Chapter 1

Synthesis, *In Vitro* Antiproliferative Activity and *In Silico* Studies of Indole-Piperidine Hybrids Bearing Amide and Urea Linkages

1.1 Introduction

Heterocyclic compounds are fundamental to organic chemistry because of their deep biological relevance.[1] The indole and piperidine frameworks stand out due to their widespread use in medicinal and natural products.[2] A bicyclic structure consisting of a pyrrole ring fused to a benzene ring, indole is a favored scaffold present in many physiologically active substances, such as natural alkaloids like vincristine and reserpine, and neurotransmitters like serotonin.[3] It is a crucial structural motif in medicinal chemistry because of its distinct electrical characteristics, planarity, and capacity for π-stacking and hydrogen bonding interactions.[4]

The saturated six-membered heterocycle piperidine, on the other hand, is one of the most common structures found in medications.[5] Improvements in solubility, metabolic stability, and receptor binding affinity are among the advantageous physicochemical characteristics that the piperidine ring bestows.[6]

When designing new pharmacologically active compounds, the clever combination of piperidine and indole moieties inside a single structural framework has shown to be a potent strategy.[7] These hybrid structures frequently have synergistic effects that result in improved biological activities, such as antiviral,[8] anticancer,[9] antibacterial,[10] and anti-inflammatory qualities.[11] By combining the biological adaptability of the piperidine ring with the indole core, the combination enables the modification of binding affinities and selectivity profiles toward a variety of biological targets.

Piperidine-containing indole derivatives can be created synthetically using a variety of methods, including multicomponent processes, Pictet-Spengler reactions, and contemporary transition-metal-catalyzed cross-coupling techniques.[12] As part of a larger movement toward sustainable chemistry, recent developments have also placed an emphasis on green chemistry techniques, such as solvent-free and microwave-assisted syntheses.[13]

Some of the indole derivatives with piperidine moiety have demonstrated potential due to the wide biological significance shown like antidepressant (Indalpine, **1**),[14] antiviral (Ajmalicine, **2**),[15] anticancer (Mitraphylline, **3**),[16] antidepresents (Mitragynine, **4**),[17] anti-HIV (Atevirdine, **5**),[18] anti-HIV (Delavirdine, **6**),[19] anti-tumorigenic drug (Brivanib, **7**).[20] Perticularly, in the recent past many indole-based molecules such as Tadalafil (**8**),[21] Alectinib (**9**),[22] Apaziquinone (**10**),[23] Panobinostat (**11**)[24] have been approved against different types of cancer, demonstrating their potential for new lead generation (**Figure 1**).

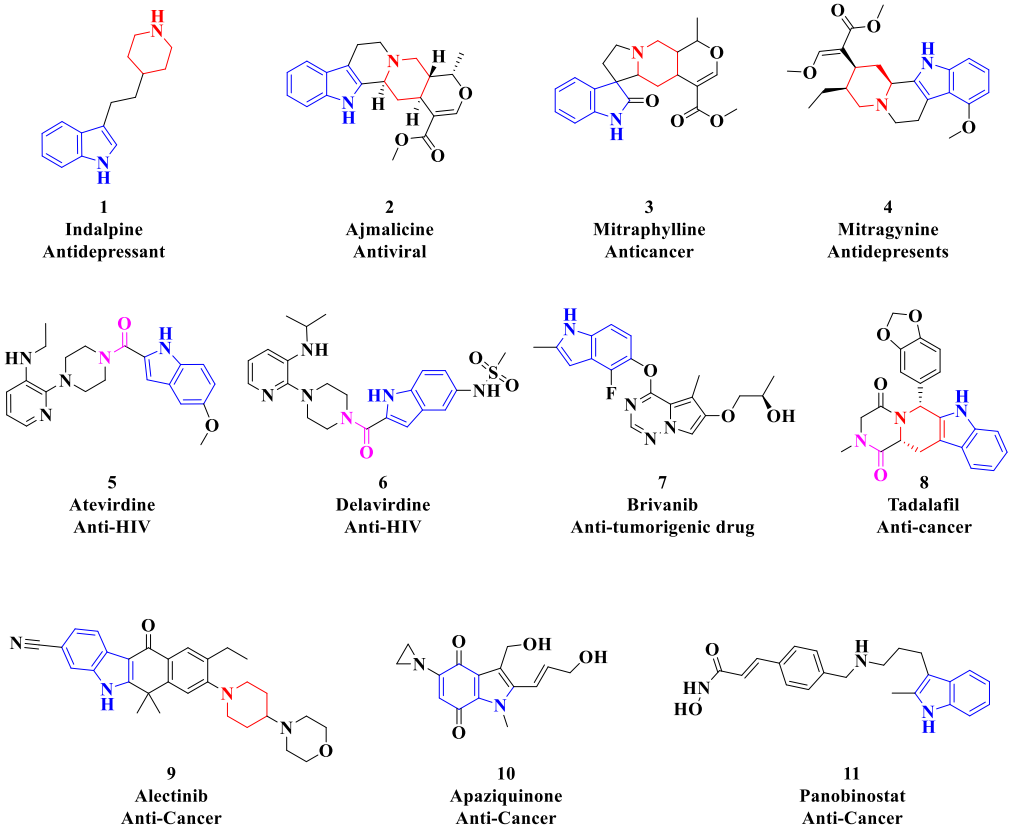


Figure 1: Marketed drugs and important compounds containing indole and piperidine motifs.

1.1.1 Synthetic methodologies for the substituted indole and piperidine framework and its biological significance

The sulphonamide of 1*H*-indole (**12**) stirred with NaH in THF, and the reaction mixture was stirred at 0 °C for 15 min, after 15 min the corresponding benzenesulfonyl chloride derivatives (**13**) was added, and reaction was stirred at 25 °C for 16h, yielded 1-(phenylsulfonyl)-1*H*-indole derivatives (**14**) (**Figure 2**).[25]

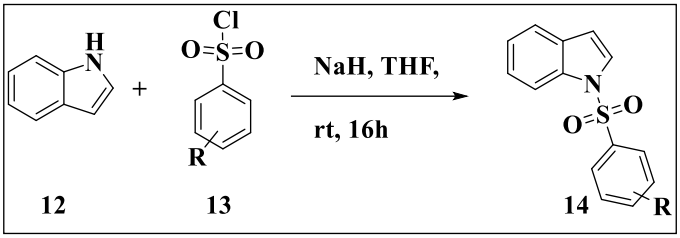


Figure 2

1*H*-Indole (**12**) was dissolved in DMSO, the reaction was stirred at 180 °C for 2h after adding of KOH, $CuCeO_2$, 1,10-phenanthroline, and 4-bromobenzene derivatives (**15**) to get produced 1-phenyl-1*H*-indole derivatives (**16**) with a good yield (**Figure 3**).[26]

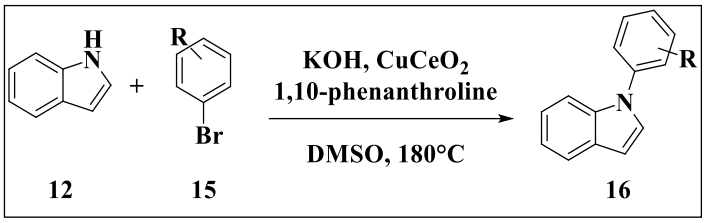


Figure 3

At ambient temperature, a combination of allyl chloride, NaOH, and 1*H*-indole (**12**) was agitated with DMSO for 3h under argon environment to get **18** (**Figure 4**).[27]

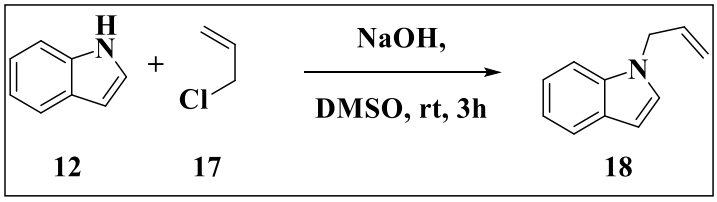


Figure 4

A soludion of 1*H*-indole (**12**) and aryl halide (**19**) in DMF, CuI, Metformin hydrochloride and CS_2CO_3 were added and the reaction was stirred at 130 °C for 4h to get derivatives of **20** (**Figure 5**).[28]

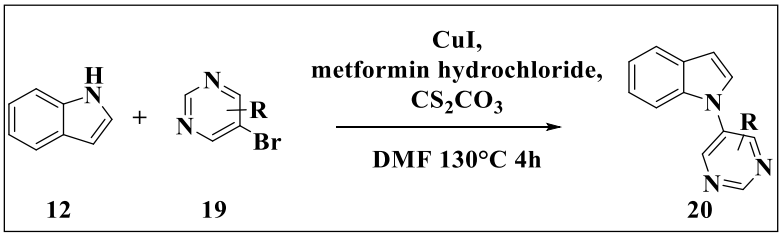


Figure 5

The nitrogen of 1*H*-indole (**12**) was protected by derivatized benzyl halide, by using NaH in THF, and the reaction mixture was stirred for 30 min 25 °C. After 30 minutes, substituted benzyl chloride (**21**) was added, and the reaction was stirred at 25 °C for 4h to give derivatives of **22** (**Figure 6**).[29]

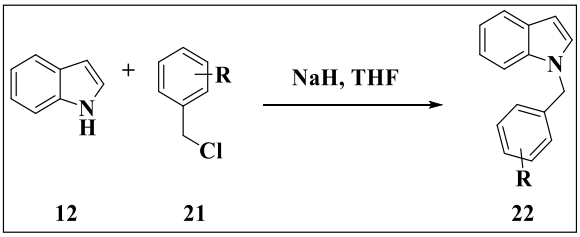


Figure 6

The amide formation via acid amine coupling reaction in between 1-benzyl-1*H*-indole-2-carboxylic acid derivatives (**23**) and ethyl piperidine-4-carboxylate (**24**) in the presence of EDC.HCl, HOBT, DIPEA in DCM, and reaction was stirred at 25 °C for 16h to get the crude product. Crude was through crystallization to get derivatives of ethyl 1-(1-benzyl-1*H*-indole-2-carbonyl)piperidine-4-carboxylate (**25**) (**Figure 7**).[30]

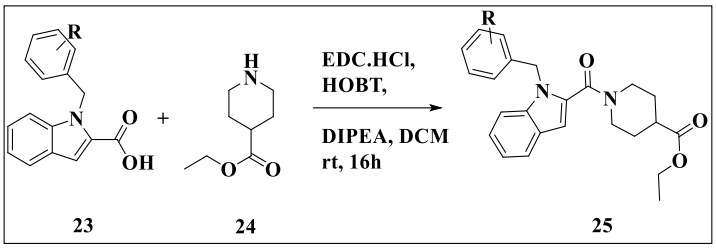


Figure 7

The 1-methyl-1*H*-indole-2-carboxylic acid derivatives (**26**) were reacted with 1-hydroxypyrrolidine-2,5-dione (**27**) in DCM, EDC.HCl, HOBT and DIPEA were added and the reaction was stirred at 25 °C for 16h. To get 2,5-dioxopyrrolidin-1-yl 1-methyl-1*H*-indole-2-carboxylate derivatives (**28)** was isolated via precipitation (**Figure 8**).[31]

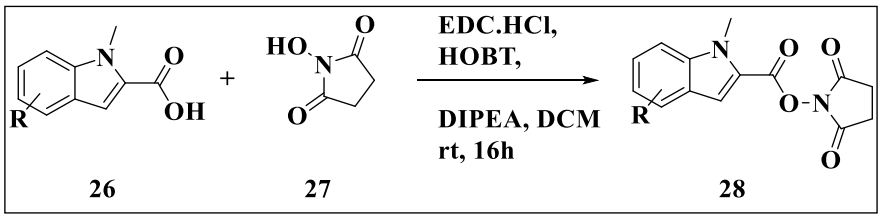


Figure 8

2-chloro-4,6-dimethoxy-1,3,5-triazine (**29**) was dissolved in toluene. Correspond indole acid (**26**) and *N*-methyl morpholine were added and reaction was stirred at 25 °C for 16h to get derivatives of **30** (**Figure 9**).[32]

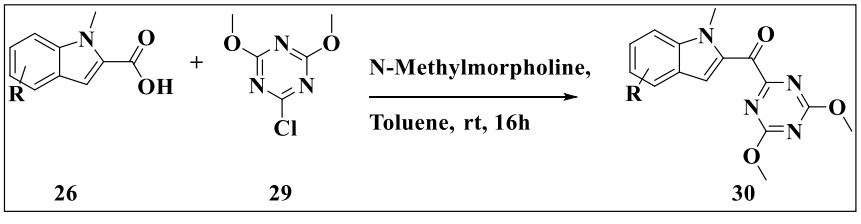


Figure 9

HATU was added to a solution of 1*H*-indole-3-carboxylic acid (**31**), piperidine-4-carboxamide (**32**), and DIPEA in DMF. The mixture was stirred for 16h at 25 °C, after completion of reaction reaction mixture was filter through celite bed and filtrate was evaporated to dryness to get 1-(1*H*-indole-3-carbonyl)piperidine-4-carboxamide (**33**) (**Figure 10**).[33]

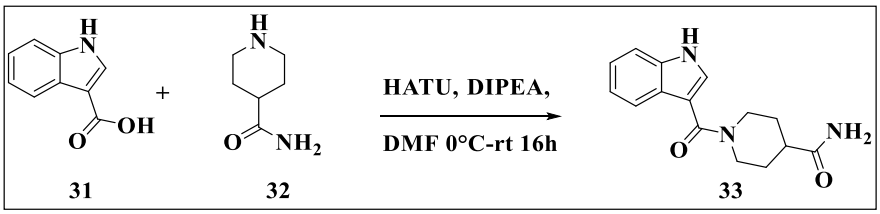


Figure 10

Some indole derivatives have good biological activity, such as antiinflammatory (**34**), antitubercular (**35**),[34] antioxidant (**36**), antidiabetic (**37**),[35] antifungal (**38**),[36] antipsychotic (**39**),[37] antiviral (**40**),[38] and carbonic anhydrase inhibitor (**41**)[39] as shown in **Figure 11**.

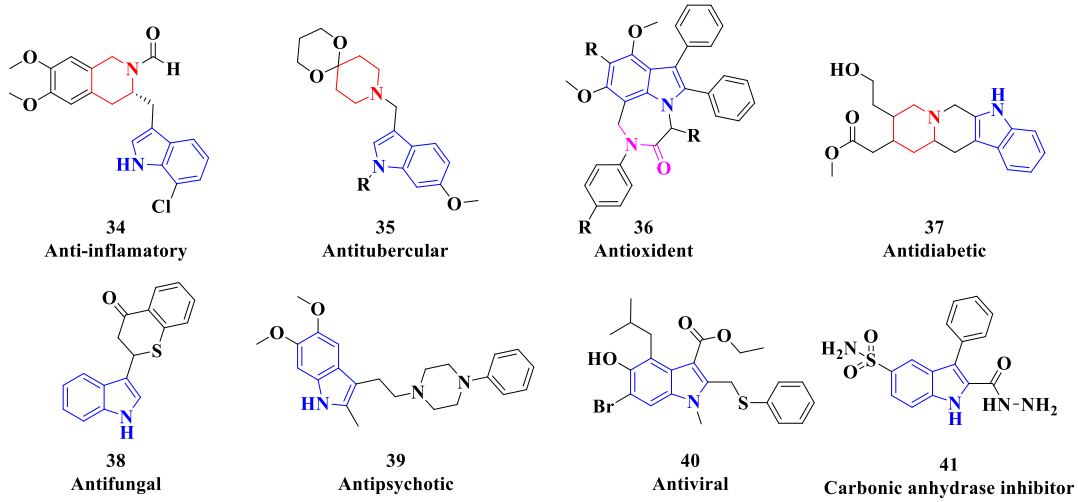


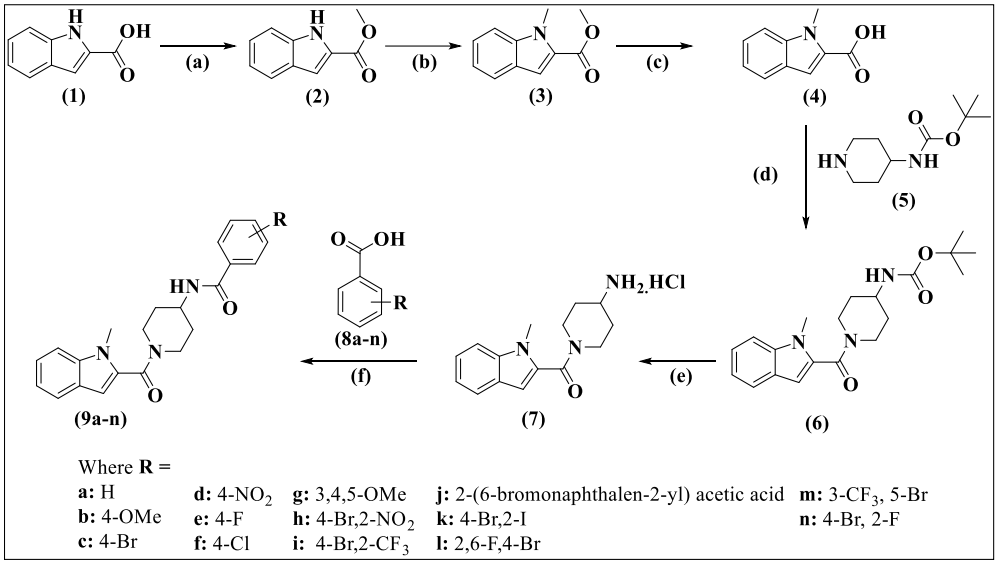
Figure 11: Important biologically active compounds containing indole and piperidine motifs.

1.2 Results and Discussion

1.2.1 Chemistry

In order to investigate a variety of chemical and possible pharmacological features, a series of processes aiming at functional group modification were used to synthesize the indole piperidine hybrid with amide linkage (**9a-n**). 1*H*-indole-2-carboxylic acid (**1**) was esterified to produce methyl 1*H*-indole-2-carboxylate (**2**) in a 70% yield.[40] In the

presence of K_2CO_3, compound (**2**) further reacted with methyl iodide for *N*-alkylation, yielding methyl 1-methylindole-2-carboxylate (**3**) with an 88% yield.[41] Its molecular ion peak $[M+1]^+$ at 190 *m/z* and 100% purity were confirmed by LC-MS analysis. 1-methylindole-2-carboxylic acid (**4**) was generated by hydrolyzing *N*-methyled indole ester (**3**) with KOH and then acidifying it with 1N HCl, as determined by ^{1}H NMR data.[42] Compound **4** and tert-butyl piperidin-4-yl carbamate (**5**) underwent a conventional acid-amine reaction to produce compound tert-butyl [1-(1-methylindole-2-carbonyl)piperidin-4-yl]carbamate (**6**), which was validated by LC-MS (*m/z* = 358) to have a 63% yield.[43] Using a 4M HCl solution in dioxane, the Boc deprotection process produced (4-aminopiperidin-1-yl)(1-methylindol-2-yl)methanone hydrochloride (**7**) with an 85% yield.[44] Using HATU and DIPEA in DMF as a solvent, compounds (**9a-n**) were created by acid-amine coupling compound **7** with substituted benzoic acids (**8a-n**) (Scheme 1). FTIR spectroscopy, ^{1}H NMR, ^{13}C NMR were used to confirm the structures of compounds **9a-n**.

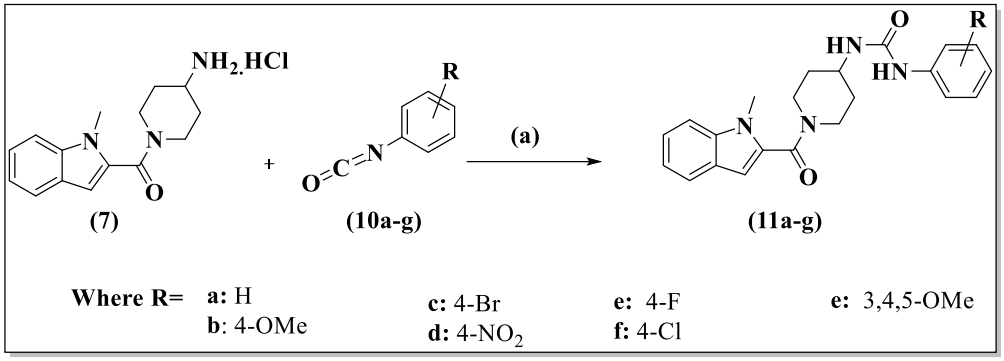


Reaction conditions: a) H_2SO_4 (Cat.), MeOH, 70 °C, 24h; b) K_2CO_3 (3 eq), MeI (2 eq), DMF, 25 °C, 16h; c) KOH (3 eq), MeOH, H_2O, 25 °C, 16h; d) Compound **5** (1 eq), HATU (1.5 eq), DIPEA (3 eq), DMF 0 °C, 25 °C, 3h; e) 4M HCl in 1,4-dioxane, 25 °C, 16h; f) R-COOH (**8a-n**), HATU (1.5 eq), DIPEA (3 eq), DMF, 0 °C-25 °C, 16h.

Scheme 1: Synthesis of indole-piperidine hybrid with amide linkage (**9a-n**).

As listed in Table 1, many experiments have been conducted to couple (4-aminopiperidin-1-yl)(1-methylindol-2-yl)methanone hydrochloride (**7**) with different anilines/isocyantes in order to produce indole piperidine hybrid compounds with phenylurea linkage (**11a-g**). Initially, CDI (Method-A) and triphosgene (Method-B)

were used, which primarily resulted in aniline self-urea production instead of the intended result, as confirmed by LC-MS analysis. However, compound **7** showed a 50–60% conversion rate for the intended products when directly substituted phenyl isocyanates (**10a-g**) were utilized to react with it under basic conditions (Method-C). This approach was used to synthesize seven phenylurea derivatives (**11a-g**) (Scheme 2) and isolate them with a purity of over 95% by LC-MS, which was confirmed by elemental analysis, ^{1}H NMR, ^{13}C NMR, and FTIR spectroscopy.



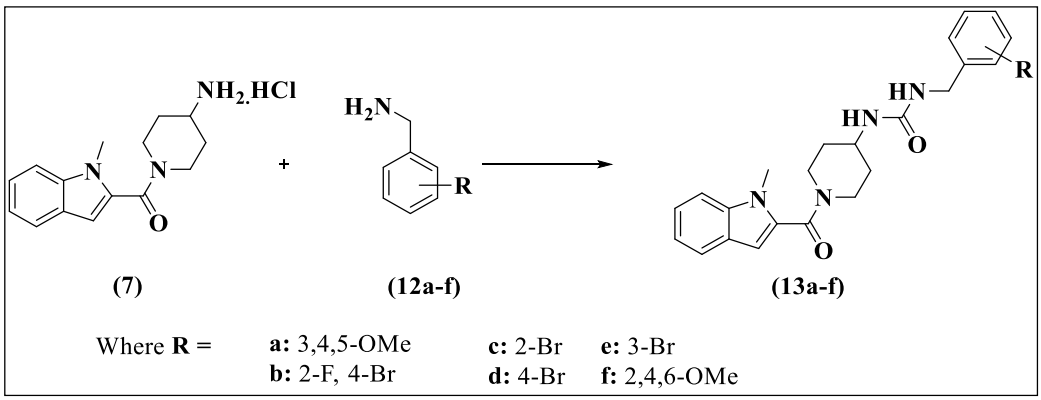
Reaction conditions: a) Compound **7** (1 eq), aryl isocyanates (**10a-g**) (0.9 eq), TEA (5.0 eq), THF, 0 °C to 25 °C, 8h.

Scheme 2: Synthesis of indole-piperidine hybrid with phenylurea linkage (**11a-g**).

Table 1: Optimization of reaction conditions for indole piperidine hybrid with phenylurea linkage (**11a-g**).

Method	Amine (7)	Substituted aniline/ Isocyanate	Reagent	Base	Reaction Condition	LC-MS observation
A	0.6 eq	Aniline (1 eq)	CDI (1 eq)	TEA (3 eq)	DCM 25 °C, 16h	Self-urea formation of aniline
B	0.6 eq	Aniline (1 eq)	Triphosgene (1 eq)	TEA (3 eq)	THF 70 °C, 3h	Self-urea formation of aniline
C	1 eq	Isocyanate (0.9 eq)	-	TEA (5 eq)	THF 25 °C, 16h	50-60% Product conversion

Optimization attempts were also conducted in order to create indole piperidine hybrid compounds with benzylurea derivatives (**13a-f**). As can be seen in Table 2, triphosgene did not provide the anticipated result when used in DCM (Method A) with TEA present. When the solvent was switched from DCM to THF (Method B), the situation improved and **13a** was produced in a 30% yield. Fortunately, 70% conversion was seen when this reaction was conducted using CDI (Method-C) with TEA present, yielding the required **13a**. Six benzylurea derivatives (**13a-f**) (Scheme 3) with purity over 95% by LC-MS were isolated by following the conditions of Method-C. These were confirmed by elemental analysis, ^{1}H NMR, ^{13}C NMR, and FTIR spectroscopy.



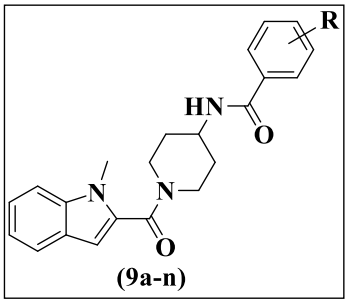
Reaction conditions: a) Compound **7** (1 eq), Substituted benzylamines (**12a-f**) (1 eq), CDI (1.0 eq), TEA (6.0 eq), DCM, 0 °C to 25 °C, 16h.

Scheme 3: Synthesis of indole-piperidine hybrid with benzyl urea linkage (**13a-f**).

Table 2: Optimization of reaction conditions for indole-piperidine hybrid with benzylurea linkage (**13a-f**).

Method	Amine (7)	Substituted benzyl amines (12a-f)	Reagent	Base	Reaction Condition	LC-MS Result
A	1 eq	1 eq	Triphosgene (0.7 eq)	TEA (3 eq.)	DCM (10 vol) 25°C, 16h	amine (**7**) remains unreacted
B	1 eq	1 eq	Triphosgene (0.8 eq)	TEA (3 eq.)	THF 70°C, 6h	30% Product conversion
C	1 eq	1 eq	CDI (1 eq)	TEA (6 eq)	DCM (10 vol) 25°C, 16h	72% Product conversion

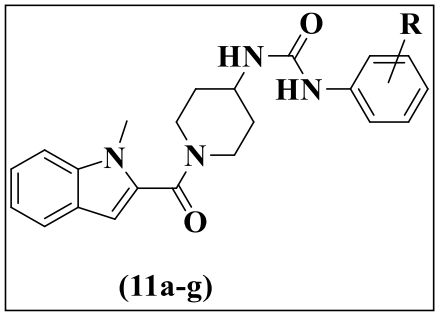
Table 3: Physicochemical characteristics of the novel piperidine containing indole derivatives **9a-n**.



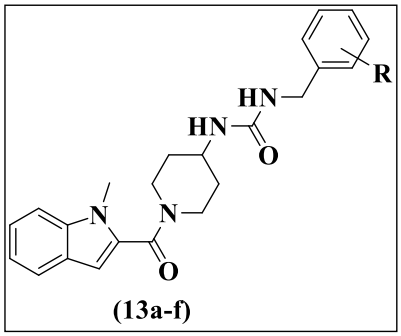
(9a-n)

Compounds	R	Molecular Weight	Molecular Formula	Yield (%)	Melting Point (°C)
9a	H	361.45	$C_{22}H_{23}N_3O_2$	85	194-196
9b	4-Ome	391.47	$C_{23}H_{25}N_3O_3$	93	193-196
9c	4-Br	440.34	$C_{22}H_{22}BrN_3O_2$	91	192-195
9d	4-NO_2	406.44	$C_{22}H_{22}N_4O_4$	92	190-192
9e	4-F	379.44	$C_{22}H_{22}FN_3O_2$	83	176-179
9f	4-Cl	395.89	$C_{22}H_{22}ClN_3O_2$	91	184-186
9g	3,4,5-Ome	451.52	$C_{25}H_{29}N_3O_5$	94	185-188
9h	4-Br,2-NO_2	485.34	$C_{22}H_{21}BrN_4O_4$	88	155-158
9i	4-Br,2-CF_3	508.34	$C_{23}H_{21}BrF_3N_3O_2$	92	160-162
9j	2-(6-bromonaphthalen-2-yl) acetic acid	504.43	$C_{27}H_{26}BrN_3O_2$	89	189-191
9k	4-Br,2-I	566.24	$C_{22}H_{21}BrIN_3O_2$	86	185-187
9l	2,6-F,4-Br	476.32	$C_{22}H_{20}BrF_2N_3O_2$	80	192-195
9m	3-CF3, 5-Br	508.34	$C_{23}H_{21}BrF_3N_3O_2$	92	162-165
9n	4-Br, 2-F	458.33	$C_{22}H_{21}BrFN_3O_2$	90	186-189

Table 4: Physicochemical characteristics of the novel piperidine containing indole derivatives **11a-g**, and **13a-f**.



(11a-g)



(13a-f)

Compounds	R	Molecular Weight	Molecular Formula	Yield (%)	Melting Point (°C)
11a	H	376.46	$C_{22}H_{24}N_4O_2$	78	184-186
11b	4-OMe	406.49	$C_{23}H_{26}N_4O_3$	76	187-190
11c	4-Br	455.36	$C_{22}H_{23}BrN_4O_2$	81	194-197
11d	4-NO_2	421.46	$C_{22}H_{23}N_5O_4$	73	194-197
11e	4-F	394.45	$C_{22}H_{23}FN_4O_2$	78	185-188
11f	4-Cl	410.90	$C_{22}H_{23}ClN_4O_2$	75	176-179
11g	3,4,5-OMe	466.54	$C_{25}H_{30}N_4O_5$	71	145-148
13a	3,4,5-OMe	480.57	$C_{26}H_{32}N_4O_5$	76	140-143
13b	2-F,4-Br	487.37	$C_{23}H_{24}BrFN_4O_2$	60	187-190
13c	2-Br	469.38	$C_{23}H_{25}BrN_4O_2$	78	187-190
13d	4-Br	469.38	$C_{23}H_{25}BrN_4O_2$	75	194-197
13e	3-Br	469.38	$C_{23}H_{25}BrN_4O_2$	75	195-198
13f	2,4,6-OMe	480.57	$C_{26}H_{32}N_4O_5$	76	194-197

1.3 Anticancer Activity

The potential anticancer activity of each of the recently synthesized hybrid indole-piperidine derivatives with substituted amide (**9a-n**) and urea linkage (**11a-g**, **13a-f**) against a variety of cancer cell lines, including leukemia, non-small cell lung cancer, colon cancer, CNS cancer, melonoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer analyzed by Developmental Therapeutics Program, that falls under Division of Cancer Treatment & Diagnosis (DCTD) of National Cancer Institute, National Institute of Health (NIH), Germantown, USA. Among them, compounds **9c**, **11d**, **13b**, and **13e** shown noteworthy effects against renal cancer (UO-31), compound

11f demonstrated noteworthy action against breast cancer (MDA-MB-468) and leukemia (RPMI-8286), and compound **9j** shown remarkable activity against CNS cancer (SNB-75). Moreover, compound **11b** has moderate action against the CNS cancer subpanels (SF-268, SNB-19, SNB-75, and U251), and compound **11c** also exhibits moderate activity against these subpanels.

Table 5. Average of Percentage Growth (% ± Standard Deviation) of the NCI-60 cancer subpanels by amide derivatives **9a–n** calculated from one dose assay results.

Subpanels	Compounds													
	9a	**9b**	**9c**	**9d**	**9e**	**9f**	**9g**	**9h**	**9i**	**9j**	**9k**	**9l**	**9m**	**9n**
Leukemia (6)*	103.01	96.65	74.95	76.79	95.40	86.74	93.00	83.35	88.42	82.64	89.76	99.93	79.85	104.24
	± 16.26	± 12.75	± 14.61	± 11.79	± 9.86	± 12.25	± 8.95	± 8.38	± 7.74	± 9.34	± 17.31	± 12.46	± 18.46	± 17.92
Non-Small Cell Lung	100.16	92.97	86.20	85.90	97.00	93.76	88.68	88.04	97.31	68.28	87.17	90.95	83.83	91.16
Cancer (9)	± 7.65	± 9.53	± 17.52	± 22.16	± 11.89	± 9.43	± 12.63	± 18.49	± 13.68	± 16.20	± 6.06	± 10.64	± 11.54	± 10.46
Colon Cancer (6)	108.03	101.25	94.47	98.35	104.78	103.75	101.88	97.53	105.04	87.44	101.50	105.18	96.68	104.67
	± 6.35	± 4.17	± 11.44	± 9.17	± 7.18	± 7.25	± 8.03	± 7.33	± 7.67	± 13.73	± 7.76	± 12.70	± 9.88	± 9.28
CNS Cancer (6)	98.19	95.68	80.29	89.21	97.14	97.27	94.36	83.79	88.67	**35.88**	88.47	92.61	78.22	96.60
	± 12.49	± 7.08	± 12.91	± 13.86	± 10.66	± 7.97	± 15.35	± 10.28	± 10.27	**± 26.53**	± 9.30	± 11.00	± 17.13	± 9.28
Melanoma (9)	97.94	91.26	83.26	84.68	98.46	96.84	100.03	93.88	100.93	93.92	71.59	108.69	95.80	86.17
	± 12.05	± 12.96	± 29.98	± 20.89	± 15.78	± 22.16	±13.85	± 16.66	± 12.67	± 11.91	± 25.9	± 8.44	± 14.69	± 20.58
Ovarian Cancer (7)	110.13	101.46	92.24	94.09	108.51	103.05	97.21	96.58	100.51	65.59	95.68	94.61	82.49	97.27
	± 16.06	± 9.26	± 12.25	± 11.77	± 14.95	± 9.45	± 8.03	± 13.12	± 5.24	± 22.75	± 12.84	± 5.81	± 8.29	± 4.33
Renal Cancer (7)	96.91	93.85	**76.13**	89.45	101.85	102.12	114.29	103.49	97.95	81.04	105.92	105.31	94.11	113.23
	± 9.02	± 10.76	**± 45.19**	± 15.45	± 15.34	± 18.52	± 36.29	± 29.99	± 16.45	± 27.83	± 32.53	± 36.96	± 31.5	± 36.54
Prostate Cancer (2)	102.43	98.39	82.07	86.90	100.01	96.59	99.16	92.22	99.62	78.02	94.32	97.69	83.57	100.18
	± 10.10	± 8.36	± 7.66	± 6.66	± 19.42	± 14.07	± 16.33	± 11.14	± 8.71	± 18.09	± 1.81	± 9.56	± 12.68	± 9.89
Breast Cancer (6)	100.10	92.64	88.59	93.72	109.62	100.38	92.00	79.37	88.94	68.36	94.64	103.79	88.42	89.17
	± 16.61	± 12.65	± 28.48	± 27.56	± 38.02	± 29.87	± 29.30	± 12.41	± 9.17	± 22.74	± 50.92	± 48.73	± 40.56	± 29.72

*Value in paranthasis represents No. of subpanel taken for average calculation

Table 6. Average of Percentage Growth (% ± Standard Deviation) of the NCI-60 cancer subpanels by phenylurea derivatives **11a-g** and benzylurea derivatives **13a-f** calculated from one dose assay results.

Subpanels	**Compounds**													
	11a	**11b**	**11c**	**11d**	**11e**	**11f**	**11g**	**13a**	**13b**	**13c**	**13d**	**13e**	**13f**	**Imatinib[#]**
Leukemia (6)*	97.73	102.35	93.45	66.97	89.42	**22.45**	98.89	98.16	83.34	83.47	102.84	89.56	87.63	33.73 ±
	± 13.55	± 11.23	± 11.59	± 14.98	± 19.80	**± 20.33**	± 5.46	± 14.28	± 23.75	± 16.60	± 15.49	± 16.19	± 15.00	31.32 (6)*
Non-Small Cell Lung	93.26	92.81	85.76	86.57	83.31	77.6	108.44	98.27	85.78	97.24	90.65	87.49	95.91	77.52 ±
Cancer (9)	± 8.50	± 28.62	± 20.49	± 27.83	± 20.65	± 55.81	± 20.08	± 12.88	± 24.92	± 12.88	± 16.59	± 10.81	± 6.59	15.88 (9)
Colon Cancer (6)	100.61	102.03	98.15	91.58	90.19	70.56	109.35	105.49	101.88	102.67	105.79	96.64	103.69	72.67 ±
	± 6.91	± 8.69	± 7.77	± 11.59	± 16.20	± 13.86	± 7.51	± 2.35	± 12.38	± 8.86	± 4.38	± 10.52	± 5.21	18.91 (6)
CNS Cancer (6)	90.67	**40.89**	**46.24**	83.91	81.39	68.55	94.52	93.29	83.07	89.73	57.10	84.18	90.60	70.38 ±
	± 9.94	**± 21.48**	**± 23.45**	± 10.73	± 25.82	± 28.86	± 8.69	± 4.38	± 11.01	± 7.31	± 21.12	± 6.73	± 10.38	19.20 (6)
Melanoma (9)	96.03	92.34	82.52	73.71	93.92	71.59	108.69	95.81	86.17	92.76	94.67	89.31	97.08	71.95 ±
	± 10.06	± 11.53	± 12.99	± 21.65	± 11.91	± 25.9	± 8.44	± 14.69	± 20.58	± 13.10	± 12.81	± 11.54	± 12.39	18.49 (8)
Ovarian Cancer (7)	100.43	93.21	79.40	83.29	83.58	62.95	101.14	111.27	79.15	102.85	88.99	89.68	105.22	91.23 ±
	± 6.31	± 23.92	± 23.89	± 13.09	± 9.83	± 21.89	± 8.23	± 30.13	± 14.71	± 21.92	± 32.29	± 11.46	± 15.03	12.48 (7)
Renal Cancer (7)	90.14	95.17	80.90	**68.46**	82.62	74.12	104.8	95.81	**42.06**	84.94	84.12	**60.63**	95.23	81.80 ±
	± 30.84	± 18.76	± 32.26	**± 55.52**	± 12.70	± 23.56	± 14.87	± 7.83	**± 69.58**	± 32.32	± 34.36	**± 64.62**	± 8.9	10.35 (7)
Prostate Cancer (2)	100.44	104.01	91.96	95.77	90.32	69.79	115.00	97.28	92.33	95.23	98.01	89.71	96.48	80.10 ±
	± 2.56	± 13.89	± 0.11	± 7.90	± 1.64	± 11.48	± 3.53	± 8.64	± 12.64	± 6.96	± 6.01	± 8.55	± 4.00	11.46 (2)
Breast Cancer (6)	92.49	94.99	95.15	87.15	73.75	**40.09**	120.84	108.00	92.05	94.50	94.27	101.30	92.50	65.86 ±
	± 6.69	± 44.86	± 50.78	± 30.77	± 20.04	**± 39.12**	± 45.44	± 27.66	± 36.01	± 16.82	± 23.08	± 32.16	± 7.58	11.02 (5)

*Value in paranthasis represents no. of subpanel taken for average calculation, [#]Data were referred from NCI data warehouse index

1.4 Structure Activity Relationship (SAR)

We assessed the anticancer potential of all the newly synthesized hybrid indole-piperidine compounds with substituted amide (**9a-n**) and urea linkages (**11a-g**, **13a-f**). The most effective compound among them was compound **13b** (4-Br, 2-F) with benzylurea linkage, which showed a significant inhibition of -83.76%, showing greater kidney cancer (UO-31) action in comparison to the other compounds. With phenylurea linkage, compound **11d** (4-NO_2) had remarkable activity against the same cell line, demonstrating its strong anticancer effects across a range of cancer types with negative inhibition values of -49.98%. Compounds **9c** (4-Br) with amide linkage and **13e** (3-Br) with benzylurea linkage also shown significant action in kidney carcinoma (UO-31) with negative inhibition values of matching -22.98% and -82.75. The phenylurea-linked compound **11f** (4-Cl) showed impressive action, with negative inhibition values of -18.24% in breast cancer (MDA-MB-468) and -7.80% in leukemia (RPMI-8286). Compound **9j** [2-(6-bromonaphthalen-2-yl) acetic acid] with amide linkage also showed impressive action in CNS cancer (SNB-75) with negative inhibition calues of -7.41%. All things considered, the derivatives of most substances that include an electron-withdrawing group at position 4 on the side chain aromatic ring greatly increase their anticancer activity.

1.5 Molecular Docking

In the course of many human illnesses, including cancer, angiogenesis the creation of new blood vessels from the preexisting vasculature is crucial for the growth, spread, and survival of tumors. Vascular endothelial growth factor (VEGF), a potent angiogenic agent that stimulates the development of tumors, is one of several growth factors and cytokines that control this intricate process. Through its interaction with two main receptor tyrosine kinases (RTKs) expressed on endothelial cells, VEGF receptor 1 (VEGFR-1) and VEGF receptor 2 (VEGFR-2), VEGF stimulates endothelial cell proliferation, migration, and tube formation, hence promoting tumor development. Current research indicates that VEGFR-2 mediates the majority of VEGF's angiogenic actions, whereas the relationship between VEGF and VEGFR-1 plays a minor part in angiogenesis. Thus, in the creation of anticancer drugs, VEGF and VEGFR-2 have both become significant therapeutic targets.

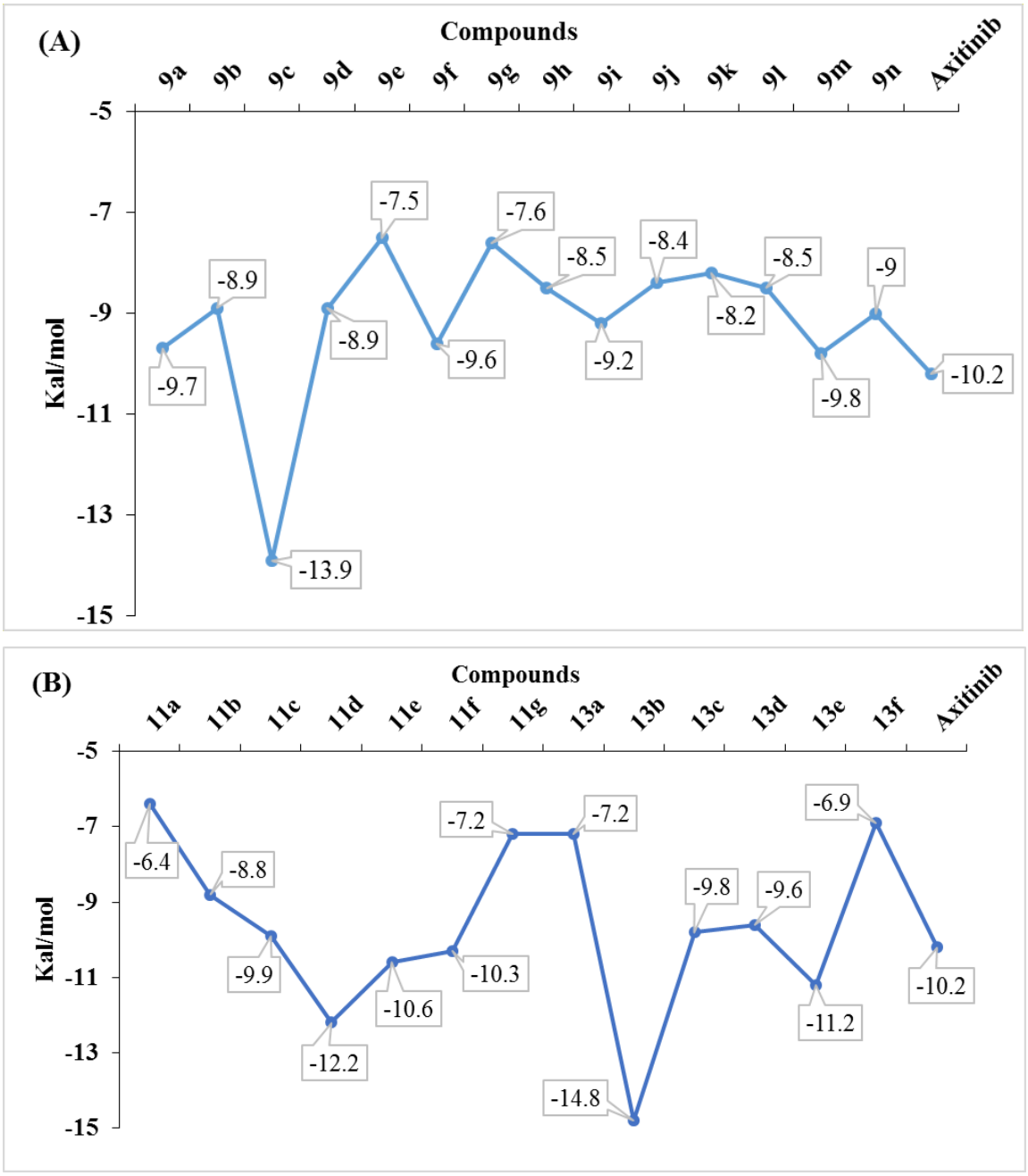


Figure 12: Docking score of (**A**) compounds **9a-n**, and (**B**) compounds **11a-g** and **13a-f** against VEGFR.

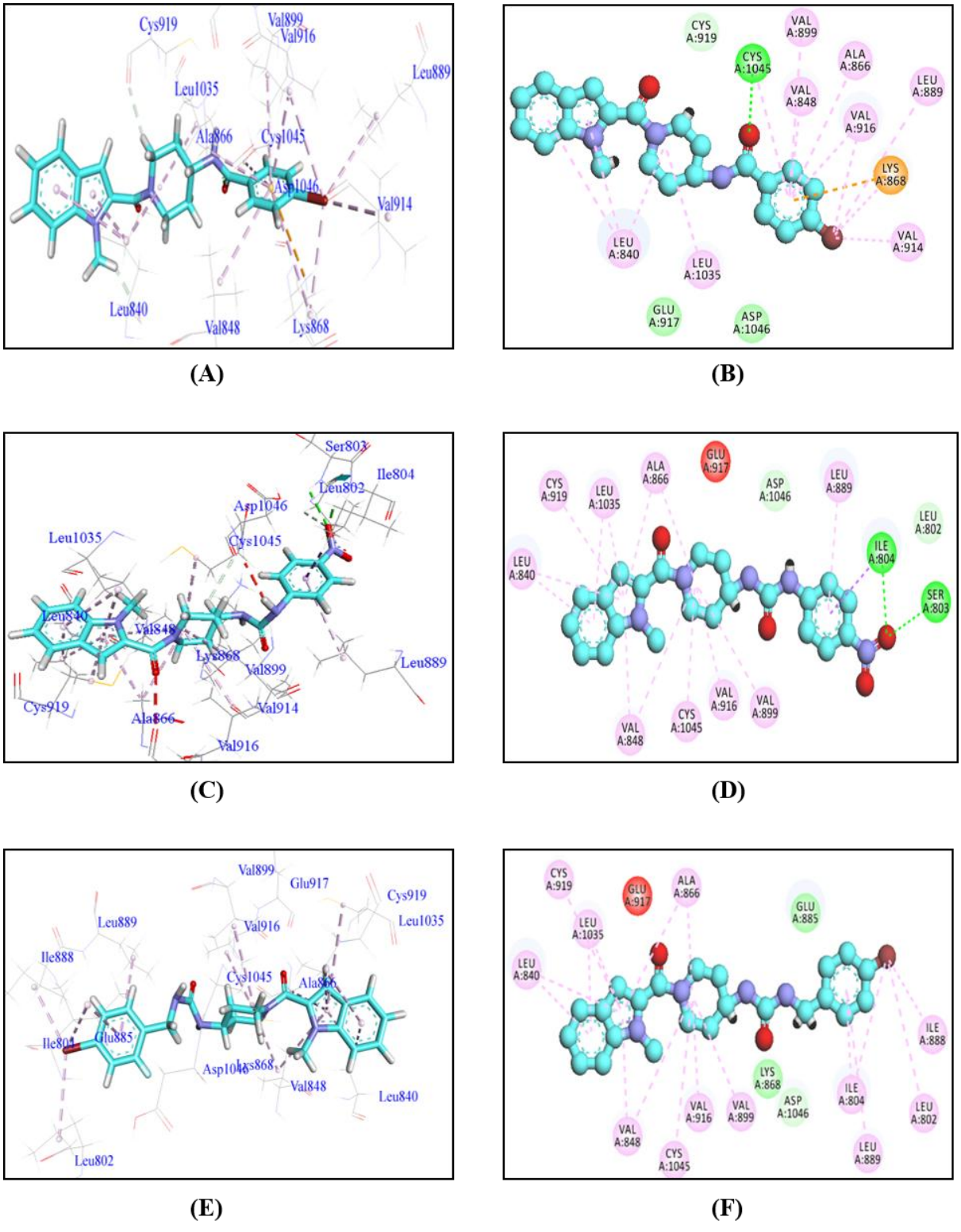


Figure 13: Docking images of compounds **9c, 11d** and **13b** : (A) 3D view; (B) 2D view of compound **9c**; (C) 3D view; (D) 2D view of **11d**; (E) 3D view and (F) 2D view of **13b**. H-bond denoted by green dash line, pink and gray dash line-lipophilic contacts, orange color lines represents pi-cation interaction.

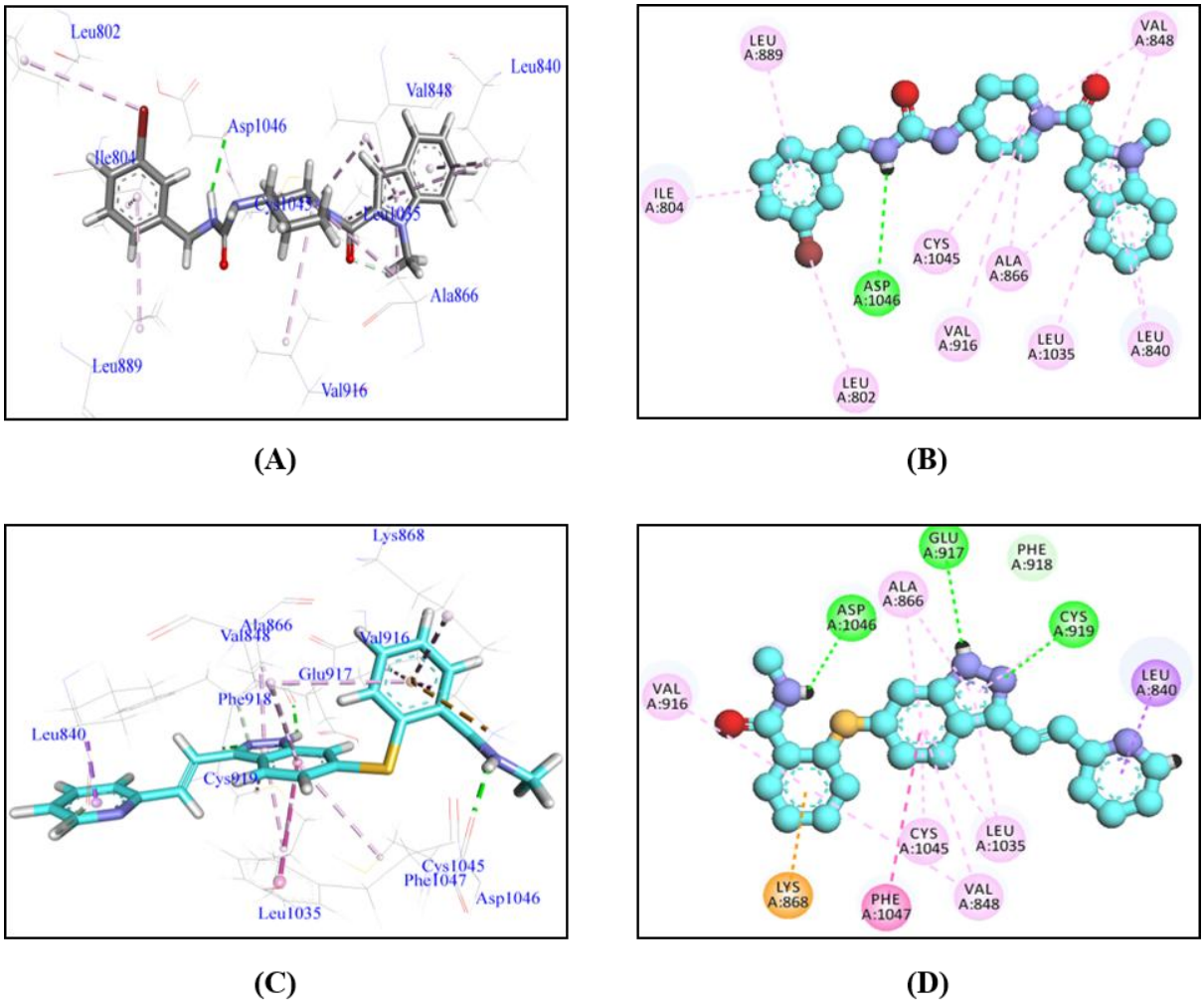


Figure 14: Docking images of compounds **13e** and axitinib: (A) 3D view; (B) 2D view of compound **13e**; (C) 3D view; (D) 2D view of axitinib. H-bond denoted by green dash line, pink and gray dash line-lipophilic contacts, orange color lines represents pi-cation interaction.

1.6 ADMET evaluation

Developing novel treatments requires ensuring the safety and effectiveness of the pharmaceutical molecules, and *in silico* pharmacokinetic profiling delivers a useful method for evaluating these variables early in the drug development process.[45] In this investigation, we used Lipinski's criteria, which are generally acknowledged as important markers of first pharmacological viability to assess the synthetic compounds' drug-likeness. Lipinski's rule of five states that an oral active chemical should have a molecular weight of less than 500 Daltons, a Log P value of less than 5, and no more than five hydrogen bond donors or ten hydrogen bond acceptors. A violation of these rules is permitted at most once.[46] with a processing score of 0.55, the findings, which

are presented in Table **7**. Show that, with a few exceptions, almost all molecules meet the 500-Dalton molecular weight barrier. With values for all indole derivatives ranging from -4.10 to -6.34, the analysis showed that the water solubility (Log S) of most of the produced compounds may be used as a gauge of their bioavailability. Favorable membrane permeability was suggested by the lipophilicity (Log Po/w) values, which were determined to be below 6, especially ranged from 2.74 to 5.77. Furthermore, synthetic accessibility was used to evaluate the structural complexity of the recently synthesized compounds. The findings show that, according to their scores, all indole derivatives have a rather simple synthetic pathway.[47]

Table 7. Physicochemical, Pharmacokinetic and medicinal chemistry properties of the synthesized molecules **9a-n**, **11a-g** and **13a-f**.

Physicochemical properties							**Pharmacokinetics**		**Medicinal chemistry**	
Compound	**MW**	**HBA**	**HBD**	**TPSA**	**Log $P_{o/w}$**	**Log S**	**GIA**	**Log kp**	**ROF**	**SA**
9a	361.44	2	1	54.34	2.83	-4.34	High	-6.05	0	2.4
9b	391.46	3	1	63.57	2.84	-4.41	High	-6.25	0	2.57
9c	440.33	2	1	54.34	3.59	-5.25	High	-6.04	0	2.5
9d	406.43	4	1	100.16	2.74	-4.32	High	-6.54	0	2.71
9e	379.43	3	1	54.34	3.39	-4.5	High	-6.09	0	2.5
9f	395.88	2	1	54.34	3.49	-4.94	High	-5.81	0	2.47
9g	451.51	5	1	82.03	2.86	-4.49	High	-6.75	0	3.09
9h	485.33	4	1	100.16	3.50	-5.23	High	-6.53	0	3.04
9i	508.33	5	1	54.34	5.77	-6.03	High	-5.92	1	2.85
9j	504.42	2	1	54.34	4.68	-6.27	High	-5.68	1	2.89
9k	566.23	2	1	54.34	4.2	-6.34	High	-6.45	1	2.79
9l	476.31	4	1	54.34	4.71	-5.49	High	-6.22	0	2.69
9m	508.33	5	1	54.34	5.77	-6.03	High	-5.92	1	2.9
9n	458.32	3	1	54.34	4.15	-5.32	High	-6.18	0	2.67
11a	376.45	2	2	66.37	3.03	-4.10	High	-6.43	0	2.62
11b	406.48	3	2	75.6	3.04	-4.17	High	-6.64	0	2.77
11c	455.35	2	2	66.37	3.8	-5.01	High	-6.42	0	2.72
11d	421.45	4	2	112.19	2.94	-4.16	High	-6.83	0	2.88
11e	394.44	3	2	66.37	3.59	-4.26	High	-6.47	0	2.67
11f	410.9	2	2	66.37	3.69	-4.69	High	-6.19	0	2.67

11g	466.53	5	2	94.06	3.06	-4.33	High	-7.04	0	3.31
13a	480.56	5	2	94.06	2.78	-4.3	High	-7.17	0	3.33
13b	487.36	3	2	66.37	4.07	-5.14	High	-6.59	0	2.98
13c	469.37	2	2	66.37	3.51	-4.98	High	-6.55	0	2.9
13d	469.37	2	2	66.37	3.51	-4.98	High	-6.55	0	2.82
13e	469.37	2	2	66.37	3.51	-4.98	High	-6.55	0	2.88
13f	480.56	5	2	94.06	2.78	-4.3	High	-7.17	0	3.34

Molecular Weight (MW), hydrogen bond acceptors (HBA), hydrogen bond donors (HBD), topological polar surface area (TPSA), lipophilicity (Log Po/w), water solubility (Log S), gastrointestinal absorption (GIA), skin permeation (Log Kp), Lipinski's rule of five (RoF) and encompassing synthetic accessibility (SA).

1.7 Conclusion

Using LC-MS and NMR spectrum analysis, a new series of hybrid molecules of indole-piperidine derivatives with urea linkage (**11a-g**, **13a-f**) and substituted amide (**9a-n**) were characterised at NIH US, the anticancer potential of all 27 produced compounds was assessed. While compounds **9c**, **11d**, **13b**, and **13e** had noteworthy anticancer effects against kidney cancer (UO-31), Compound **11f** demonstrated noteworthy anticancer action against breast cancer (MDA-MB-468) and leukemia (RPMI-8286), with inhibition levels indicating their potential for therapeutic use. While compound **9j** (SNB-75) had efficacy against CNS cancer. Compounds **13b** and **13e** exhibited greater activity in renal cancer, as evidenced by their respective negative inhibition values of -82.75 and -83.76% (UO-31). Additionally, these indole-piperidine hybrids were shown to connect with the receptor well using molecular docking research using the Vascular Endothelial Growth Factor (VEGFR-2) protein, generating a stable protein-ligand complex that highlights the hybrids' potential as anticancer drugs.

1.8 Experimental Section

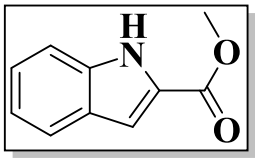
1.8.1 Material and methods for characterization of the compound

All of the melting points on an electrothermal device (HTLP Digital Melting Point Apparatus) were found using the open-capillary technique, and the findings have been adjusted. Reverse phase combi flash chromatography with UV light at 220 and 254 nm was used to purify the compounds. To record infrared spectra, a Shimadzu IR spirit spectrometer (4000–400 region) was used. Using tetramethyl silane (TMS) as an

internal standard, ^{1}H NMR and ^{13}CMR (100 MHz) spectra in DMSO-d_6, D_2O, and MeOD were recorded using a Bruker Ascend TM 400 (400 MHz) spectrometer. Chemical shifts are expressed in parts per million. Agilent water using a direct intake probe, LC-MS (purity data) spectra were recorded using an LC-MS spectrometer. The elemental analysis data was obtained using the Euro Vector EA 3000 CHNS-O analyzer. Spectrochem, TCI, and Sigma-Aldrich were the suppliers of all the chemicals, which were utilized without further purification.

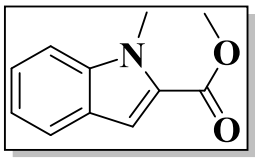
1.8.2 Chemistry

Synthesis of methyl 1*H*-indole-2-carboxylate (2)



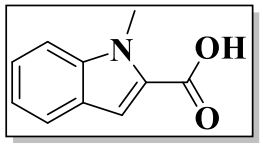
Compound methyl 1*H*-indole-2-carboxylate (**2**) was synthesized using previously reported method with yield: 70%. mp: 150-151 °C (Reported mp: 152-153 °C).[40]

Synthesis of methyl 1-methyl-1*H*-indole-2-carboxylate (3)



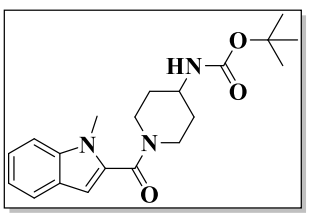
Compound methyl 1-methyl-1*H*-indole-2-carboxylate (**3**) was synthesized using previously reported method with yield: 88%. mp: 92-93 °C (Reported mp: 92-93 °C).[41]

Synthesis of 1-methyl-1*H*-indole-2-carboxylic acid (4)



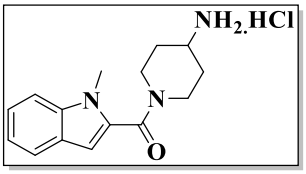
Compound 1-methyl-1*H*-indole-2-carboxylic acid (**4**) was synthesized using previously reported method with yield: 75%. mp: 120-121 °C (Reported mp: 120-122 °C).[42]

Procedure for synthesis of tert-butyl [1-(1-methyl-1*H*-indole-2-carbonyl) piperidin-4-yl] carbamate (6)



DMF (80 mL) was used to dissolve 1-methyl-1*H*-indole-2-carboxylic acid (**4**) (7.7 g, 43.95 mmol) in single-neck RBF. HATU (25.08 g, 65.92 mmol) was then added, and the reaction mixture was stirred at 25 °C for 1h. DIPEA (17 g, 131.85 mmol) and tert-butyl piperidin-4-yl carbamate (**5**) (13.2 g, 65.92 mmol) were then added, and the mixture was stirred for an additional 120 min. at 25 °C.[41] On TLC, the first indications of product formation and commencing material consumption were found. The reaction was completed by adding water, filtering the precipitates, washing them with water, adding n-pentane, and then drying them thoroughly under vacuum to get a white solid (10 g, 63% yield) tert-butyl [1-(1-methyl-1*H*-indole-2-carbonyl) piperidin-4-yl] carbamate (**6**).[43] mp: 150-152 °C. IR (KBr) ν_{max}/cm^{-1}: 3328 (NH), 3056 (aromatic-CH), 2931 (aliphatic-CH), 1677 (C=O-NH), 1621 (C=C), 1164 (C-N). ^{1}H NMR (400MHz, *DMSO-d*$_6$): δppm 7.62-7.60 (d, *J* = 8Hz, 1H, C=O-NH), 7.53-7.51 (d, *J* = 8Hz, 1H, Ar-CH), 7.27-7.24 (t, *J* = 6.8Hz, 1H, Ar-CH), 7.12-7.09 (t, *J* = 7.2Hz, 1H, Ar-CH), 6.95-6.93 (d, *J* = 6Hz, 1H, Ar-CH), 6.61 (s,1H, Ar-CH), 4.36 (bs, 1H, CH), 3.92 (bs, 1H, CH), 3.75 (s, 3H, N-CH_3), 3.57 (bs, 1H, CH), 3.35 (s, 2H, CH_2), 3.18 (bs, 2H, CH_2), 1.81 (s, 2H, CH_2), 1.40 (s, 9H, O-tBu). ^{13}C NMR (100 MHz, *DMSO-d*$_6$): δppm 162.42, 155.29, 137.64, 132.96, 126.50, 123.18, 121.58, 120.40, 110.74, 102.37, 78.12, 47.61, 46.44, 32.54, 31.23, 28.71. LCMS (*m/z*): $[M+1]^+$: 358. Anal. Calcd. $C_{20}H_{27}N_3O_3$ (357.45): C, 67.20; H, 7.61; N, 11.76%. Found C, 67.14; H, 7.62; N, 11.68%.

Procedure for synthesis of (4-aminopiperidin-1-yl)(1-methyl-1*H*-indol-2-yl)methanone [hydrochloride] (7)



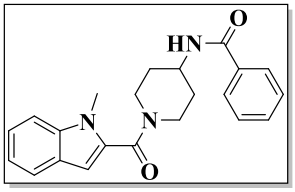
4M HCl solution in dioxane (50 mL) was added dropwise at 0 °C to a solution of tert-butyl [1-(1-methyl-1*H*-indole-2-carbonyl)piperidin-4-yl]carbamate (**6**) (10 g, 28.01 mmol) in dioxane (100 mL) in a single neck RBF.[42] The reaction was then left to stir at 25 °C for 16h. The reaction's volatile components were removed by vacuum evaporation, and the residue was then triturated with n-pentane to produce a white solid (7 g, 85% yield) in the form of (4-aminopiperidin-1-yl)(1-methyl-1*H*-indol-2-yl)methanone [hydrochloride] (**7**).[44] mp: 190-192 °C. IR (KBr) ν_{max}/cm^{-1}: 3423-3330 (NH_2), 3127 (aromatic-CH), 2886 (aliphatic-CH), 1701 (C=O-NH), 1608 (C=C), 1164 (C-N). ^{1}H NMR (400MHz, *DMSO-d*$_6$): δppm 7.61-7.59 (d, *J* = 7.6Hz, 1H, Ar-CH),

7.51-7.49 (d, *J* = 8.4Hz, 1H, Ar-CH), 7.27-7.23 (t, *J* = 7.6Hz, 1H, Ar-CH), 7.11-7.08 (t, *J* = 7.6Hz, 1H, Ar-CH), 4.35 (bs, 3H, 3CH), 3.56 (s, 1H, CH), 1.98 (s, 2H, CH_2), 1.57-1.52 (m, 2H, CH_2). ^{13}C NMR (100 MHz, *DMSO-d₆*): δppm 162.59, 137.72, 132.59, 126.43, 123.31, 121.65, 120.44, 110.80, 102.63, 66.80, 47.79, 46.44, 31.33, 30.32. LC-MS (*m/z*): $[M+1]^+$: 258. Anal. Calcd. $C_{15}H_{19}N_3O$ (257.34): C, 70.01; H, 7.44; N, 16.33%. Found C, 70.05; H, 7.40; N, 16.25%.

General procedure for the synthesis of indole-piperidine hybrid compounds with amide linkage (*9a-n*)

A solution of substituted acid (**8a-n**) (1 eq) in DMF in a single neck RBF under nitrogen atmosphere was mixed with HATU (1.5 eq) at 0 °C and stirred for 1h. DIPEA (3 eq) and {(4-aminopiperidin-1-yl)[(1-methyl-1*H*-indol-2-yl)]methanone} [hydrochloride] (**7**) (1.2 eq) were then added. At 25 °C, the resultant mixture was left to stir for an additional sixteen hours. After the reaction was finished, cold water was added to the reaction mass while being stirred, and the reaction's progress was tracked using TLC. To get the solid as the matching intended product, the separated solid precipitate was filtered, washed with cold water, then n-pentane and thoroughly dried under vacuum to get compounds **9a-n**.

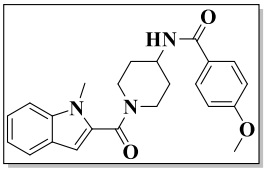
***N*-{1-[(1-methyl-1*H*-indol-2-yl)carbonyl]piperidin-4-yl}benzamide (9a)**



Compound **9a** was prepared from **8a** (0.2 g, 1.783 mmol), HATU (1.016 g, 2.675 mmol) in DMF (4 mL), DIPEA (0.690 g, 5.349 mmol) and **7** (0.628 g, 2.140 mmol). Off white solid (0.5 g, 85% yield). mp: 194-196 °C. IR (KBr) ν_{max}/cm^{-1}: 3296 (NH), 3054 (aromatic-CH), 2935 (aliphatic-CH), 1623 (C=O), 1164 (C-N). ^{1}H NMR (400MHz, *DMSO-d₆*): δppm 8.10-8.09 (d, *J* = 7.2Hz, 1H, C=O-NH), 7.86-7.84 (d, *J* = 8Hz, 2H, 2 x Ar-CH), 7.62-7.60 (d, *J* = 8Hz, 1H, Ar-CH), 7.53-7.43 (m, 4H, 4 x Ar-CH), 7.27-7.23 (t, *J* = 8Hz, 1H), 7.11-7.08 (t, *J* = 7.2Hz, 1H, Ar-CH), 6.61 (s, 1H, Ar-CH), 4.24-4.13 (m, 3H, CH), 3.77 (s, 3H, N-CH_3), 3.22-3.16 (t, *J* = 12Hz, 2H), 1.95-1.92 (d, *J* = 12Hz, 2H), 1.66-1.57 (m, 2H). ^{13}C NMR (100 MHz, *DMSO-d₆*): δppm 166.37, 162.74, 137.88, 135.45, 133.40, 131.38, 128.55, 127.72, 126.79, 123.17, 121.57, 120.38, 110.62, 102.37, 47.10, 43.93, 32.09, 31.18. LC-MS (*m/z)*: 97% $[M+1]^+$: 362. Anal. Calcd.

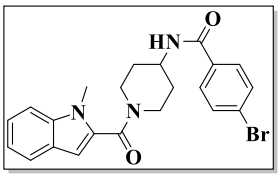
$C_{22}H_{23}N_3O_2$ (361.45): C, 73.11; H, 6.41; N, 11.63%. Found: C, 72.95; H, 6.48; N, 11.55%.

4-Methoxy-*N*-{1-[(1-methyl-1*H*-indol-2-yl)carbonyl]piperidin-4-yl}benzamide (9b)



Compound **9b** was prepared from **8b** (0.2 g, 1.314 mmol), HATU (0.750 g, 1.971 mmol) in DMF (4 mL), DIPEA (0.508 g, 3.943 mmol) and **7** (0.463 g, 1.577 mmol). Off white solid (0.480 g, 93% yield). mp: 193-196 °C. IR (KBr) ν_{max}/cm^{-1}: 3296 (NH), 3054 (aromatic-CH), 2987 (aliphatic-CH), 1653 (C=O-NH), 1623 (C=O), 1164 (C-N). ^{1}HNMR (400MHz, *DMSO-d*$_6$): δppm 7.95-7.93 (d, *J* = 8Hz, 1H, C=O-NH), 7.84-7.82 (d, *J* = 8Hz, 2H, 2 x Ar-CH), 7.62-7.60 (d, *J* = 8Hz, 1H, Ar-CH), 7.50-7.48 (d, *J* = 8Hz, 1H, Ar-CH), 7.27-7.23 (t, *J* = 8Hz, 1H, Ar-CH), 7.12-7.08 (t, *J* = 8Hz, 1H, Ar-CH), 6.99-6.97 (d, *J* = 8Hz, 2H, 2 x Ar-CH), 6.61 (s, 1H, Ar-CH), 4.25-4.21 (m, 2H, CH_2), 4.13-4.11 (m, 1H, CH), 3.80 (s, 3H, O-CH_3), 3.77 (s, 3H, NCH_3), 3.22-3.12 (m, 2H, CH_2), 1.94-1.90 (d, *J* = 16Hz, 2H, CH_2), 1.64-1.56 (m, 2H, CH_2). ^{13}C NMR (100 MHz, *DMSO-d*$_6$): δppm 165.84, 162.72, 162.15, 137.87, 133.40, 129.53, 127.72, 126.78, 123.17, 121.57, 120.38, 113.97, 110.62, 102.36, 55.89, 47.01, 43.85, 32.18, 31.17. LC-MS (*m/z*): 97% $[M+1]^+$: 392. Anal. Calcd. $C_{23}H_{25}N_3O_3$ (391.47): C, 70.57; H, 6.44; N, 10.73%. Found C, 70.65; H, 6.50; N, 10.80%.

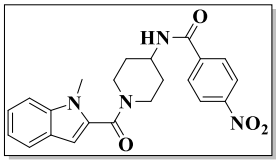
4-Bromo-*N*-{1-[(1-methyl-1*H*-indol-2-yl)carbonyl]piperidin-4-yl}benzamide (9c)



Compound **9c** was prepared from **8c** (0.2 g, 0.994 mmol), HATU (0.567 g, 1.492 mmol) in DMF (4 mL), DIPEA (0.385 g, 2.984 mmol) and **7** (0.350 g, 1.193 mmol). White solid (0.400 g, 91% yield). mp: 192-195 °C. IR (KBr) ν_{max}/cm^{-1}: 3333 (NH), 3058 (aromatic-CH), 2933 (aliphatic-CH), 1654(C=O-NH), 1612 (C=O), 1181 (C-N). ^{1}H NMR (400MHz, *DMSO-d*$_6$): δppm 8.22 (s, 1H, C=O-NH), 7.89-7.87 (d, *J* = 8Hz, 2H, 2 Ar-CH), 7.63-7.61 (d, *J* = 8H, 1H, Ar-CH), 7.53-7.49 (t, *J* = 8Hz, 3H, Ar-CH), 7.28-7.24 (t, *J* = 8Hz, 1H, Ar-CH), 7.13-7.09 (t, *J* = 8Hz, 1H, Ar-CH), 6.62 (s, 1H, Ar-CH), 4.24 (bs, 2H, CH_2), 4.13 (bs, 1H, CH), 3.78 (s, 3H, N-CH_3), 3.12-3.11 (m, 2H, CH_2),

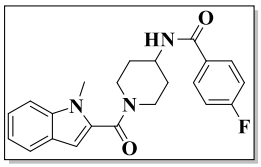
1.95-1.92 (d, *J* = 12Hz, 2H, CH_2), 1.62-1.59 (m, 2H, CH_2). ^{13}CMR (100 MHz, *DMSO-d6*): δppm 165.14, 162.51, 137.69, 134.12, 133.00, 131.71, 129.92, 126.54, 125.35, 123.24, 121.61, 120.44, 110.78, 102.43, 47.09, 31.26. LC-MS (*m/z*): 97.50% $[M^{79}Br^{+1}]^+$: 440, $[M^{81}Br^{+1}]^+$: 442. Anal. Calcd. $C_{22}H_{22}BrN_3O_2$ (440.34): C, 60.01; H, 5.04; N, 9.54%. Found C, 59.96; H, 5.09; N, 9.58%.

4-Nitro-*N*-{1-[(1-methyl-1*H*-indol-2-yl)carbonyl]piperidin-4-yl}benzamide (9d)



Compound **9d** was prepared from **8d** (0.2 g, 1.196 mmol), HATU (0.682 g, 1.795 mmol) in DMF (4 mL), DIPEA (0.463 g, 3.590 mmol) and **7** (0.422 g, 1.436 mmol). Off white solid (0.450 g, 92% yield). mp: 190-192 °C. IR (KBr) ν_{max}/cm^{-1}: 3328 (NH), 3058 (aromatic-CH), 2931 (aliphatic-CH), 1660 (C=O-NH), 1612 (C=O), 1107 (C-N). ^{1}H NMR (400MHz, *DMSO-d6*): δppm 8.48-8.47 (d, *J* = 6Hz, 1H, C=O-NH), 8.30-8.27 (d, *J* = 8Hz, 2H, 2 x Ar-CH), 8.09-8.08 (d, *J* = 8.8Hz, 2H, 2 x Ar-CH), 7.62-7.60 (d, *J* = 7.6Hz, 1H, Ar-CH), 7.50-7.48 (d, *J* = 8.4Hz, 1H, Ar-CH), 7.27-7.23 (t, *J* = 8Hz, 1H, Ar-CH), 7.11-7.08 (t, *J* = 7.2Hz, 1H, Ar-CH), 6.61 (s, 1H, Ar-CH), 4.26-4.15 (m, 3H, CH_2, CH), 3.78 (m, 3H, N-CH_3), 3.24-3.19 (t, *J* = 11.6Hz, 2H, CH_2), 2.05-1.94 (m, 2H, CH_2), 1.66-1.59 (m, 2H, CH_2). ^{13}C NMR (100 MHz, *DMSO-d6*): δppm 164.48, 162.53, 149.47, 140.67, 137.70, 132.98, 129.30, 126.53, 123.94, 123.25, 121.63, 120.45, 110.79, 102.45, 47.31, 31.98, 31.27. LC-MS (*m/z*): 100% $[M+1]^+$: 407. Anal. Calcd. $C_{22}H_{22}N_4O_4$ (406.44): C, 65.01; H, 5.46; N, 13.78%. Found C, 64.95; H, 5.42; N, 13.72%.

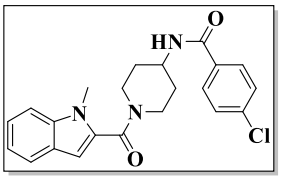
4-Fluoro-*N*-{1-[(1-methyl-1*H*-indol-2-yl)carbonyl]piperidin-4-yl}benzamide (9e)



Compound **9e** was prepared from **8e** (0.2 g, 1.427 mmol), HATU (0.813 g, 2.141 mmol) in DMF (4 mL), DIPEA (0.552 g, 4.282 mmol) and **7** (0.503 g, 1.712 mmol). Off white solid (0.450 g, 83% yield). mp: 176-179 °C. IR (KBr) ν_{max}/cm^{-1}: 3308 (NH), 3060 (aromatic-CH), 2948 (aliphatic-CH), 1654 (C=O-NH), 1612 (C=O), 1149 (C-N). ^{1}H NMR (400MHz, *DMSO-d6*): δppm 8.23 (s, 1H, C=O-NH), 7.89-7.87 (d, *J* = 8Hz, 2H, 2 x Ar-CH), 7.63-7.61 (d, *J* = 8Hz, 1H, Ar-CH), 7.57-7.49 (m, 3H, 3 x Ar-CH), 7.28-

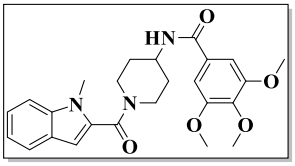
7.24 (t, *J* = 8Hz, 1H, Ar-CH), 7.13-7.09 (t, *J* = 8Hz, 1H, Ar-CH), 6.62 (s, 1H, Ar-CH), 4.24-4.12 (m, 3H, CH_2, CH), 3.78 (s, 3H, N-CH_3), 3.23-3.12 (m, 2H, CH_2), 1.95-1.92 (d, *J* = 12Hz, 2H, CH_2), 1.62-1.59 (m, 2H). ^{13}CMR (100 MHz, *DMSO-d6*): δppm 165.54, 165.05, 163.07, 162.51, 137.69, 133.01, 131.50, 130.44, 130.35, 126.54, 123.23, 121.61, 120.43, 115.69, 115.47, 110.77, 102.41, 47.05, 36.25, 32.26, 31.25. LC-MS (*m/z*): 96% $[M+1]^+$: 380. Anal. Calcd. $C_{22}H_{22}FN_3O_2$ (379.44): C, 69.64; H, 5.84; N, 11.07%. Found C, 69.58; H, 5.78; N, 11.08%.

4-Chloro-*N*-{1-[(1-methyl-1*H*-indol-2-yl)carbonyl]piperidin-4-yl}benzamide (9f)



Compound **9f** was prepared from **8f** (0.2 g, 1.276 mmol), HATU (0.813 g, 1.91 mmol) in DMF (4 mL), DIPEA (0.494 g, 3.829 mmol) and **7** (0.450 g, 1.538 mmol). White solid (0.460 g, 91% yield). mp: 184-186 °C. IR (KBr) ν_{max}/cm^{-1}: 3311 (NH), 3058 (aromatic-CH), 2939 (aliphatic-CH), 1654 (C=O-NH), 1612 (C=O), 1149 (C-N). ^{1}H NMR (400MHz, *DMSO-d6*): δppm 8.17 (s, 1H, C=O-NH), 7.95-7.91 (t, *J* = 8Hz, 2H, 2 x Ar-CH), 7.63-7.61 (d, *J* = 8Hz, 1H, Ar-CH), 7.51-7.49 (d, *J* = 8Hz, 1H, Ar-CH), 7.28-7.24 (m, 3H, 3 x Ar-CH), 7.13-7.09 (t, *J* = 8Hz, 1H, Ar-CH), 6.62 (s, 1H, Ar-CH), 4.24-4.11 (m, 3H,CH_2, CH), 3.78 (s, 3H, N-CH_3), 3.23-3.17 (m, 2H, CH_2), 1.95-1.92 (d, *J* = 12Hz, 2H, CH_2), 1.65-1.56 (m, 2H, CH_2). ^{13}C NMR (100 MHz, *DMSO-d6*): δppm 165.05, 162.52, 137.69, 136.44, 133.75, 133.00, 129.71, 128.77, 126.54, 123.24, 121.61, 120.44, 110.77, 102.41, 47.08, 32.26, 31.25. LC-MS (*m/z*): 96% $[M^{35}Cl^{+1}]^+$: 396, $[M^{37}Cl^{+1}]^+$: 398. Anal. Calcd. $C_{22}H_{22}ClN_3O_2$ (395.89): C, 66.75; H, 5.60; N, 10.61%. Found C, 66.70; H, 5.70; N, 10.62%.

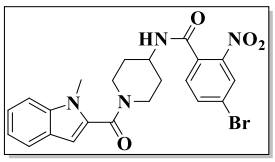
3,4,5-Trimethoxy-*N*-{1-[(1-methyl-1*H*-indol-2-yl)carbonyl]piperidin-4-yl}benzamide (9g)



Compound **9g** was prepared from **8g** (0.2 g, 0.939 mmol), HATU (0.535 g, 1.409 mmol) in DMF (4 mL), DIPEA (0.363 g, 2.818 mmol) and **7** (0.331 g, 1.127 mmol). An off white solid (0.400 g, 94% yield). mp: 185-188 °C. IR (KBr) ν_{max}/cm^{-1}: 3289 (NH), 3058 (aromatic-CH), 2937 (aliphatic-CH), 1697 (C=O-NH), 1623 (C=O), 1123 (C-N). ^{1}H

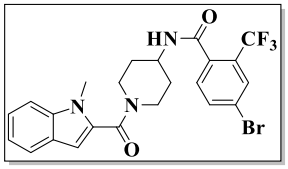
NMR (400 MHz, *DMSO-d_6*): δppm 8.29-8.27 (d, *J* = 7.6Hz, 1H, C=O-NH), 7.65-7.63 (d, *J* = 7.6Hz, 1H, Ar-CH), 7.55-7.53 (d, *J* = 8.4Hz, 1H, Ar-CH), 7.29-7.26 (t, *J* = 7.6Hz, 1H, Ar-CH), 7.19 (s, 2H, 2 x Ar-CH), 7.14-7.10 (t, *J* = 7.6Hz, 1H, Ar-CH), 6.66 (s, 1H, Ar-CH), 4.53 (s, 2H, CH_2), 4.16-4.14 (m, 2H, CH_2), 3.85 (s, 6H, 2 x OCH_3), 3.79 (s, 3H, N-CH_3), 3.72 (s, 3H, O-CH_3), 2.71-2.70 (m, 1H, CH), 1.93 (s, 2H, CH), 1.59-1.57 (m, 2H, CH_2). ^{13}C NMR (100 MHz, *DMSO-d_6*): δppm 165.41, 162.44, 153.00, 140.40, 137.69, 132.95, 130.17, 126.51, 123.26, 121.63, 120.45, 110.79, 31.29, 105.37, 102.49, 60.55, 56.53, 47.13, 31.94. LCMS (*m/z*): 99 % $[M+1]^+$: 452. Anal. Calcd. $C_{25}H_{29}N_3O_5$ (451.52): C, 66.50; H, 6.47; N, 9.31%. Found C, 66.55; H, 6.42; N, 9.28%.

4-Bromo-2-nitro-*N*-{1-[(1-methyl-1*H*-indol-2-yl)carbonyl]piperidin-4-yl}benzamide (9h)



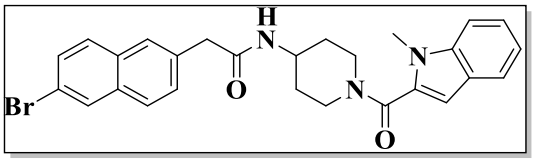
Compound **9h** was prepared from **8h** (0.2 g, 0.812 mmol), HATU (0.463 g, 1.219 mmol) in DMF (4 mL), DIPEA (0.314 g, 2.438 mmol) and **7** (0.286 g, 0.975 mmol). Yellow solid (0.350 g, 88% yield). mp: 155-158 °C. IR (KBr) ν_{max}/cm^{-1}: 3375 (NH), 3054 (aromatic-CH), 2922 (aliphatic-CH), 1606 (C=O-NH), 1526 (C=O), 1140 (C-N). ^{1}H NMR (400 MHz, *DMSO-d_6*): δppm 8.52-8.50 (d, *J* = 6.4Hz, 1H, C=O-NH), 8.24 (s, 1H, Ar-CH), 8.00-7.99 (d, *J* = 6.4Hz, 1H, Ar-CH), 7.62-7.60 (d, *J* = 7.6Hz, 1H, Ar-CH), 7.58-7.56 (d, *J* = 8Hz, 1H, Ar-CH), 7.50-7.48 (d, *J* = 8Hz, 1H, Ar-CH), 7.27-7.23 (t, *J* = 7.2Hz, 1H, Ar-CH), 7.12-7.08 (t, *J* = 7.2Hz, 1H, Ar-CH), 6.61 (s, 1H, Ar-CH), 4.16-4.07 (m, 3H, CH_2, CH), 3.76 (s, 3H, N-CH_3), 3.30-3.25 (t, *J* = 11.2 Hz, 2H, CH_2), 1.97-1.95 (d, *J* = 10.4Hz, 2H, CH_2), 1.57-1.50 (m, 2H, CH_2). ^{13}C NMR (100 MHz, *DMSO-d_6*): δppm 164.45, 162.56, 148.15, 137.71, 136.78, 132.92, 131.96, 131.25, 127.23, 126.53, 123.24, 123.19, 121.64, 120.44, 110.79, 31.27, 46.88, 102.50, 46.88, 31.27. LC-MS (*m/z*):100% $[M^{79}Br^{+1}]^+$: 485, $[M^{81}Br^{+1}]^+$: 487. Anal. Calcd. $C_{22}H_{21}BrN_4O_4$ (485.34): C, 54.44; H, 4.36; N, 11.54%. Found C, 54.38; H, 4.34; N, 11.42%.

4-Bromo-2-(trifluoromethyl)-*N*-{1-[(1-methyl-1*H*-indol-2-yl)carbonyl]piperidin-4-yl}benzamide (9i)



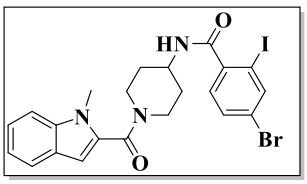
Compound **9i** was prepared from **8i** (0.2 g, 0.757 mmol), HATU (0.431 g, 1.136 mmol) in DMF (4 mL), DIPEA (0.293 g, 2.272 mmol) and **7** (0.267 g, 0.909 mmol). Yellow solid (0.350 g, 92% yield). mp: 160-162 °C. IR (KBr) ν_{max}/cm^{-1}: 3278 (NH), 3054 (aromatic-CH), 2939 (aliphatic-CH), 1718 (C=O-NH), 1615 (C=O), 1127 (C-N). ^1H NMR (400 MHz, *DMSO-d₆*): δppm 8.39 (s, 1H, C=O-NH), 7.94 (s, 2H, Ar-CH), 7.62-7.60 (d, *J* = 8Hz, 1H, Ar-CH), 7.50-7.47 (m, 2H, Ar-CH), 7.27-7.23 (t, *J* = 7.2Hz, 1H, Ar-CH), 7.12-7.08 (t, *J* = 7.2Hz, 1H, Ar-CH), 4.17-4.03 (m, 3H, CH_2, CH), 3.76 (s, 3H, N-CH_3), 3.29-3.20 (m, 2H, CH_2), 1.99-1.92 (m, 2H, CH_2), 1.54-1.49 (m, 2H, CH_2). ^{13}C NMR (100 MHz, *DMSO-d₆*): δppm 165.96, 162.52, 137.67, 136.13, 135.87, 14.54, 132.87, 131.15, 129.41, 128.40, 128.08, 127.35, 126.49, 124.62, 123.22, 122.88, 121.89, 121.61, 120.42, 110.77, 102.46, 60.22, 46.75, 31.24, 21.23. LC-MS (*m/z*): 100% $[M^{79}Br^{+1}]^+$: 508, $[M^{81}Br^{+1}]^+$: 510. Anal. Calcd. $C_{23}H_{21}BrF_3N_3O_2$ (508.34): C, 54.34; H, 4.16; N, 8.27%. Found C, 54.28; H, 4.21; N, 8.23%.

2-(6-Bromonaphthalen-2-yl)-*N*-{1-[(1-methyl-1*H*-indol-2-yl)carbonyl]piperidin-4-yl}acetamide (9j)



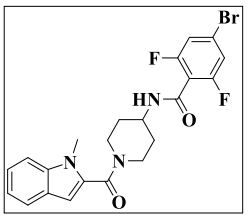
Compound **9j** was prepared from **8j** (0.2 g, 0.754 mmol), HATU (0.430 g, 1.131 mmol) in DMF (4 mL), DIPEA (0.292 g, 2.263 mmol), and **7** (0.266 g, 0.905 mmol). White solid (0.340 g, 89% yield). mp: 189-191 °C. IR (KBr) ν_{max}/cm^{-1}: 3283 (NH), 3058 (aromatic-CH), 2935 (aliphatic-CH), 1647 (C=O-NH), 1627 (C=O), 1140 (C-N). ^1H NMR (400 MHz, *DMSO-d₆*): δppm 8.13 (s, 1H, C=O-NH), 7.93 (s, 1H, Ar-CH), 7.84-7.78 (m, 3H, Ar-CH), 7.59-7.49 (m, 4H, 4 x Ar-CH), 7.25-7.10 (m, 2H, 2 x Ar-CH), 6.60 (s, 1H, Ar-CH), 4.11 (s, 2H, CH_2), 3.91 (s, 1H, CH), 3.75 (s, 3H, N-CH_3), 3.61 (s, 2H, CH_2), 3.22-3.16 (t, *J* = 11.2Hz, 2H, CH_2), 1.87-1.84 (d, *J* = 10.8Hz, 2H, CH_2), 1.46-1.44 (d, J = 10Hz, 2H, CH_2). ^{13}C NMR (100 MHz, *DMSO-d₆*): δppm 169.57, 162.45, 137.65, 135.41, 133.40, 132.90, 131.94, 130.17, 129.82, 129.47, 129.22, 127.72, 127.34, 126.48, 123.21, 121.60, 120.41, 119.04, 110.77, 102.45, 31.24, 46.30, 42.87, 32.00. LC-MS (*m/z*): 100% $[M^{79}Br^{+1}]^+$: 504, $[M^{81}Br^{+1}]^+$: 506. Anal. Calcd. $C_{27}H_{26}BrN_3O_2$ (504.43): C, 64.29; H, 5.20; N, 8.33%. Found C, 64.24; H, 5.26; N, 8.37%.

4-Bromo-2-iodo-*N*-[1-(1-methyl-1*H*-indole-2-carbonyl)piperidin-4-yl]benzamide (9k)



Compound **9k** was prepared from **8k** (0.2 g, 0.611 mmol), HATU (0.348 g, 0.917 mmol) in DMF (4 mL), DIPEA (0.236 g, 1.835 mmol) and **7** (0.215 g, 0.734 mmol). White solid (0.300 g, 86% yield). mp: 185-187 °C. IR (KBr) ν_{max}/cm^{-1} 3295 (NH), 3047 (aromatic-CH), 2939 (aliphatic-CH), 1638 (C=O-NH), 1571 (C=C), 1131 (C-N). ^{1}H NMR (400 MHz, *DMSO-d*$_6$): δppm 8.25 (s, 1H, C=O-NH), 8.06 (s, 1H, Ar-CH), 7.66-7.60 (m, 2H, Ar-CH), 7.50-7.48 (d, *J* = 8Hz, 1H, Ar-CH), 7.29-7.23 (m, 2H, Ar-CH), 7.12-7.08 (t, J = 8Hz, 1H, Ar-CH), 6.61 (s, 1H, Ar-CH), 4.18-4.09 (m, 3H, CH_2, CH), 3.76 (s, 3H, N-CH_3), 3.31-3.25 (t, *J* = 12Hz, 2H, CH_2), 1.99-1.95 (m, 2H, CH_2), 1.63-1.53 (m, 2H, CH_2). ^{13}C NMR (100 MHz, *DMSO-d*$_6$): δppm 168.10, 162.56, 142.85, 140.88, 137.70, 132.96, 131.40, 129.83, 126.54, 123.24, 122.98, 121.63, 120.45, 110.79, 102.45, 95.54, 46.72, 31.28. LC-MS (*m/z*): 99% $[M^{79}Br^{+1}]^+$: 566, $[M^{81}Br^{+1}]^+$: 568. Anal. Calcd. $C_{22}H_{21}BrIN_3O_2$ (566.24): C, 46.67; H, 3.74; N, 7.42%. Found C, 46.53; H, 3.70; N, 7.38%.

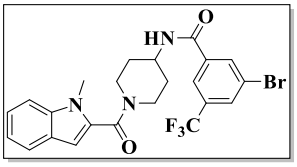
4-Bromo-2,6-difluoro-*N*-[1-(1-methyl-1*H*-indole-2-carbonyl)piperidin-4-yl]benzamide (9l)



Compound **9l** was prepared from **8l** (0.2 g, 0.843 mmol), HATU (0.481 g, 1.265 mmol) in DMF (4 mL), DIPEA (0.326 g, 2.531 mmol), and **7** (0.297 g, 1.012 mmol). Off white solid (0.320 g, 80% yield). mp: 192-195 °C. IR (KBr) ν_{max}/cm^{-1}: 3259 (NH), 3073 (aromatic-CH), 2939 (aliphatic-CH), 1645 (C=O-NH), 1619 (C=O), 1101 (C-N). ^{1}H NMR (400 MHz, *DMSO-d*$_6$): δppm 8.85-8.83 (d, *J* = 7.2Hz, 1H, C=O-NH), 7.62-7.59 (m, 3H, 3 x Ar-CH), 7.53-7.51 (d, *J* = 8.4Hz, 1H, Ar-CH), 7.27-7.23 (t, *J* = 7.2Hz, 1H, Ar-CH), 7.12-7.08 (t, *J* = 7.6Hz, 1H, Ar-CH), 6.64 (s, 1H, Ar-CH), 4.33 (bs, 1H, CH), 4.08 (s, 2H, CH_2), 3.75 (s, 3H, N-CH_3), 3.23 (m, 2H, CH_2), 1.92 (s, 2H, CH_2), 1.48-1.45 (m, 2H, CH_2). ^{13}C NMR (100 MHz, *DMSO-d*$_6$): δppm 162.53, 160.53, 160.44,

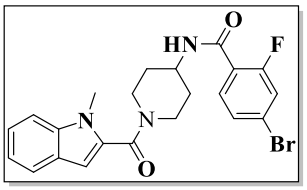
158.58, 158.03, 157.94, 137.68, 132.83, 126.48, 123.23, 123.01, 121.62, 120.41, 116.37, 116.10, 115.52, 110.77, 102.53, 46.92, 46.05, 32.05, 31.25. LC-MS (*m/z*): 100% $[M^{79}Br^{+1}]^+$: 476, $[M^{81}Br^{+1}]^+$ 478. Anal. Calcd. $C_{22}H_{20}BrF_2N_3O_2$ (476.32): C, 55.48; H, 4.23; N, 8.82%. Found C, 55.42; H, 4.15; N, 8.90%.

3-Bromo-5-(trifluoromethyl)-*N*-{1-[(1-methyl-1*H*-indole-2-carbonyl)piperidin-4-yl]}benzamide (9m)



Compound **9m** was prepared from **8m** (0.2 g, 0.743 mmol), HATU (0.424 g, 1.115 mmol) in DMF (4 mL), DIPEA (0.287 g, 2.230 mmol), and **7** (0.262 g, 0.892 mmol). Off white solid (0.350 g, 92% yield). mp: 162-165 °C. IR (KBr) ν_{max}/cm^{-1} 3293 (NH), 3063 (aromatic-CH), 2931 (aliphatic-CH), 1636 (C=O-NH), 1617 (C=O), 1127 (C-N). ^{1}H NMR (400 MHz, *DMSO-d$_6$*): δppm 8.72-8.70 (d, *J* = 8.0Hz, 1H, C=O-NH), 8.36 (s, 1H, Ar-CH), 8.20 (s, 2H, 2 x Ar-CH), 7.63-7.61 (d, *J* = 8.0Hz, 1H, Ar-CH), 7.54-7.52 (d, *J* = 8Hz, 1H, Ar-CH), 7.28-7.24 (t, *J* = 8Hz, 1H, Ar-CH), 7.13-7.09 (t, *J* = 8Hz, 1H, Ar-CH), 6.64 (s, 1H, Ar-CH), 4.49 (s, 1H, CH), 4.15 (s, 2H, CH_2), 3.78 (s, 3H, N-CH_3), 3.18-3.17 (m, 2H, CH_2), 1.94 (s, 2H, CH_2), 1.58-1.55 (m, 2H, CH_2). ^{13}C NMR (100 MHz, *DMSO-d$_6$*): δppm 163.11, 162.52, 137.77, 137.72, 134.67, 132.97, 131.70, 131.37, 131.03, 127.55, 126.54, 124.84, 123.68, 123.26, 122.97, 122.12, 121.63, 120.46, 110.80, 102.49, 47.40, 46.57, 32.02, 31.28, 29.50. LC-MS (*m/z*): 97 % $[M^{79}Br^{+1}]^+$: 508, $[M^{81}Br^{+1}]^+$: 510. Anal. Calcd. $C_{23}H_{21}BrF_3N_3O_2$ (508.34): C, 54.34; H, 4.16; N, 8.27%. Found C, 54.40; H, 4.11; N, 8.20%.

4-Bromo-2-fluoro-*N*-{1-[(1-methyl-1*H*-indole-2-carbonyl)piperidin-4-yl]}benzamide (9n)



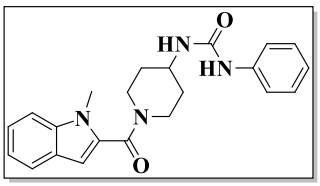
Compound **9n** was prepared from **8n** (0.2 g, 0.913 mmol), HATU (0.520 g, 1.369 mmol) in DMF (4 mL), DIPEA (0.353 g, 2.739 mmol), and **7** (0.322 g, 1.095 mmol). White solid (0.380 g, 90% yield). mp: 186-189 °C. IR (KBr) ν_{max}/cm^{-1} 3296 (NH), 3084 (aromatic-CH), 2946 (aliphatic-CH), 1623 (C=O-NH), 1602 (C=O), 1110 (C-N). ^{1}H

NMR (400 MHz, *DMSO-d_6*): δppm 8.43-8.41 (d, *J* = 8Hz, 1H, C=O-NH), 7.69-7.67 (d, *J* = 8Hz, 1H, Ar-CH), 7.62-7.60 (d, *J* = 7.9Hz, 1H, Ar-CH), 7.56-7.50 (m, 3H, 3 x Ar-CH), 7.27-7.24 (t, *J* = 8Hz, 1H, Ar-CH), 7.12-7.08 (t, *J* = 8Hz, 1H, Ar-CH), 6.63 (s, 1H, Ar-CH), 4.38 (s, 1H, CH), 4.09 (s, 2H, CH_2), 3.76 (s, 3H, N-CH_3), 3.18-3.14 (m, 2H, CH_2), 1.91 (s, 2H, CH_2), 1.53-1.50 (m, 2H, CH_2). ^{13}C NMR (100 MHz, *DMSO-d_6*): δppm 162.84, 162.50, 137.67, 132.93, 131.94, 128.12, 126.51, 124.30, 123.22, 121.61, 120.42, 120.05, 119.79, 110.76, 102.44, 46.93, 32.02, 31.25. LC-MS (*m/z*): 97 % $[M^{79}Br^{+1}]^+$: 458, $[M^{81}Br^{+1}]^+$: 460. Anal. Calcd. $C_{22}H_{21}BrFN_3O_2$ (458.33): C, 57.65; H, 4.62; N, 9.17%. Found C, 57.55; H, 4.60; N, 9.11%.

General procedure for the synthesis of indole-piperidine hybrid compounds with urea linkage by using phenyl isocyanate derivatives (*11a-g*)

To a stirred solution of **7** (1 eq) in dry THF, TEA (5 eq) was added at 0 °C under nitrogen atmosphere and the reaction was stirred for 10 min followed by the addition of corresponding isocyanate (**10a-g**, 0.9 eq) and the reaction was stirred for another 16h at 25 °C. After completion of the reaction, the reaction mixture was poured into ice water and extracted with ethyl acetate (3 times). The combined organic layer was washed with water and brine, the separated organic layer was dried over sodium sulphate, concentrated to dryness, the obtained crude product was purified by reverse phase chromatography on C18 column with 15µ size using acetonitrile: 0.1% Formic acid in H_2O as mobile phase, obtained eluent was evaporated under vacum to give the corresponding desired product **11a-g**.

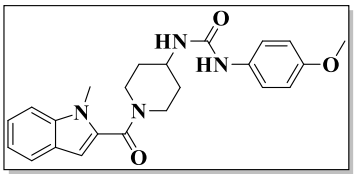
1-[1-(1-Methyl-1*H*-indole-2-carbonyl)piperidin-4-yl]-3-phenylurea (11a)



Compound **11a** was prepared from **7** (0.2 g, 0.680 mmol), TEA (0.344 g, 3.403 mmol) in THF (4 mL) and **10a** (0.073 g, 0.612 mmol). White solid (0.2 g, 78% yield). mp: 184-186 °C. IR (KBr) ν_{max}/cm^{-1} 3295 (NH), 3091 (aromatic-CH), 2942 (aliphatic-CH), 1625 (C=O-NH), 1593 (C=O), 1138 (C-N). ^{1}H NMR (400MHz, *DMSO-d_6*): δppm 8.18 (s, 1H, C=O-NH), 7.62-7.60 (d, *J* = 7.6Hz, 1H, Ar-CH), 7.50-7.48 (d, *J* = 8.4Hz, 1H, Ar-CH), 7.39-7.37 (d, *J* = 7.6Hz, 2H, 2 x Ar-CH), 7.27-7.20 (m, 3H, 3 x Ar-CH), 7.12-7.08 (t, *J* = 7.6Hz, 1H, Ar-CH), 6.92-6.88 (t, *J* = 7.2Hz, 1H, Ar-CH), 6.63 (s, 1H, C=O-NH), 6.13-6.11 (d, *J* = 6.8Hz, 1H, Ar-CH), 4.13-4.10 (d, *J* = 11.6Hz, 2H,CH_2), 3.82-

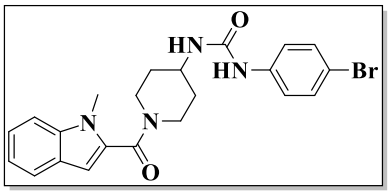
3.81 (bs, 1H, CH), 3.77 (s, 3H, N-CH_3), 3.29-3.23 (t, *J* = 11.6Hz, 2H, CH_2), 1.95-1.93 (d, *J* = 10.4Hz, 2H, CH_2), 1.48-1.40 (m, 2H, CH_2). ^{13}C NMR (100 MHz, *DMSO-d6*): δppm 162.48, 154.97, 140.87, 137.69, 133.00, 129.11, 126.54, 123.19, 121.59, 120.40, 118.13, 110.74, 102.48, 46.66, 32.02, 31.25. LC-MS (*m/z*): 100% $[M+1]^+$: 377. Anal. Calcd. $C_{22}H_{24}N_4O_2$ (376.46): C, 70.19; H, 6.43; N, 14.88%. Found C, 70.10; H, 6.38; N, 14.90%.

1-(4-Methoxyphenyl)-3-[1-(1-methyl-1*H*-indole-2-carbonyl)piperidin-4-yl]urea (11b)



Compound **11b** was prepared from **7** (0.2 g, 0.680 mmol), TEA (0.344 g, 3.403 mmol) in THF (4 mL) and **10b** (0.092 g, 0.612 mmol). White solid (0.210 g, 76% yield). mp: 187-190 °C. IR (KBr) ν_{max}/cm^{-1} 3306 (NH), 3058 (aromatic-CH), 2922 (aliphatic-CH), 1625 (C=O-NH), 1567 (C=O), 1101 (C-N). ^{1}H NMR (400MHz, *DMSO-d6*): δppm 8.60 (s, 1H, C=O-NH), 7.63-7.61 (d, *J* = 8Hz, 1H, Ar-CH), 7.52-7.50 (d, *J* = 8Hz, 1H, Ar-CH), 7.31-7.24 (m, 3H, 3 x Ar-CH), 7.13-7.09 (t, *J* = 8Hz, 1H, Ar-CH), 6.84-6.81 (d, *J* = 12Hz, 2H, 2 x Ar-CH), 6.64 (s, 1H, C=O-NH), 6.13-6.11 (d, *J* = 8Hz, 1H, Ar-CH), 4.12 (bs, 2H, CH_2), 3.78 (s, 4H, N-CH_3, CH), 3.72 (s, 3H, O-CH_3), 3.29-3.23 (t, *J* = 12Hz, 2H, CH_2), 1.95-1.92 (d, *J* = 12Hz, 2H, CH_2), 1.46-1.43 (m, 2H, CH_2). ^{13}C NMR (100 MHz, *DMSO-d6*): δppm 162.44, 155.34, 154.29, 137.67, 134.26, 133.00, 126.52, 123.19, 121.60, 120.40, 119.77, 114.32, 110.75, 102.46, 55.59, 46.58, 32.74, 31.26. LC-MS (*m/z*): 100% $[M+1]^+$: 407. Anal. Calcd. $C_{23}H_{26}N_4O_3$ (406.49): C, 67.96; H, 6.45; N, 13.78%. Found C, 67.84; H, 6.52; N, 13.83%.

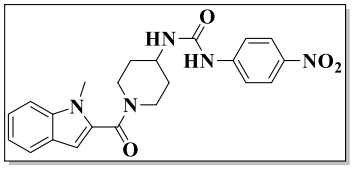
1-(4-Bromophenyl)-3-[1-(1-methyl-1*H*-indole-2-carbonyl)piperidin-4-yl]urea (11c)



Compound **11c** was prepared from **7** (0.2 g, 0.680 mmol), TEA (0.344 g, 3.403 mmol) in THF (4 mL) and **10c** (0.121 g, 0.612 mmol). White solid (0.250 g, 81% yield). mp: 194-197 °C. IR (KBr) ν_{max}/cm^{-1} 3336-3293 (NH), 3088 (aromatic-CH), 2946

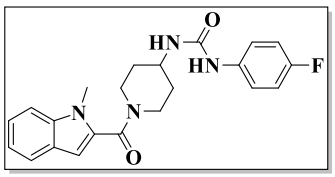
(aliphatic–CH), 1623 (C=O-NH), 1589 (C=O), 1138 (C-N). ^{1}H NMR (400MHz, *DMSO-d6*): δppm 8.38 (s, 1H, C=O-NH), 7.63-7.61 (d, *J* = 7.6 Hz, 1H, Ar-CH), 7.51-7.49 (d, *J* = 8.4Hz, 1H, Ar-CH), 7.38 (s, 4H, 4 x Ar-CH), 7.28-7.24 (t, *J* = 7.2Hz, 1H, Ar-CH), 7.13-7.09 (t, *J* = 7.2Hz, 1H, Ar-CH), 6.64 (s, 1H, C=O-NH), 6.20-6.18 (d, *J* = 6.8Hz, 1H, Ar-CH), 3.28-3.23 (t, *J* = 10.4Hz, 2H, CH_2), 4.11 (bs, 2H, CH_2), 3.85-3.75 (m, 4H, N-CH_3, CH), 1.95-1.93 (d, *J* = 10.4Hz, 2H, CH_2). ^{13}C NMR (100 MHz, *DMSO-d6*): δppm 162.67, 154.85, 137.84, 133.26, 131.75, 126.72, 123.15, 121.56, 120.35, 120.29, 110.61, 102.44, 43.46, 32.65, 31.17. LC-MS (*m/z*): 100% $[M^{79}Br^{+1}]^{+}$: 455, $[M^{81}Br^{+1}]^{+}$: 457. Anal. Calcd. $C_{22}H_{23}BrN_4O_2$ (455.36): C, 58.03; H, 5.09; Br, N, 12.30%. Found C, 58.12; H, 5.12; N, 12.22% .

1-[1-(1-Methyl-1*H*-indole-2-carbonyl)piperidin-4-yl]-3-(4-nitrophenyl)urea (11d)



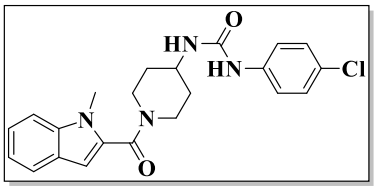
Compound **11d** was prepared from **7** (0.2 g, 0.680 mmol), TEA (0.344 g, 3.403 mmol) in THF (4 mL) and **10d** (0.1 g, 0.612 mmol). White solid (0.210 g, 73% yield). mp: 194-197 °C. IR (KBr) ν_{max}/cm^{-1}: 3345-3293 (NH), 3080 (aromatic–CH), 2946 (aliphatic-CH), 1694 (C=O-NH), 1604 (C=O), 1108 (C-N). ^{1}H NMR (400MHz, *DMSO-d6*): δppm 9.01 (s, 1H, C=O-NH), 8.12-8.14 (d, *J* = 8Hz, 2H, 2 Ar-CH), 7.62-7.60 (d, *J* = 8.4Hz, 3H, 3 x Ar-CH), 7.51-7.49 (d, *J* = 7.6Hz, 1H, Ar-CH), 7.28-7.24 (t, *J* = 7.2Hz, 1H, Ar-CH), 7.13-7.09 (t, *J* = 7.2Hz, 1H, Ar-CH), 6.64 (s, 1H, C=O-NH), 6.45-6.44 (d, *J* = 4Hz, 1H, Ar-CH), 4.15-4.11 (d, *J* = 11.2Hz, 2H, CH_2), 3.85 (s, 1H, CH), 3.77 (s, 3H, N-CH_3), 3.30-3.24 (t, *J* = 10.8Hz, 2H, CH_2), 1.98-1.94 (d, *J* = 9.6Hz, 2H, CH_2), 1.50-1.47 (m, 2H, CH_2). ^{13}CMR (100 MHz, *DMSO-d6*): 162.53, 154.21, 147.53, 141.03, 137.73, 133.01, 126.56, 125.57, 123.21, 121.59, 120.41, 117.37, 110.73, 102.51, 46.92, 32.47, 31.26. LC-MS (*m/z*): 100% $[M+1]^{+}$: 422. Anal. Calcd. $C_{22}H_{23}N_5O_4$ (421.46): C, 62.70; H, 5.50; N, 16.62%. Found C, 62.59; H, 5.39; N, 16.71%.

1-(4-Fluorophenyl)-3-[1-(1-methyl-1*H*-indole-2-carbonyl)piperidin-4-yl]urea (11e)



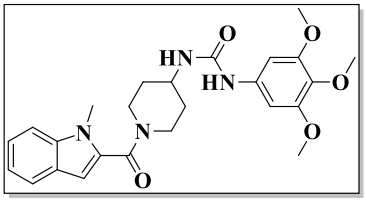
Compound **11e** was prepared from **7** (0.2 g, 0.680 mmol), TEA (0.344 g, 3.403 mmol) in THF (4 mL) and **10e** (0.084 g, 0.612 mmol). White solid (0.210 g, 78% yield). mp: 185-188 °C. IR (KBr) ν_{max}/cm^{-1}: 3324-3298 (NH), 3060 (aromatic-CH), 2920 (aliphatic-CH), 1625 (C=O-NH), 1567 (C=O), 1158 (C-N). ^{1}H NMR (400MHz, *DMSO-d6*): δppm 8.22 (s, 1H, C=O-NH), 7.61-7.59 (d, *J* = 8Hz, 1H, Ar-CH), 7.49-7.47 (d, *J* = 8.4Hz, 1H, Ar-CH), 7.40-7.36 (m, 2H, 2 x Ar-CH), 7.26-7.22 (m, 1H, Ar-CH), 7.11-7.07 (t, *J* = 6.8Hz, 1H, Ar-CH), 7.04-7.00 (m, 2H, 2 x Ar-CH), 6.62 (s, 1H, C=O-NH), 6.10-6.09 (d, *J* = 7.2Hz, 1H, Ar-CH), 4.12-4.09 (d, *J* = 12Hz, 2H, CH_2), 3.81-3.79 (m, 1H, CH), 3.77 (s, 3H, N-CH_3), 3.27-3.21 (t, *J* = 10.8Hz, 2H, CH_2), 1.95-1.91 (m, 2H, CH_2), 1.48-1.39 (m, 2H, CH_2). ^{13}C NMR (100 MHz, *DMSO-d6*): δppm 161.96, 158.05, 155.70, 154.52, 137.19, 136.76, 132.47, 126.02, 122.71, 121.11, 119.92, 119.26, 119.19, 115.19, 114.97, 110.27, 102.00, 46.22, 32.15, 30.78. LC-MS (*m/z*): 100% $[M+1]^+$: 395. Anal. Calcd. $C_{22}H_{23}FN_4O_2$ (394.45): C, 66.99; H, 5.88; N, 14.20%. Found C, 67.08; H, 5.78; N, 14.28%.

1-(4-Chlorophenyl)-3-[1-(1-methyl-1*H*-indole-2-carbonyl)piperidin-4-yl]urea (11f)



Compound **11f** was prepared from **7** (0.2 g, 0.680 mmol), TEA (0.344 g, 3.403 mmol) in THF (4 mL) and **10f** (0.094 g, 0.612 mmol). Off white solid (0.210 g, 75% yield). mp: 176-179 °C. IR (KBr) ν_{max}/cm^{-1}: 3296 (NH), 3052 (aromatic-CH), 2926 (aliphatic-CH), 1623 (C=O-NH), 1559 (C=C), 1138 (C-N). ^{1}H NMR (400MHz, *DMSO-d6*): δppm 8.34 (s, 1H, C=O-NH), 7.61-7.59 (d, *J* = 8Hz, 1H, Ar-CH), 7.49-7.47 (d, *J* = 8.4Hz, 1H, Ar-CH), 7.42-7.39 (m, 2H, 2 x Ar-CH), 7.26-7.22 (m, 3H, 3 x Ar-CH), 7.11-7.07 (t, *J* = 7.2Hz, 1H, Ar-CH), 6.62 (s, 1H, C=O-NH), 6.17-6.15 (d, *J* = 7.6Hz, 1H, Ar-CH), 4.12-4.09 (d, *J* = 12.8Hz, 2H, CH_2), 3.81-3.76 (m, 1H, CH), 3.75 (s, 3H, N-CH_3), 3.27-3.21 (t, *J* = 10.8Hz, 2H, CH_2), 1.95-1.91 (m, 2H, CH_2), 1.49-1.39 (m, 2H, CH_2). ^{13}C NMR (100 MHz, *DMSO-d6*): δppm 161.96, 154.31, 139.40, 137.19, 132.46, 128.46, 126.02, 124.49, 122.72, 121.11, 119.92, 119.10, 110.27, 102.01, 46.22, 32.20, 30.78. LC-MS (*m/z*): 94% $[M^{35}Cl^{+1}]^+$: 411, $[M^{37}Cl^{+1}]^+$: 413. Anal. Calcd. $C_{22}H_{23}ClN_4O_2$ (410.90): C, 64.31; H, 5.64; N, 13.64%. Found C, 64.28; H, 5.68; N, 13.70%.

1-[1-(1-Methyl-1*H*-indole-2-carbonyl)piperidin-4-yl]-3-(3,4,5-trimethoxyphenyl)urea (11g)

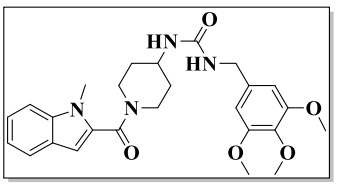


Compound **11g** was prepared from **7** (0.2 g, 0.680 mmol), TEA (0.344 g, 3.403 mmol) in THF (4 mL) and **10g** (0.128 g, 0.612 mmol). Off white solid (0.225 g, 71% yield). mp: 145-148 °C. IR (KBr) ν_{max}/cm^{-1}: 3349 (NH), 3088 (aromatic-CH), 2931 (aliphatic-CH), 1684 (C=O-NH), 1600 (C=C), 1123 (C-N). ^{1}H NMR (400MHz, *DMSO-d$_6$*): δppm 8.14 (s, 1H, C=O-NH), 7.62-7.60 (d, *J* = 8Hz, 1H, Ar-CH), 7.51-7.49 (d, *J* = 8Hz, 1H, Ar-CH), 7.28-7.24 (t, *J* = 8Hz, 1H, Ar-CH), 7.12-7.09 (t, *J* = 7.2Hz, 1H, Ar-CH). ^{13}C NMR (100 MHz, *DMSO-d$_6$*): δppm 162.44, 154.99, 153.23, 137.66, 137.05, 132.95, 132.38, 126.49, 123.19, 121.59, 120.41, 110.75, 102.49, 95.93, 66.55, 56.05, 46.71, 32.75, 31.26. LC-MS (*m/z*): 100% $[M+1]^+$: 467. Anal. Calcd. $C_{25}H_{30}N_4O_5$ (466.54): C, 64.36; H, 6.48; N, 12.01%. Found C, 64.28; H, 6.58; N, 12.10%.

General procedure for the synthesis of indole-piperidine hybrid compounds with urea linkage by using benzyl amine derivatives (*13a-f*)

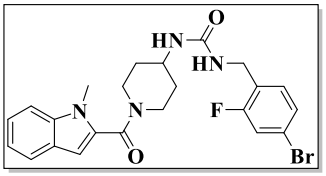
To a solution of **7** (1 eq) in DCM under nitrogen atmosphere, TEA (6 eq) was added at 25 °C and stirred it for 10 min, followed by CDI (1 eq) was added to the mixture and allowed to stirr at 25 °C for 30 min. After conversion of **7** into isocyanate intermediate, monitored by TLC (Non-Polar spot). Corresponding benzylamine (1 eq) was added and the reaction was stirred at 25 °C for 16h. After completion of the reaction, water was added and extracted with DCM (2 times), the combined organic layer was washed with water followed by brine. The separated organic layer was dried over sodium sulphate, and dried to obtain crude product, the obtained crude product was purified by reverse phase chromatography on C18 column with 15µ size using acetonitrile: 0.1% Formic acid in H_2O as mobile phase, obtained eluent was evaporated under vacum to give the corresponding desired product **13a-f**.

1-{1-[(1-Methyl-1*H*-indol-2-yl)carbonyl]piperidin-4-yl}-3-[(3,4,5-trimethoxyphenyl) methyl]urea (13a)



Compound **13a** was prepared from **7** (0.2 g, 0.680 mmol), TEA (0.412 g, 4.080 mmol) in DCM (4 mL), CDI (0.110 g, 0.680 mmol) and **12a** (0.134 g, 0.680 mmol). White solid (0.250 g, 76% yield). mp: 140-143 °C. IR (KBr) ν_{max}/cm^{-1}: 3302 (NH), 3052 (aromatic-CH), 2933 (aliphatic-CH), 1621 (C=O-NH), 1593 (C=O), 1127 (C-N). ^{1}H NMR (400MHz, *DMSO-d*$_6$): δppm 7.60-7.58 (d, *J* = 7.9Hz, 1H, C=O-NH), 7.51-7.49 (d, *J* = 8.3Hz, 1H, Ar-CH), 7.25-7.22 (t, *J* = 7.7Hz, 1H, Ar-CH), 7.10-7.07 (t, *J* = 7.4Hz, 1H, Ar-CH), 6.61 (s, 1H, Ar-CH), 6.55 (s, 2H, 2 x Ar-CH), 6.23-6.20 (t, *J* = 5.9Hz, 1H, C=O-NH), 6.03-6.01 (d, *J* = 7.8Hz, 1H, Ar-CH), 4.40-4.21 (m, 1H, Ar-CH), 4.13-4.12 (d, *J* = 5.9Hz, 2H, CH_2), 4.05-3.82 (m, 1H, CH), 3.73 (s, 9H, 3 x OCH_3), 3.61 (s, 3H, N-CH_3), 3.25-2.92 (m, 3H, CH_2, CH), 1.83 (bs, 2H, CH_2), 1.34-1.22 (m, 2H, CH_2). ^{13}C NMR (100 MHz, *DMSO-d*$_6$): δppm 162.43, 157.80, 153.24, 137.66, 136.99, 136.65, 133.00, 126.52, 123.19, 121.59, 120.41, 110.76, 104.80, 102.44, 66.46, 56.25, 46.85, 43.64, 33.28, 31.25. LC-MS (*m/z*): 97% $[M+1]^+$: 481. Anal. Calcd. $C_{26}H_{32}N_4O_5$ (480.57): C, 64.98; H, 6.71; N, 11.66%. Found C, 65.05; H, 6.70; N, 11.70%.

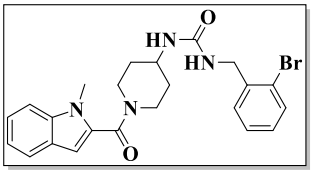
1-[(4-Bromo-2-fluorophenyl)methyl]-3-{1-[(1-methyl-1*H*-indol-2-yl)carbonyl]piperidin-4-yl}urea (13b)



Compound **13b** was prepared from **7** (0.2 g, 0.680 mmol), TEA (0.412 g, 4.080 mmol) in DCM (4 mL), CDI (0.110 g, 0.680 mmol) and **12b** (0.139 g, 0.680 mmol). White solid (0.200 g, 60% yield). mp: 187-190 °C. IR (KBr) ν_{max}/cm^{-1}: 3306 (NH), 3099 (aromatic-CH), 2927 (aliphatic-CH), 1617 (C=O-NH), 1571 (C=O), 1127 (C-N). ^{1}H NMR (400MHz, *DMSO-d*$_6$): δppm 7.63-7.61 (d, *J* = 8.0Hz, 1H, C=O-NH), 7.51-7.49 (d, *J* = 8.4Hz, 1H, Ar-CH), 7.45-7.39 (m, 2H, 2 x Ar-CH), 7.33-7.25 (m, 2H, 2 x Ar-CH), 7.14-7.10 (t, *J* = 7.7Hz, 1H, Ar-CH), 6.62 (s, 1H, Ar-CH), 6.23-6.20 (m, 1H, C=O-NH), 5.99-5.97 (d, *J* = 7.5Hz, 1H, Ar-CH), 4.26-4.25 (d, *J* = 6.0Hz, 2H, CH_2), 4.12-

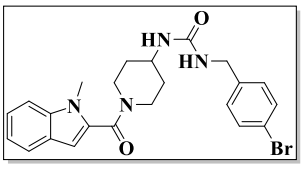
4.10 (bs, 2H, CH_2), 3.77 (s, 4H, N-CH_3, CH), 3.25-3.19 (t, *J* = 11.9Hz, 2H, CH_2), 1.91-1.88 (d, *J* = 12.9Hz, 2H, CH_2), 1.41-1.38 (d, *J* = 11.7Hz, 2H, CH_2). ^{13}C NMR (100 MHz, *DMSO-d6*): δppm 162.43, 161.56, 159.08, 157.65, 137.66, 132.99, 131.36, 131.31, 127.89, 127.74, 126.52, 123.19, 121.60, 120.41, 120.23, 120.14, 118.93, 118.69, 110.76, 102.44, 46.90, 36.89, 33.03, 31.26. LC-MS (*m/z*): 100% $[M^{79}Br^{+1}]^+$: 487, $[M^{81}Br^{+1}]^+$: 489. Anal. Calcd. $C_{23}H_{24}BrFN_4O_2$ (487.37): C, 56.68; H, 4.96; N, 11.50%. Found C, 56.64; H, 4.91; N, 11.54%.

1-[(2-Bromophenyl)methyl]-3-[1-(1-methyl-1*H*-indole-2-carbonyl)piperidin-4-yl]urea (13c)



Compound **13c** was prepared from **7** (0.2 g, 0.680 mmol), TEA (0.412 g, 4.080 mmol) in DCM (4 mL), CDI (0.110 g, 0.680 mmol) and **12c** (0.126 g, 0.680 mmol). White solid (0.250 g, 78% yield). mp: 187-190 °C. IR (KBr) ν_{max}/cm^{-1}: 3322 (NH), 3056 (aromatic-CH), 2933 (aliphatic-CH), 1623 (C=O-NH), 1578 (C=O), 1136 (C-N). ^{1}H NMR (400MHz, *DMSO-d6*): δppm 7.64-7.58 (m, 2H, Ar-CH, C=O-NH), 7.52-7.50 (d, *J* = 8Hz, 1H, Ar-CH), 7.39-7.37 (m, 2H, 2 x Ar-CH), 7.29-7.19 (m, 2H, 2 x Ar-CH), 7.14-7.12 (m, 1H, Ar-CH), 6.63-6.62 (d, *J* = 4Hz, 1H, Ar-CH), 6.22 (m, 1H, C=O-NH), 6.05 (s, 1H, Ar-CH), 4.32-4.29 (m, 2H, CH_2), 4.10 (bs, 2H, CH_2), 3.79-3.77 (m, 4H, CH_3, CH), 3.27-3.21 (t, *J* = 12Hz, 2H, CH_2), 1.93-1.90 (d, *J* = 12Hz, 2H, CH_2), 1.43-1.41 (m, 2H, CH_2). ^{13}C NMR (100 MHz, *DMSO-d6*): δppm 162.45, 157.68, 139.85, 137.67, 133.00, 132.73, 129.15, 128.16, 126.53, 123.20, 122.72, 121.60, 120.42, 110.76, 102.45, 46.88, 43.77, 33.05, 31.26. LC-MS (*m/z*): 99% $[M^{79}Br^{+1}]^+$: 469, $[M^{81}Br^{+1}]^+$: 471. Anal. Calcd. $C_{23}H_{25}BrN_4O_2$ (469.38): C, 58.85; H, 5.37; N, 11.94%. Found C, 58.74; H, 5.41; N, 11.86%.

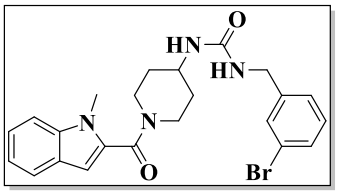
1-[(4-Bromophenyl)methyl]-3-[1-(1-methyl-1*H*-indole-2-carbonyl)piperidin-4-yl]urea (13d)



Compound **13d** was prepared from **7** (0.2 g, 0.680 mmol), TEA (0.412 g, 4.080 mmol) in DCM (4 mL), CDI (0.110 g, 0.680 mmol) and **12d** (0.126 g, 0.680 mmol). White

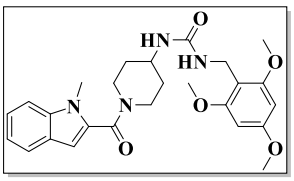
solid (0.240 g, 75% yield). mp: 194-197 °C. IR (KBr) ν_{max}/cm^{-1}: 3300 (NH), 3082 (aromatic-CH), 2920 (aliphatic-CH), 1615 (C=O-NH), 1559 (C=O), 1149 (C-N). ^1H NMR (400MHz, *DMSO-d6*): δppm 7.63-7.61 (d, *J* = 8Hz, 1H, C=O-NH), 7.51-7.49 (d, *J* = 8Hz, 3H, 3 x Ar-CH), 7.29-7.23 (m, 3H, 3 x Ar-CH), 7.14-7.10 (t, *J* = 8Hz, 1H, Ar-CH), 6.62 (s, 1H, Ar-CH), 6.21-6.19 (m, 1H, C=O-NH), 5.93-5.91 (d, *J* = 8Hz, 1H, Ar-CH), 4.22-4.21 (d, *J* = 4Hz, 2H, CH_2), 4.13-4.09 (d, *J* = 16Hz, 2H, CH_2), 3.77 (s, 4H, N-CH_3, CH), 3.25-3.19 (t, *J* = 12Hz, 2H, CH_2), 1.91-1.88 (d, *J* = 12Hz, 2H, CH_2), 1.44-1.39 (m, 2H, CH_2). ^{13}C NMR (100 MHz, *DMSO-d6*): δppm 162.43, 157.77, 141.01, 137.66, 133.00, 131.52, 129.70, 126.52, 123.19, 121.60, 120.41, 119.94, 110.76, 102.43, 46.91, 42.69, 32.95, 31.26. LC-MS (*m/z*):100% $[M^{79}Br^{+1}]^+$: 469, $[M^{81}Br^{+1}]^+$: 471. Anal. Calcd. $C_{23}H_{25}BrN_4O_2$ (469.38): C, 58.85; H, 5.37; N, 11.94%. Found C, 58.74; H, 5.42; N, 11.89%.

1-[(3-Bromophenyl)methyl]-3-[1-(1-methyl-1*H*-indole-2-carbonyl)piperidin-4-yl]urea (13e)



Compound **13e** was prepared from **7** (0.2 g, 0.680 mmol), TEA (0.412 g, 4.080 mmol) in DCM (4 mL), CDI (0.110 g, 0.680 mmol), and **12e** (0.126 g, 0.680 mmol). White solid (0.240 g, 75% yield). mp: 195-198 °C. IR (KBr) ν_{max}/cm^{-1}: 3295 (NH), 3056 (aromatic-CH), 2924 (aliphatic-CH), 1617 (C=O-NH), 1565 (C=O), 1101 (C-N). ^1H NMR (400MHz, *DMSO-d6*): δppm 7.63-7.61 (d, *J* = 8Hz, 1H, C=O-NH), 7.51-7.41 (m, 3H, 3 x Ar-CH), 7.31-7.25 (m, 3H, 3 x Ar-CH), 7.14-7.10 (t, *J* = 8Hz, 1H, Ar-CH), 6.63 (s, 1H, Ar-CH), 6.25-6.21 (m, 1H, C=O-NH), 5.96-5.94 (d, *J* = 8Hz, 1H, Ar-CH), 4.26-4.24 (d, *J* = 8Hz, 2H, CH_2), 4.10 (bs, 2H, CH_2), 3.78 (s, 4H, N-CH_3, CH), 3.25-3.19 (t, *J* = 12Hz, 2H, CH_2), 1.92-1.89 (d, *J* = 12Hz, 2H, CH_2), 1.46-1.27 (m, 2H, CH_2). ^{13}C NMR (100 MHz, *DMSO-d6*): δppm 162.41, 157.75, 144.48, 137.64, 132.98, 130.88, 130.13, 129.79, 126.51, 123.18, 122.04, 121.59, 120.40, 110.76, 102.43, 46.91, 42.72, 31.25. LC-MS (*m/z*): 100% $[M^{79}Br^{+1}]^+$: 469, $[M^{81}Br^{+1}]^+$: 471. Anal. Calcd. $C_{23}H_{25}BrN_4O_2$ (469.38): C, 58.85; H, 5.37; N, 11.94%. Found C, 58.74; H, 5.42; N, 11.88%.

1-[(2,4,6-Trimethoxyphenyl)methyl]-3-[1-(1-methyl-1*H*-indole-2-carbonyl)piperidin-4-yl]urea (13f)



Compound **13f** was prepared from **7** (0.2 g, 0.680 mmol), TEA (0.412 g, 4.080 mmol) in DCM (4 mL), CDI (0.110 g, 0.680 mmol), and **12f** (0.134 g, 0.680 mmol). White solid (0.250 g, 76% yield). mp: 194-197 °C. IR (KBr) ν_{max}/cm^{-1}: 3321 (NH), 3049 (aromatic-CH), 2939 (aliphatic-CH), 1627 (C=O-NH), 1556 (C=O), 1058 (C-N). ^{1}H NMR (400MHz, *DMSO-d6*): δppm 7.63-7.61 (d, *J* = 8Hz, 1H, C=O-NH), 7.51-7.49 (d, *J* = 8Hz, 1H, Ar-CH), 7.29-7.25 (t, *J* = 8Hz, 1H, Ar-CH), 7.14-7.10 (t, *J* = 8Hz, 1H, Ar-CH), 6.62 (s, 1H, Ar-CH), 6.26 (s, 2H, Ar-CH, C=O-NH), 5.89-5.88 (d, *J* = 4Hz, 1H, Ar-CH), 5.40 (bs, 1H, Ar-CH), 4.18-4.16 (d, *J* = 8Hz, 2H, CH_2), 4.06 (bs, 2H, CH_2), 3.81-3.77 (m, 13H, 3 OCH_3, N-CH_3, CH), 3.27-3.21 (t, *J* = 12Hz, 2H, CH_2), 1.89-1.86 (t, *J* = 12Hz, 2H, CH_2), 1.36-1.29 (m, 2H, CH_2). ^{13}C NMR (100 MHz, *DMSO-d6*): δppm 162.64, 160.99, 159.52, 157.66, 137.81, 133.35, 126.74, 123.13, 121.56, 120.35, 110.60, 108.55, 102.36, 91.96, 56.44, 55.83, 46.67, 44.15, 33.07, 32.61, 31.15. LC-MS (*m/z*): 100% $[M+1]^+$: 481. Anal. Calcd. $C_{26}H_{32}N_4O_5$ (480.57): C, 64.98; H, 6.71; N, 11.66%. Found C, 64.90; H, 6.65; N, 11.68%.

1.8.3 Protocol of Anti Cancer Activity

At the National Cancer Institute (NCI US), all the newly synthesized compounds were submitted for screening of NCI 60 cell lines underwent an initial evaluation at a single high dosage concentration of 10^{-5} M across all NCI 60 cell lines. The cells were cultured for 48 hours following the addition of drugs at the specified concentration. The growth percentage (GP) of treated cells, which was calculated in relation to the number of cells at zero time and untreated control cells, was the resultant **Figure**. Every screening was conducted by NCI US guidelines.[48-49]

1.8.4 Protocol of Molecular Docking Study

We utilized the Autodock Vina PyRx program (version 0.8) to study molecular interactions. To put it briefly, the protein database was retrieved to retrieve the protein VEGFR2 (PDB ID: 4AGC). After being sketched with ChemDraw software, the

compound's structures were polished into three-dimensional conformers. Excess water and metals were removed to prepare the protein, the energy level was lowered, and hydrogen atoms were added. By adding polar hydrogen atoms and ions and lowering the energy state, the ligand was created. The active torsion was then set to 6 and the file was stored in pdbqt. With center characteristics (X = -23.1, Y = 0.7, and Z = -11.1) and size (X = 18.2, Y = 16.1, and Z = 15.4), the grid box for VEGFR2 was created. The exhaustiveness was set at eight, and the maximum number of conformers was 10. Software called Discovery Studio Visualization (version 4) was used to record the binding interaction. Interaction photos were stored in JPG format, and docking scores were noted.[50-51]

1.8.5 Protocol of the ADMET Study

To assess the novel drug candidates' pharmacokinetic characteristics, *in silico* ADME experiments were carried out using the SwissADME server, which is a component of the Swiss Institute of Bioinformatics' Advanced Model for Drug Evaluation. As part of this procedure, a number of physicochemical properties were evaluated, including molecular weight, polar surface area, water solubility, pharmacokinetics, drug-likeness, and the existence of donors and acceptors for hydrogen bonds.[52-53]

1.9 Representative spectral data

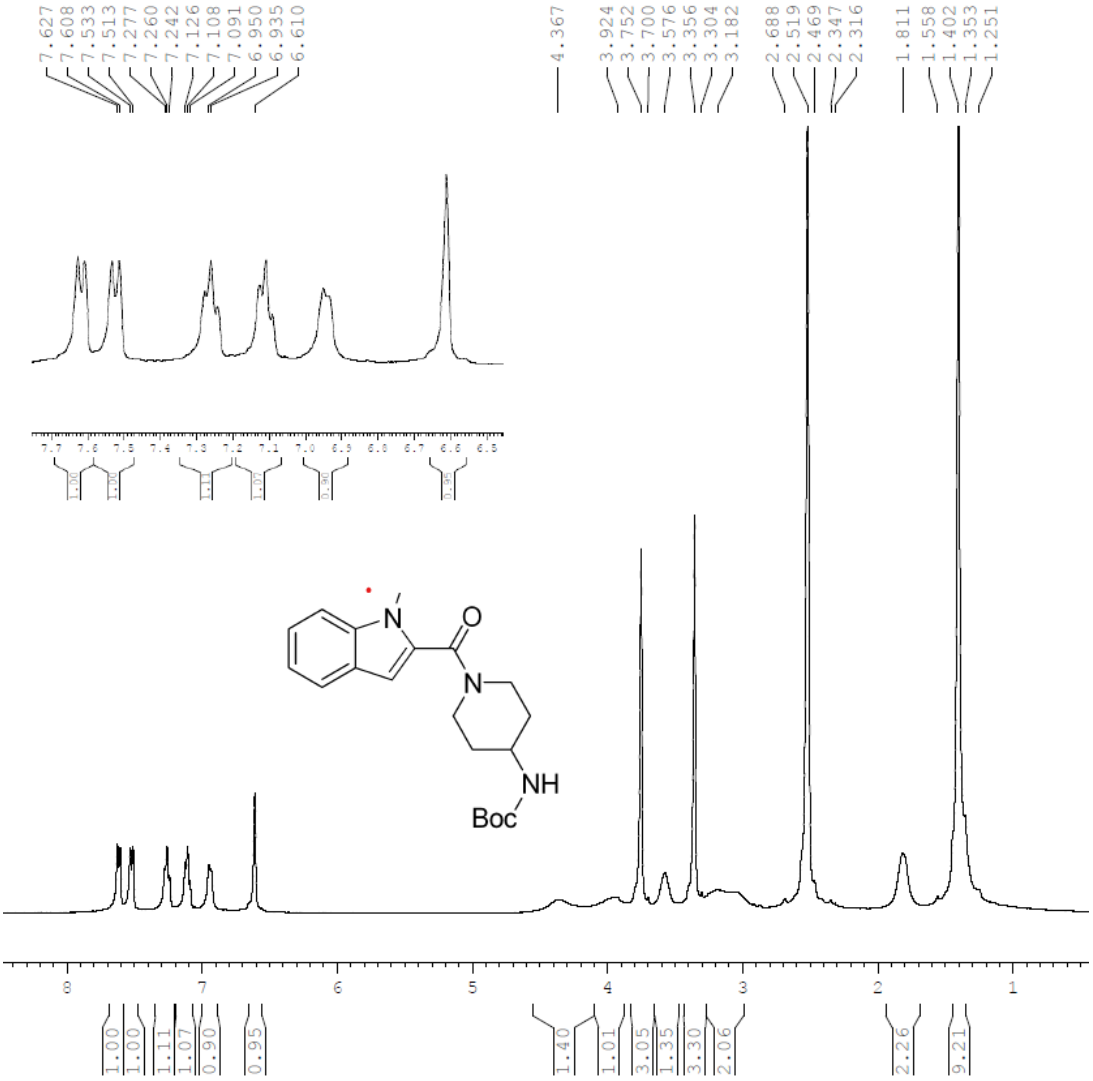


Figure 15: ^{1}H NMR of compound **6.**

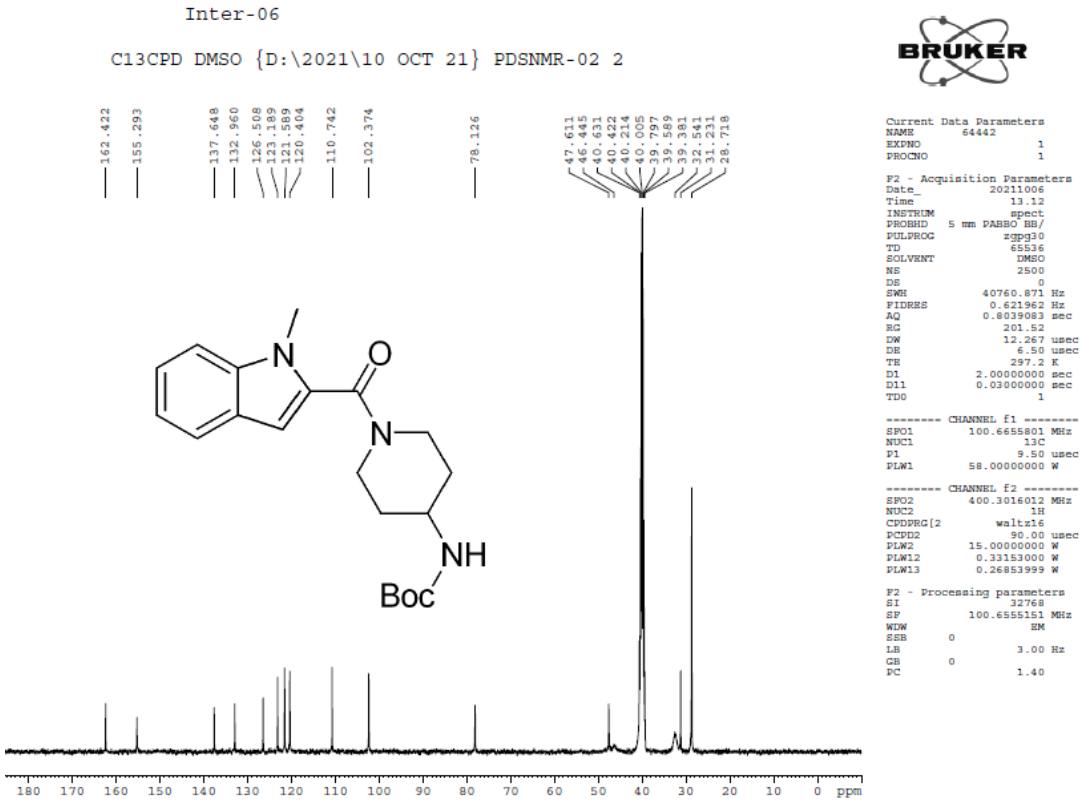
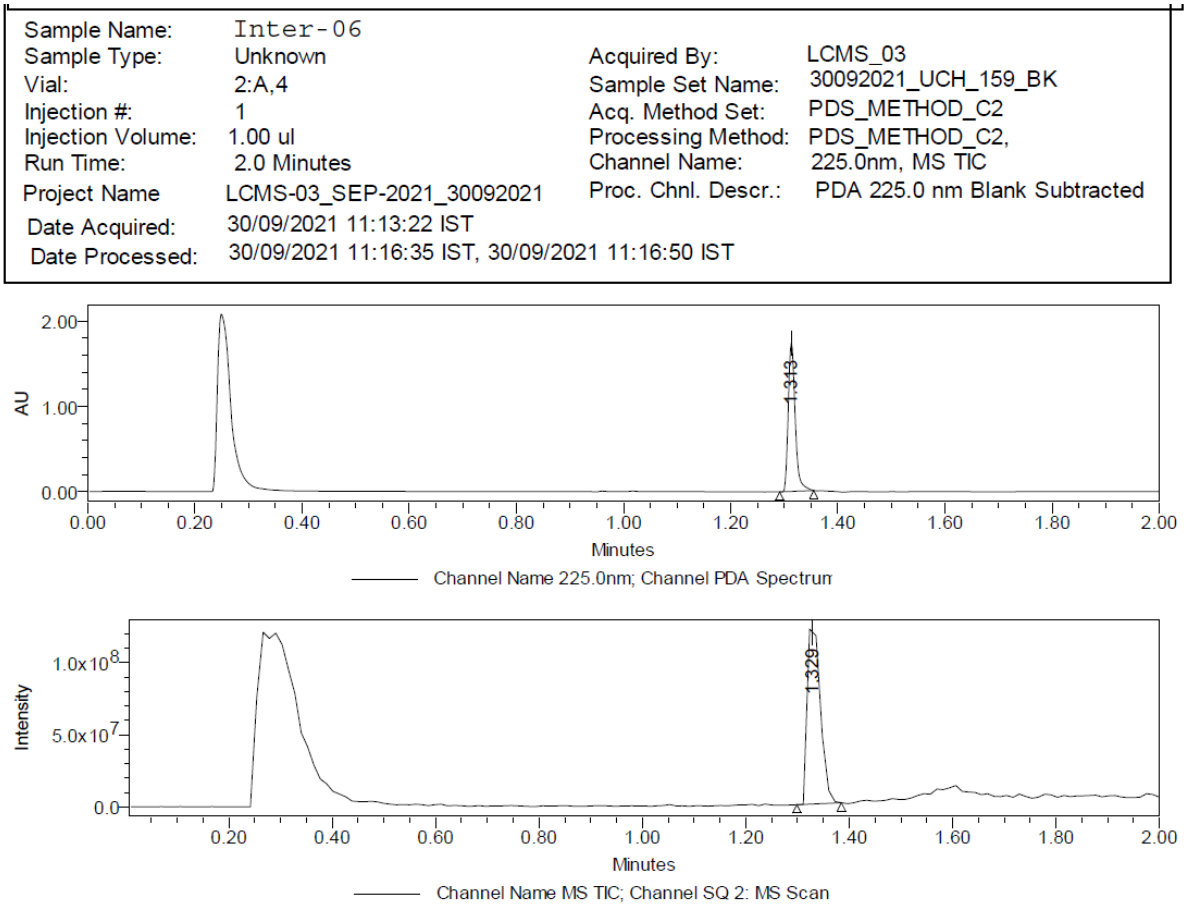
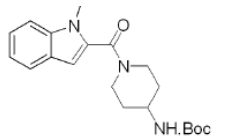


Figure 16: ^{13}C NMR of compound **6.**

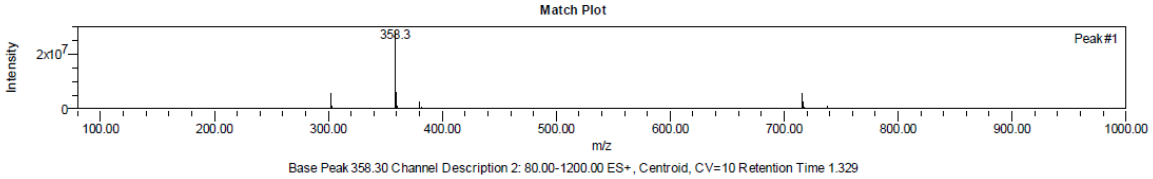


Peak Results
Channel: PDA Spectrum

	Retention Time (min)	Base Peak (m/z)	Height (µV)	Area (µV*sec)	% Area	Channel	Channel Name
1	1.313		1739551	1565833	100.00	PDA Spectrum	225.0nm



Chemical Formula: $C_{20}H_{27}N_3O_3$
Molecular Weight: 357.45



Base Peak 358.30 Channel Description 2: 80.00-1200.00 ES+, Centroid, CV=10 Retention Time 1.329

Figure 17: LC-MS of compound **6.**

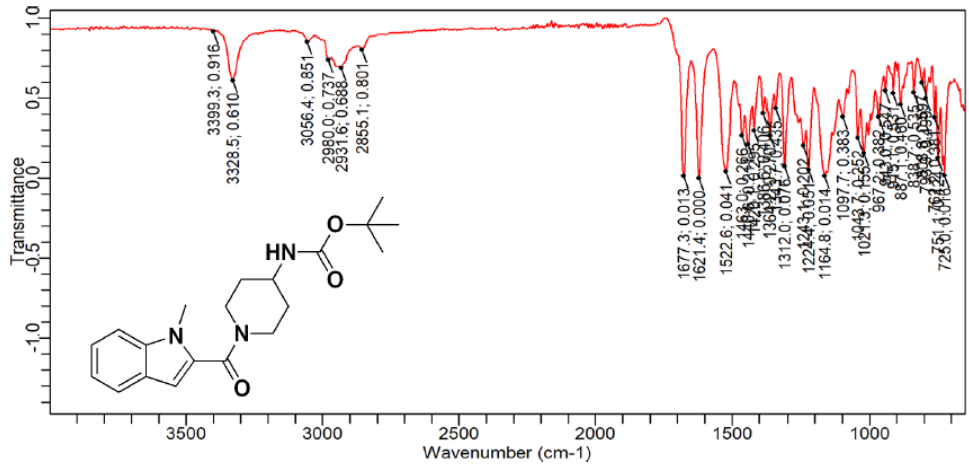


Figure 18: IR of compound **6.**

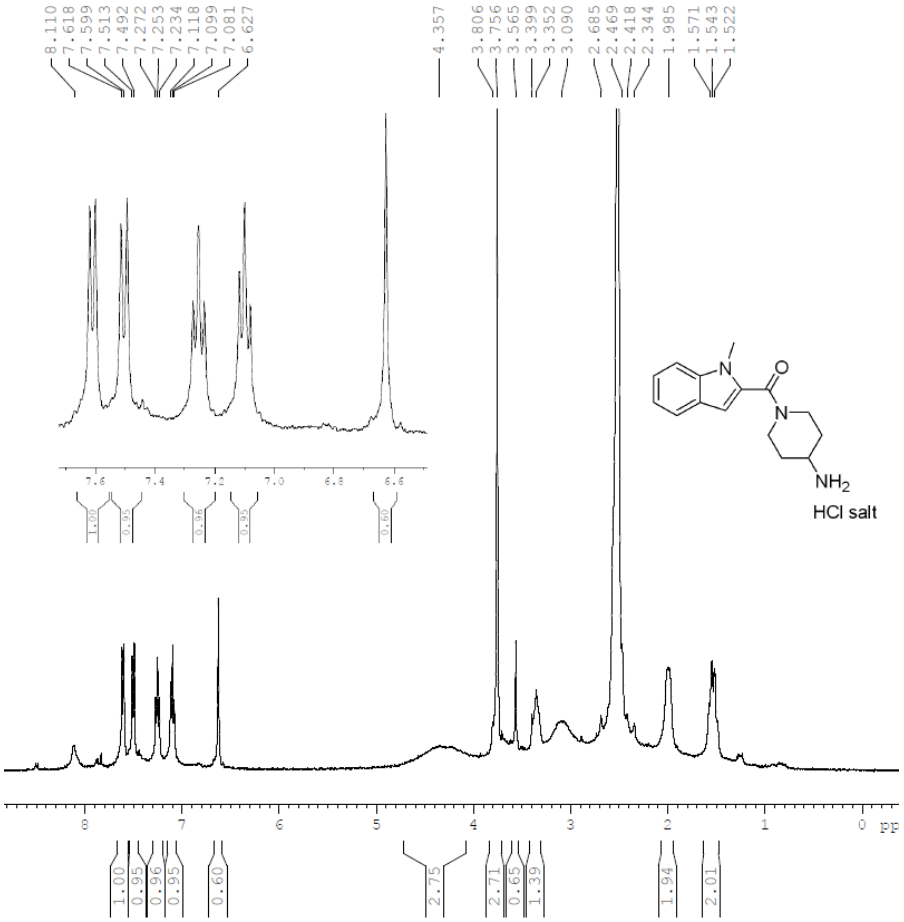


Figure 19: ^{1}H NMR of compound **7.**

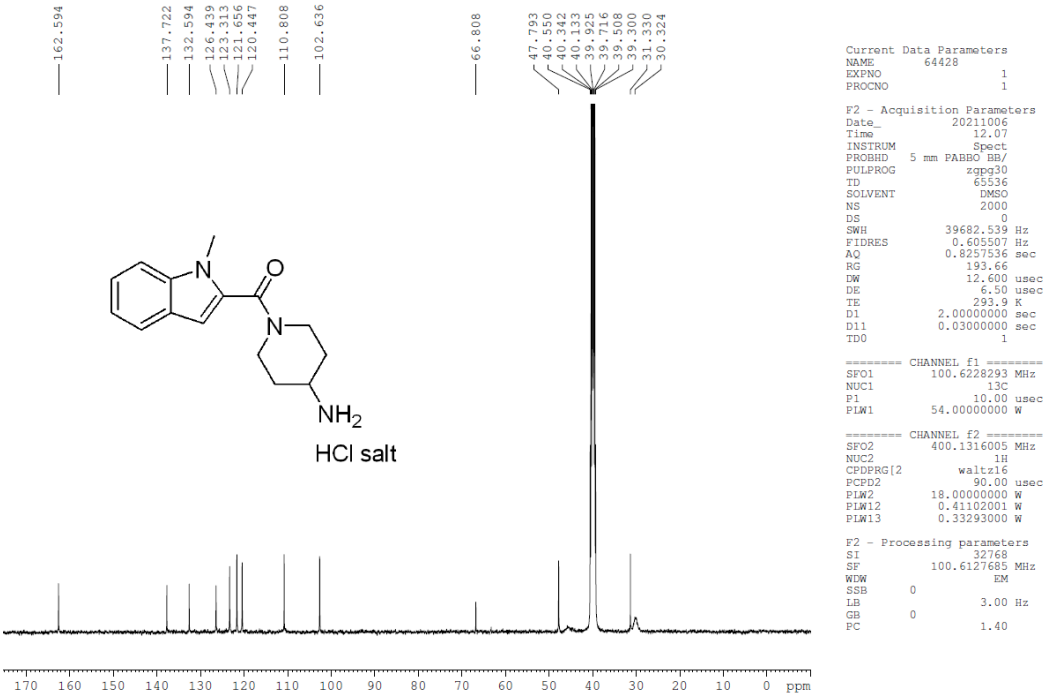
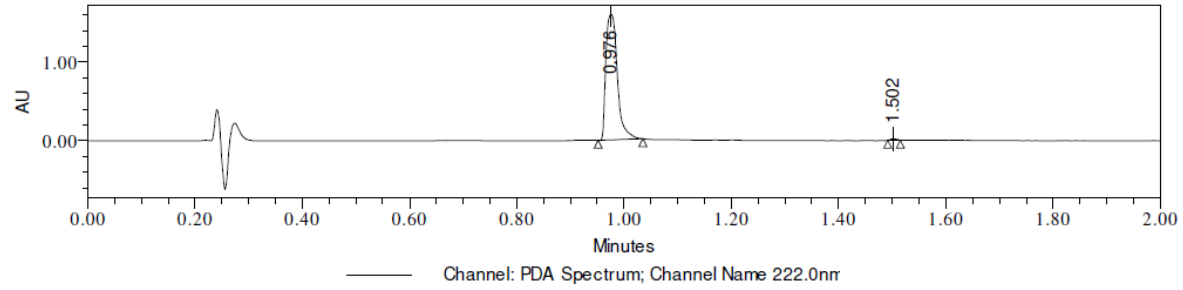
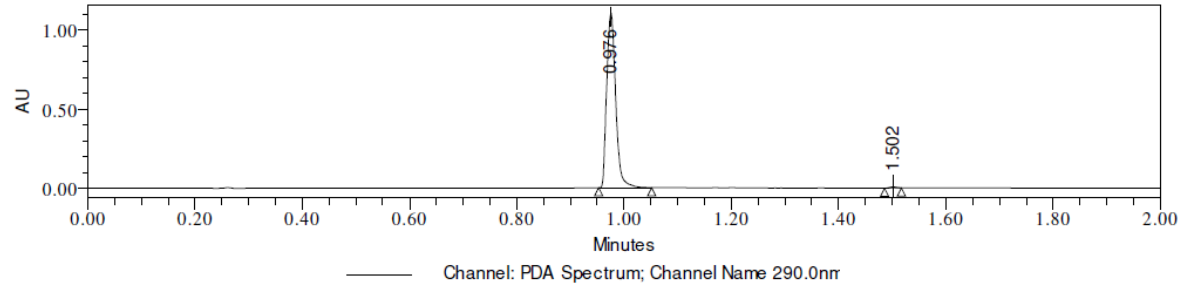
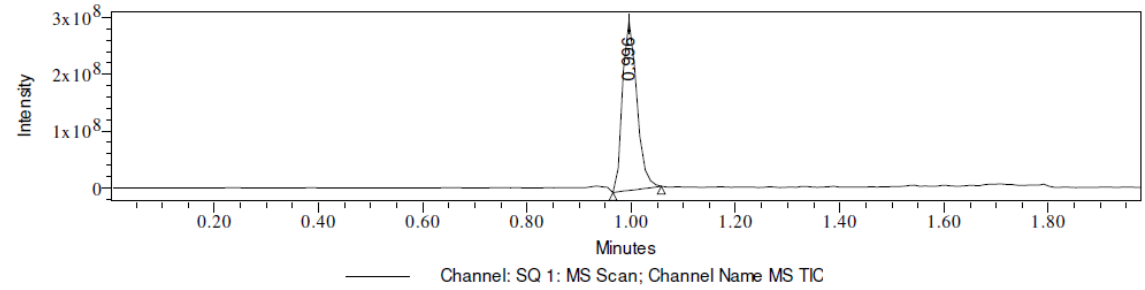


Figure 20: ^{13}C NMR of compound **7.**

Sample Name:	Inter-07_Amine		
Sample Type:	Unknown	Acquired By:	LCMS-02
Vial:	1:A,4	Sample Set Name:	01102021 UCH 154 AG
Injection #:	1	Acq. Method Set:	LCMS METHOD C2
Injection Volume:	1.00 ul	Processing Method:	LCMS METHOD C2, LCMS
Run Time:	2.0 Minutes	Channel Name:	222.0nm, MS TIC, 290.0nm
Project Name	LCMS-02_OCT-2021_01102021	Proc. Chnl. Descr.:	SQ 1: MS Scan MS TIC, Smoothed
Date Acquired:	01/10/2021 13:48:09 IST		
Date Processed:	01/10/2021 13:59:48 IST, 01/10/2021 14:00:12 IST, 01/10/2021 14:00:26 IST		

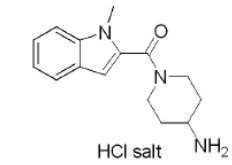






Peak Results
Channel: PDA Spectrum

	Retention Time (min)	Base Peak (m/z)	Height (µV)	Area (µV*sec)	% Area	Channel	Channel Name
1	0.976		1102479	1286592	99.49	PDA Spectrum	290.0nm
2	0.976		1597912	2373739	99.40	PDA Spectrum	222.0nm
3	1.502		7761	6638	0.51	PDA Spectrum	290.0nm
4	1.502		18504	14209	0.60	PDA Spectrum	222.0nm



Chemical Formula: $C_{15}H_{19}N_3O$
Molecular Weight: 257.34

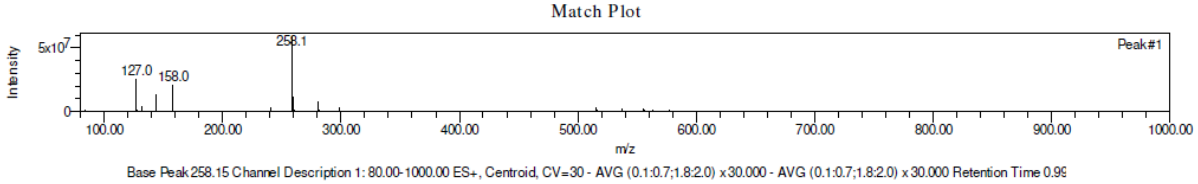


Figure 21: LC-MS of compound **7.**

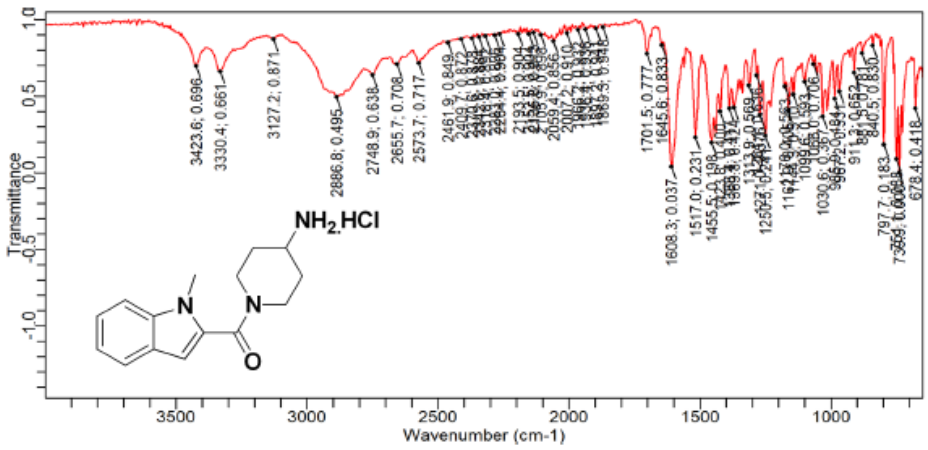


Figure 22: IR of compound **7.**

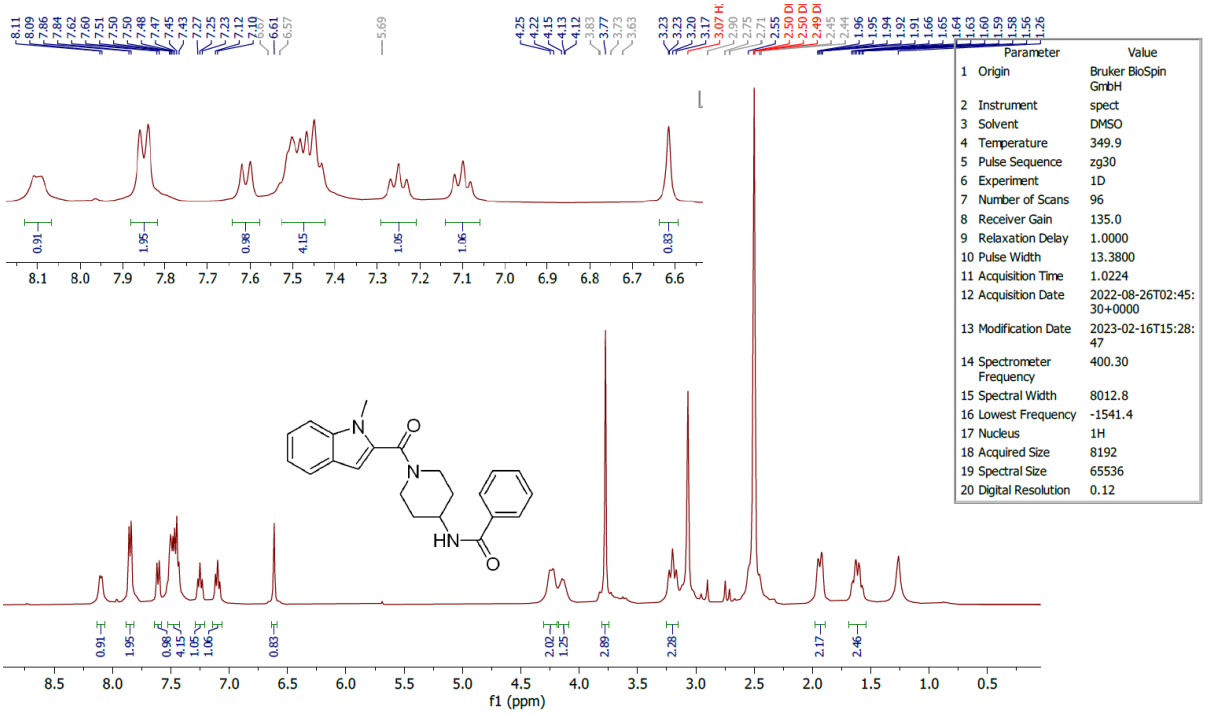


Figure 23: ^{1}H NMR of compound **9a.**

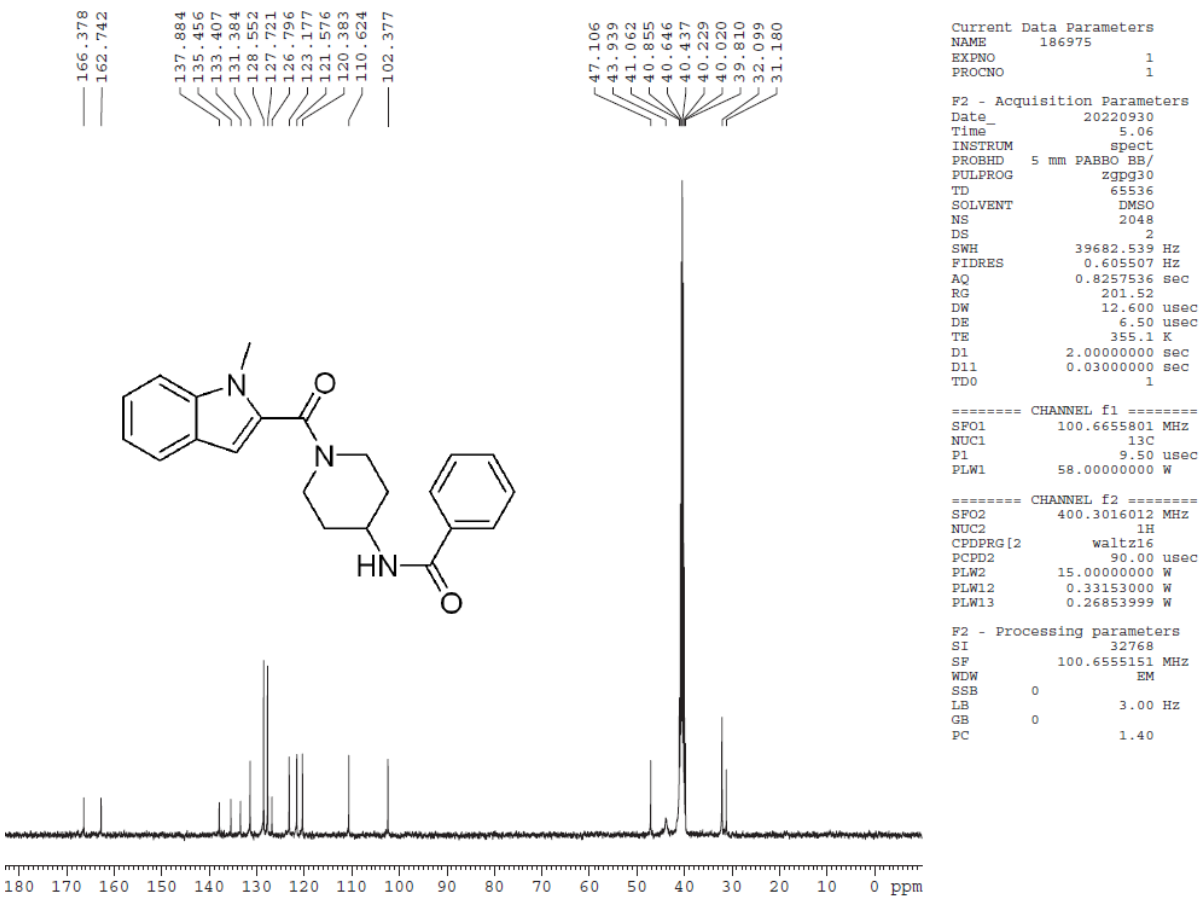
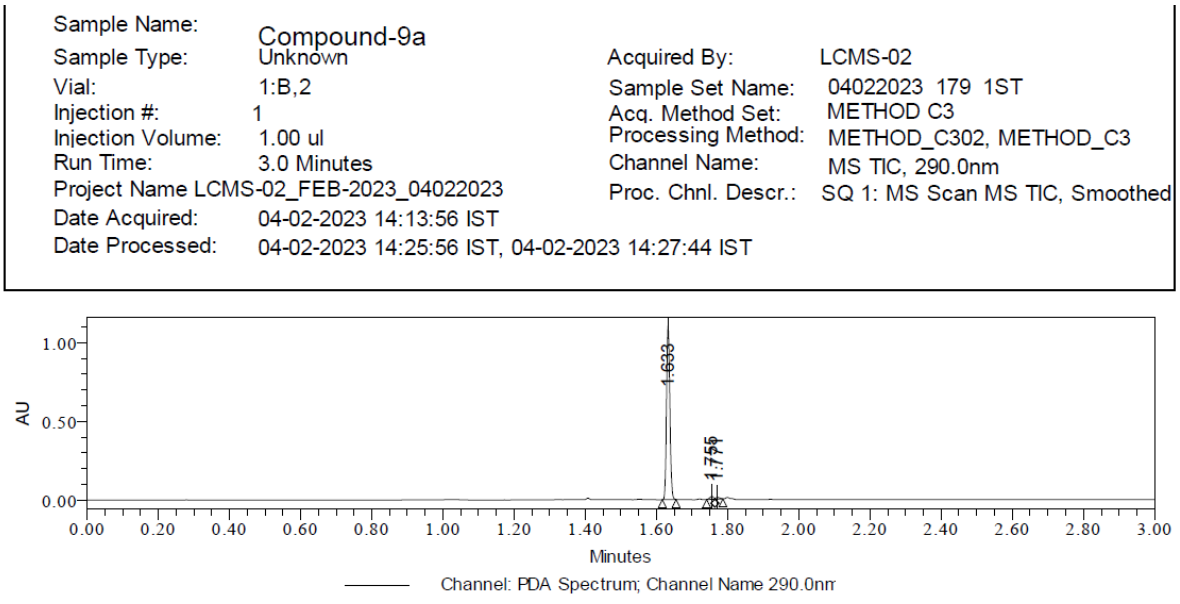
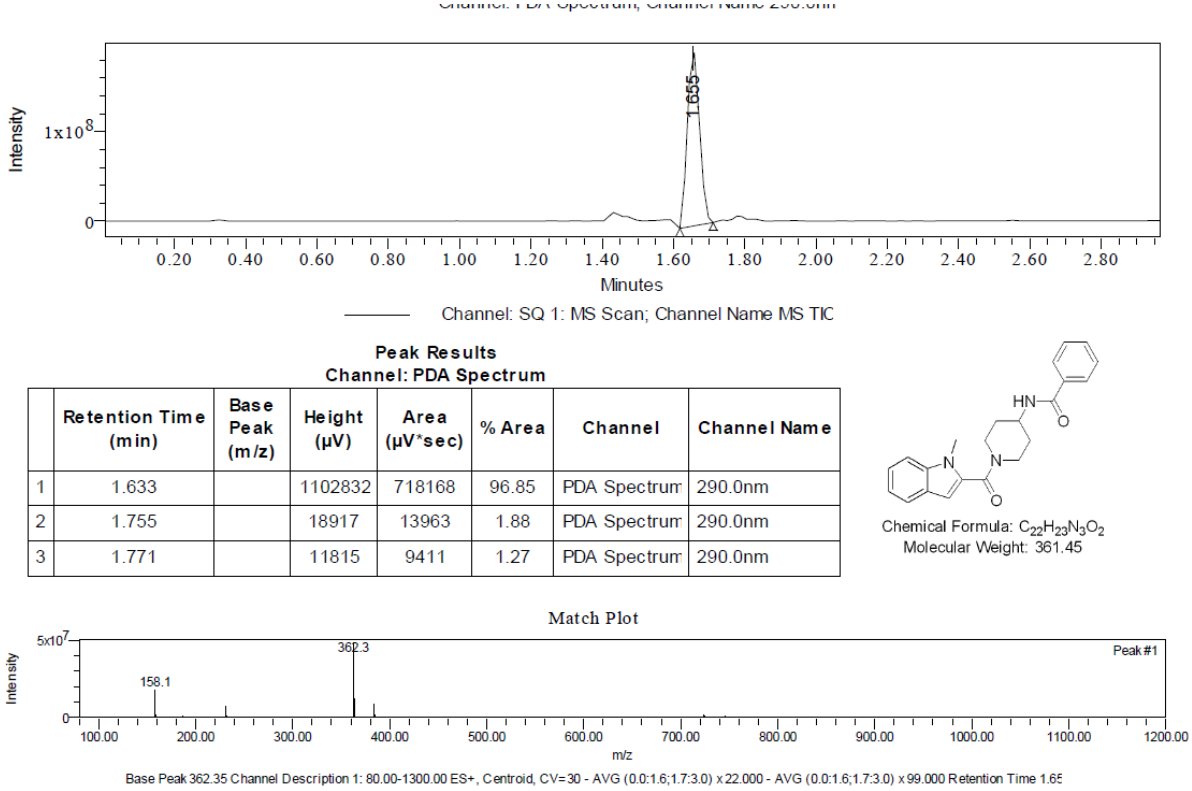


Figure 24: ^{13}C NMR of compound **9a.**





Peak Results
Channel: PDA Spectrum

	Retention Time (min)	Base Peak (m/z)	Height (µV)	Area (µV*sec)	% Area	Channel	Channel Name
1	1.633		1102832	718168	96.85	PDA Spectrum	290.0nm
2	1.755		18917	13963	1.88	PDA Spectrum	290.0nm
3	1.771		11815	9411	1.27	PDA Spectrum	290.0nm

Chemical Formula: $C_{22}H_{23}N_3O_2$
Molecular Weight: 361.45

Figure 25: LC-MS of compound **9a.**

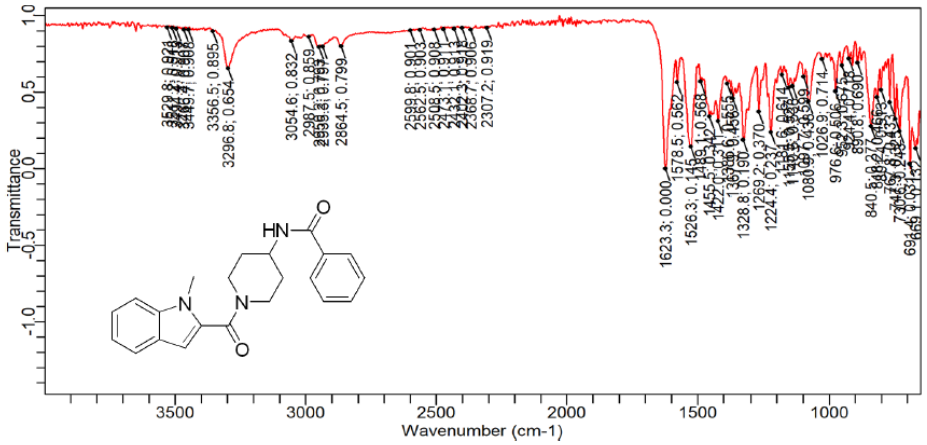


Figure 26: IR of compound **9a.**

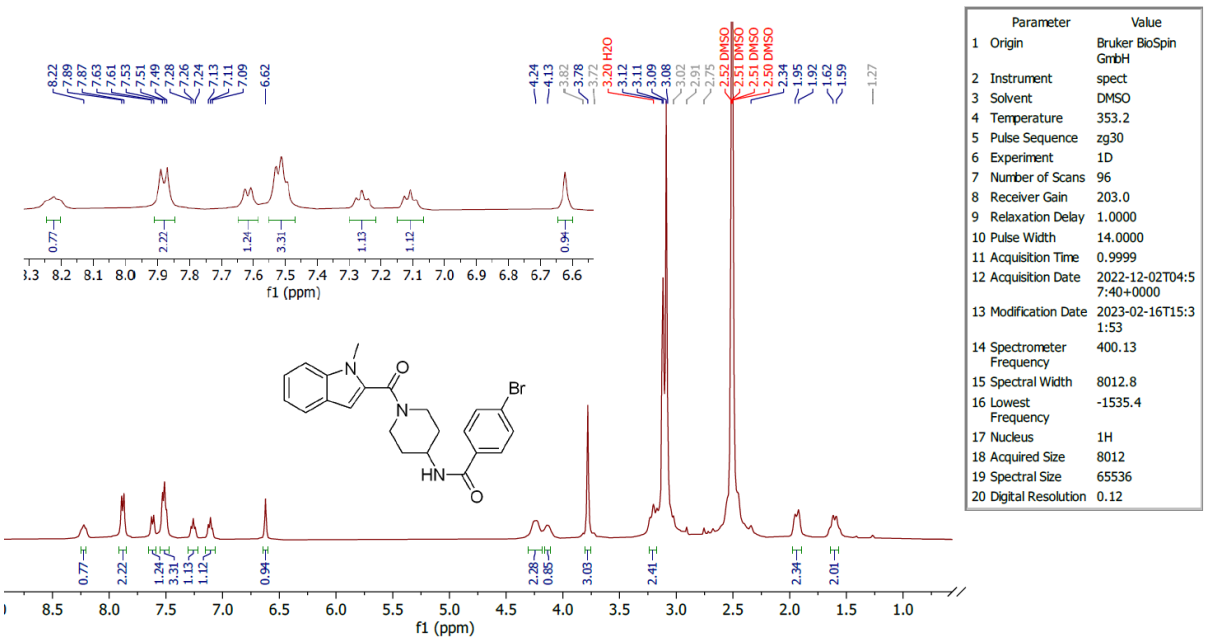


Figure 27: ^{1}H NMR of compound **9c.**

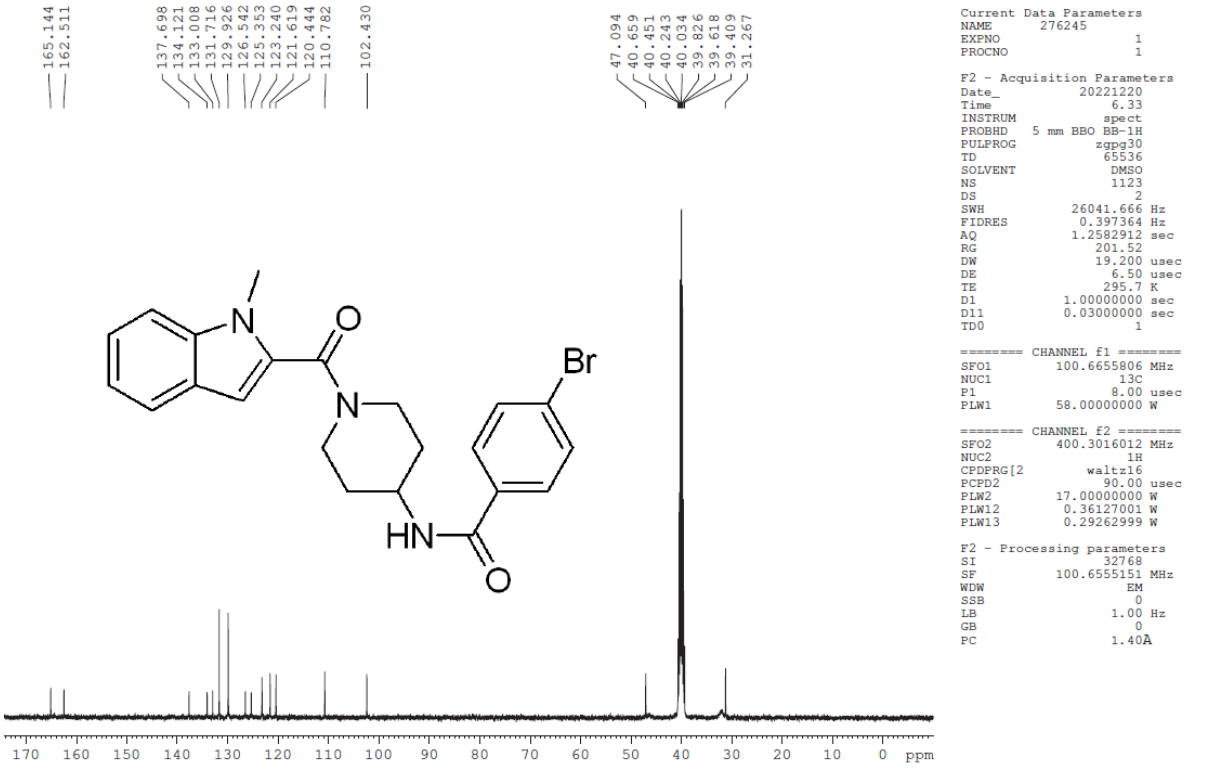
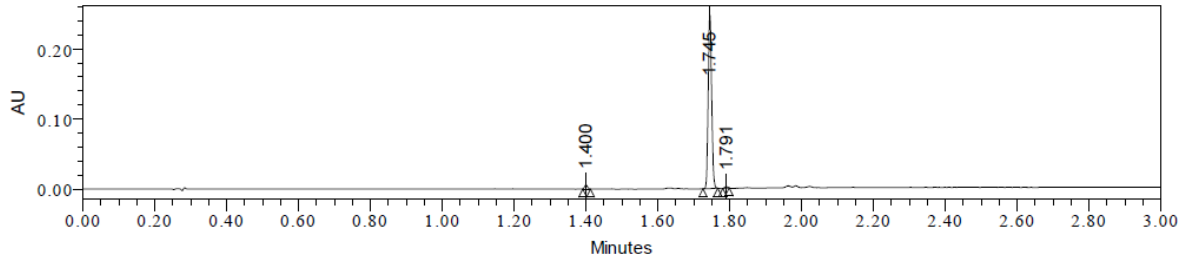
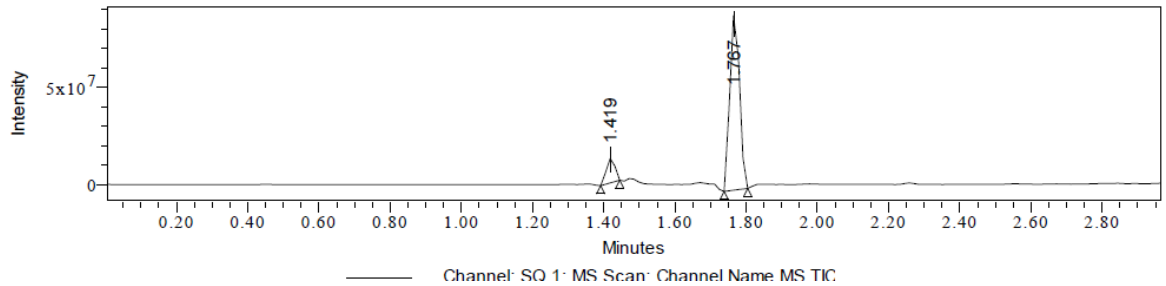


Figure 28: ^{13}C NMR of compound **9c.**

LCMS Analysis Report

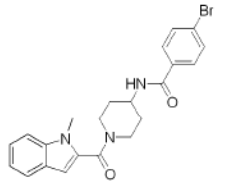
Sample Name:	Compound-9c		
Sample Type:	Unknown	Acquired By:	LCMS-02
Vial:	1:B,4	Sample Set Name:	04022023 179 1ST
Injection #:	1	Acq. Method Set:	METHOD C3
Injection Volume:	1.00 ul	Processing Method:	METHOD_C302, METHOD_C3
Run Time:	3.0 Minutes	Channel Name:	285.0nm, MS TIC
Project Name	LCMS-02_FEB-2023_04022023	Proc. Chnl. Descr.:	PDA 285.0 nm Blank Subtracted
Date Acquired:	04-02-2023 14:22:06 IST		
Date Processed:	04-02-2023 14:31:27 IST, 04-02-2023 14:31:49 IST		





Peak Results
Channel: PDA Spectrum

	Retention Time (min)	Base Peak (m/z)	Height (µV)	Area (µV*sec)	% Area	Channel	Channel Name
1	1.400		5499	3147	1.85	PDA Spectrum	285.0nm
2	1.745		248361	166181	97.50	PDA Spectrum	285.0nm
3	1.791		2053	1115	0.65	PDA Spectrum	285.0nm



Chemical Formula: $C_{22}H_{22}BrN_3O_2$
Molecular Weight: 440.34

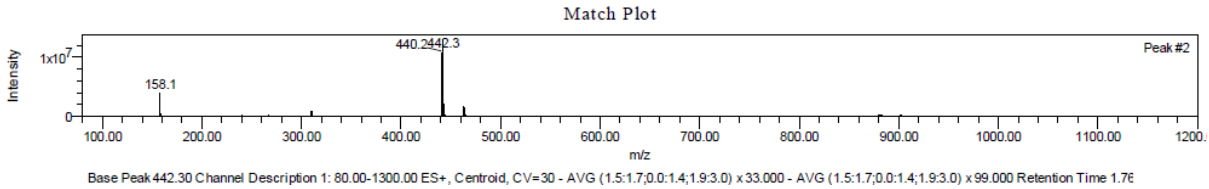


Figure 29: LC-MS of compound **9c.**

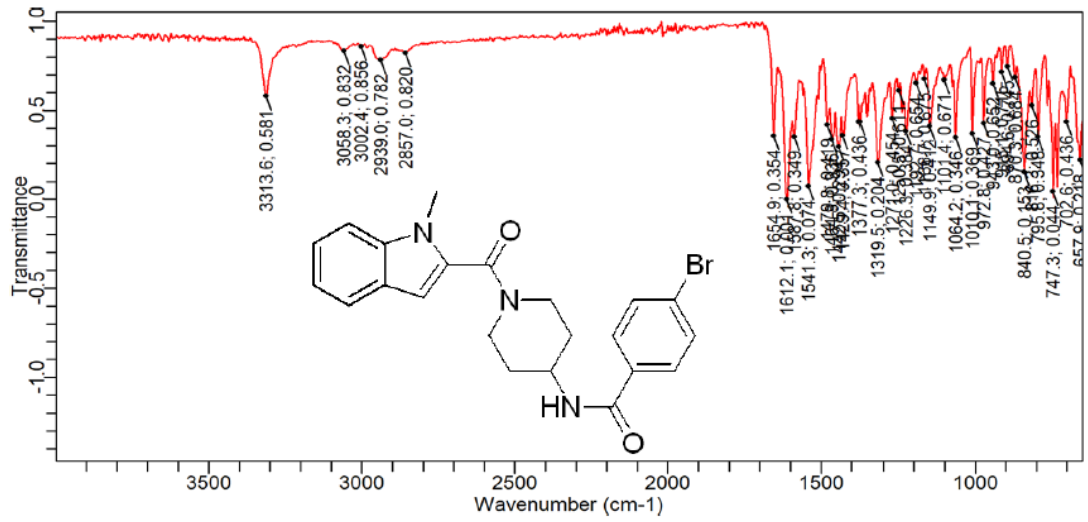


Figure 30: IR of compound **9c.**

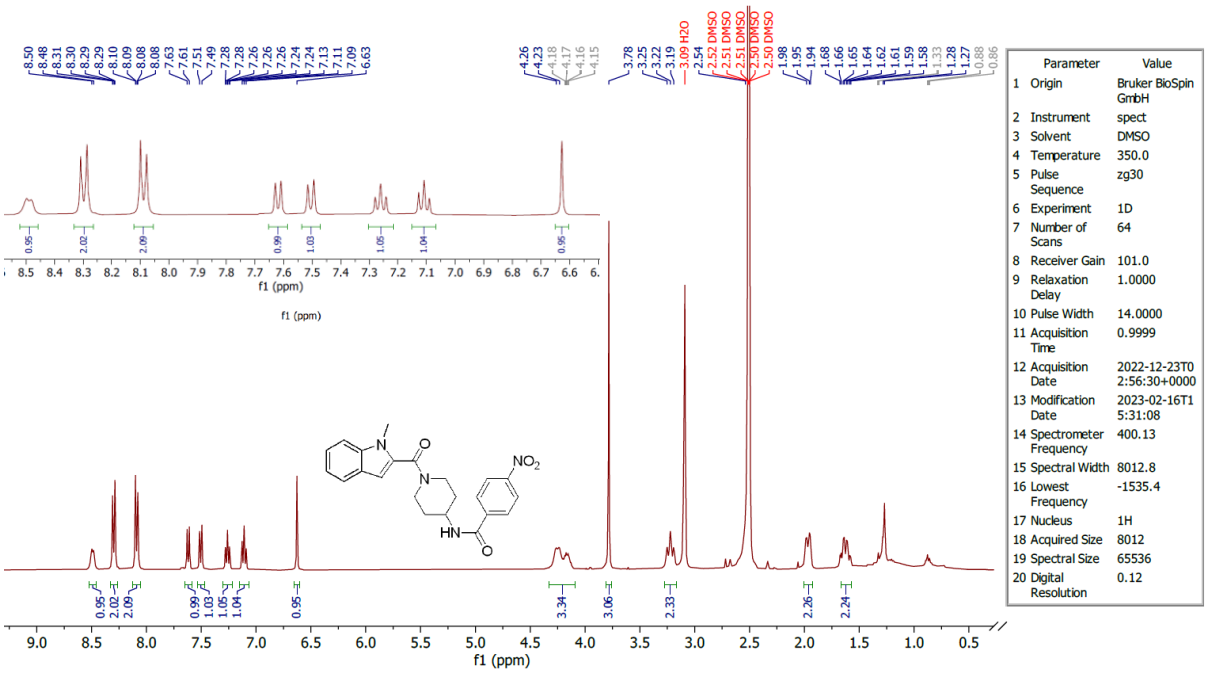


Figure 31: ^{1}H NMR of compound **9d.**

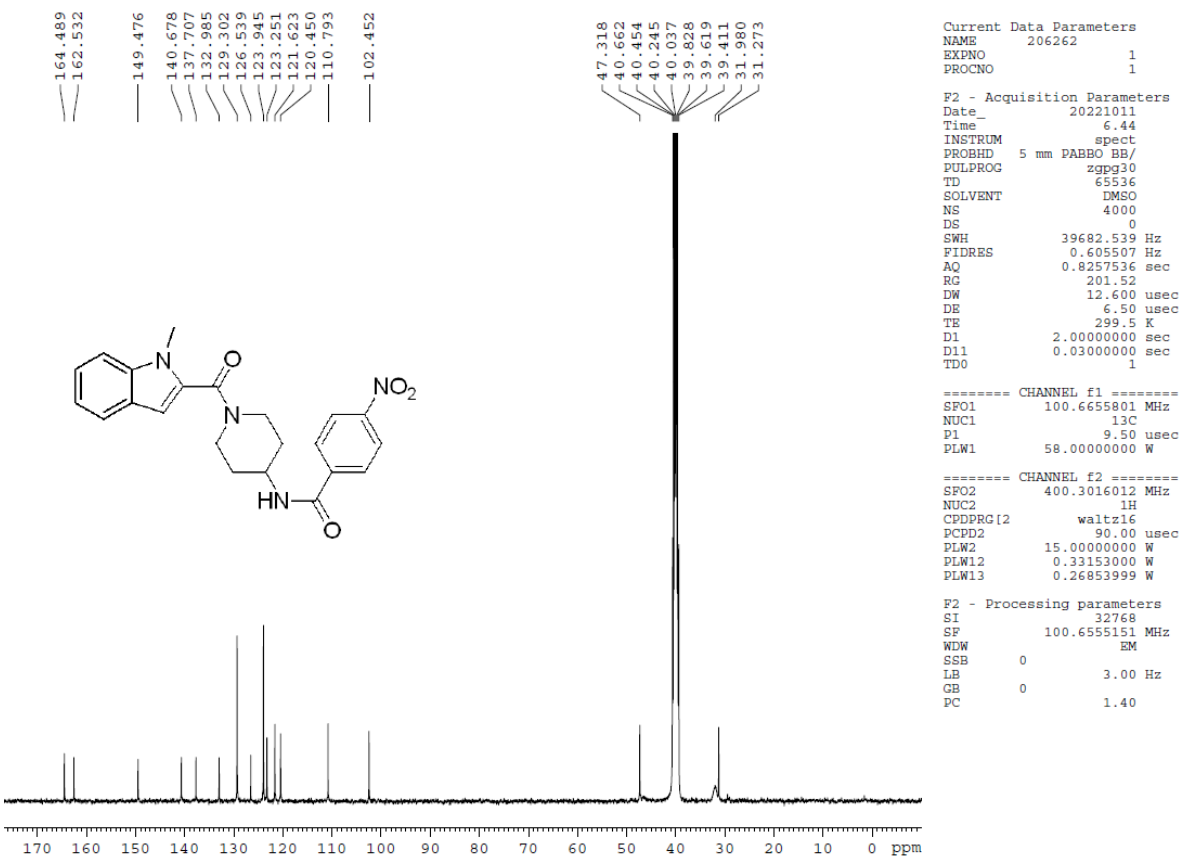
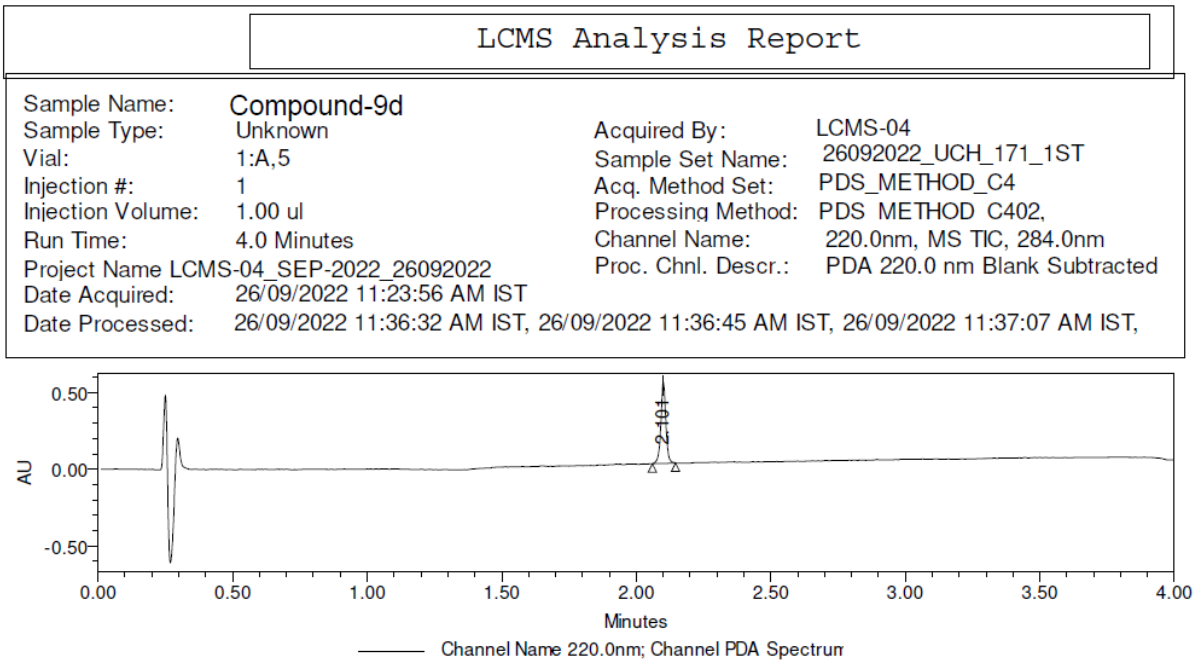
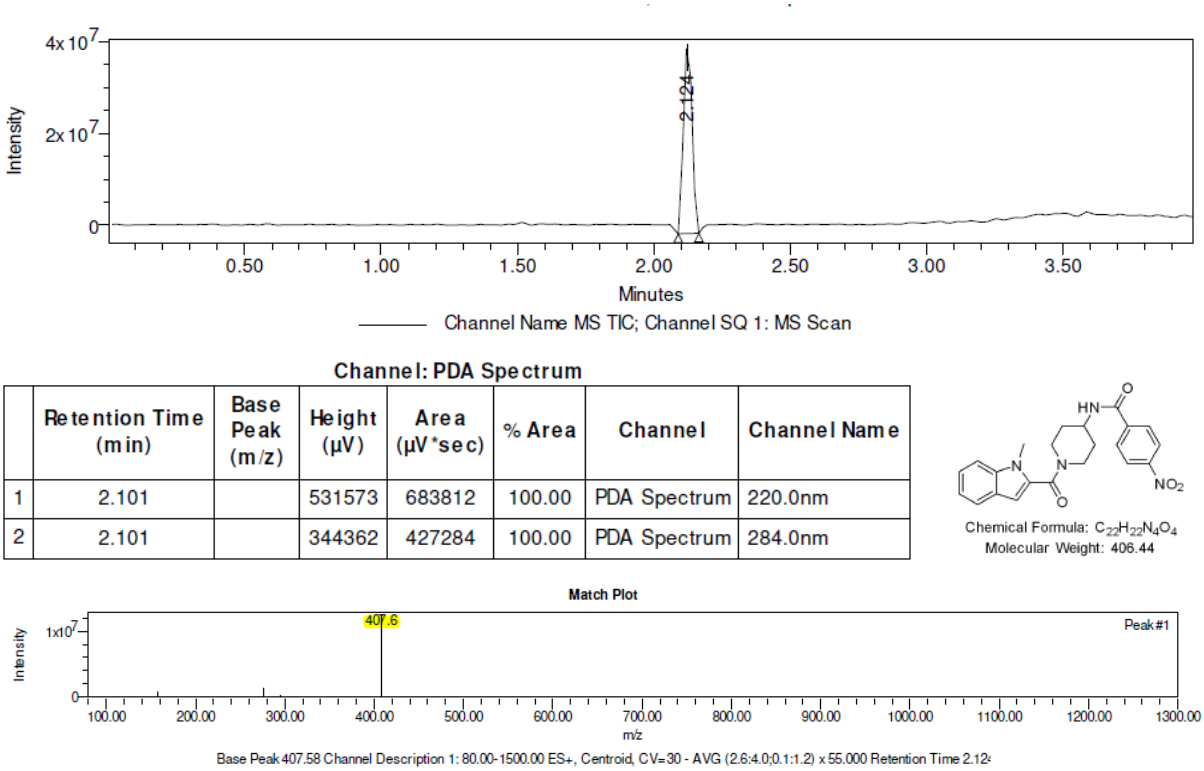


Figure 32: ^{13}C NMR of compound **9d.**





Channel: PDA Spectrum

	Retention Time (min)	Base Peak (m/z)	Height (µV)	Area (µV*sec)	% Area	Channel	Channel Name
1	2.101		531573	683812	100.00	PDA Spectrum	220.0nm
2	2.101		344362	427284	100.00	PDA Spectrum	284.0nm

Chemical Formula: $C_{22}H_{22}N_4O_4$
Molecular Weight: 406.44

Figure 33: LC-MS of compound **9d.**

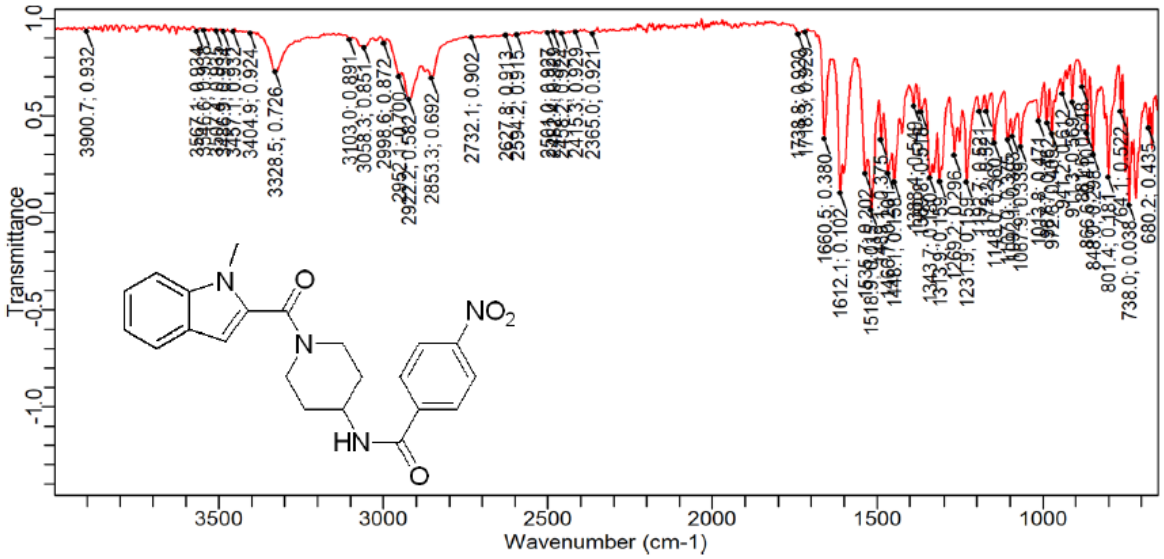


Figure 34: IR of compound **9d.**

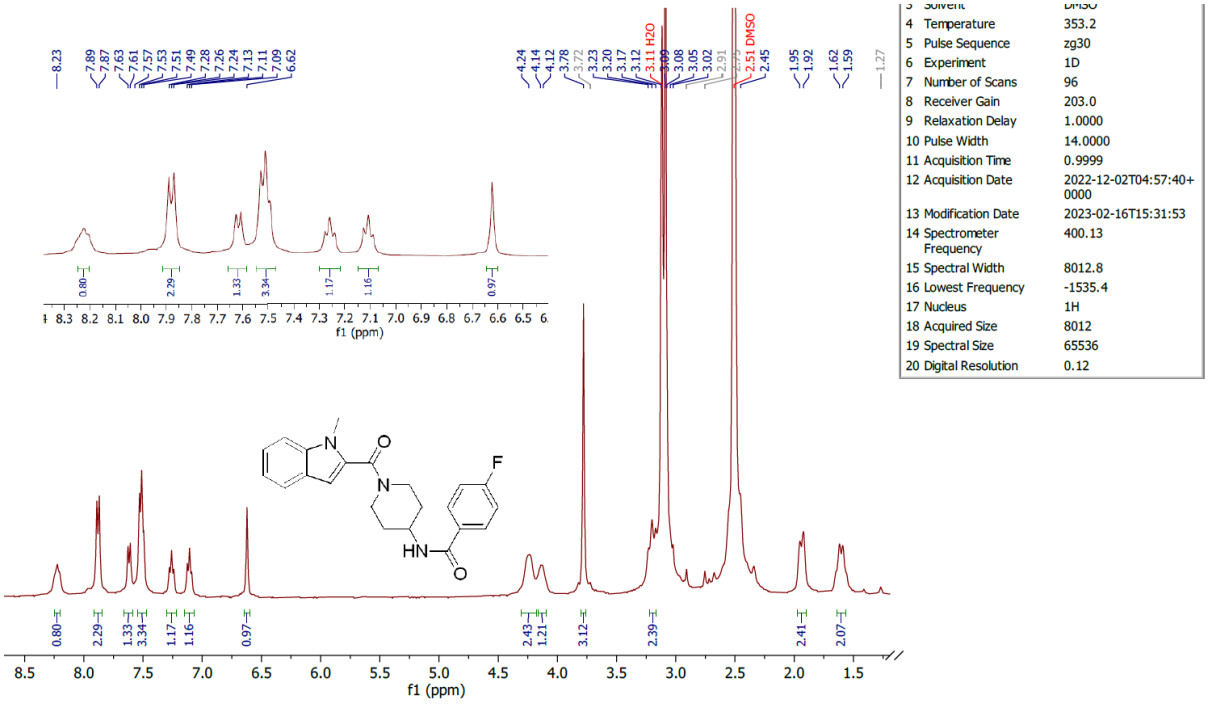


Figure 35: ^{1}H NMR of compound **9e.**

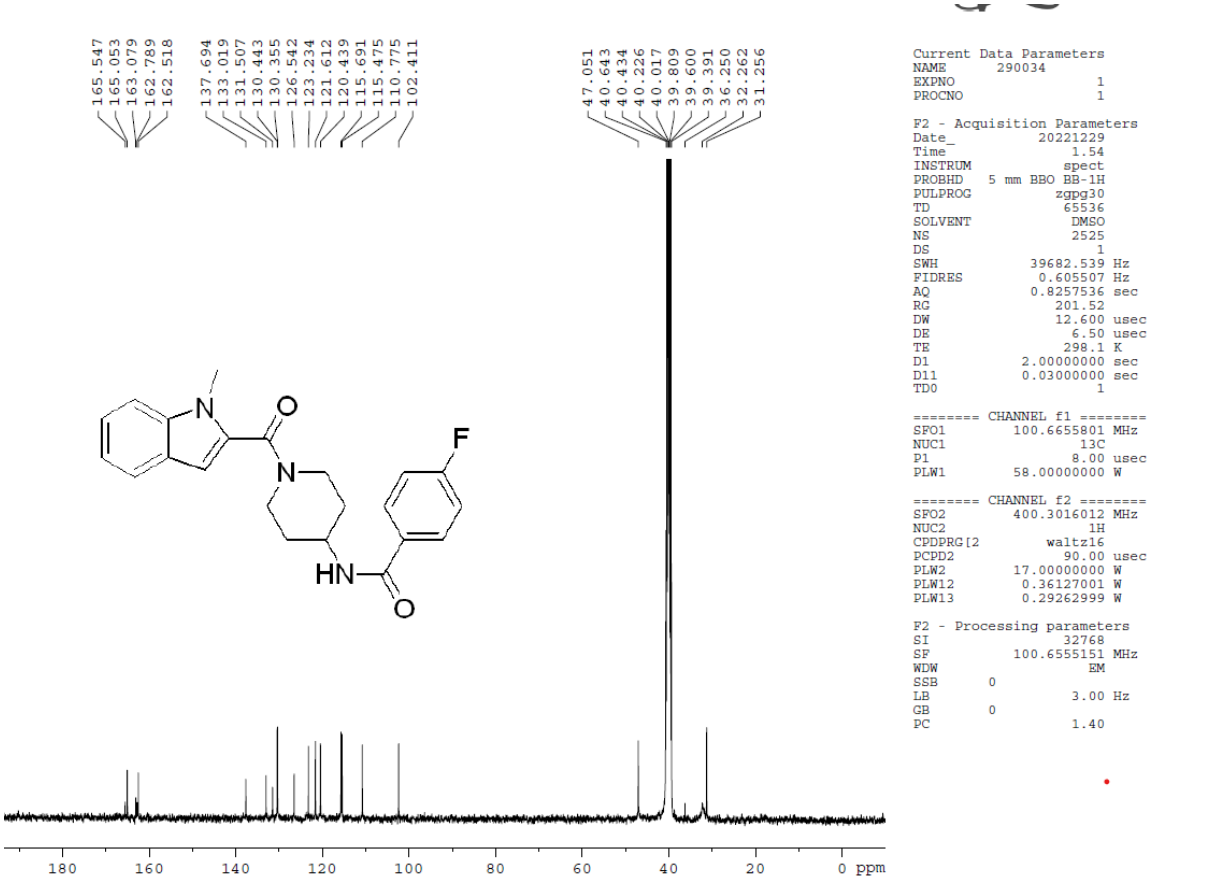
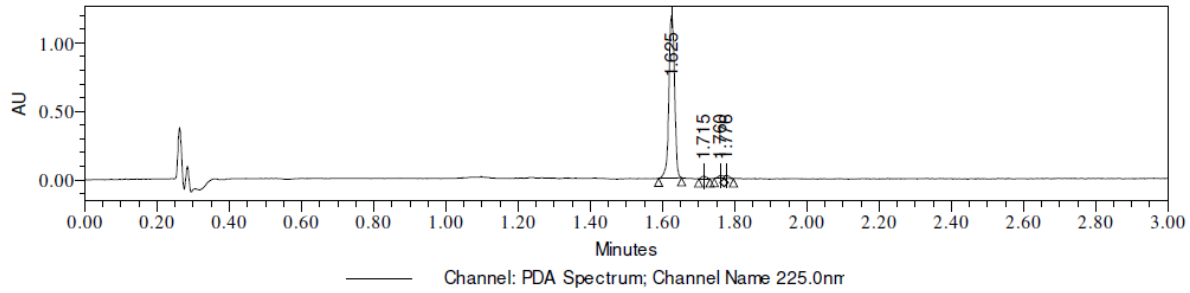
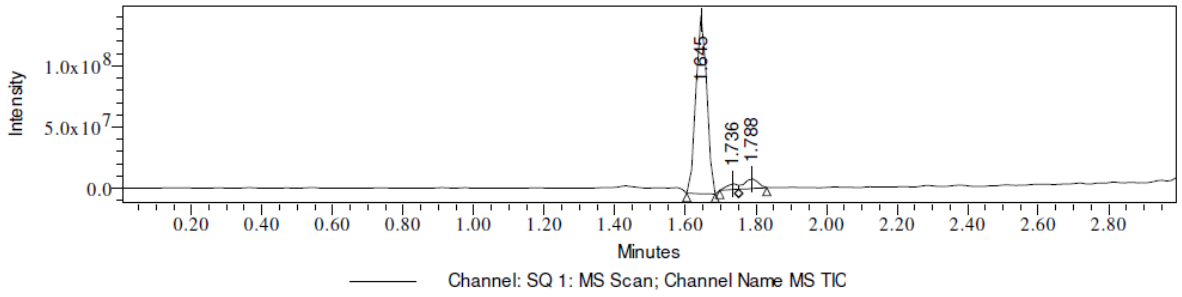


Figure 36: ^{13}C NMR of compound **9e.**

LCMS Analysis Report

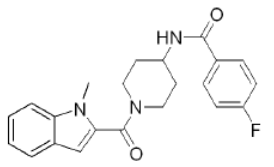
Sample Name:	Compound-9e		
Sample Type:	Unknown	Acquired By:	LCMS-02
Vial:	1:D,3	Sample Set Name:	28112022 UCH 177
Injection #:	1	Acq. Method Set:	METHOD C3
Injection Volume:	1.00 ul	Processing Method:	METHOD_C3_2, METHOD_C3
Run Time:	3.0 Minutes	Channel Name:	225.0nm, MS TIC, 290.0nm
Project Name	LCMS-02_NOV-2022_28112022	Proc. Chnl. Descr.:	PDA 290.0 nm Blank Subtracted
Date Acquired:	28-11-2022 23:28:21 IST		
Date Processed:	29-11-2022 00:30:47 IST, 29-11-2022 00:30:56 IST, 29-11-2022 00:31:18 IST		





Peak Results
Channel: PDA Spectrum

	Retention Time (min)	Base Peak (m/z)	Height (µV)	Area (µV*sec)	% Area	Channel	Channel Name
1	1.625		511079	511560	99.02	PDA Spectrum	290.0nm
2	1.625		1187639	1289107	95.57	PDA Spectrum	225.0nm
3	1.714		6290	5062	0.98	PDA Spectrum	290.0nm
4	1.715		18643	16547	1.23	PDA Spectrum	225.0nm
5	1.760		22712	21925	1.63	PDA Spectrum	225.0nm
6	1.776		22192	21218	1.57	PDA Spectrum	225.0nm



Chemical Formula: $C_{22}H_{22}FN_3O_2$
Molecular Weight: 379.44

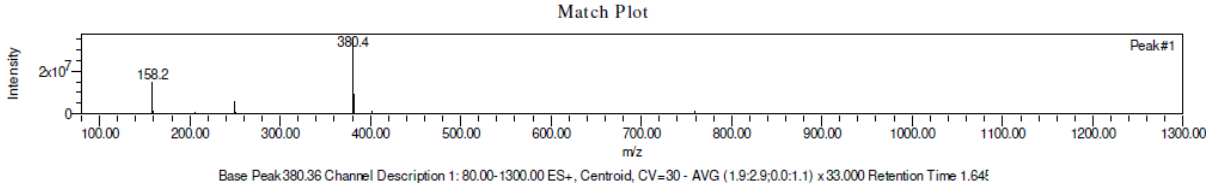


Figure 37: LC-MS of compound **9e.**

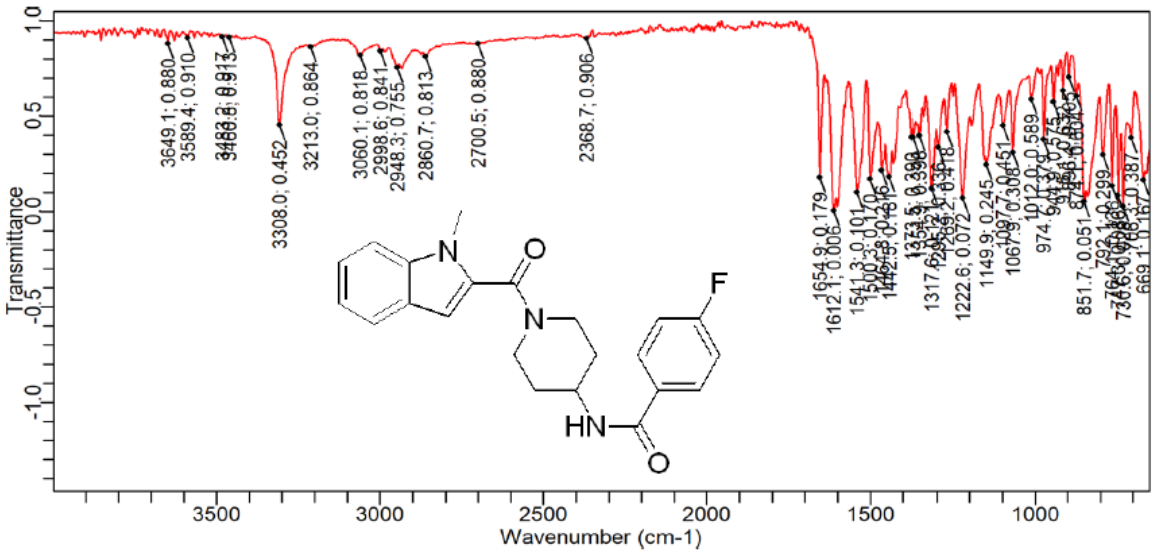


Figure 38: IR of compound **9e.**

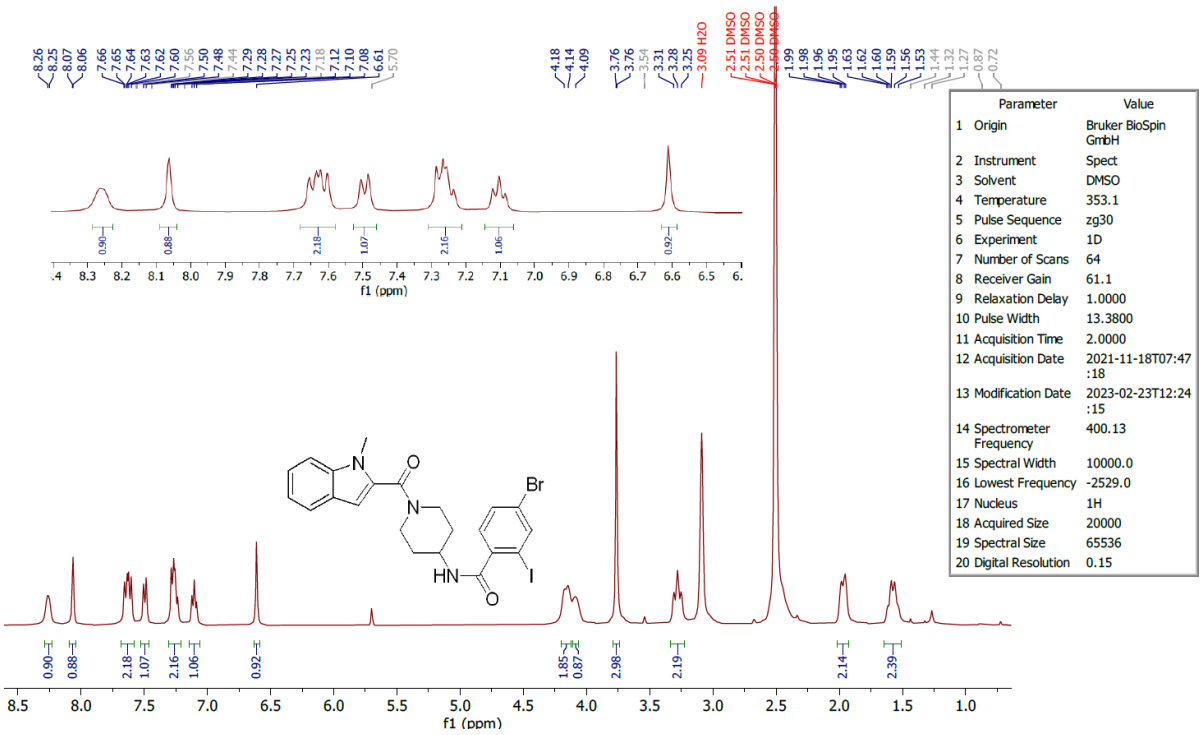


Figure 39: ^{1}H NMR of compound **9k.**

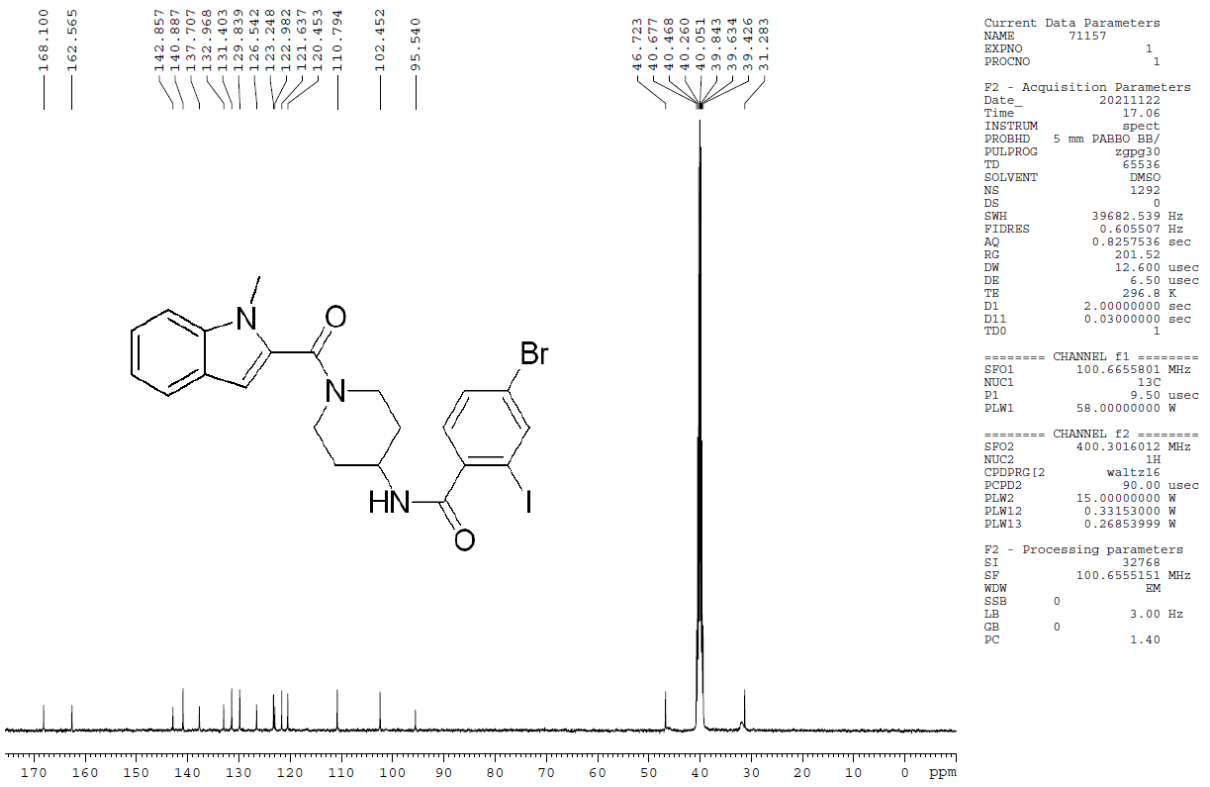
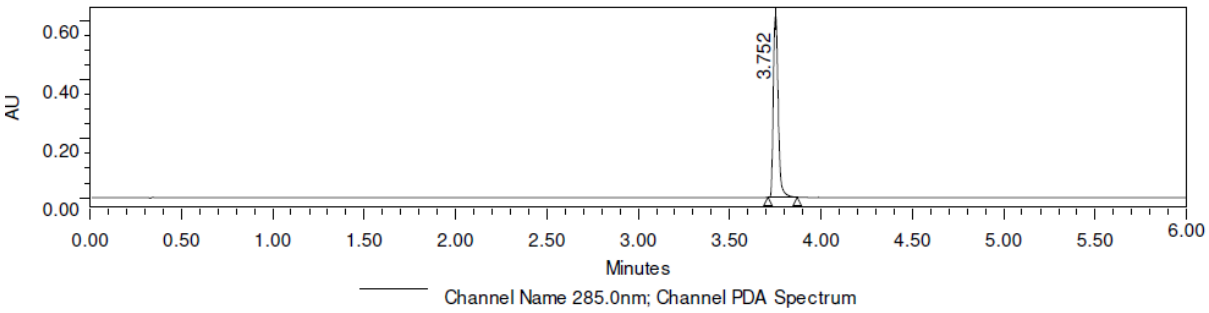
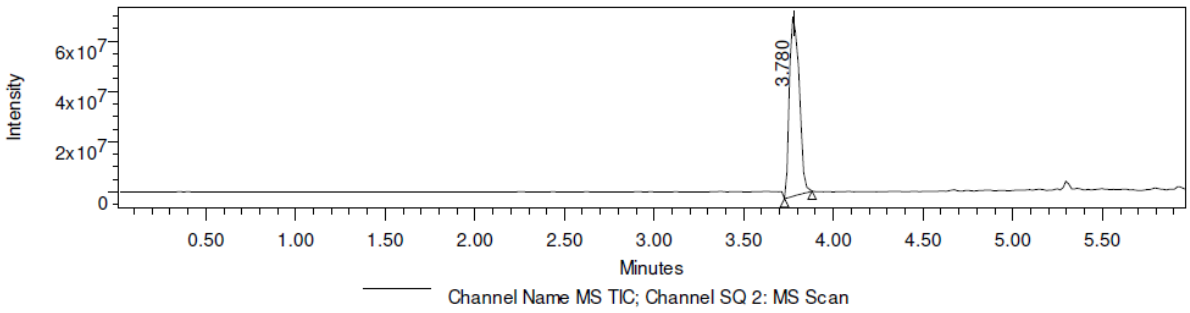


Figure 40: ^{13}C NMR of compound **9k.**

LCMS Analysis Report

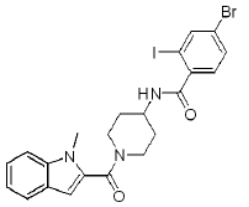
Sample Name:	Compound-9k		
Sample Type:	Unknown	Acquired By:	LCMS_03
Vial:	1:E,2	Sample Set Name:	16112021_UCH_160_JS
Injection #:	1	Acq. Method Set:	PDS_METHOD_J2
Injection Volume:	2.00 ul	Processing Method:	PDS_METHOD_J2,
Run Time:	6.0 Minutes	Channel Name:	202.0nm, 285.0nm, MS TIC
Project Name	LCMS-03_NOV-2021_16112021	Proc. Chnl. Descr.:	SQ 2: MS Scan MS TIC,
Date Acquired:	16/11/2021 22:18:11 IST		
Date Processed:	16/11/2021 22:26:58 IST, 16/11/2021 22:27:22 IST, 16/11/2021 22:27:45 IST		



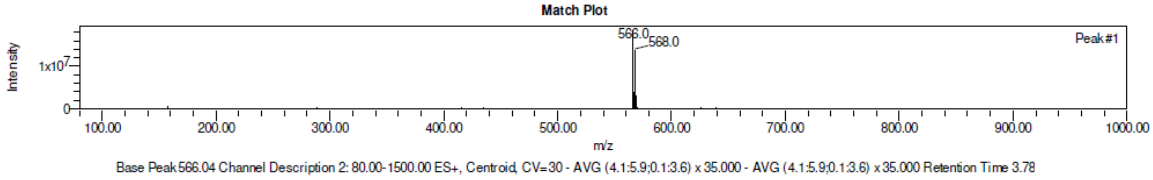


Peak Results
Channel: PDA Spectrum

	Retention Time (min)	Base Peak (m/z)	Height (µV)	Area (µV*sec)	% Area	Channel	Channel Name
1	3.751		1206357	2628517	99.64	PDA Spectrum	202.0nm
2	3.752		612252	1142915	100.00	PDA Spectrum	285.0nm
3	3.892		6354	9481	0.36	PDA Spectrum	202.0nm



Chemical Formula: $C_{22}H_{21}BrIN_3O_2$
Molecular Weight: 566.24



Base Peak 566.04 Channel Description 2: 80.00-1500.00 ES+, Centroid, CV=30 - AVG (4.1:5.9;0.1:3.6) x 35.000 - AVG (4.1:5.9;0.1:3.6) x 35.000 Retention Time 3.78

Figure 41: LC-MS of compound **9k.**

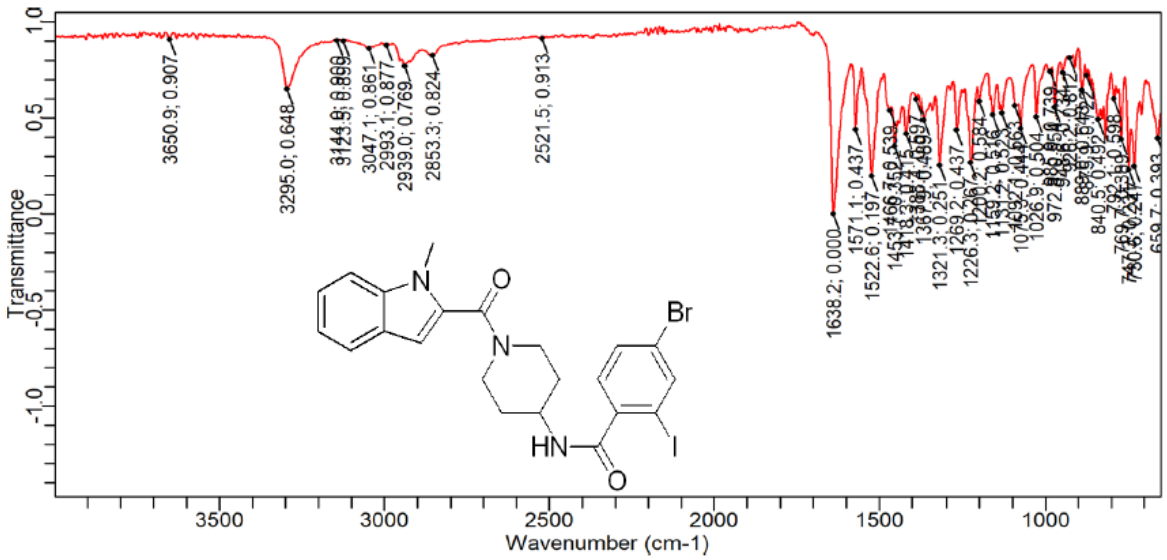


Figure 42: IR of compound **9k.**

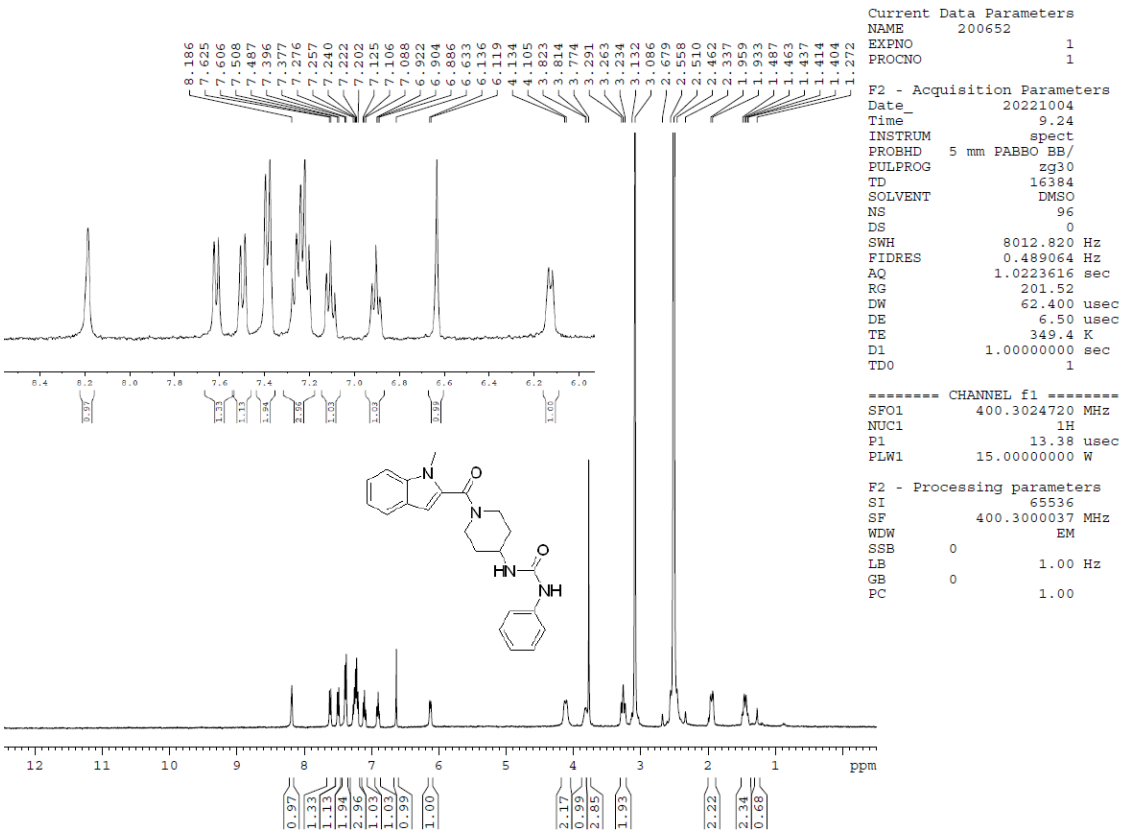


Figure 43: ^{1}H NMR of compound **11a.**

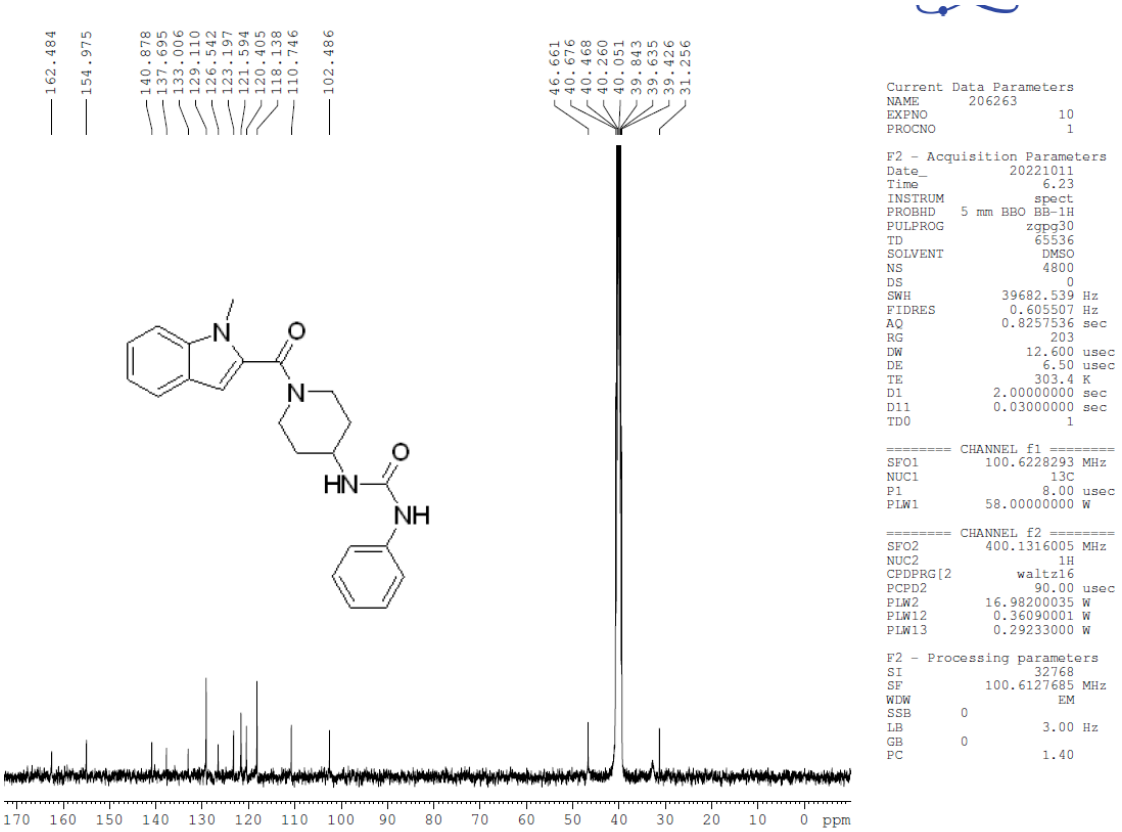


Figure 44: ^{13}C NMR of compound **11a.**

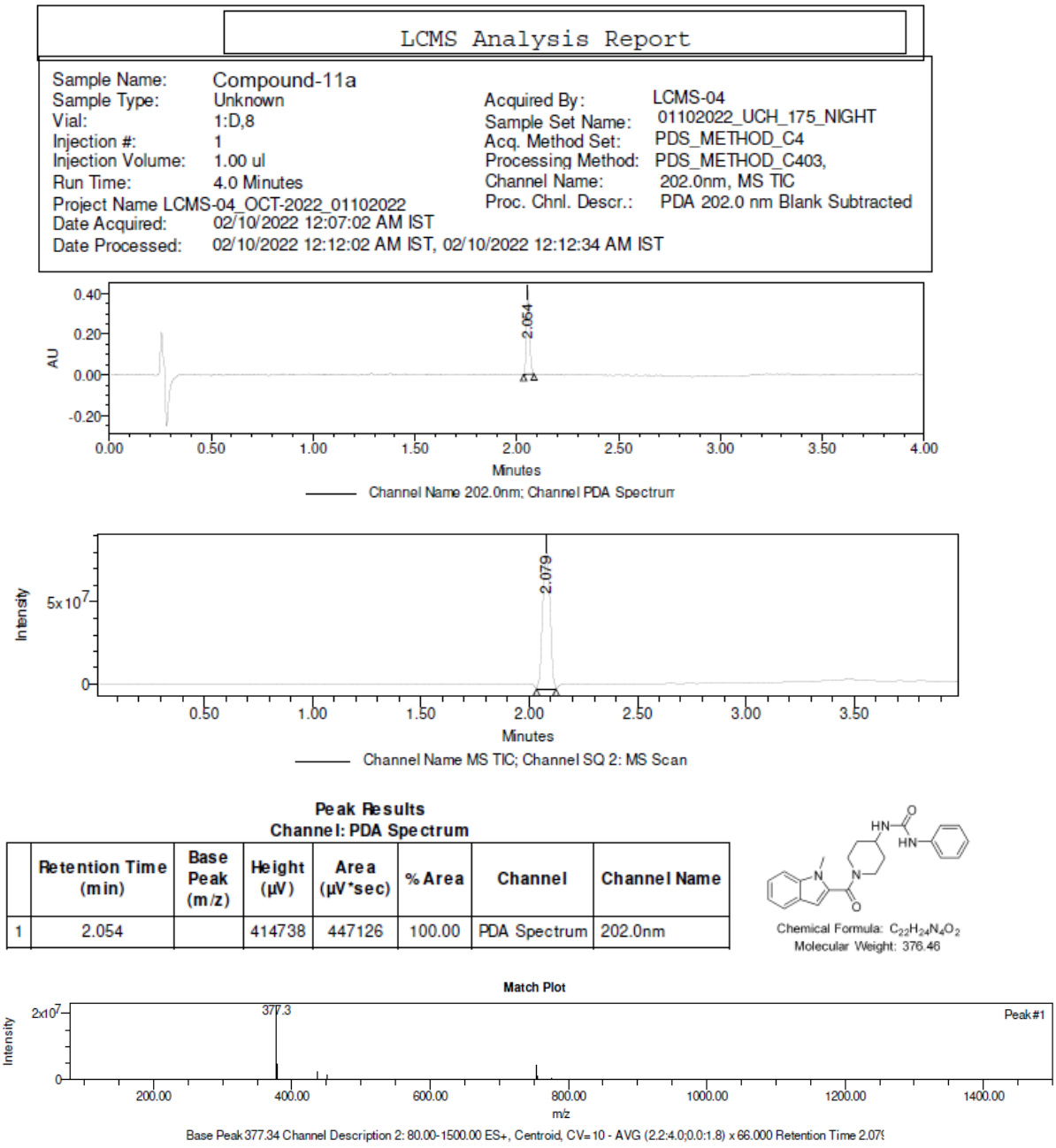


Figure 45: LC-MS of compound **11a.**

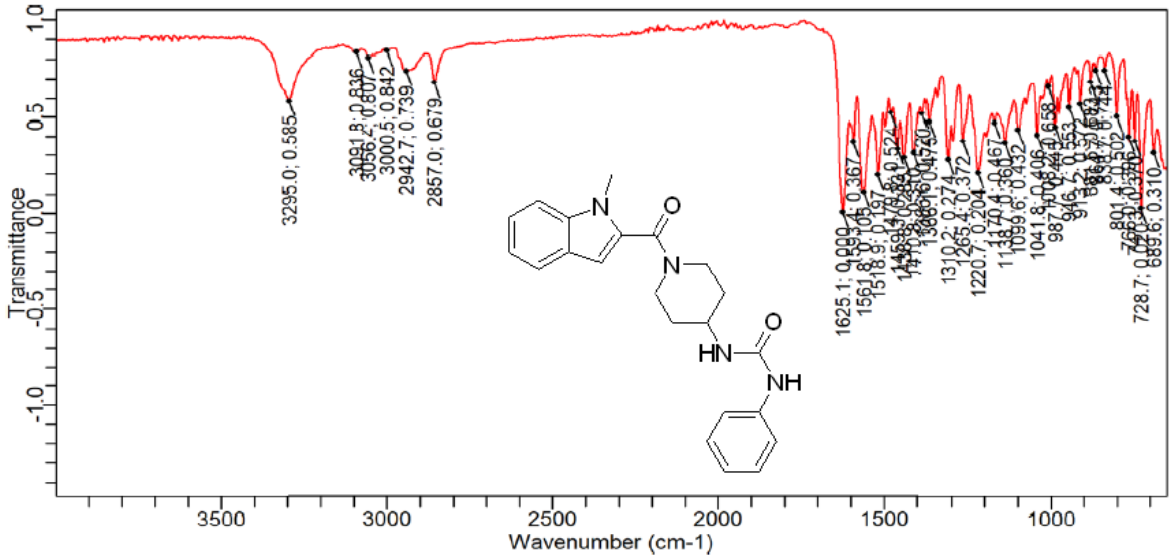


Figure 46: IR of compound **11a.**

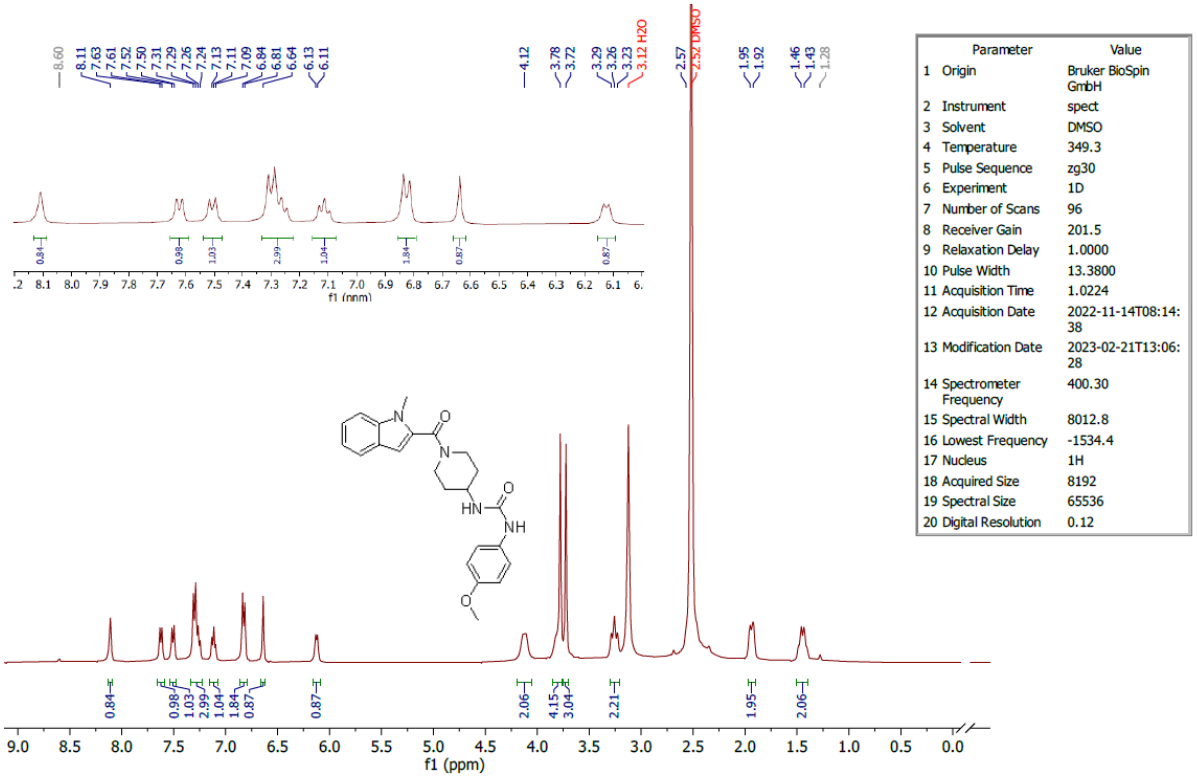


Figure 47: ^{1}H NMR of compound **11b.**

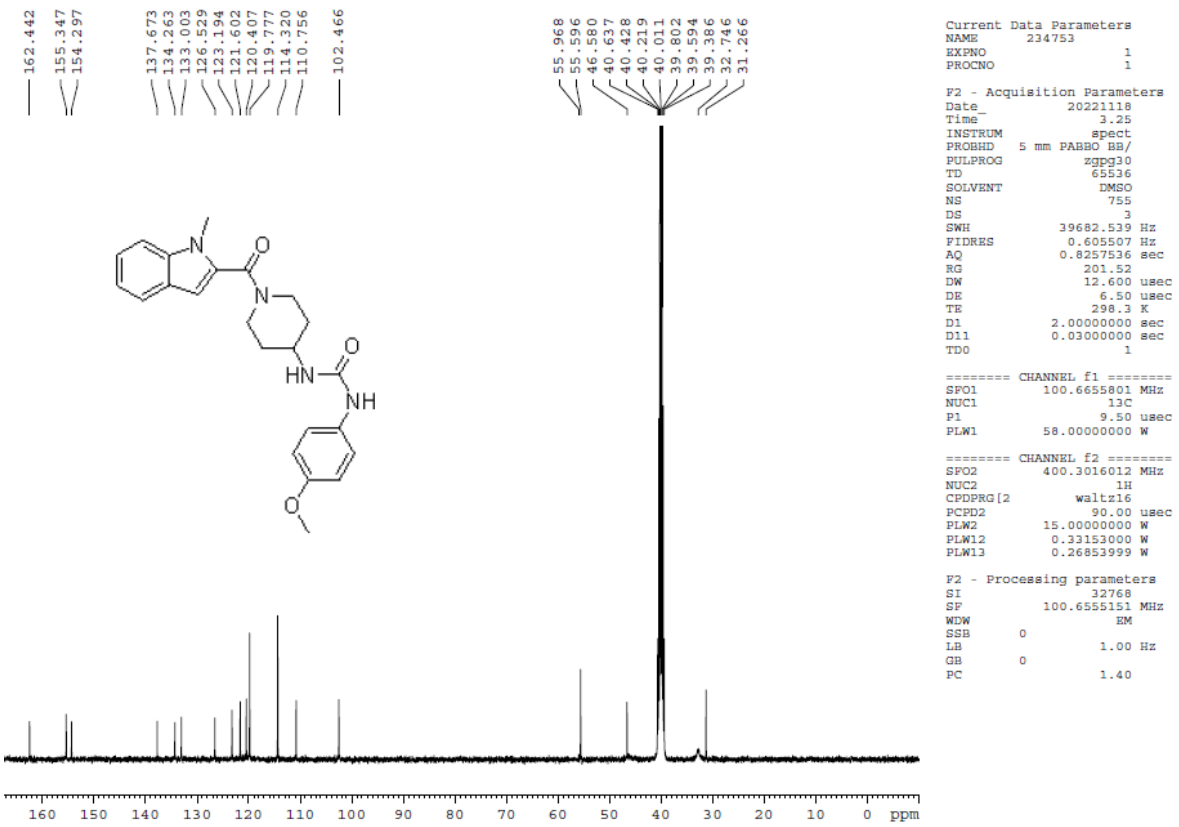
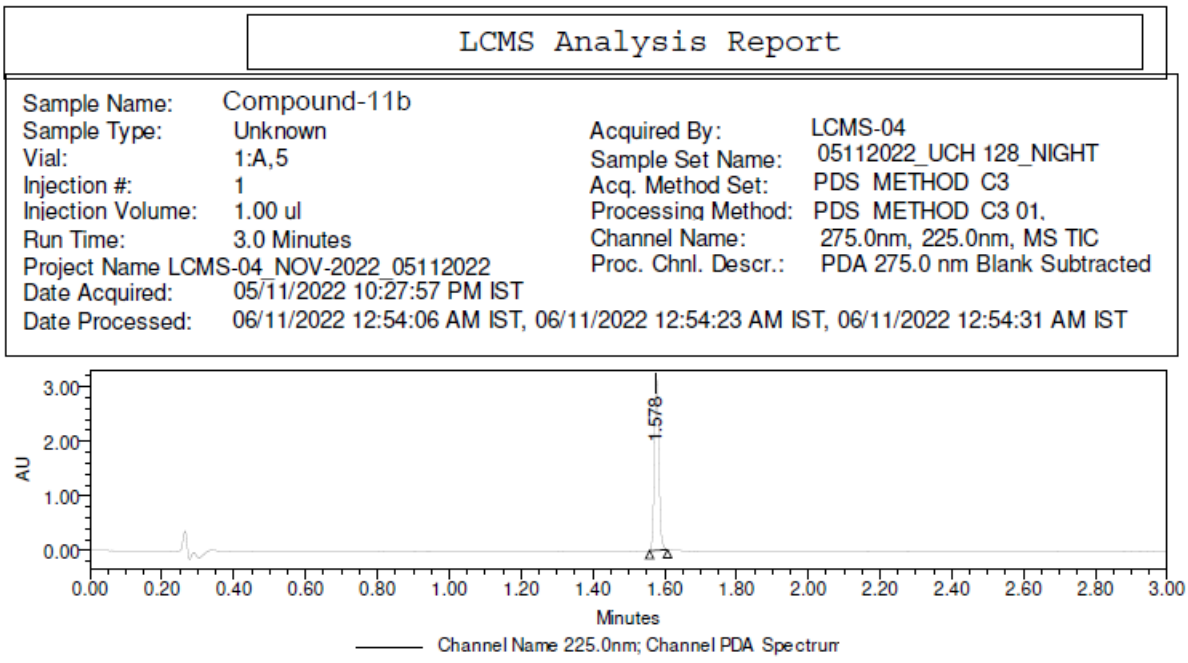
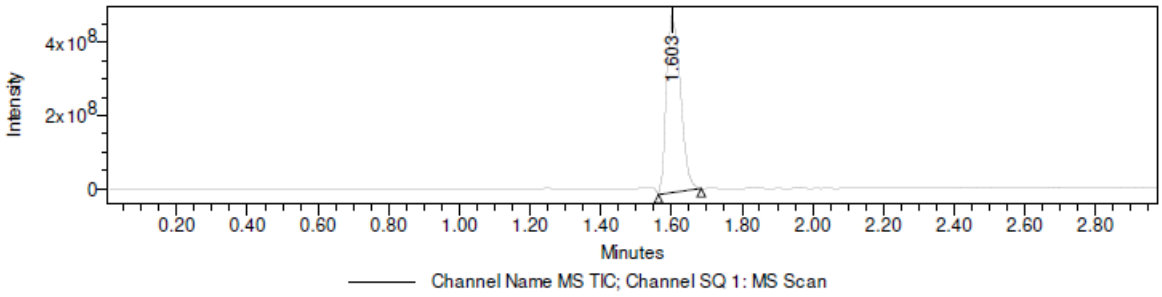


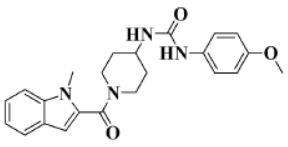
Figure 48: ^{13}C NMR of compound **11b.**



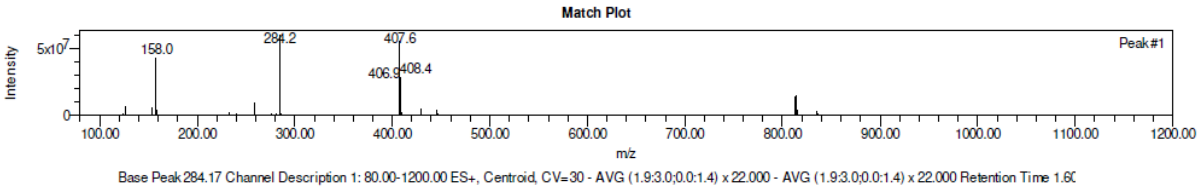


Peak Results
Channel: PDA Spectrum

	Retention Time (min)	Base Peak (m/z)	Height (µV)	Area (µV*sec)	% Area	Channel	Channel Name
1	1.578		457204	461993	100.00	PDA Spectrum	275.0nm
2	1.578		3121795	2696687	100.00	PDA Spectrum	225.0nm



Chemical Formula: $C_{23}H_{26}N_4O_3$
Molecular Weight: 406.49



Base Peak 284.17 Channel Description 1: 80.00-1200.00 ES+, Centroid, CV=30 - AVG (1.9:3.0;0.0:1.4) x 22.000 - AVG (1.9:3.0;0.0:1.4) x 22.000 Retention Time 1.6(

Figure 49: LC-MS of compound **11b.**

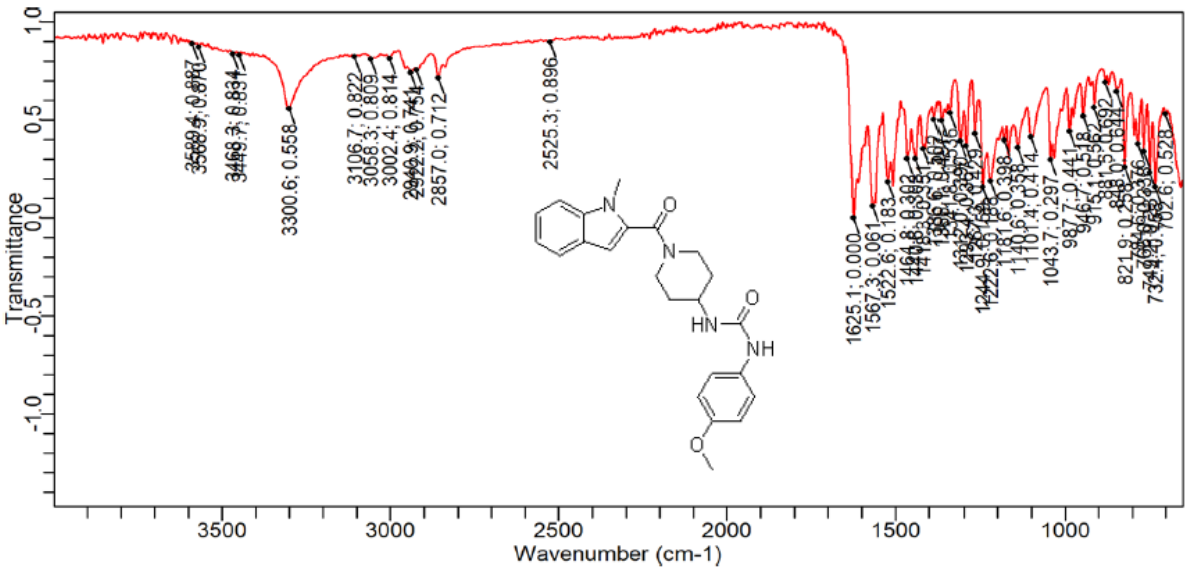


Figure 50: IR of compound **11b.**

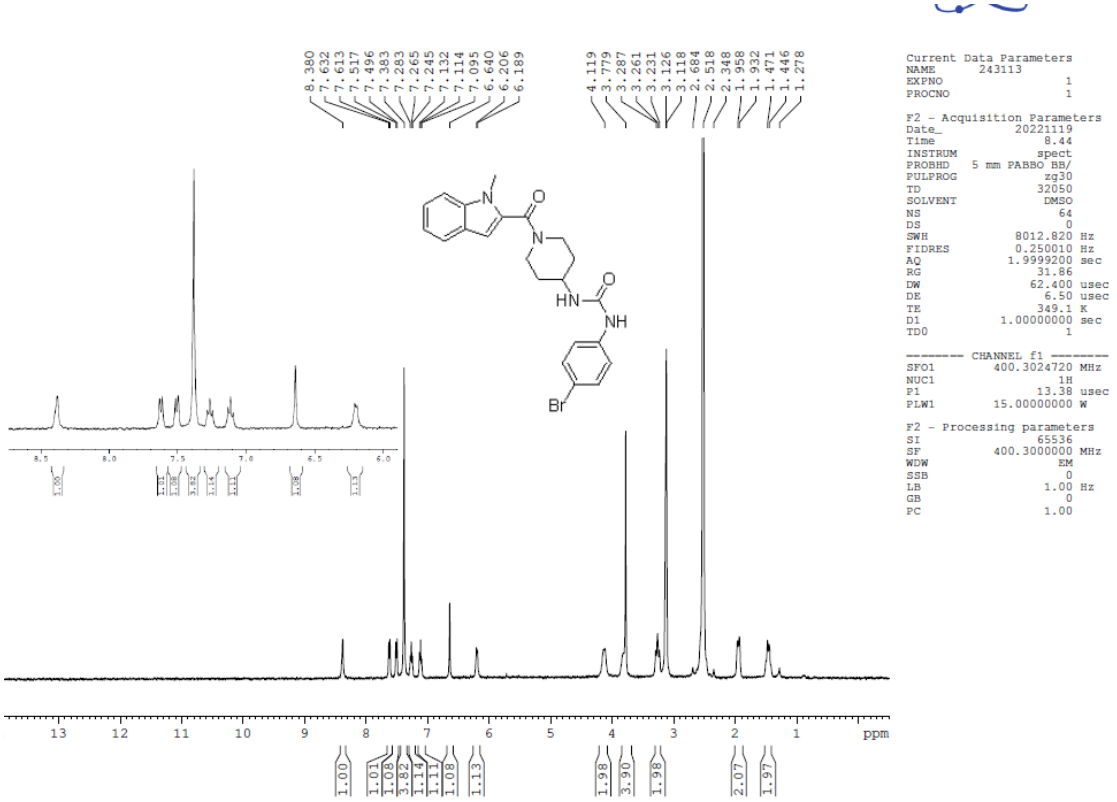


Figure 51: ^{1}H NMR of compound **11c.**

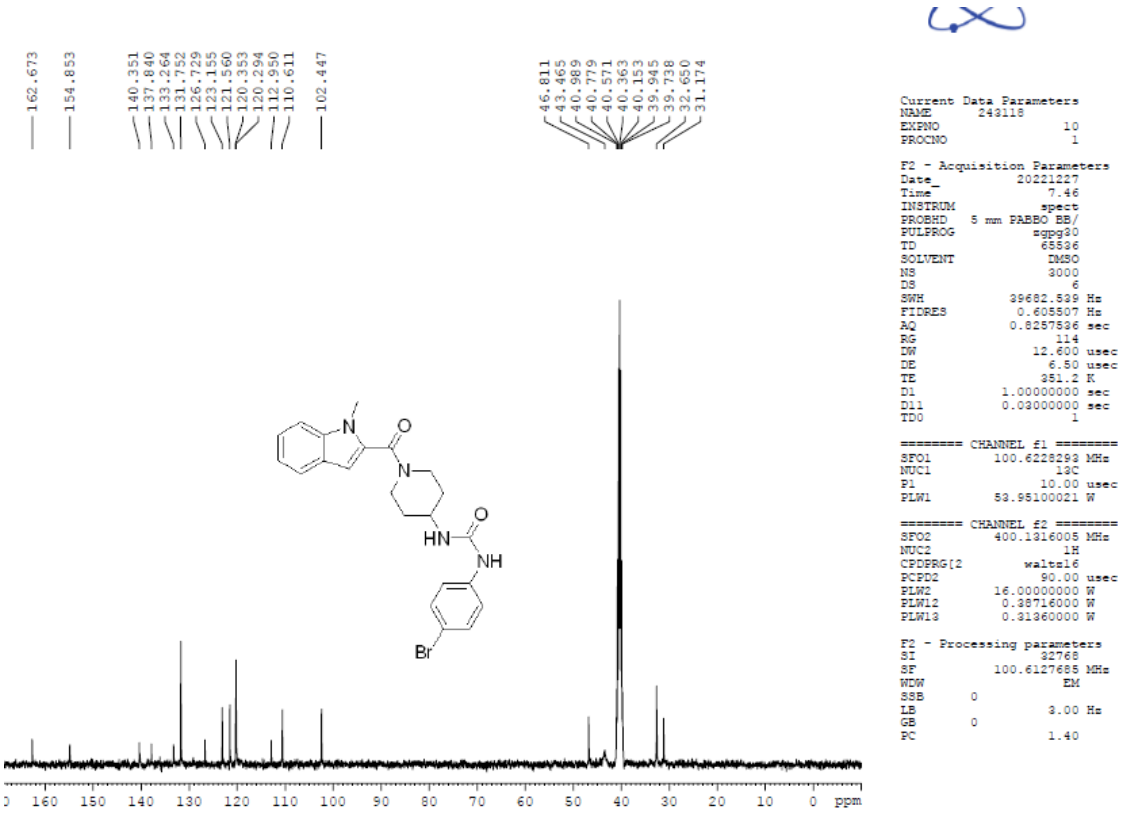


Figure 52: ^{13}C NMR of compound **11c.**

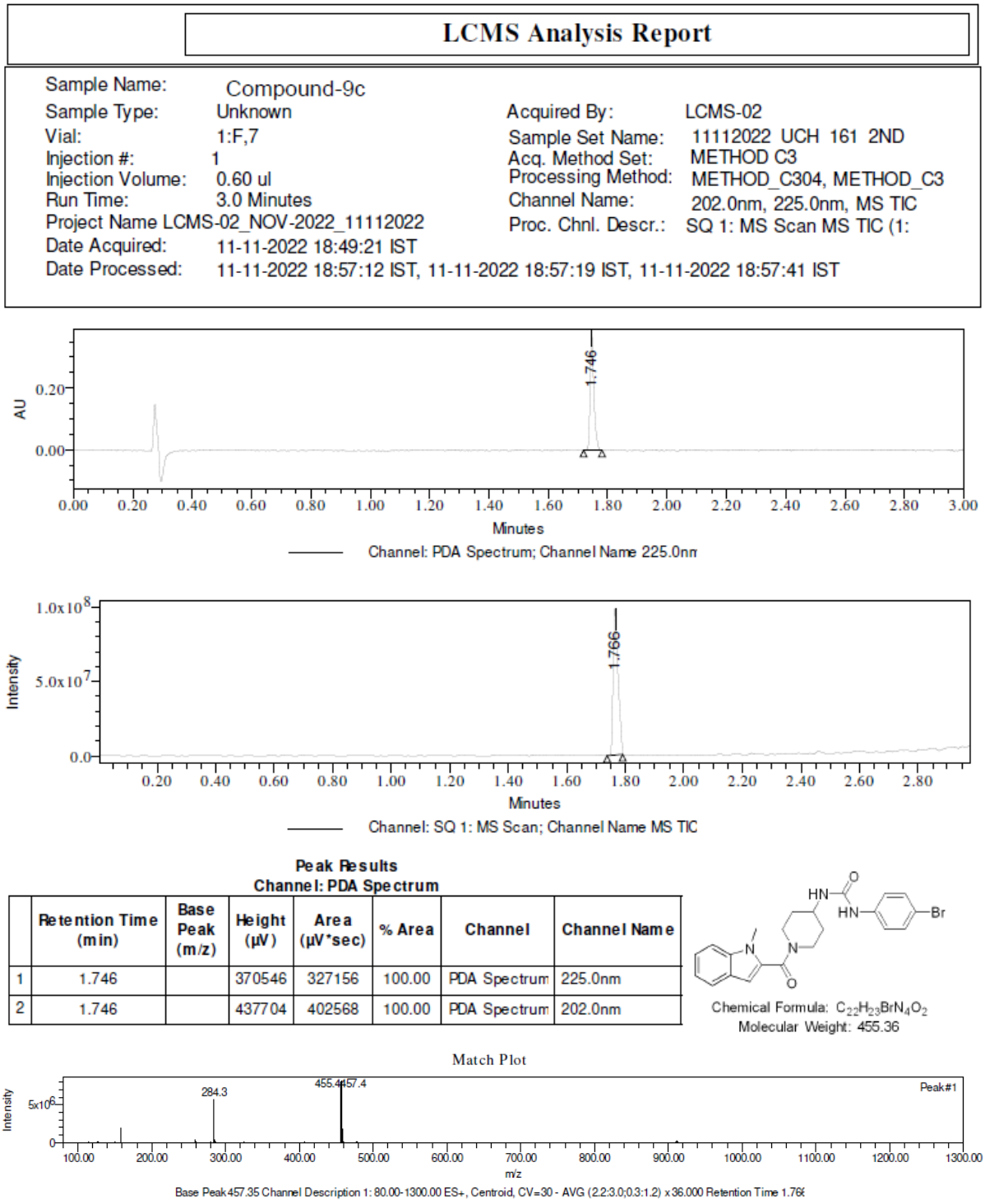


Figure 53: LC-MS of compound **11c.**

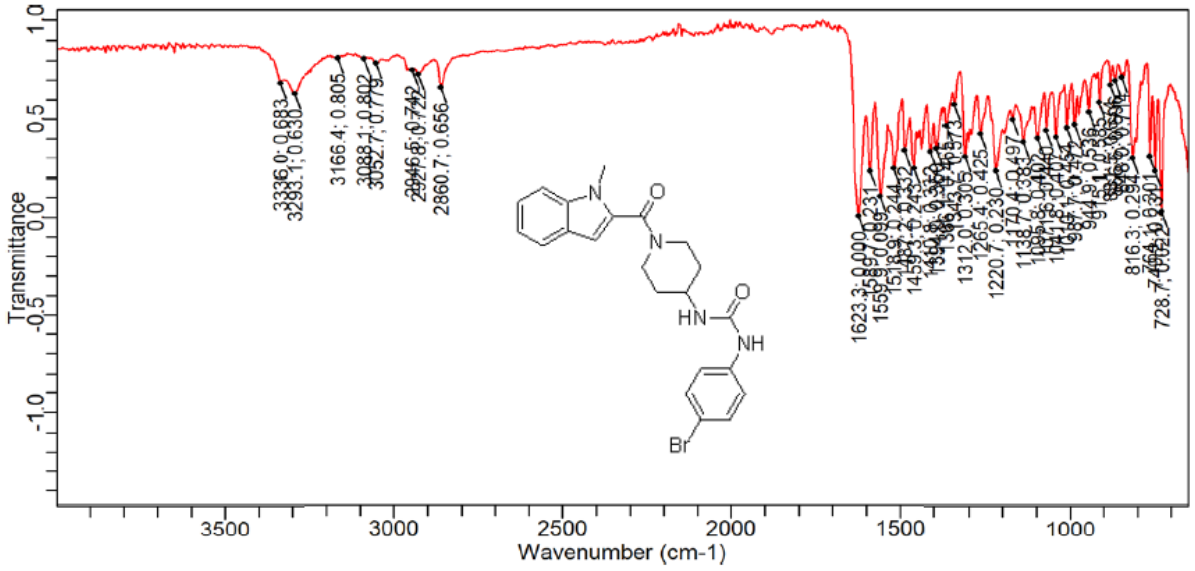


Figure 54: IR of compound **11c.**

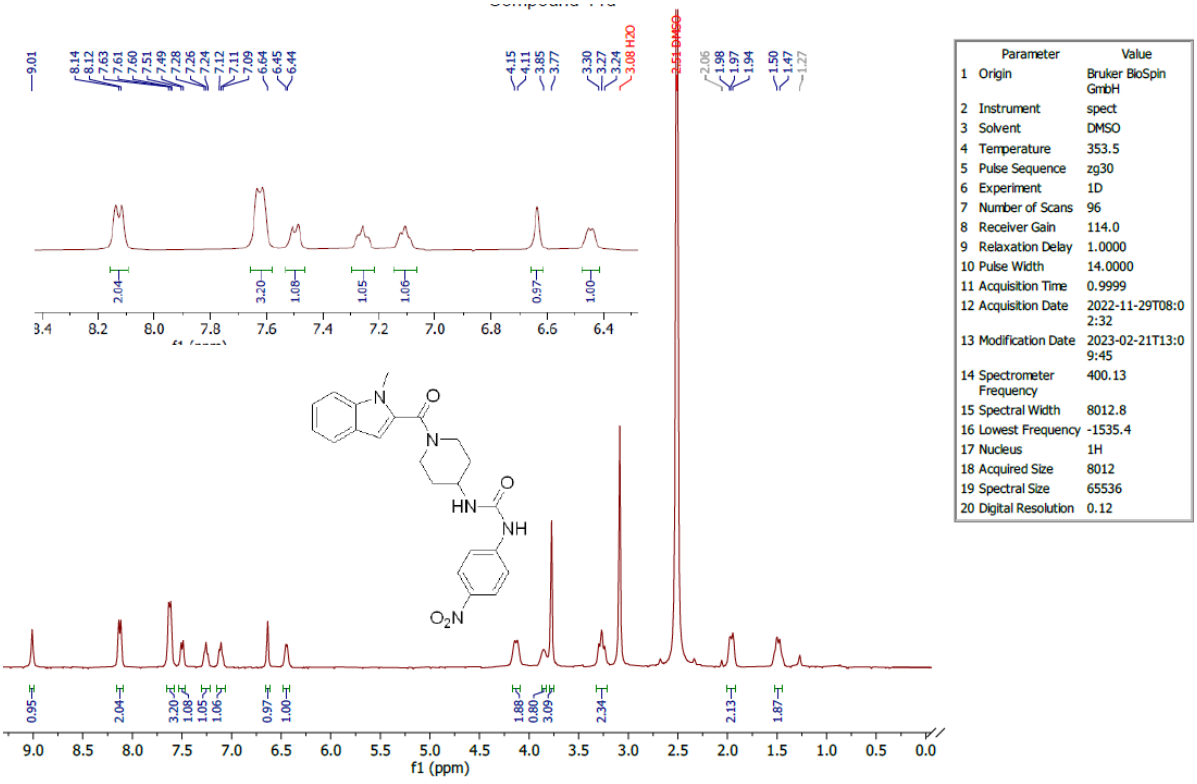


Figure 55: ^{1}H NMR of compound **11d.**

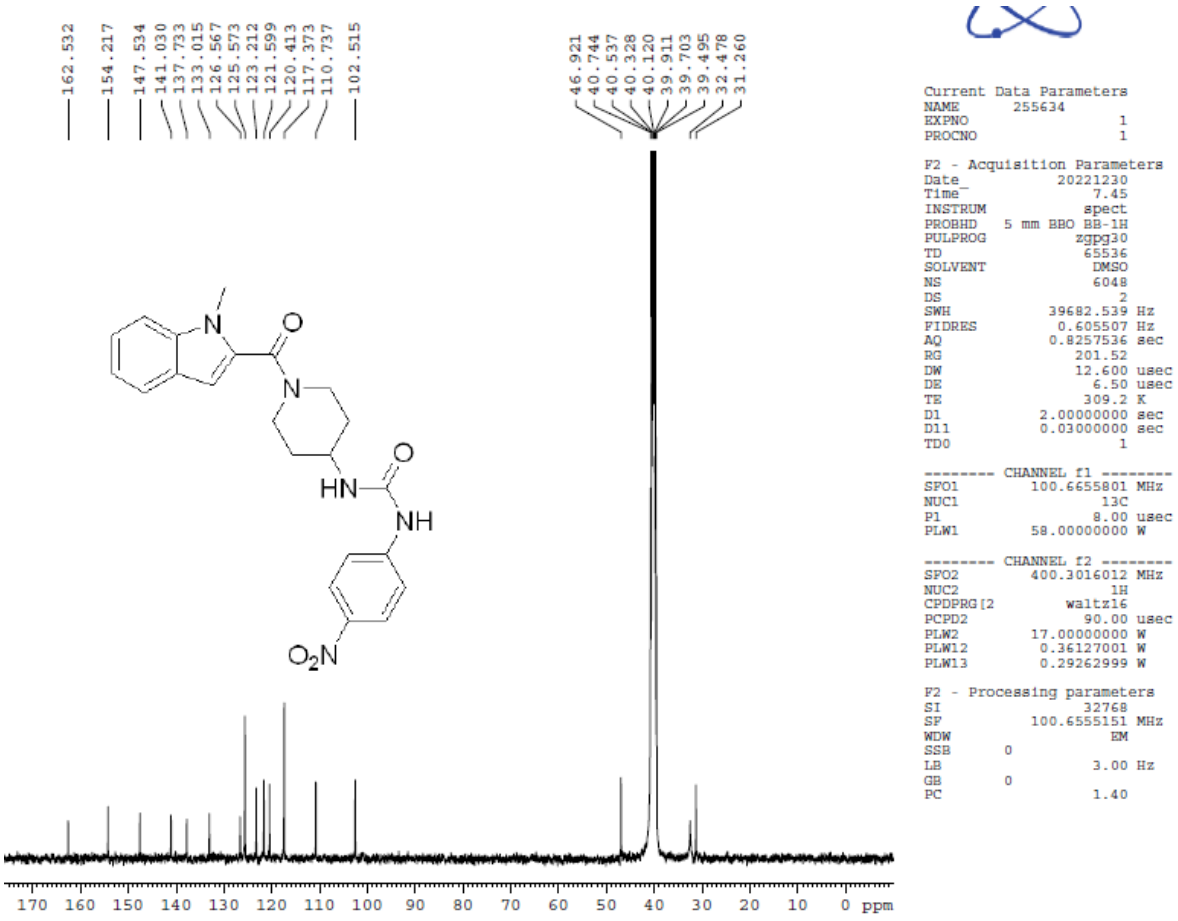
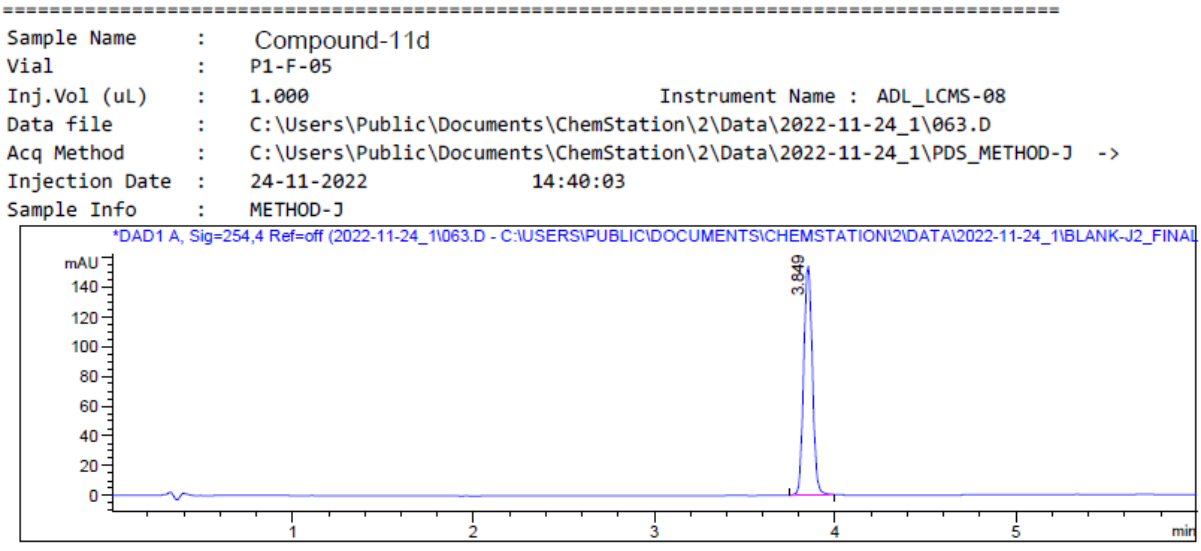
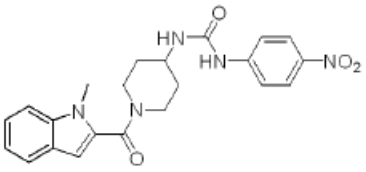


Figure 56: ^{13}C NMR of compound **11d.**



Peak No	Height	RT (min)	Area	Area %
1	154.360	3.849	510	100.00



Chemical Formula: $C_{22}H_{23}N_5O_4$
Molecular Weight: 421.46

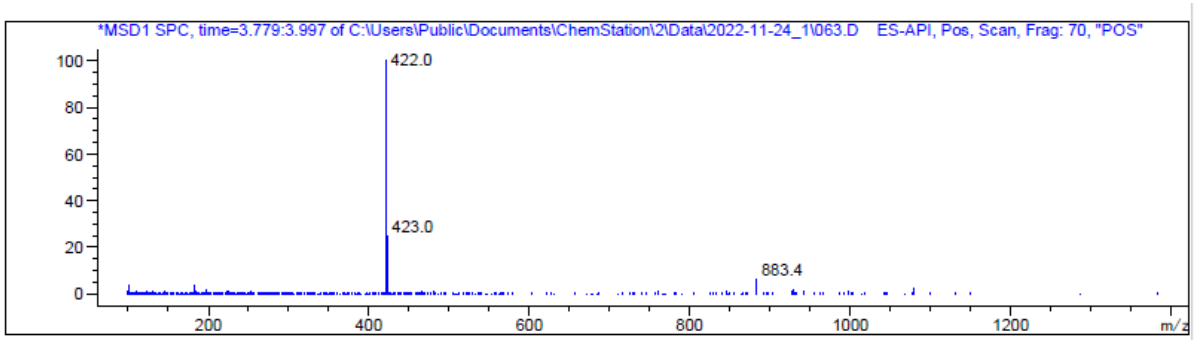


Figure 57: LC-MS of compound **11d.**

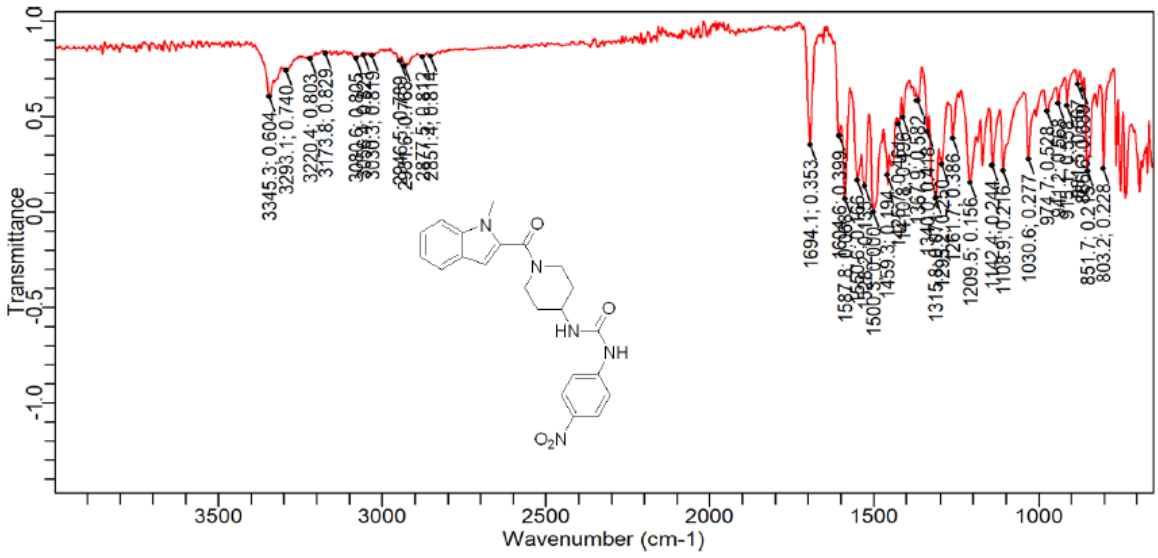


Figure 58: IR of compound **11d.**

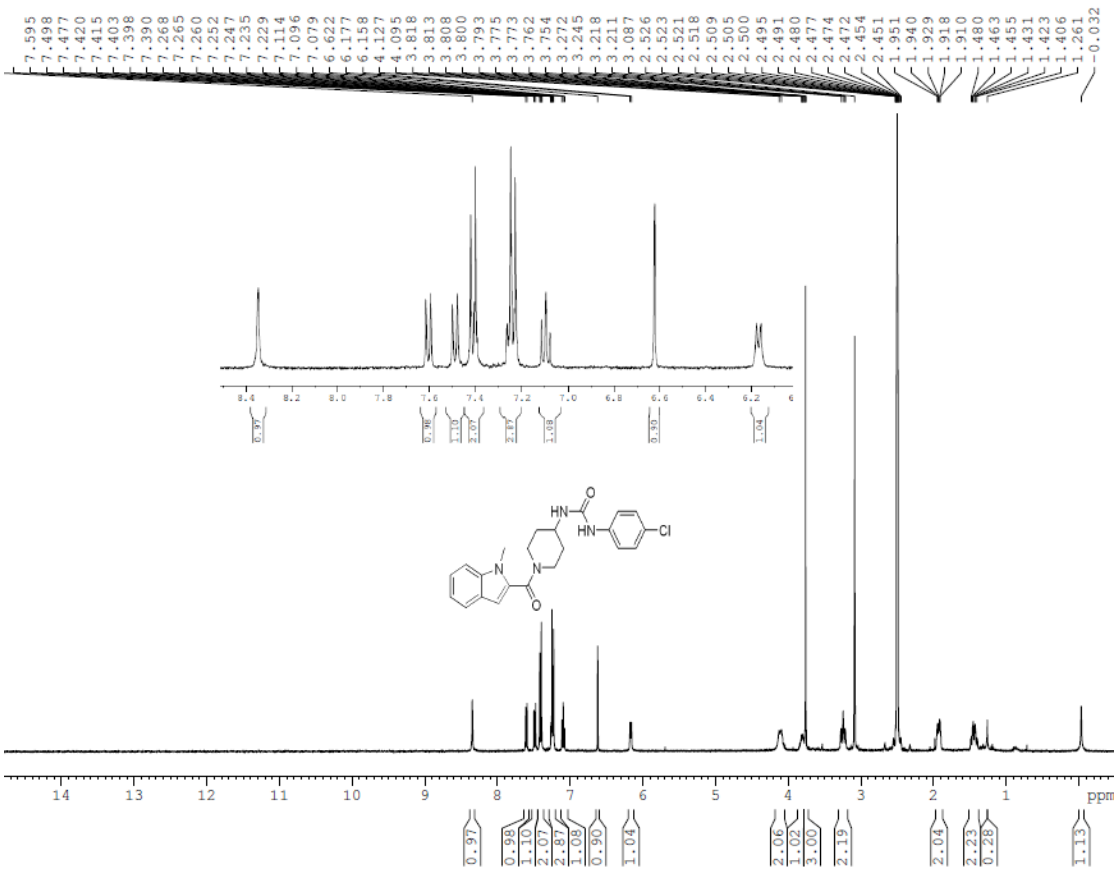
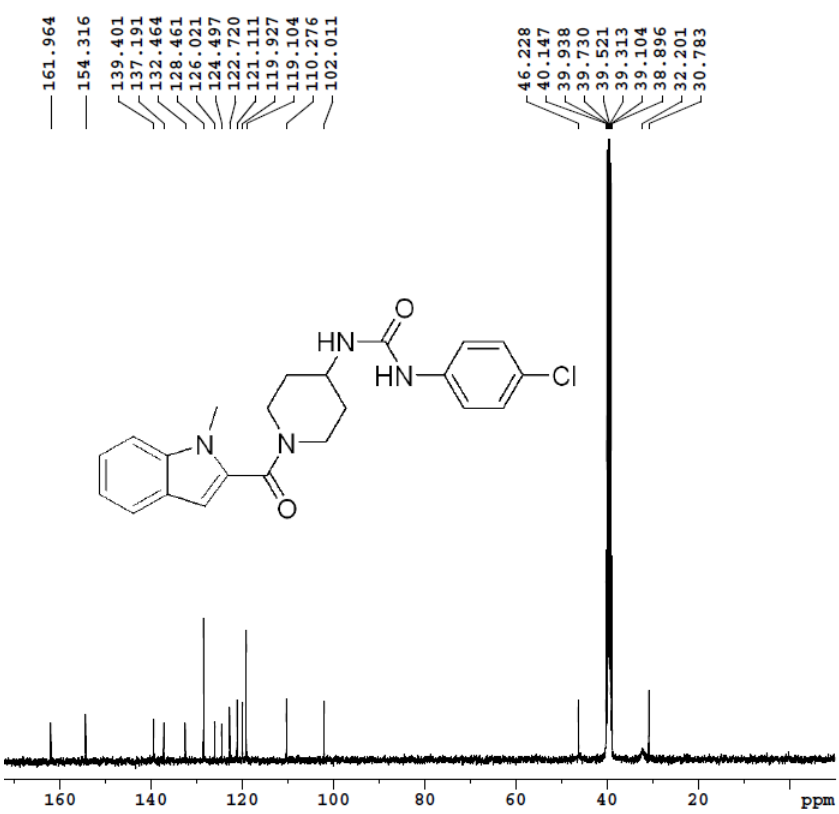


Figure 59: ^{1}H NMR of compound **11f.**

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PROCNO                 1

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TD                65536
SOLVENT            DMSO
NS                  1024
DS                     4
SWH           32051.281 Hz
FIDRES         0.978127 Hz
AQ            1.0223616 sec
RG                201.52
DW                15.600 usec
DE                 6.50 usec
TE                436.7 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                    1
SFO1         100.6655806 MHz
NUC1                 13C
P0                  3.33 usec
P1                 10.00 usec
PLW1         55.00000000 W
SFO2         400.3016012 MHz
NUC2                 1H
CPDPRG[2         waltz65
PCPD2              90.00 usec
PLW2         14.00000000 W
PLW12         0.38889000 W
PLW13         0.31500000 W

F2 - Processing parameters
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WDW                   EM
SSB                    0
LB                  2.00 Hz
GB                     0
PC                  1.40
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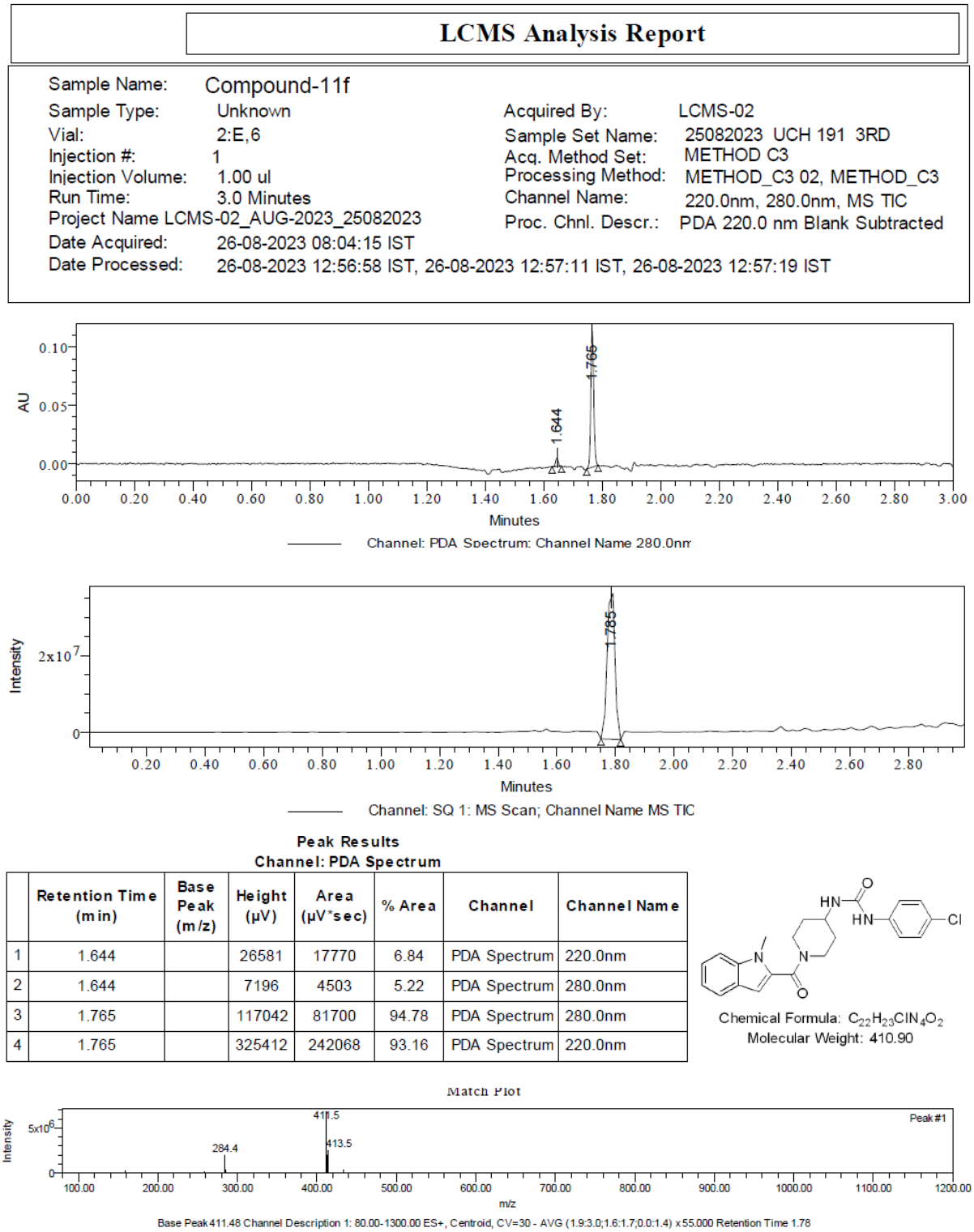
Figure 60: ^{13}C NMR of compound **11f.**



	Retention Time (min)	Base Peak (m/z)	Height (µV)	Area (µV*sec)	% Area	Channel	Channel Name
1	1.644		26581	17770	6.84	PDA Spectrum	220.0nm
2	1.644		7196	4503	5.22	PDA Spectrum	280.0nm
3	1.765		117042	81700	94.78	PDA Spectrum	280.0nm
4	1.765		325412	242068	93.16	PDA Spectrum	220.0nm

Figure 61: LC-MS of compound **11f.**

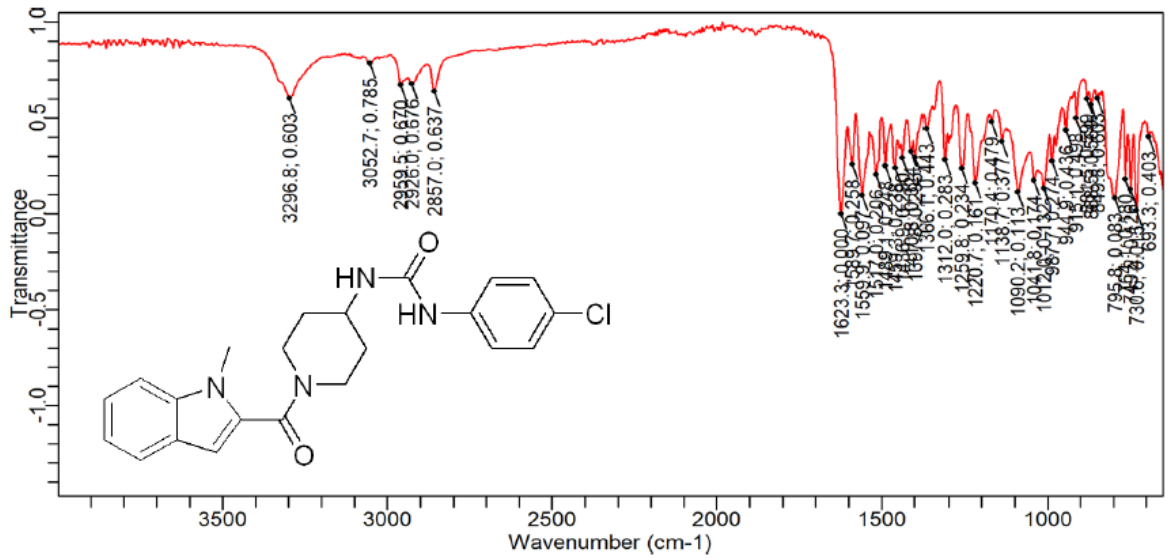


Figure 62: IR of compound **11f.**

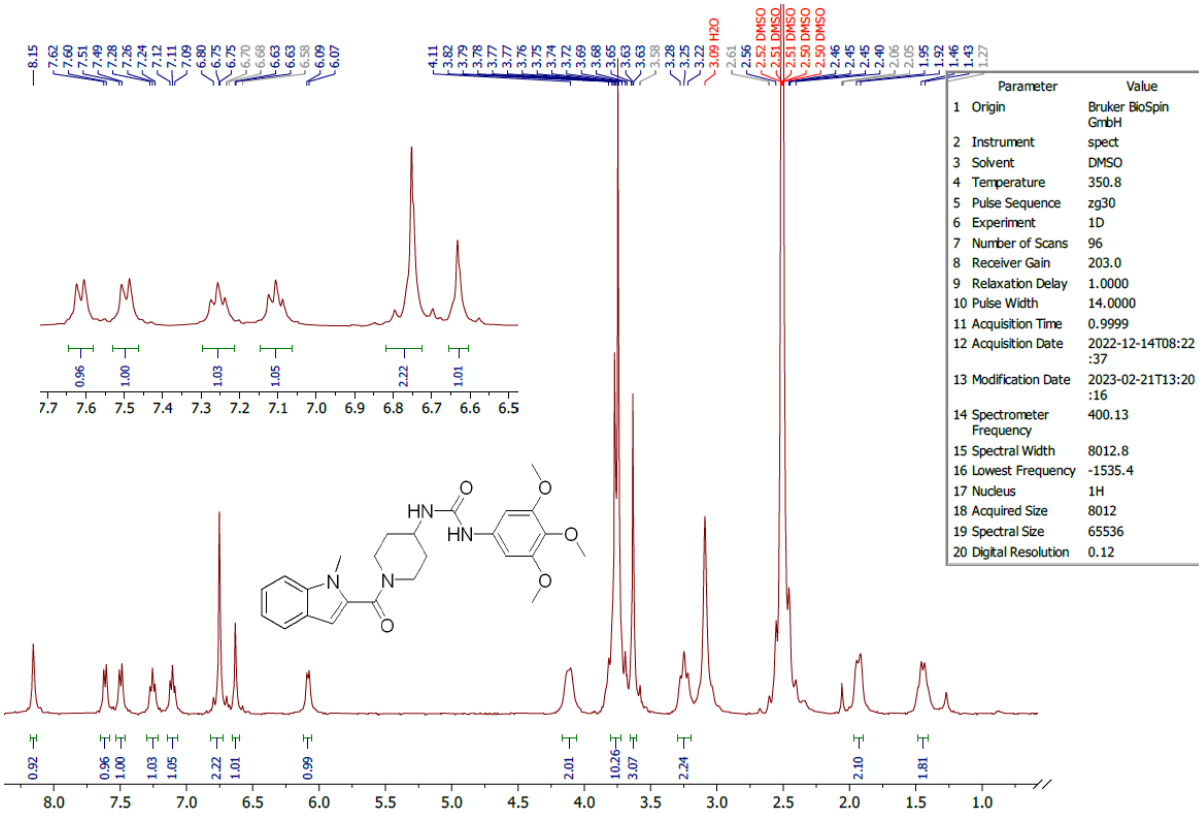


Figure 63: ^{1}H NMR of compound **11g.**

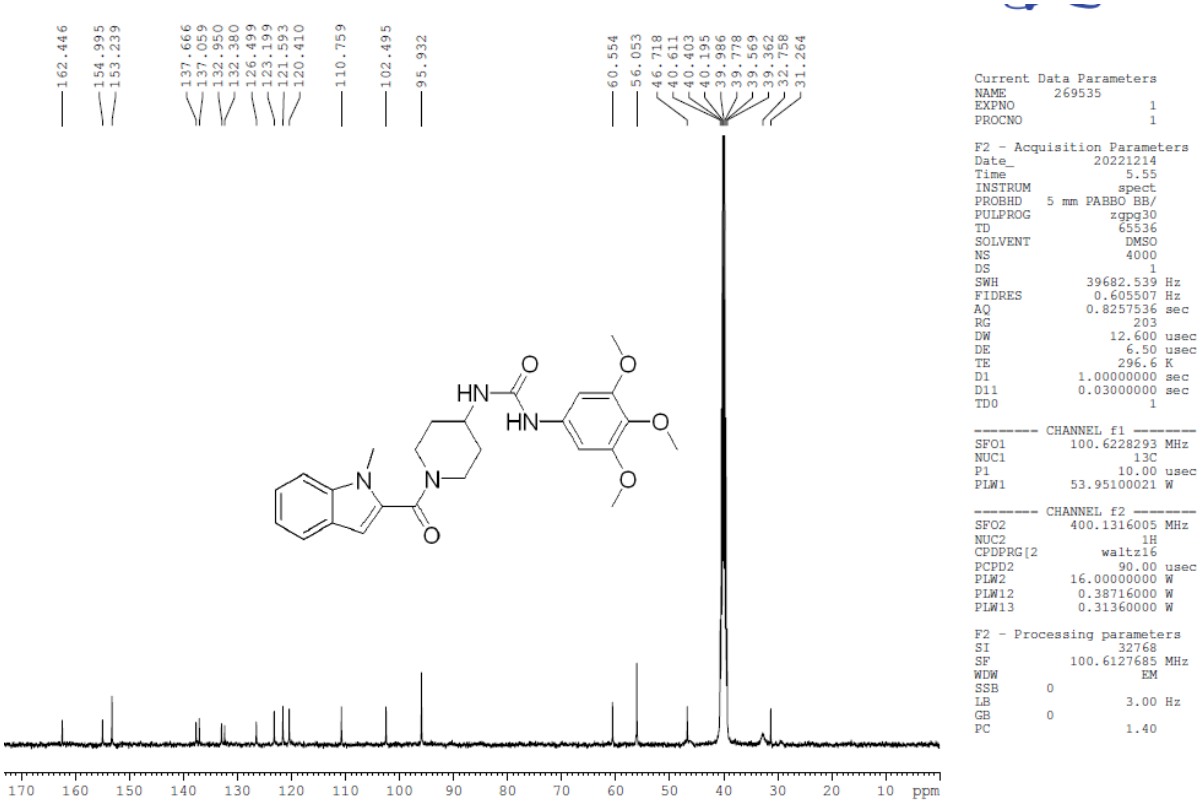
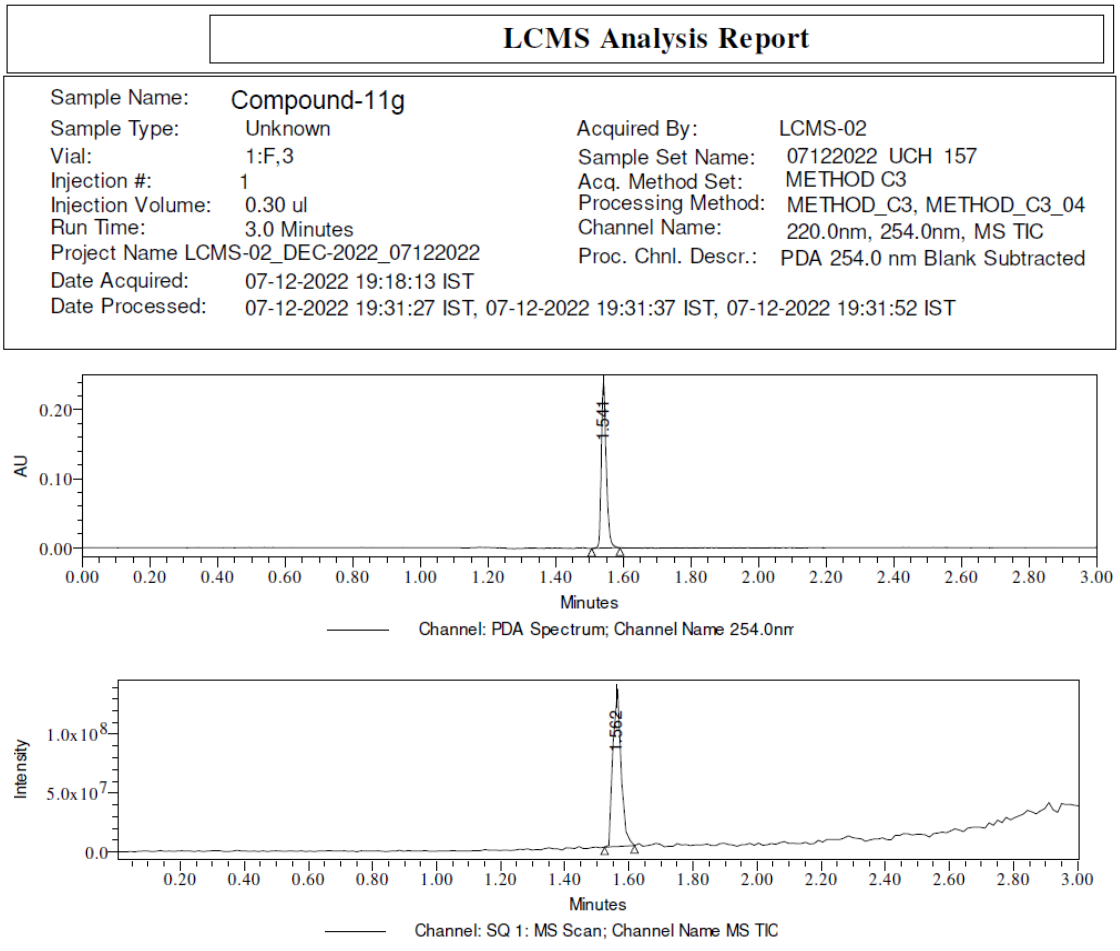
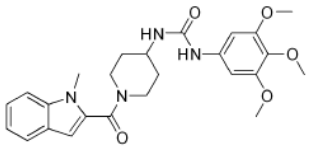


Figure 64: ^{13}C NMR of compound **11g.**

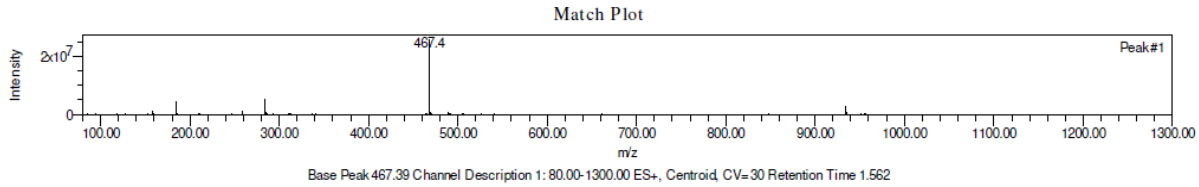


Peak Results
Channel: PDA Spectrum

	Retention Time (min)	Base Peak (m/z)	Height (µV)	Area (µV*sec)	% Area	Channel	Channel Name
1	1.541		239277	243666	100.00	PDA Spectrum	254.0nm
2	1.541		591539	614569	100.00	PDA Spectrum	220.0nm



Chemical Formula: $C_{25}H_{30}N_4O_5$
Molecular Weight: 466.54



Base Peak 467.39 Channel Description 1: 80.00-1300.00 ES+, Centroid, CV=30 Retention Time 1.562

Figure 65: LC-MS of compound **11g.**

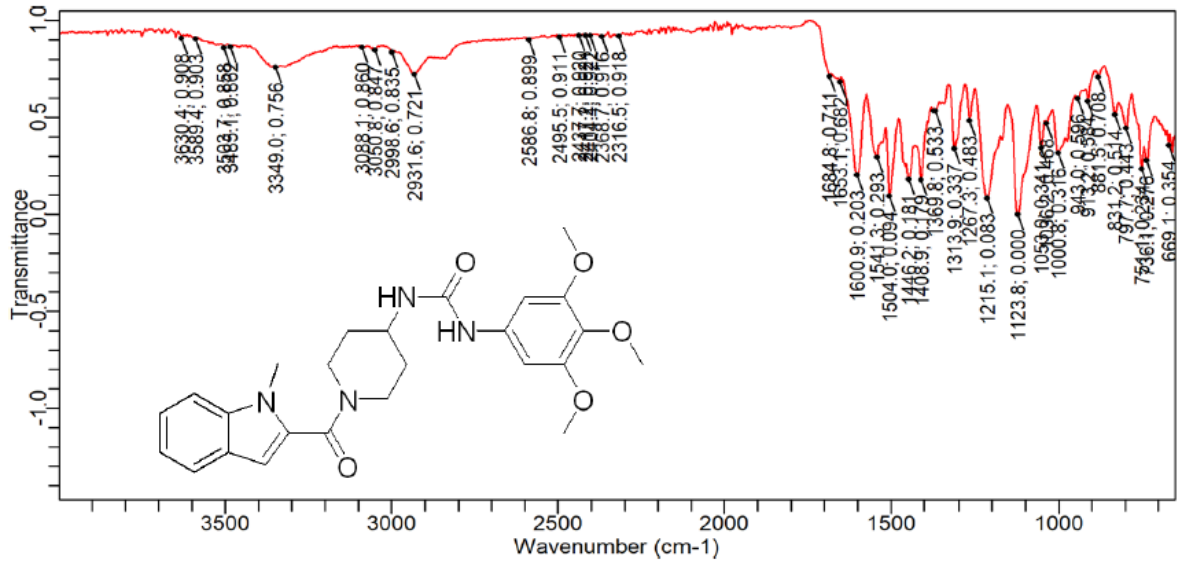


Figure 66: IR of compound **11g.**

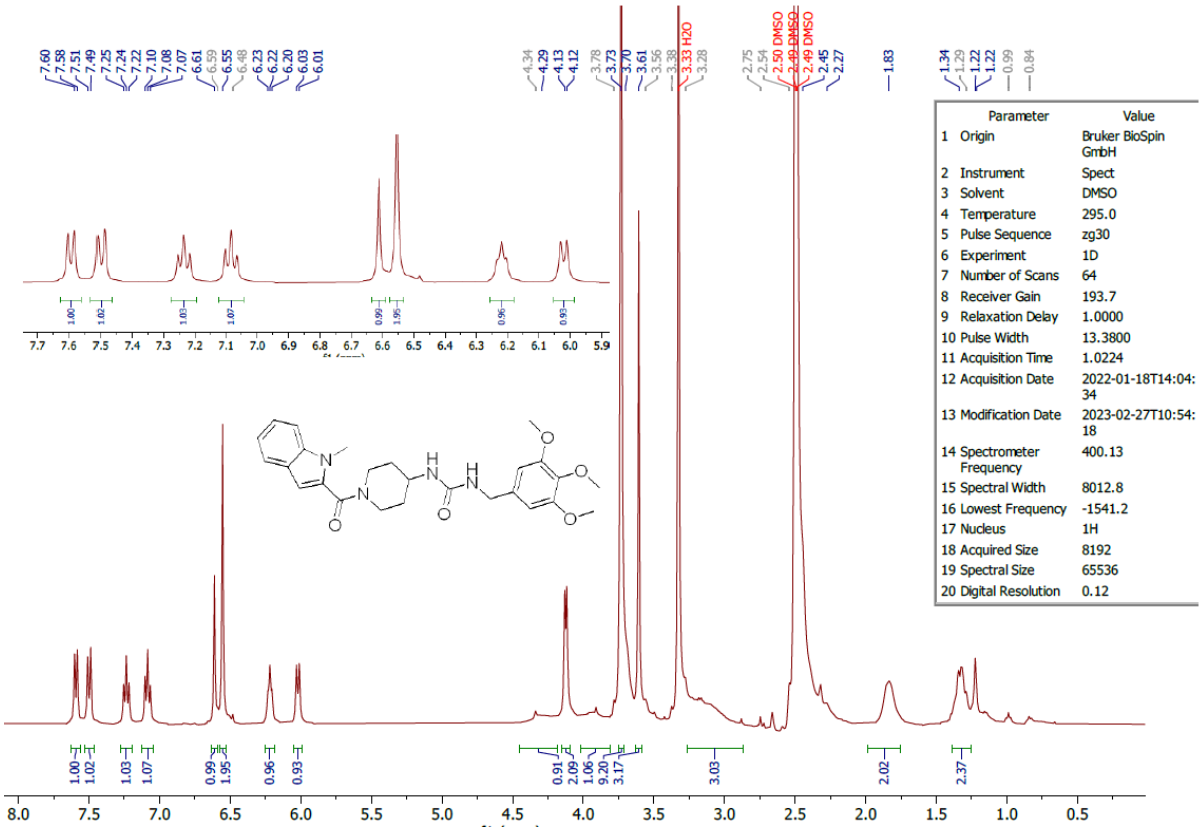


Figure 67: ^{1}H NMR of compound **13a.**

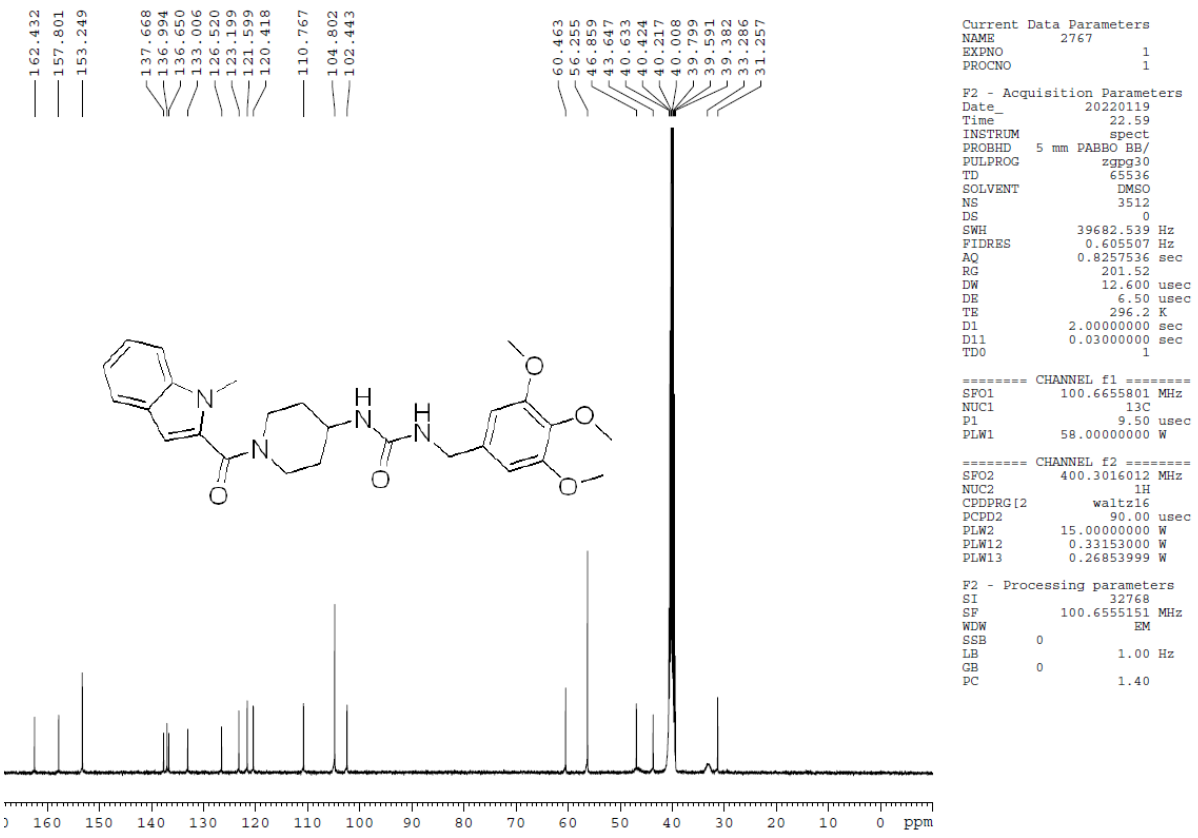
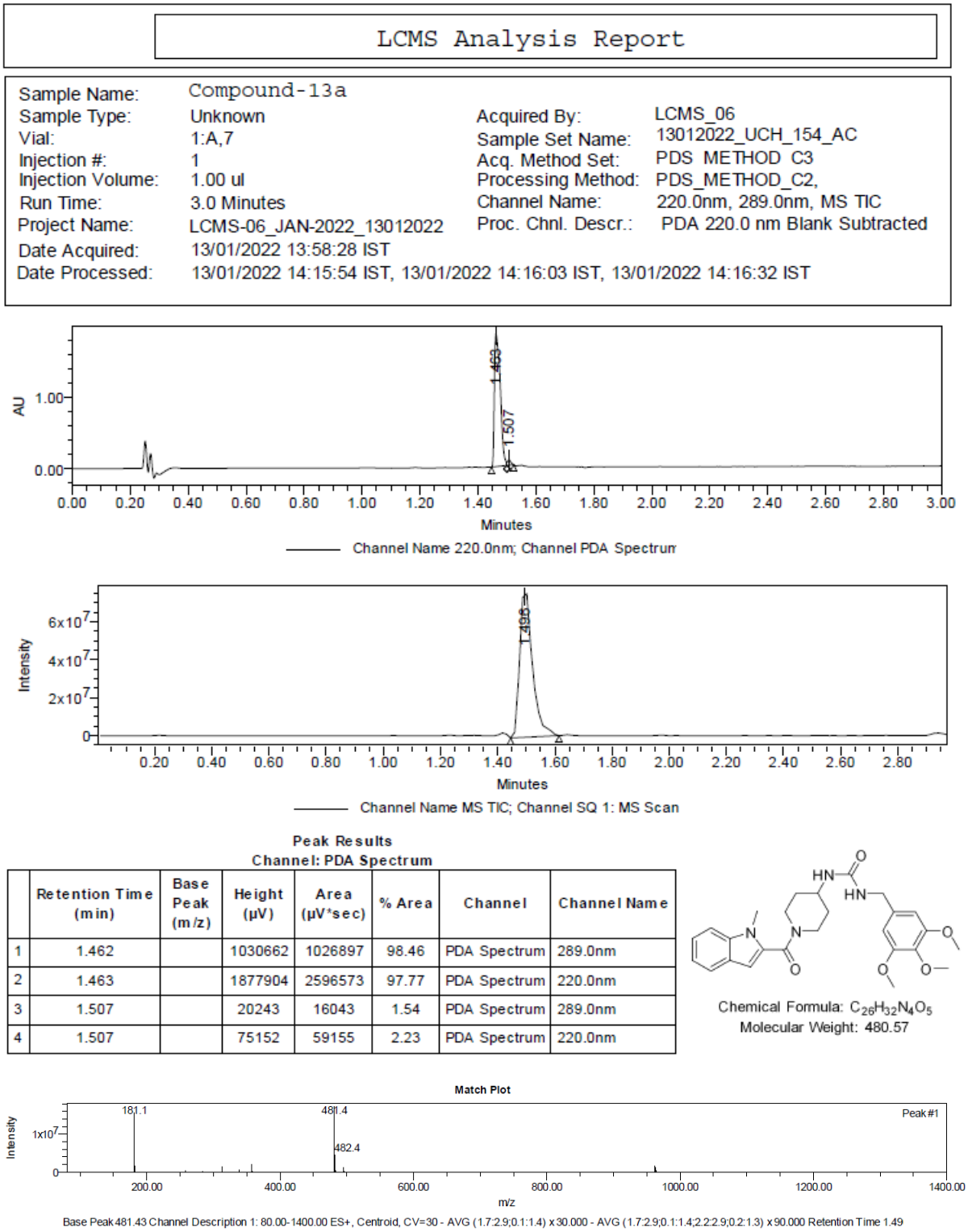


Figure 68: ^{13}C NMR of compound **13a.**



	Retention Time (min)	Base Peak (m/z)	Height (µV)	Area (µV*sec)	% Area	Channel	Channel Name
1	1.462		1030662	1026897	98.46	PDA Spectrum	289.0nm
2	1.463		1877904	2596573	97.77	PDA Spectrum	220.0nm
3	1.507		20243	16043	1.54	PDA Spectrum	289.0nm
4	1.507		75152	59155	2.23	PDA Spectrum	220.0nm

Figure 69: LC-MS of compound **13a.**

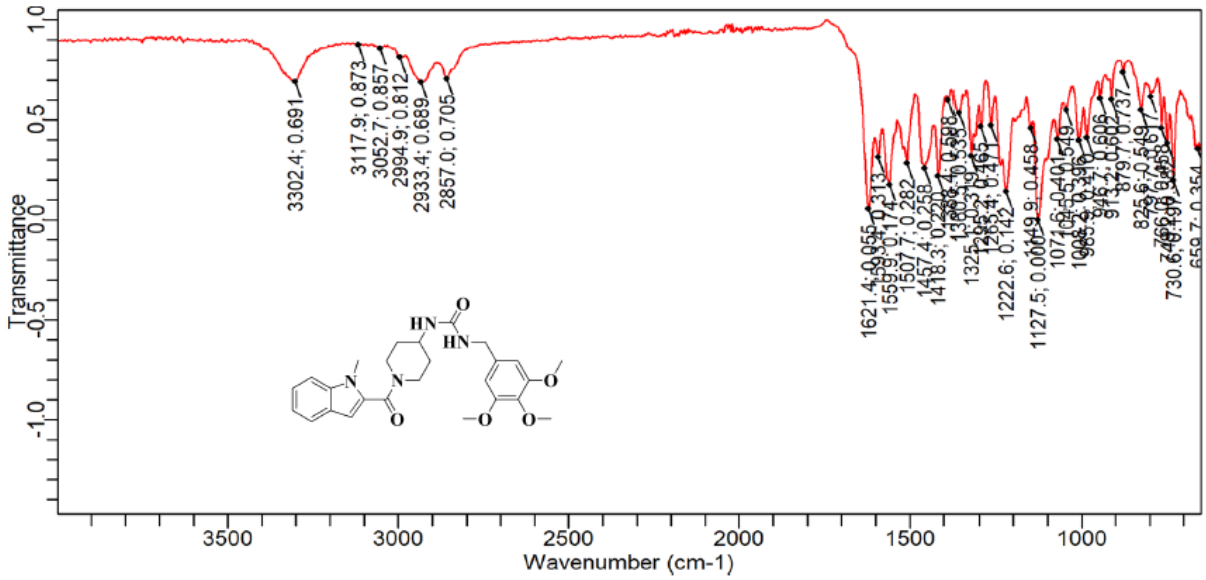


Figure 70: IR of compound **13a.**

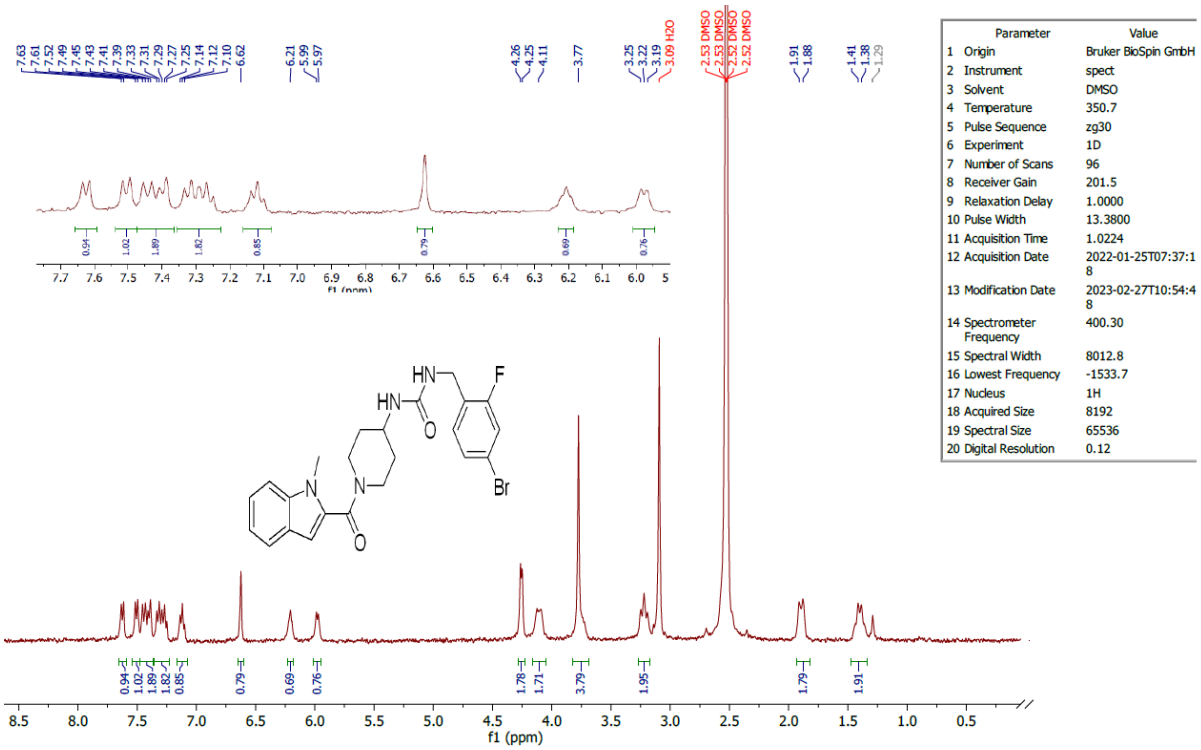


Figure 71: ^{1}H NMR of compound **13b.**

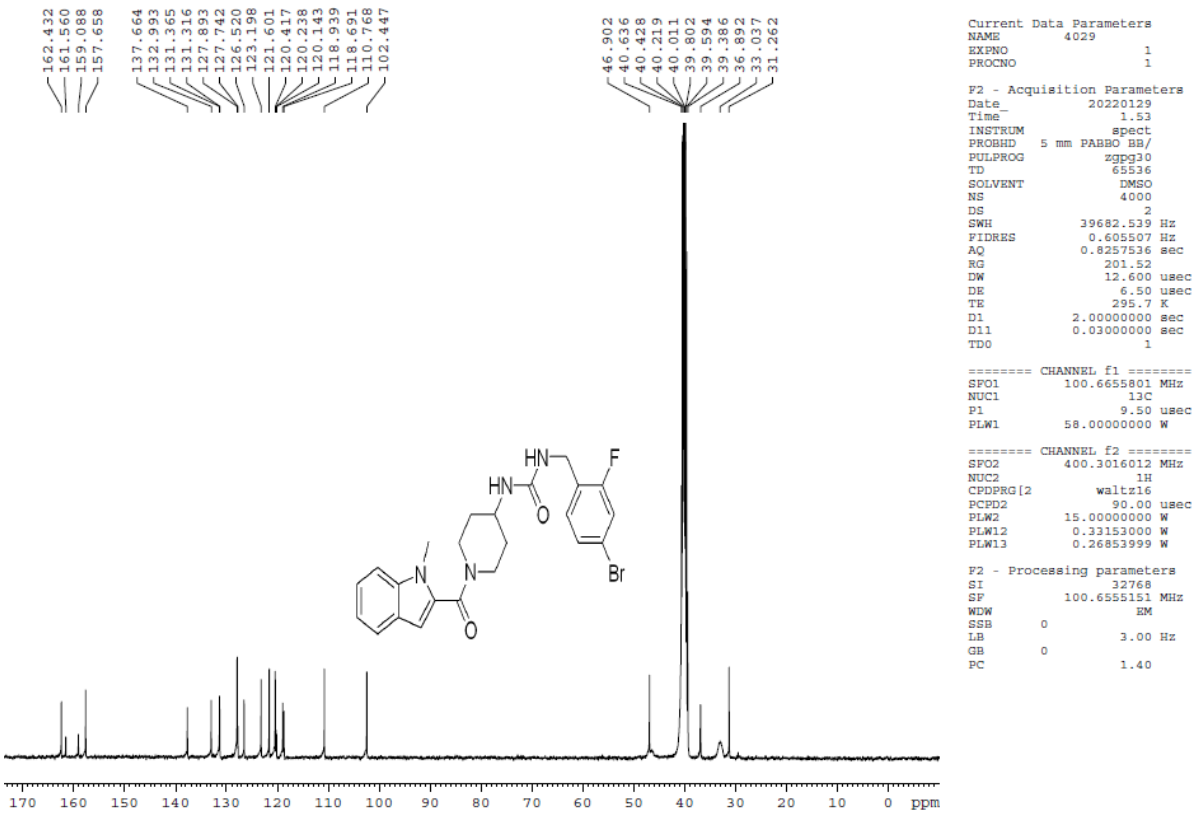
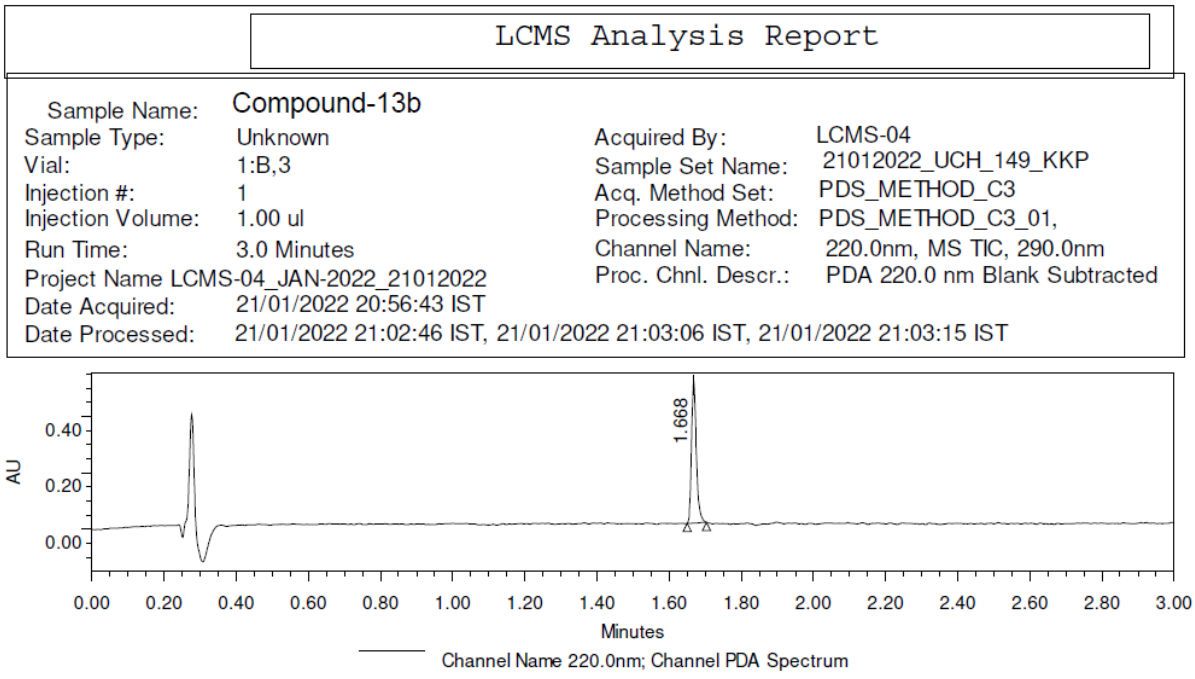
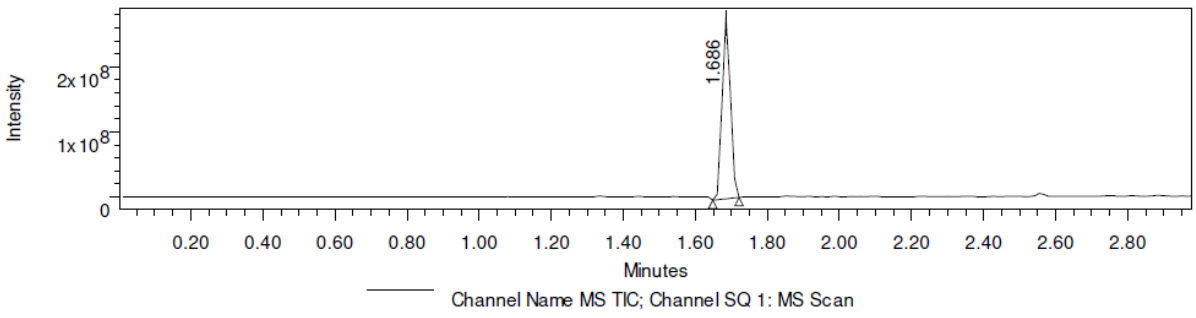


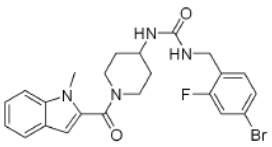
Figure 72: ^{13}C NMR of compound **13b.**



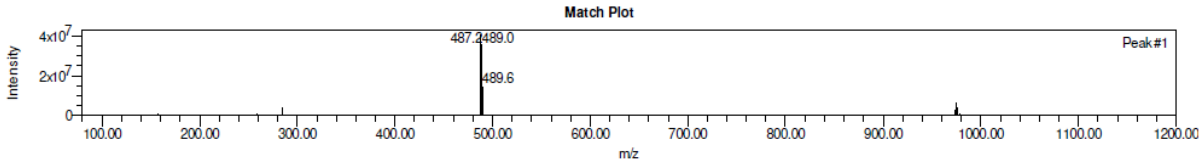


Peak Results
Channel: PDA Spectrum

	Retention Time (min)	Base Peak (m/z)	Height (µV)	Area (µV*sec)	% Area	Channel	Channel Name
1	1.668		154915	145426	100.00	PDA Spectrum	290.0nm
2	1.668		499490	468838	100.00	PDA Spectrum	220.0nm



Chemical Formula: $C_{23}H_{24}BrFN_4O_2$
Molecular Weight: 487.37



Base Peak 487.25 Channel Description 1: 80.00-1200.00 ES+, Centroid, CV=30 - AVG (0.0:1.2;2.1:3.0;0.1:1.2;2.2:3.0) x 66.000 - AVG (0.0:1.2;2.1:3.0;0.1:1.2;2.2:3.0) x 66.000 Retention Time 1.68

Figure 73: LC-MS of compound **13b.**

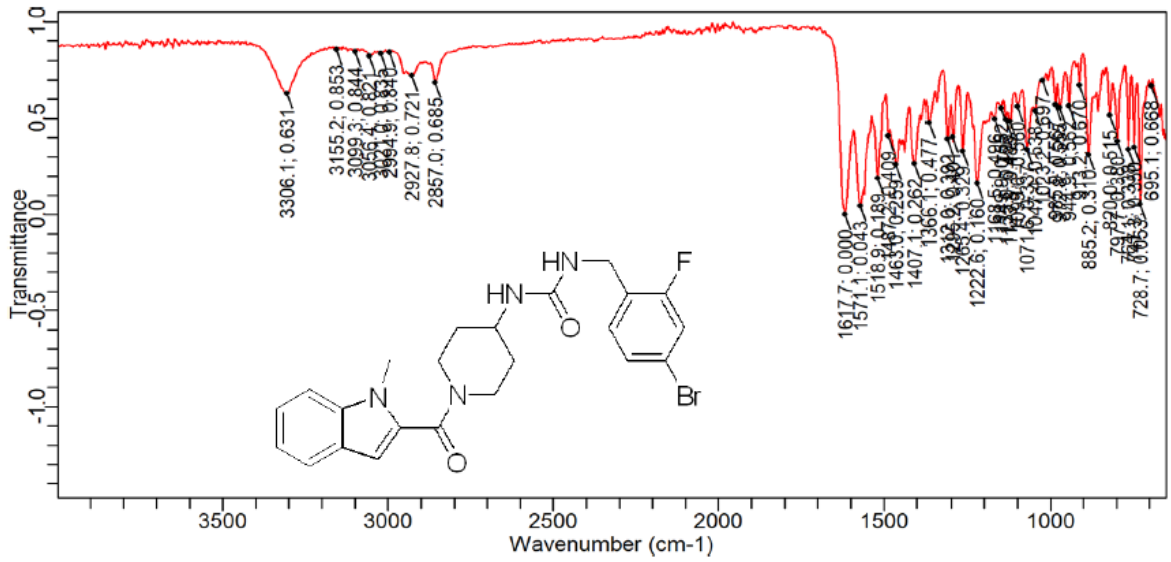
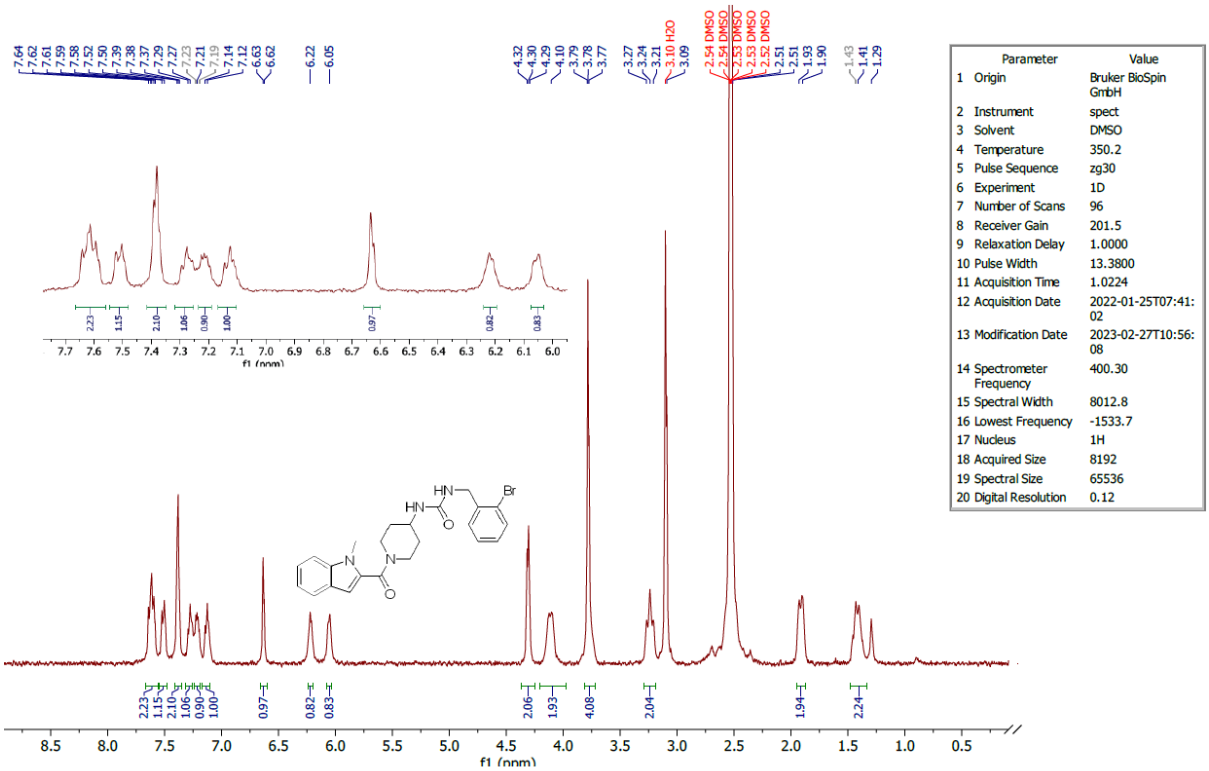
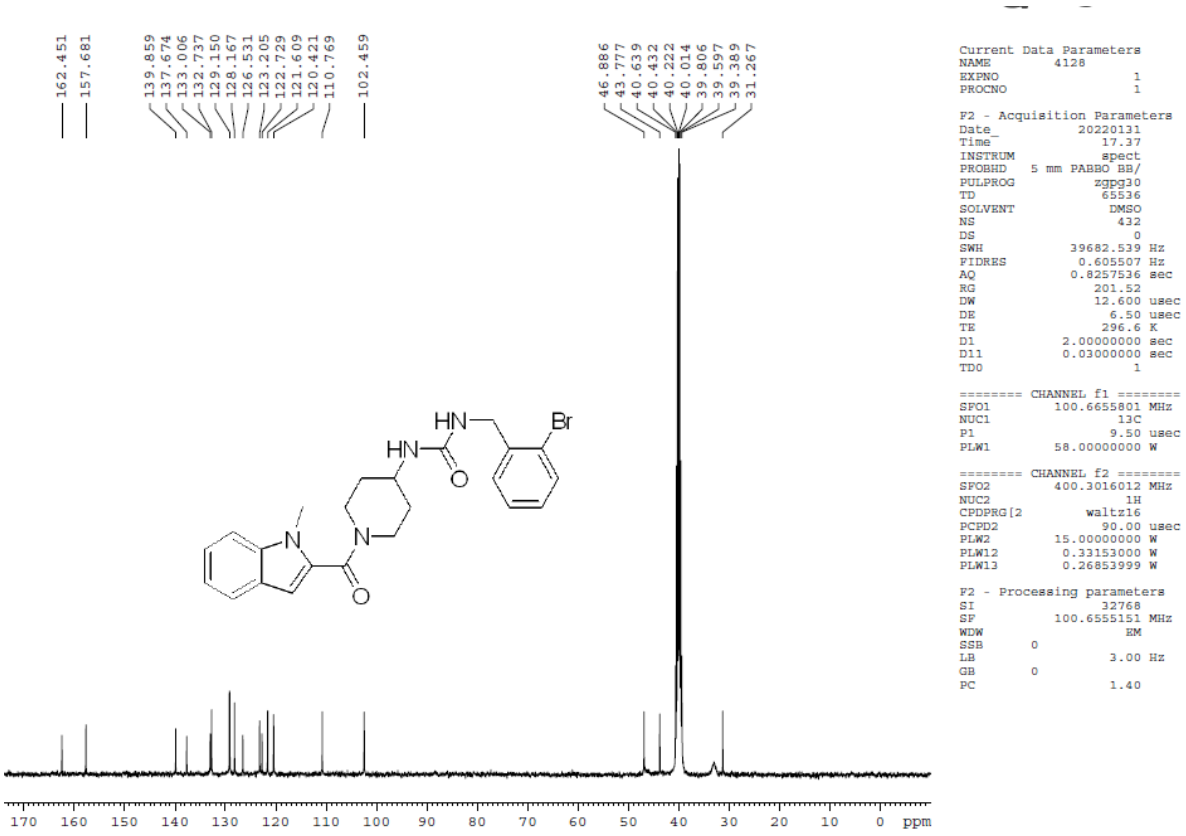


Figure 74: IR of compound **13b.**



	Parameter	Value
1	Origin	Bruker BioSpin GmbH
2	Instrument	spect
3	Solvent	DMSO
4	Temperature	350.2
5	Pulse Sequence	zg30
6	Experiment	1D
7	Number of Scans	96
8	Receiver Gain	201.5
9	Relaxation Delay	1.0000
10	Pulse Width	13.3800
11	Acquisition Time	1.0224
12	Acquisition Date	2022-01-25T07:41:02
13	Modification Date	2023-02-27T10:56:08
14	Spectrometer Frequency	400.30
15	Spectral Width	8012.8
16	Lowest Frequency	-1533.7
17	Nucleus	1H
18	Acquired Size	8192
19	Spectral Size	65536
20	Digital Resolution	0.12

Figure 75: ^{1}H NMR of compound **13c.**

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PROCNO           1

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TD             65536
SOLVENT         DMSO
NS               432
DS                 0
SWH        39682.539 Hz
FIDRES         0.605507 Hz
AQ             0.8257536 sec
RG               201.52
DW              12.600 usec
DE               6.50 usec
TE              296.6 K
D1          2.00000000 sec
D11         0.03000000 sec
TD0              1

======== CHANNEL f1 ========
SFO1       100.6655801 MHz
NUC1              13C
P1               9.50 usec
PLW1       58.00000000 W

======== CHANNEL f2 ========
SFO2       400.3016012 MHz
NUC2              1H
CPDPRG[2       waltz16
PCPD2           90.00 usec
PLW2       15.00000000 W
PLW12       0.33153000 W
PLW13       0.26853999 W

F2 - Processing parameters
SI               32768
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WDW                EM
SSB       0
LB               3.00 Hz
GB        0
PC               1.40
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Figure 76: ^{13}C NMR of compound **13c.**

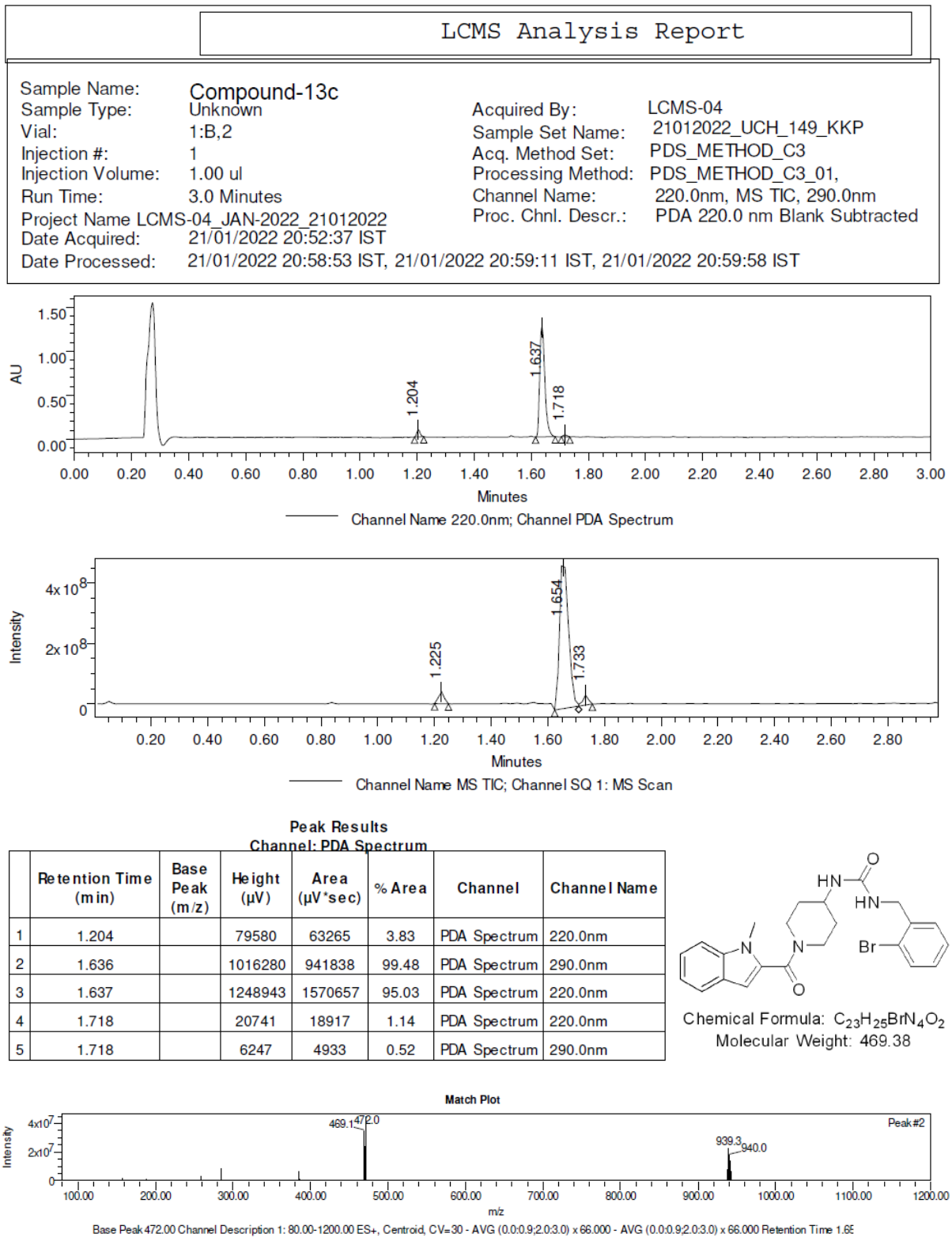


Figure 77: LC-MS of compound **13c.**

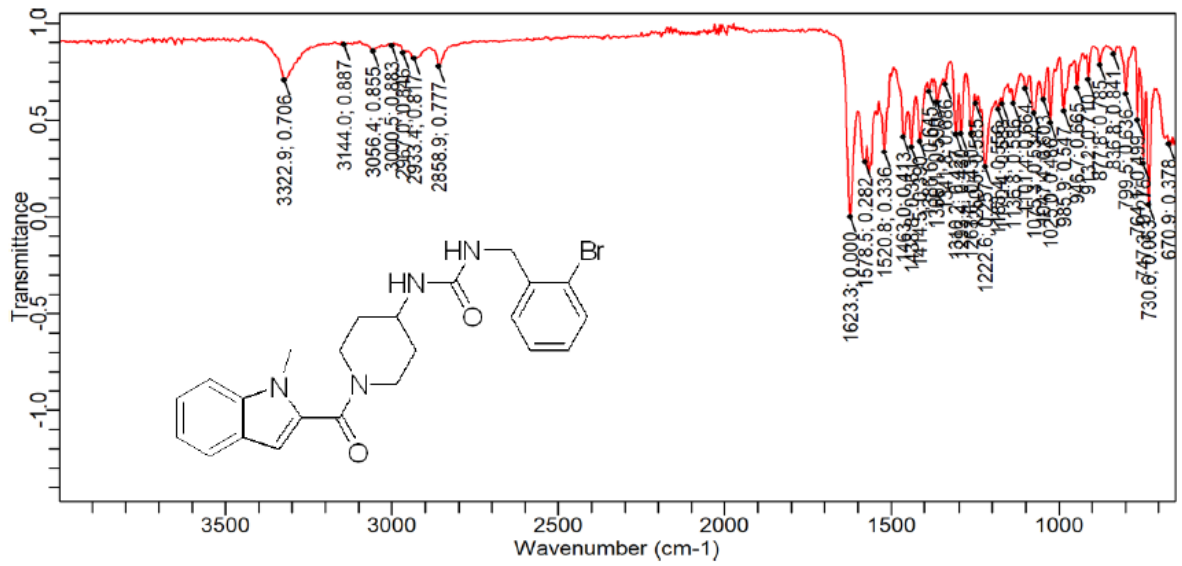


Figure 78: IR of compound **13c.**

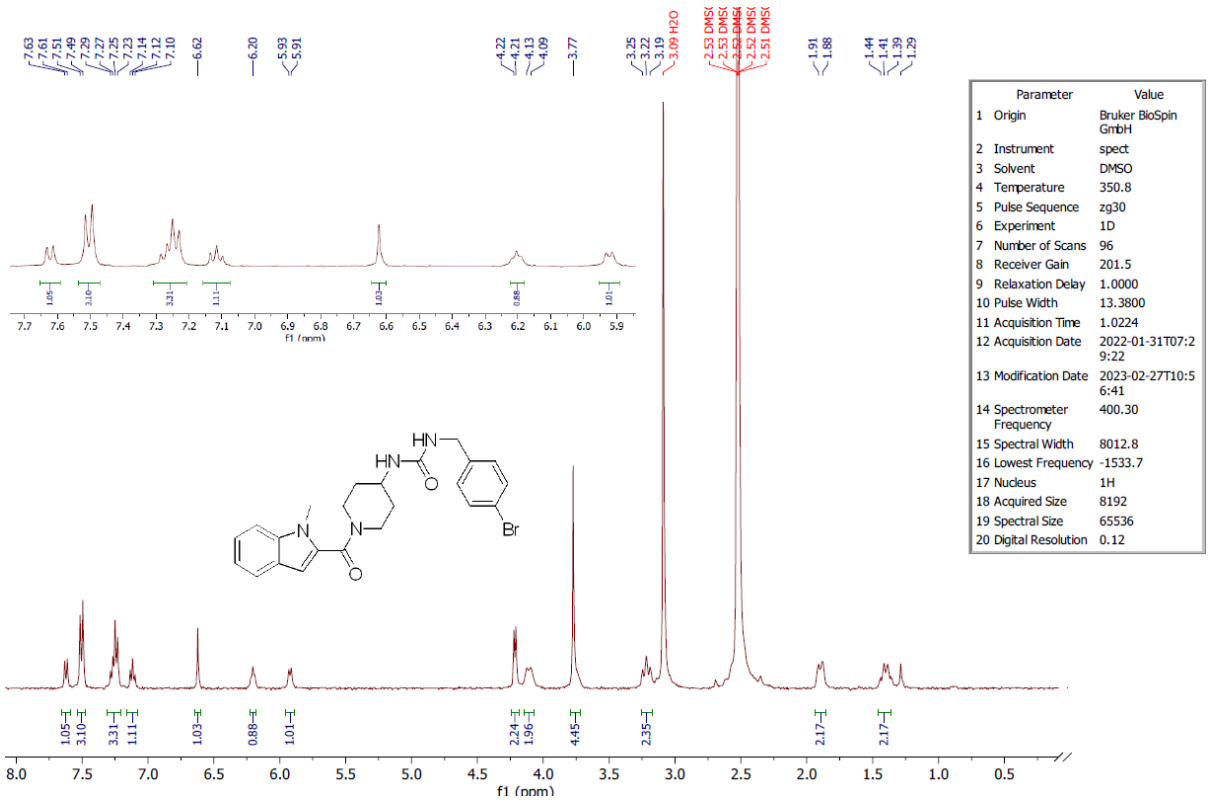


Figure 79: ^{1}H NMR of compound **13d.**

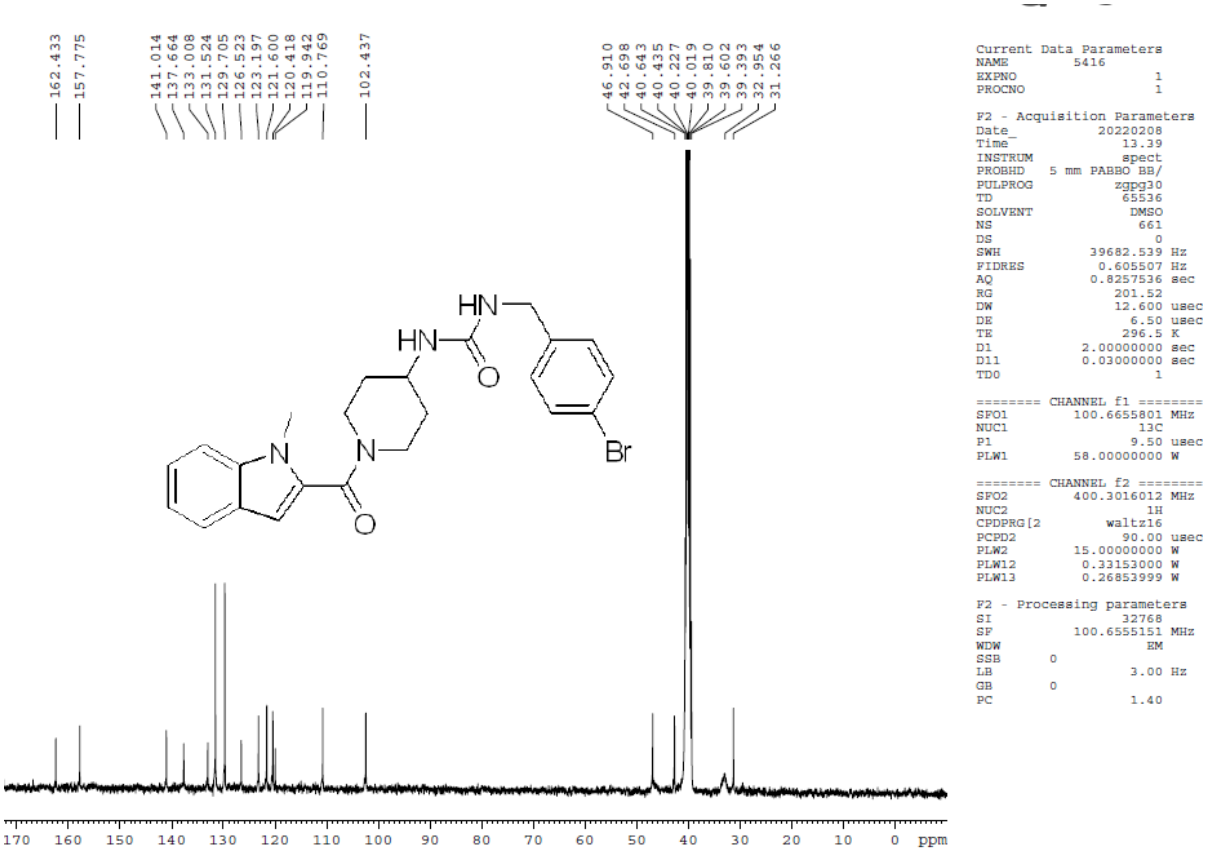
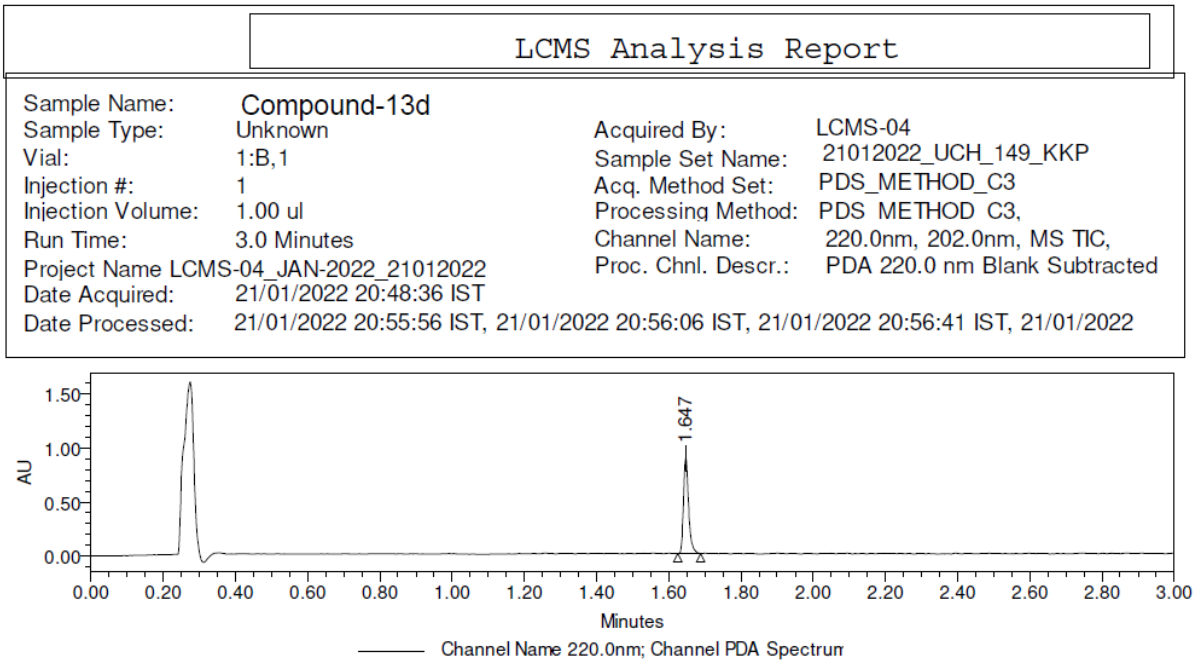
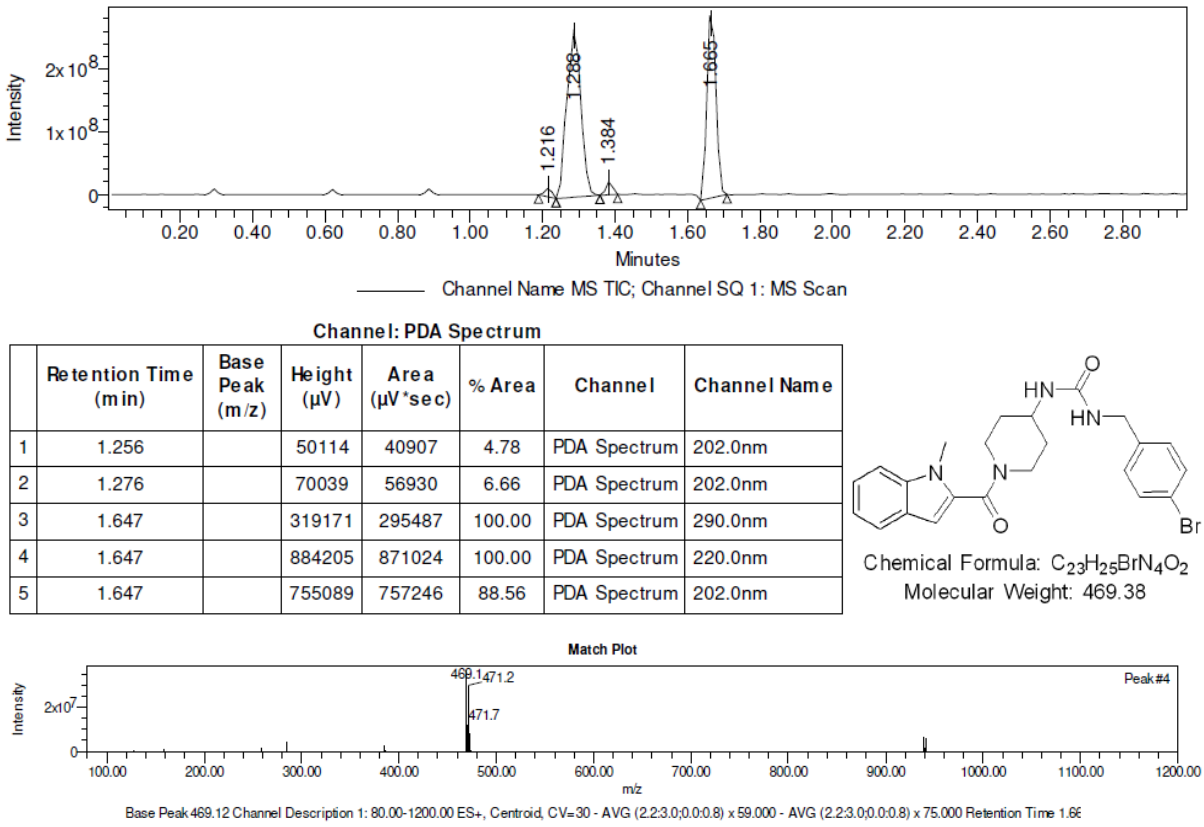


Figure 80: ^{13}C NMR of compound **13d.**





Channel: PDA Spectrum

	Retention Time (min)	Base Peak (m/z)	Height (µV)	Area (µV*sec)	% Area	Channel	Channel Name
1	1.256		50114	40907	4.78	PDA Spectrum	202.0nm
2	1.276		70039	56930	6.66	PDA Spectrum	202.0nm
3	1.647		319171	295487	100.00	PDA Spectrum	290.0nm
4	1.647		884205	871024	100.00	PDA Spectrum	220.0nm
5	1.647		755089	757246	88.56	PDA Spectrum	202.0nm

Chemical Formula: $C_{23}H_{25}BrN_4O_2$
Molecular Weight: 469.38

Figure 81: LC-MS of compound **13d.**

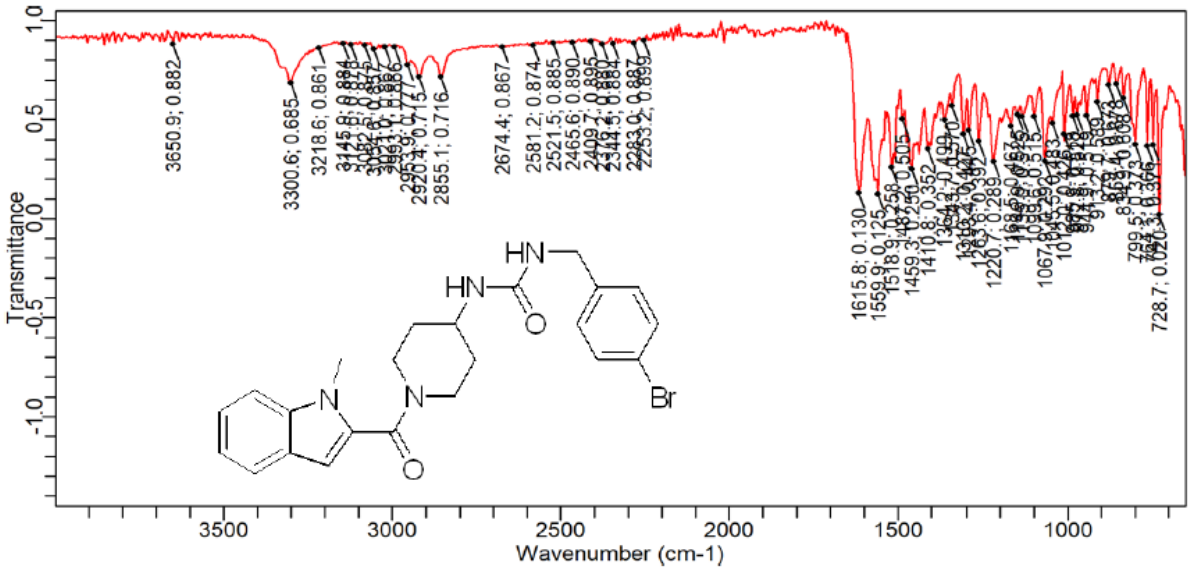


Figure 82: IR of compound **13d.**

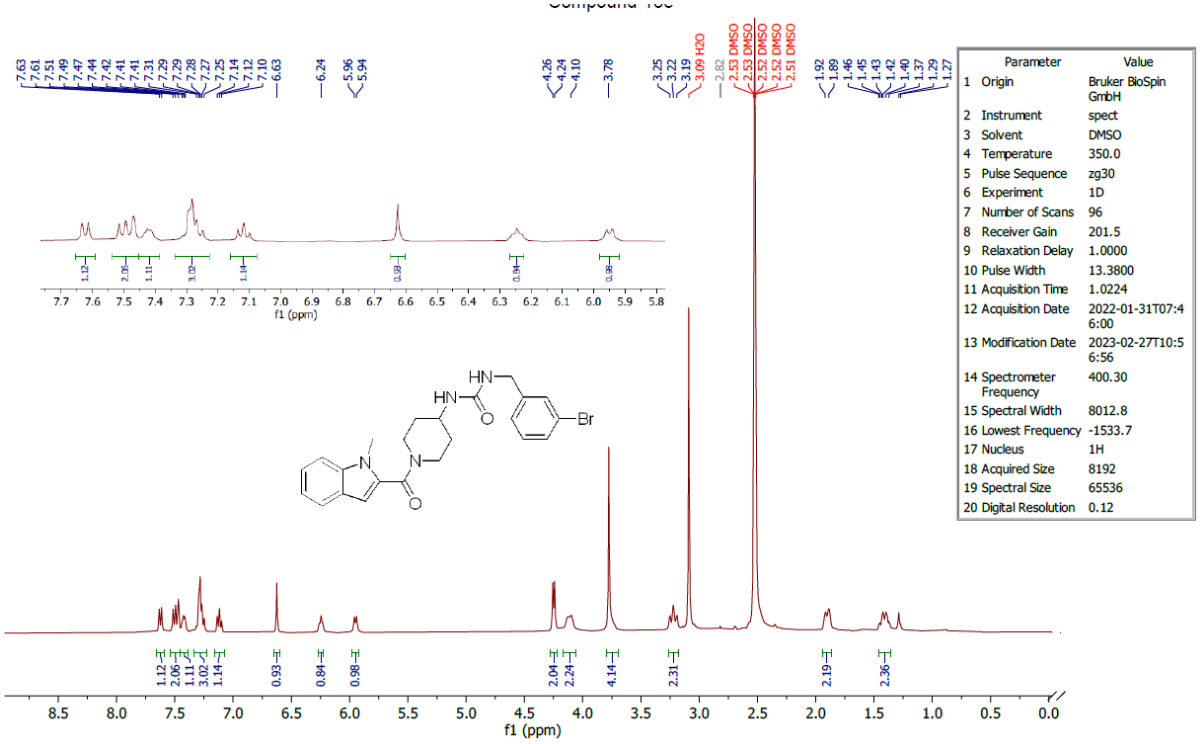


Figure 83: ^{1}H NMR of compound **13e.**

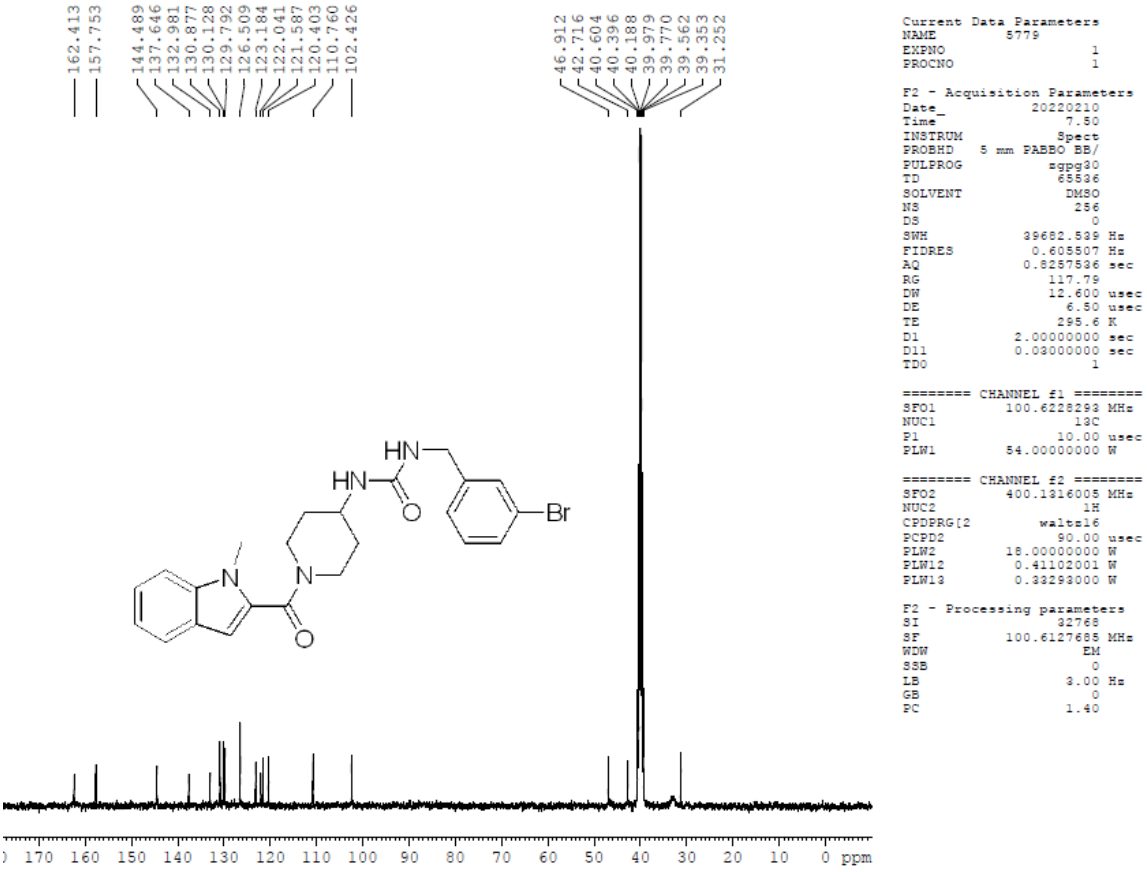


Figure 84: ^{13}C NMR of compound **13e.**

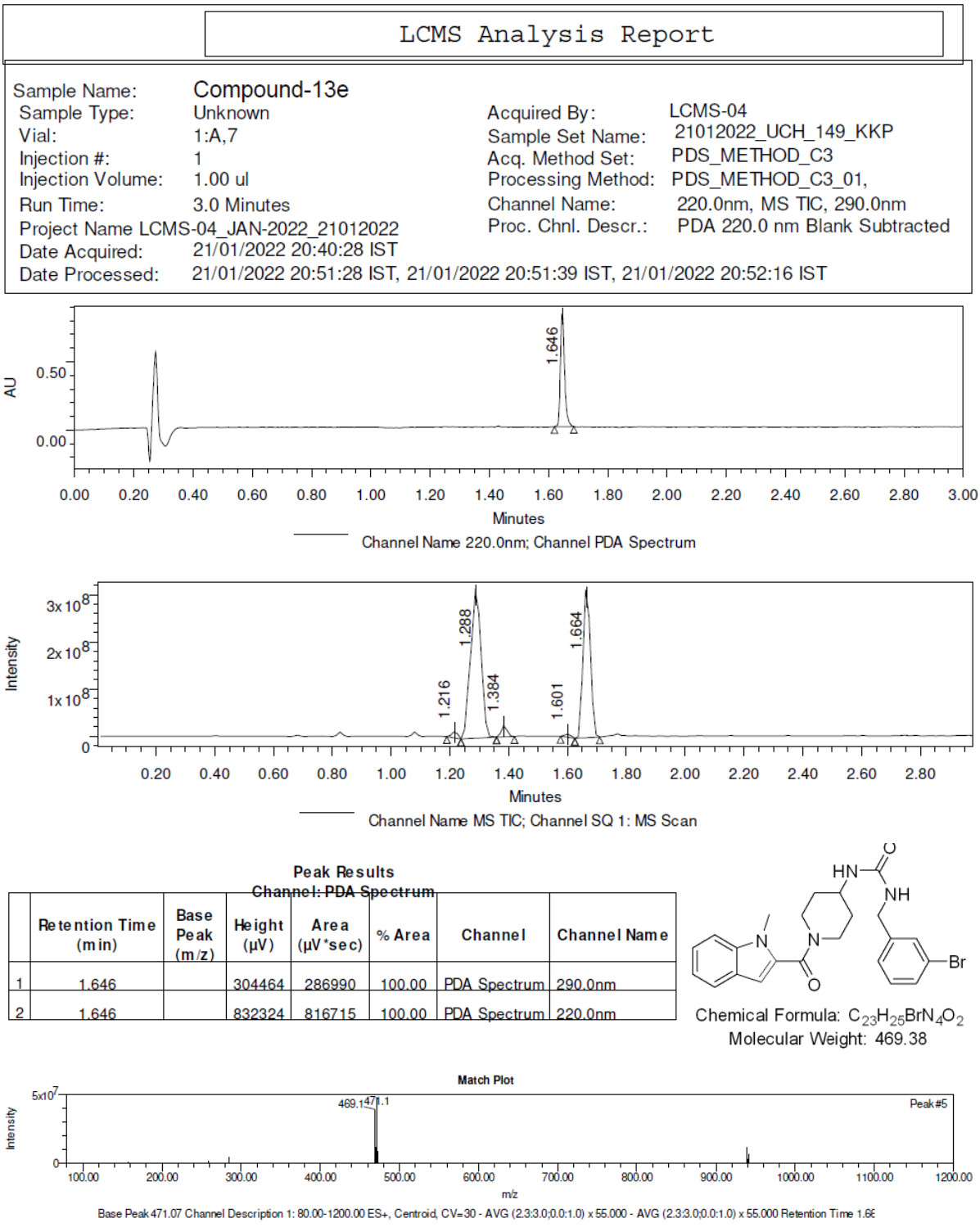


Figure 85: LC-MS of compound **13e.**

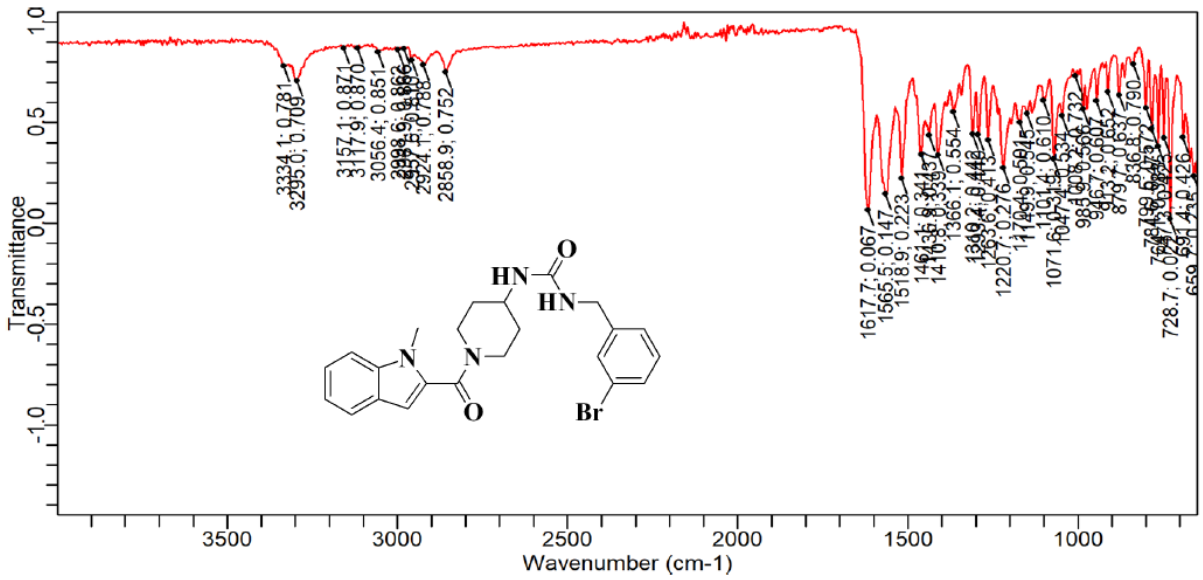


Figure 86: IR of compound **13e.**