Synthesis of New 4-Aryl-1-(Biarylmethylene) Piperidine Ligands, Structurally Related to SLV-313

BY

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DEDICATION

Dedicated to all members of my family and friends

ACKNOWLEDGMENT

All thank and praise is to Allah for giving me the power and ability to accomplish this research .his peace and blessing be upon his messenger, Muhammad, his family members, his companions and those who will follow him in righteousness to the Day of Judgment.

My deep and sincere appreciations are to my parents who stand beyond my success in my life. They support me in all the steps of my study .I don't forget the efforts of my brothers and sisters in achieving this task.

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THESIS ABSTRACT

Name: Ali Ahmed Qaid Al-Shaheri

Title: Synthesis of New 4-Aryl-1-(Biarylmethylene) Piperidine Ligands, Structurally Related to SLV-313.

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A series of new 4-aryl-1-(biarylmethylene)piperidines have been synthesized. They are structurally related to SLV-313, a potential atypical antipsychotic agent with potent D2 receptor antagonist and5-HT1A receptor agonist properties. Suzuki-Miyaura reaction of cyclic vinyl boronates, derived from the vinyl triflates of N-protected tetrahydropyridines, with appropriate aryl halides yielded 4-arylpiperidines.The reductive amination of the latter with suitable biarylaldehydes accomplished the synthesis of the new compounds.

MASTER OF SCIENCE DEGREE

KING FAHD UNIVERSITY OF PETROLEUM AND MINERALS

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ملـخص الرســالة

الاســــــــــــم:علي أحمد قايد الشاهري

عنوان الرسالة: إصطناع سلسلة جديدة من مشتقات **4-aryl-1-(biarylmethylene)piperidin**

والتي تشابه تركيبياً لمادة SLV-313.

التخصـــــــص: كيمياء

تاريخ التخـرج: يوليو ١٤٣٣هـ

تم تحضير سلسلة جديدة من مشتقات 4-aryl-1-(biarylmethylene)piperidines

والتي تشابه تركيبياً لمادةSLV-313.

بواسطة تفاعل سوزوكي-مایاورا بين بورونات الفنيال الحلقية المشتقة من تراي فلايت الفنايل لرباعي هايدروالبيريدين مع هاليدات الاريل والذي انتج مادة ٤-اريل البايبريدين تم تفاعل الاخير مع الديهايد ثنائي الاريل المناسب لإصطناع المركبات الجديدة المذكورة في الرسالة

ماجستير العلوم

جامعــة الملك فهــد للبترول والمعــادن

الظهران – المملكة العربية السعودية

يوليو ٢٠١٢م

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

1.1. INTRODUCTION

Schizophrenia is a lifelong, chronic, complex neuropsychiatric illness, afflicting approximately 1.5% of the world population irrespective of ethnic, economical, or cultural bound [1,2]. There are no specific focal characteristics for the diagnosis of schizophrenia, and no single symptom is consistently present in all patients. Consequently, its diagnosis as a single disorder, or as a variety of different disorders, is still debated [3]. Symptoms typically arise in early adulthood and lead to severe social and occupational dysfunction In general, schizophrenia involves alterations in cognitive and emotional functioning and the symptoms can be grouped as positive, negative and cognitive dysfunction. Positive symptoms include altered behavior, such as delusion, irrational fears, hallucinations, disorganized thoughts, extreme emotions, excited motor activity and incoherent speech. Negative symptoms are described as a lack of behavior, such as poverty of speech, social withdrawal, avolition, anhedonia and affective blunting, and are resistance to typical antipsychotics. Cognitive deficits include reduction in working memory, attention, and verbal fluency [4-6]. Depression is also a common feature of the condition [7]. In many patients the illness involves repeated relapses of acute psychotic episodes interspersed with stable phases of complete or partial remission.

Investigation into the neurobiological basis of schizophrenia has spanned over a century, and although definitive pathology remains elusive, certain deviations in neuroanatomy and neurochemistry are now reasonably well established. At the neuroanatomical level, there is a general enlargement of the lateral ventricles and a small

reduction in brain volume [8], which appears to be of neurodevelopmental (as opposed to neurodegenerative) origin [9]. Neuropath logical studies have provided evidence for subtle cytoarchitectural anomalies in areas such as the hippocampus and prefrontal cortex, where volume reductions are pronounced [10]. There is now also evidence for alterations in sub-cortical dopamine activity during the acute psychotic phases of the disorder [11], consistent with the proven efficacy of antipsychotics, which act on dopamine receptors, in the treatment of positive symptoms. However, it is likely that the phenotypic heterogeneity of schizophrenia at least partly reflects heterogeneity in the underlying pathological mechanisms, which are at present largely unknown. Recent developments in molecular genetics have paved the way for significant advances in our mechanistic understanding of schizophrenia and the extent to which these mechanisms are shared with other neuropsychiatric disorders.

1.2. LITERATURE REVIEW

Since the discovery antipsychotic agent chlorpromazine **1**more than 50 years ago [12], the number of antipsychotic agents for the treatment of schizophrenia has tremendously increased. The development of the first-generation antipsychotics, or typical antipsychotics, had for the first time made possible to treat the 'positive' symptoms such as delusions and hallucinations of schizophrenia, leading to the deinstitutionalization of the world's mentally ill. The typical antipsychotic drugs, however, are generally not effective at treating the 'negative' symptoms, for instance anhedoniaand lack of motivation; and cognitive dysfunction of schizophrenia and have a high liability of extrapyramidal side effects (EPS) [13].Atypical antipsychotic drugs are different from typical antipsychotic drugs by virtue of a relative lack of EPS and serum prolactin elevation as compared with typical antipsychotic drugs. Clozapine **2**itself has become the 'gold standard' antipsychotic medication because of its absence of debilitating extrapyramidal side effects and its demonstrated clinical superiority in treatment-resistant schizophrenia [14] and suicidality. The beneficial effect on negative symptoms and cognition ofclozapine**2** is unclear [13, 15].Clozapine**2**, however, is associated with serious side effects including weight gain, diabetes and an increased risk of seizures and agranulocytosis [16].The proven superiority of clozapine **2** [17, 18] over other antipsychotic drugs has led to an intense effort over the past 15–20 years to develop clozapine-like atypical antipsychotics that are safer and better tolerated than clozapine**2**. Thus multiple atypical and pseudo-atypical antipsychotic drugs, includingrisperidone**3**, olanzapine**4**, quetiapine**5** and ziprasidone**6**have been discovered. Expectations from these drugs to treat negative symptoms and cognition were initially high[19] which were, however, have not been realized[20].While most of the new drugs offer, at best, modest advantages over the typical antipsychotic drugs with regard to improvement in negative symptoms, cognitive impairment and functional capacity, the improvements are not consistent among studies[21-23]. In addition, the atypical

antipsychotics have substantial side-effect liability, specifically weight gain and the metabolic syndrome [24, 25]. Even though the introduction of antipsychotic medications has had a profound effect on the treatment of schizophrenia over the past 50 years, and the atypical antipsychotic drugs have provided a larger and more diverse armamentarium of treatment options, the advances and improvements that have been made since the discovery of the antipsychotic properties of chlorpromazine**1**have been small and incremental. Thus, enormous challenges remain in the long-term treatment of this debilitating disease and continuing with the current paradigms of drug discovery is unlikely to produce significant advances [26, 27]. It is therefore important to continue to pursue diverse molecular targets for discovering new antipsychotic compounds and to devise novel paradigms for drug discovery in schizophrenia.

The main obstacle to the discovery and development of novel treatments for schizophrenia stems from poor understanding of the biological processes involved in schizophrenia and is not sufficient to predict the therapeutic value of novel drug targets [27]. Thus, unvalidated targets are frequently left unpursued by the pharmaceutical industry and, frequently, companies have focused on alterations of existing medications (that is, separating enantiomers or marketing active metabolites; for example 9-OH-risperidoneor paliperidone **7** [28], finding additional compounds that hit known and validated targets [29]. These methods, however, cannot continue indefinitely as the number of such possibilities is limited and thus it is critical to find new approaches to drug development. Interestingly, many of the atypical will soon be going off patent, beginning with the launch of generic risperidone**3**in 2007. Thus, there is significant interest and urgency within the pharmaceutical industry and among schizophrenia basic scientists and clinicians in developing safer and more-effective treatments for schizophrenia.

While we await potential therapeutic avenues arising from improved understanding of schizophrenia susceptibility mechanisms, several novel pharmacological strategies, based largely on prior neurochemical hypotheses of

schizophrenia, have recently shown promise in clinical trials. The path physiology of this complex and uniquely human disorder is believed to be associated with dopaminergic hyperactivity in the mesolimbic system of the brain [30]. The introduction of dopamine receptor blockers such as haloperidol **8** have been treatment of choice for decades [31]. The second-generation atypical drug, emerged after almost three decades, cause no or minimal EPS at therapeutically relevant doses due to multi receptor affinity profile. For most atypical drugs (e.g., clozapine **2**, risperidone **3**, olanzapine **4** and ziprasidone **6** antagonisms at D_2 receptors is accompanied by 5-HT_{2A} receptors blockades. The ratio of 5-HT_2/D_2 rather than the absolute affinity for D_2 and 5-HT_2 receptors may be important for defining an atypical antipsychotic profile of these agents [32]. They are claimed to be active against both positive and negative symptoms, even though their superiority on negative symptoms compared with that of typical antipsychotics is by no means firmly established [33]. Except for clozapine **2** in treatment-resistant schizophrenia, comparative studies have not shown efficacy advantage for any one of these agents, and treatment discontinuation rates are very high [34].Moreover, because of their significant affinity for numerous other receptors, they do exhibit a variety of other side effects[35,36]. These include weight gain ($5HT_{2C}$ receptor blockade), postural hypotension, sedation and dizziness (α_1 adrenoceptor blockade), dry mouth (muscarinic M_1 receptor blockade), and sedation (histamine H_1 receptor blockade).

Newer atypical agents (e.g., Aripiprazole **9**, bifeprunox **10**, and SSR-181507 **11** differ in that they act as partial agonist at D_2 receptors, although also interact with array of other CNS targets. Such therapeutic strategy features the stabilization of dopamine function, instead of the inhibition of the D_2 transmission caused by previous antipsychotic drugs [37], either by post-synaptic dopamine D_2 receptor antagonism [38] and/or partial agonism [39] at presynaptic dopamine D_2 receptors.

1.3. SCHIZOPHRENIA IN SAUDI ARABIA

Schizophrenia in Saudi Arabia is traced back to the early reports in 1975 when sixty-nine schizophrenic patients of both sexes, were investigated for the phenomenology and frequency of visual hallucinations in Taif [40]. The following report was related to discover the incidence of Schneider's first-rand symptoms and their usefulness in diagnosing schizophrenia in Saudi Arabia [41, 42]. Further studies have not only demonstrated that the course of chronic schizophrenia in Saudi families had developed symptoms of delusion of pregnancy[43]but also that out of total of 1366 psychiatric patients in 10 years from different parts of the Eastern Province of the Kingdom of Saudi Arabia, 19.5% had schizophrenia[44]. The other literature reports on schizophrenia in Saudi Arabia dealt in: the comparison of the life-event histories of the schizophrenic patients [45], a familial tendency towards schizophrenia [46] a cross-cultural comparison studies between British and Saudi Arabian patients [47, 48] and quality of life of patients of schizophrenia [49]. The previous studies in the Kingdom have not addressed the core issue of treatment and remedies to the illness so far. We aim to synthesize novel, potential antipsychotic compounds to develop more effective and less toxic therapies for schizophrenia. To the best of our knowledge, this will be the first study of its nature in the Kingdom that would aim to discover the treatment and relieve to the symptoms of illness.

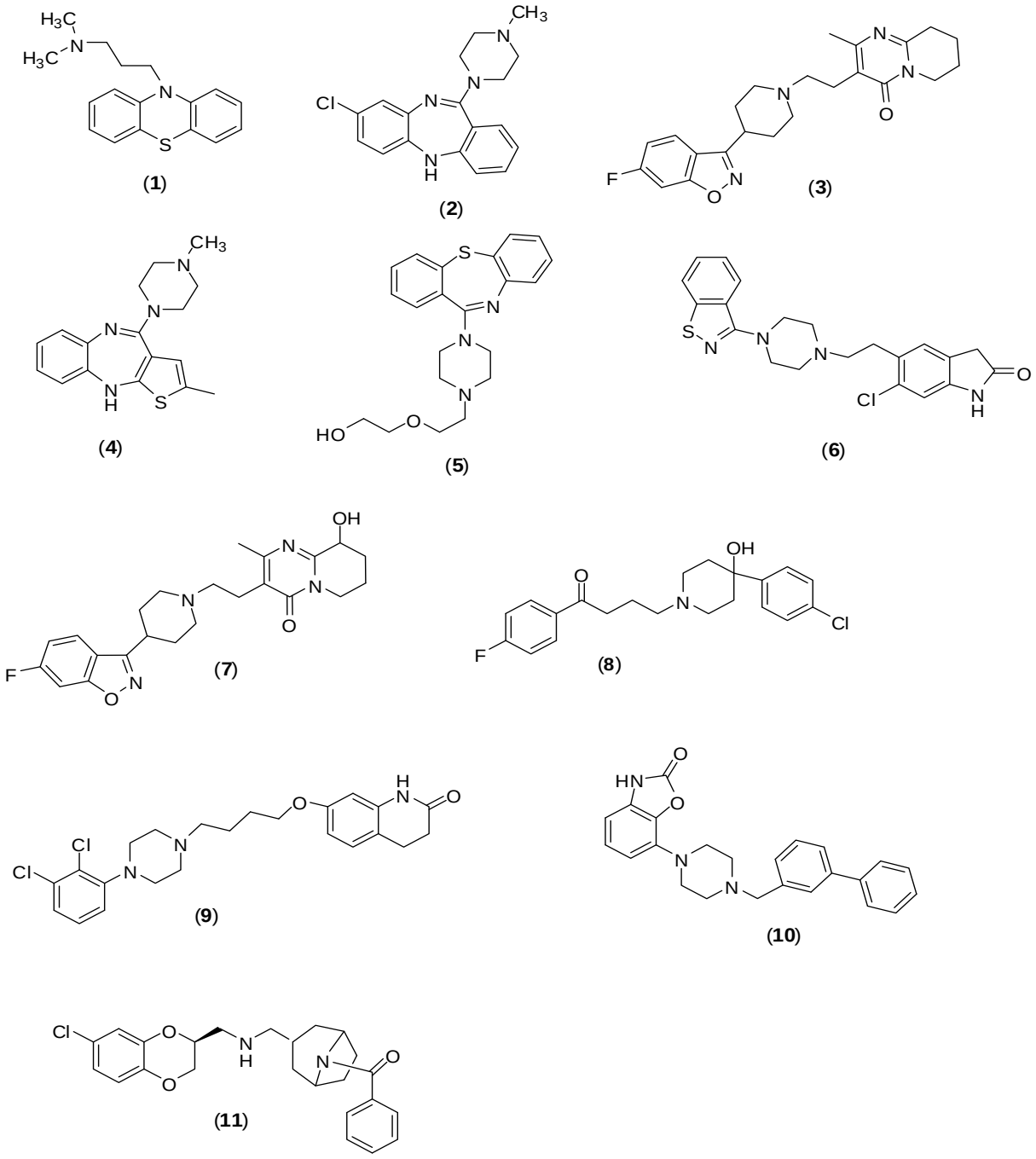


Figure 1: Typical and Newer Atypical Antipsychotics

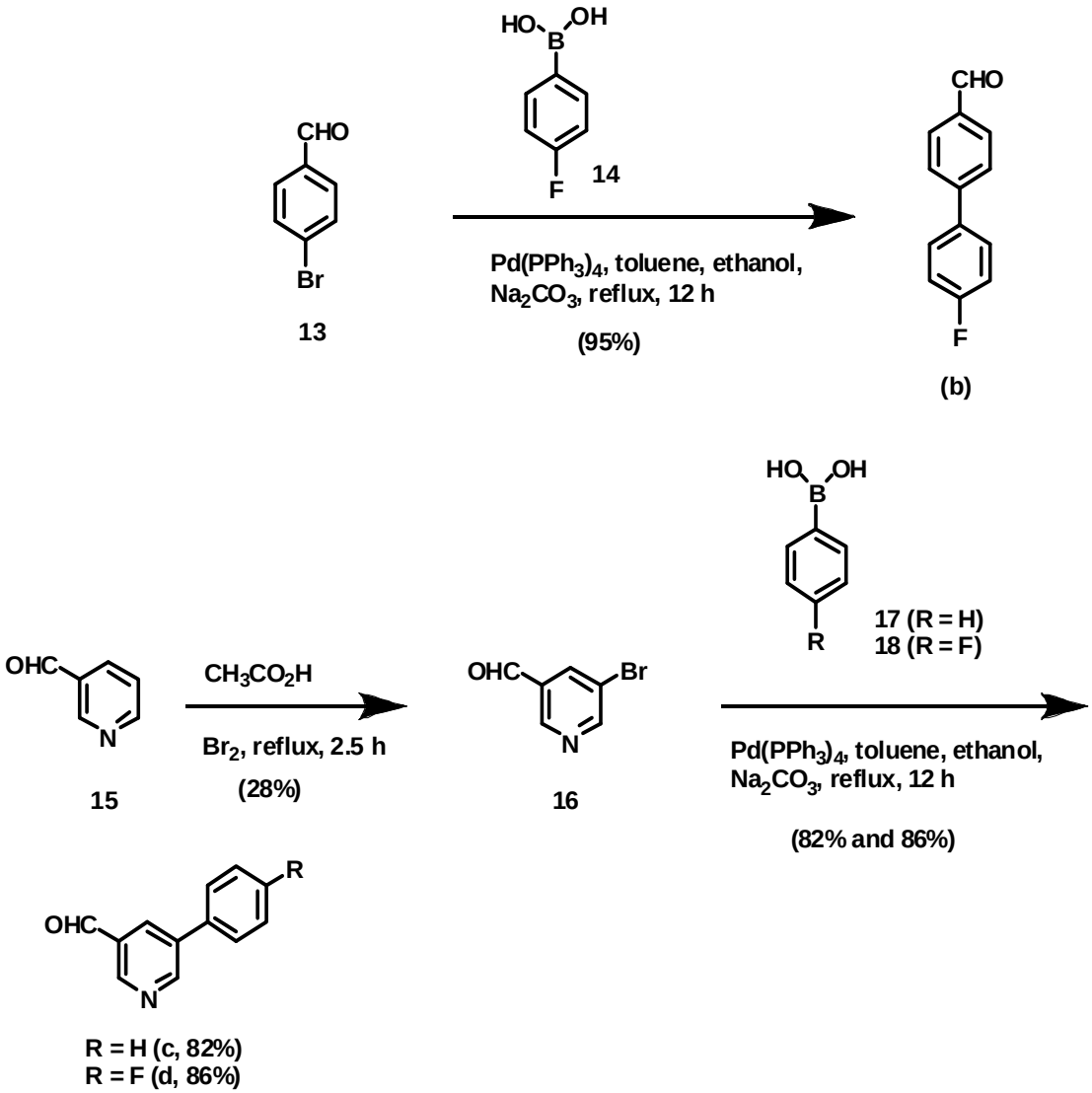
CHAPTER 2

RESULTS AND DISCUSSION

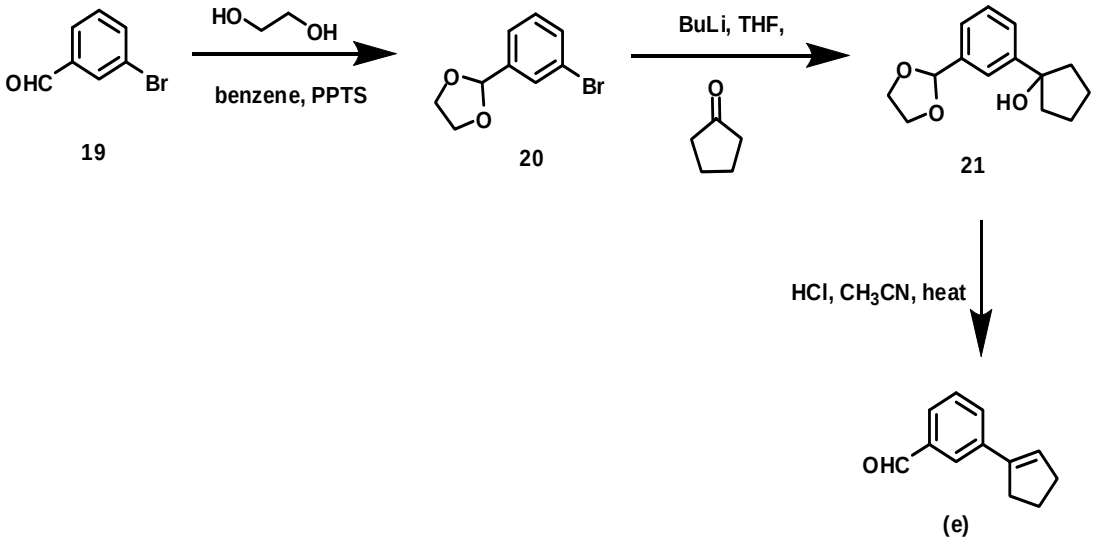
2.1. SYNTHESIS OF ALDEHYDES (B-F) AND BORONIC ESTER (30)

In order to accomplish the synthesis of the desired final compounds **(10a-10f, 11a-11f,12a-12f)**, access to aldehydes (a-f) and boronic ester **30** was imperative. Intermediate **(a)** was commercially available whereas (b) was synthesized by Suzuki reaction of aldehyde **13**with boronic acid **14** in a mixture of toluene and ethanol, using $Pd(PPh_3)_4$ as catalyst and sodium carbonate as base. To access intermediates **(c)** and **(d)**, aldehyde **15** was first converted to bromoaldehyde **16** by the action of bromine in acetic acid [51], followed by the Suzuki reaction of the latter with boronic acids **17** and **18**, under identical reaction conditions as described for intermediate (b), to produce intermediates **(c)** and **(d)**, respectively[51-54] (Scheme 1).The synthesis of the intermediate **(e)** was started with protection of aldehyde **19** to get acetal **20**. Bromine lithium exchange of **20** was ensued by treating it with n-butyllithium at lower temperature, followed by quenching the resultant lithiate with cyclopentanone afforded alcohol **21**. Acid exposure of the latter under heating furnished the desired intermediate **(e)**[55](Scheme **2**). Likewise the synthesis of the desired intermediate **(f)** was commenced from the Grignard reaction of ester **22**with alkylmagnesium bromide, originated from

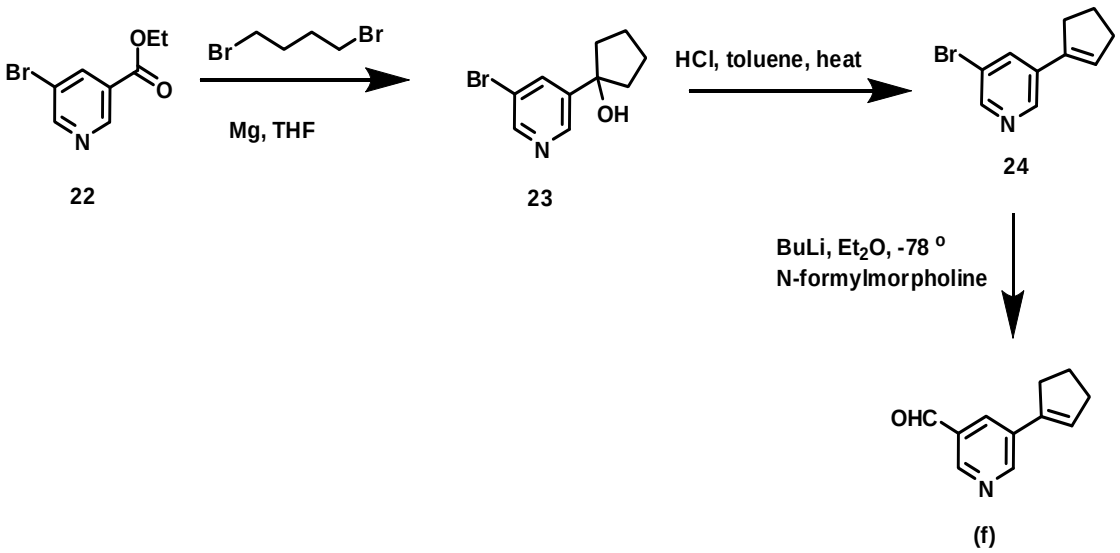
the reaction of 1, 4-dibrmoethane with magnesium in refluxing THF, to produce alcohol **23**. The dehydration of the latter with HCl in toluene produced intermediate **24** in a moderate yield. Bromine-lithium exchange of intermediate **24**by treating it with n-butyllithium at lower temperature, followed by quenching it with N-formylmorpholine yielded the desired **(f)** in a low yield (7%) [56] (Scheme **3**).



Scheme 1: Synthesis of intermediate (b-d)

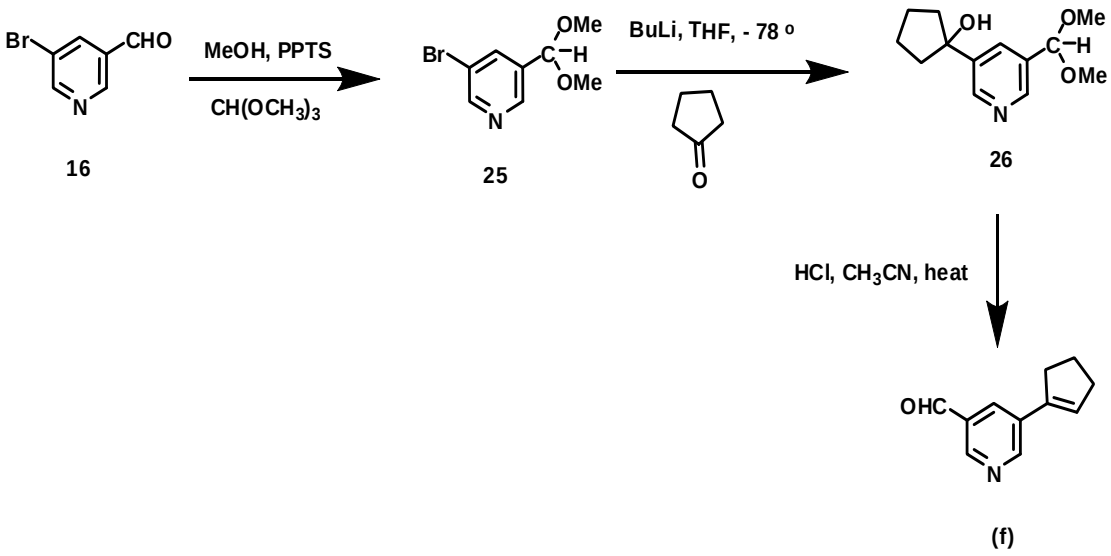


Scheme 2: Synthesis of intermediate (e)



Scheme 3: Synthesis of intermediate (f)

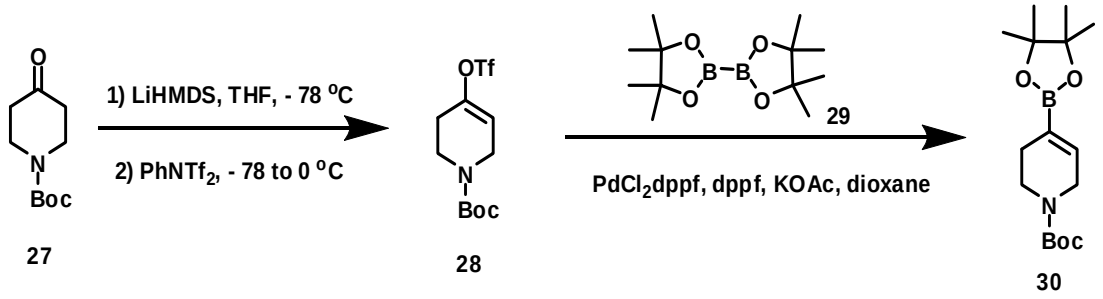
In order to improve the synthesis of **(f)**, a modified procedure was adopted as depicted in Scheme: **4**. Conversion of aldehyde **16** to its corresponding acetal **25** was accomplished with the aid of trimethylorthoformate and catalytic amount of PPTS. Bromine-lithium exchange of **25**, followed by trapping the resultant aryllithium with cyclopentanone gave alcohol **26**, which was subsequently exposed to acid in acetonitrile to generate the desired intermediate **(f)** (Scheme 4).



Scheme 4 : Synthesis of intermediate (f)

Having secured the synthesis of aldehydes **b-f**, we next moved on towards the synthesis of boronic ester [54] **30** as outlined in Scheme: 5. Reaction of lithium enolate, derived from reaction of boc-pyridone **27** with LiHMDS at lower temperature, with N-phenylbis(trifluoromethanesulfonimide) generated triflate **28**. Reaction of triflate **28** with bis(pinacolato)diboron under Suzuki reaction conditions produced the desired

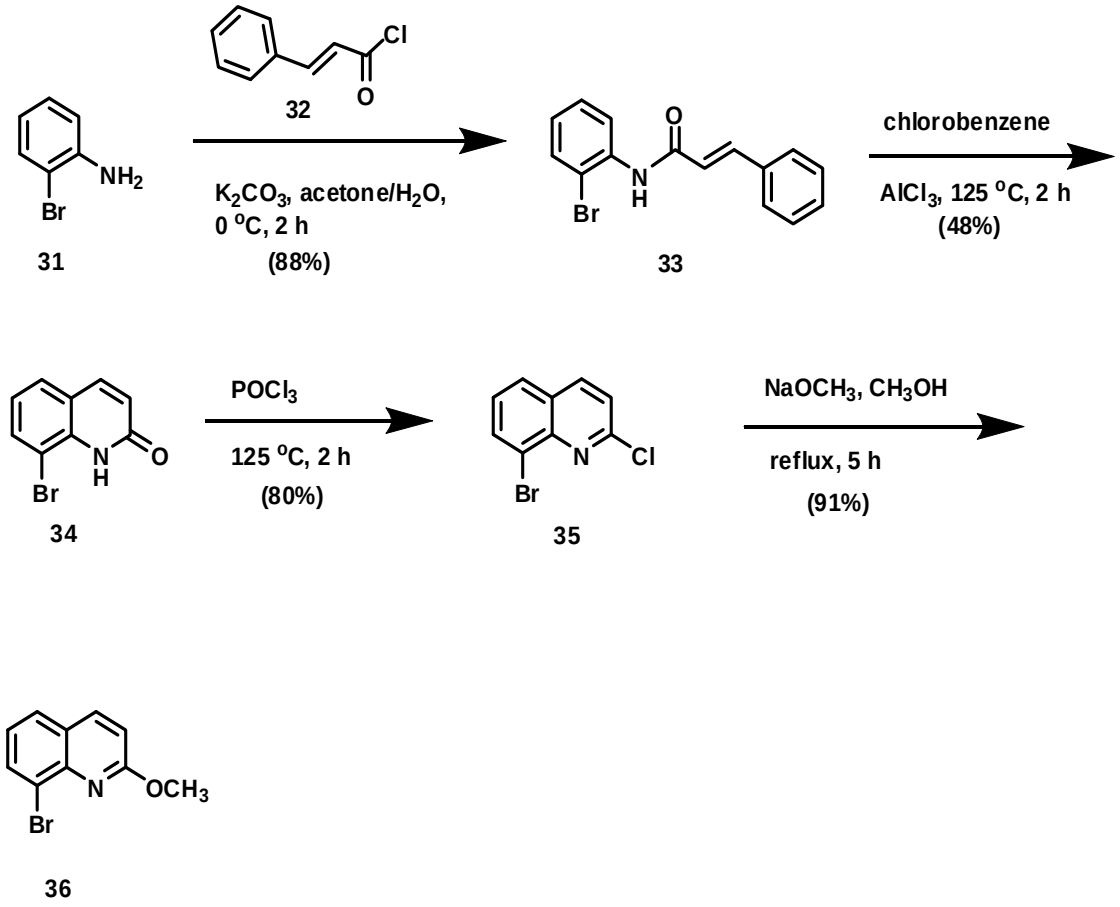
boronic ester **30**. The purifications of both **28** and **30** were proved to be quite tedious and required the use of basic alumina (Scheme **5**).



Scheme 5 : Synthesis of intermediate (30)

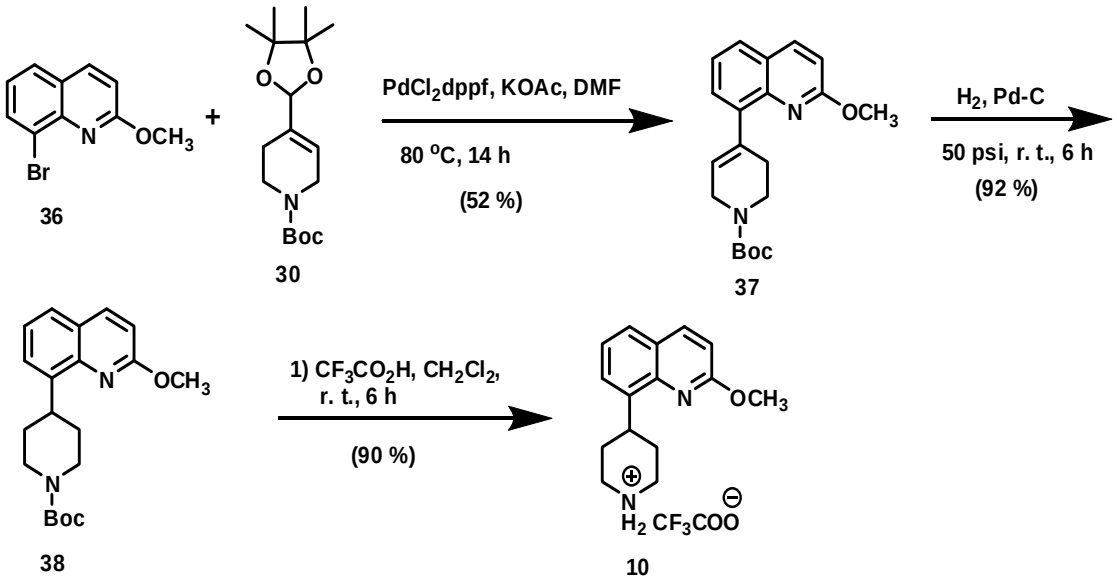
2.2. SYNTHESIS OF INTERMEDIATES (10-12)

Having accomplished the synthesis of the desired aldehydes **(b-f)** and boronic ester (**30**), we next focused on the synthesis of intermediates **10**-**12**. Access to intermediate **10** required the synthesis of intermediate **36**, which in turn was synthesized as outlined in Scheme: **7**. Acylation of bromoaniline **31** with cinnamoyl chloride **32** generated the amide **33**. Acid catalyzed cyclization of the latter in chlorobenzene at higher temperature rendered the intermediate **34**, which was exposed to phosphorous oxychloride to produce quinoline **35**.Condensation of the latter withsodium methoxide yielded the desired **36** (Scheme **6**).



Scheme 6 : Synthesis of intermediate (36)

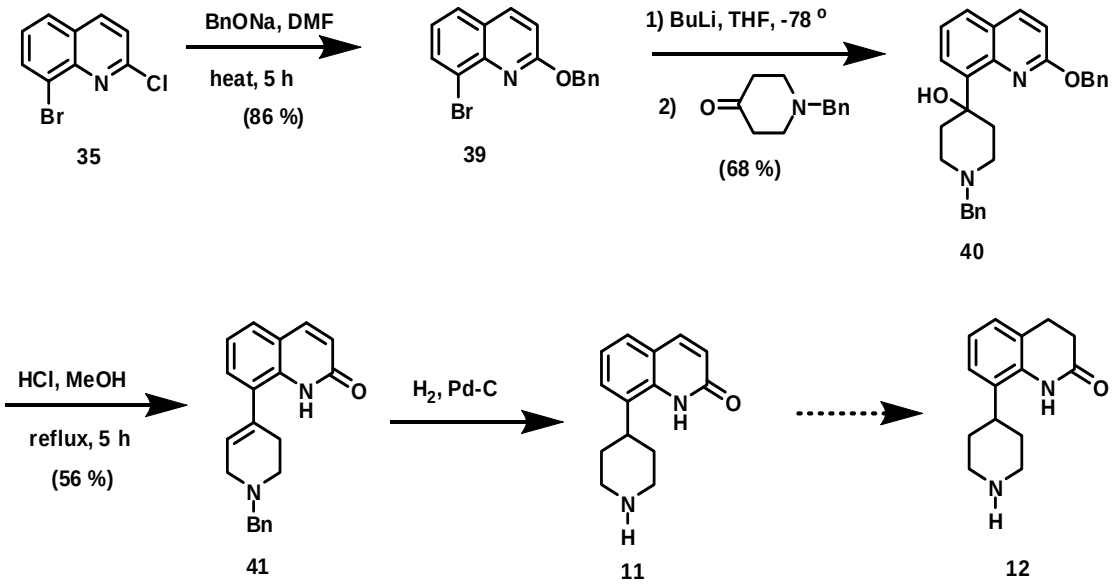
The synthesis of intermediate **36** eventually allowed us to march towards the synthesis of arylpiperidine **10**. Suzuki-Miyaura reaction of cyclic vinyl boronates **30** with bromoquinoline **36** [55].generated compound **37**, which in turn was hydrogenated at 50 psi for 6 h to furnish intermediate **38**. Exposure of the latter to trifluoroacetic acid at room temperature smoothly produced the desired intermediate **10** in an overall yield of 43% from **36** (Scheme **7**).



Scheme 7 : Synthesis of intermediate (10)

Owing to the difficulty in purifications of **28** and **30**, the synthesis of arylpiperidines **11** and **12** were initiated through a different synthetic approach. The quinoline **35** was condensed with sodium phenylmethanolate, generated by the action of benzyl alcohol and sodium hydride in DMF, to produce quinoline **39**.Lithiation of intermediate **39** in THF at -78 ^{o}C followed by quenching it with N-protected piperidinone gave alcohol **40** in 68% yield. The dehydration of latter was ensued by refluxing it in conc. HCl and MeOH to generate compound **41** in a moderate yield (56%). To produce the desired intermediate **11** from compound **41**, removal of N-protection and reduction of the double bond were required. Hence compound **41** was

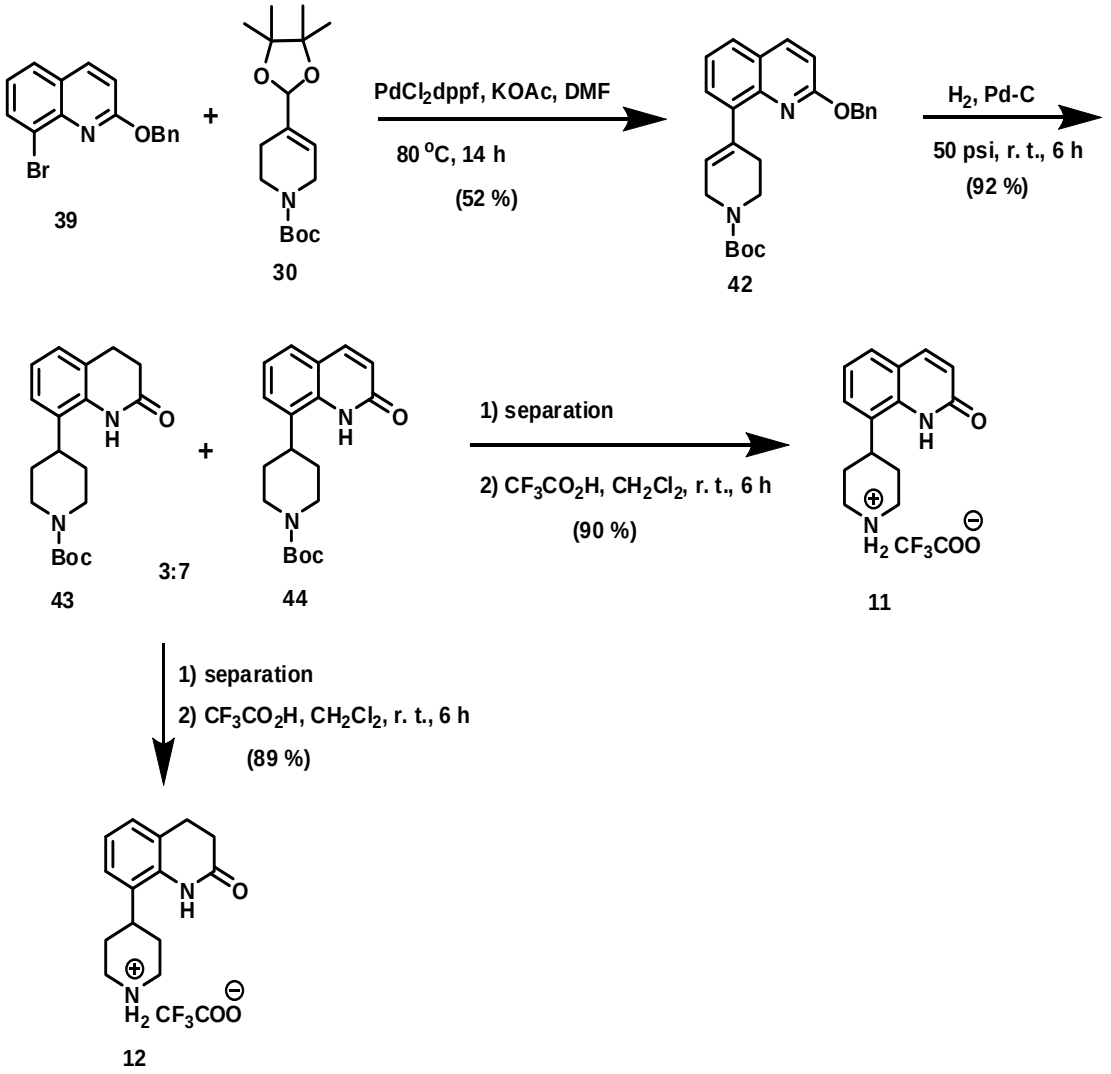
subjected to hydrogenation in a Parr apparatus at 60 psi for 5 hours. The benzyl deprotection, however, proved to be stubborn and the reaction yielded very polar mixture of products which were difficult to separate (Scheme **8**).



Scheme 8 : Synthesis of arylpiperidines (11) and (12)

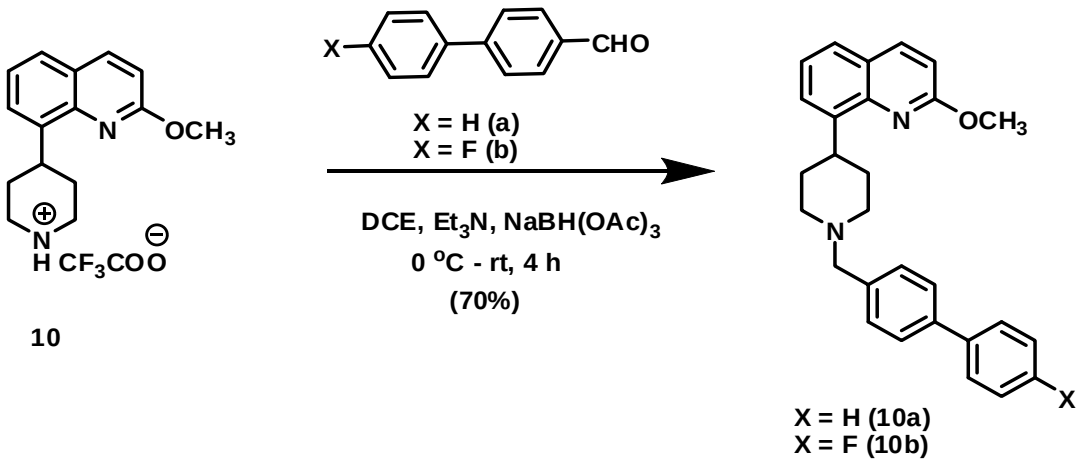
Thus the desired intermediates **11** and **12** were synthesized from an alternative route as outlined in Scheme 10. Suzuki-Miyaura reaction of cyclic vinyl boronates **30** [57].with bromoquinoline **39** generated compound **42**. Hydrogenation of intermediate **42** in a Parr apparatus at 50 psi for 6 hours followed by column chromatographic purifications on silica gel produced intermediates **43** and **44** in 3:7 ratio. Exposure of

compounds **43** and **44** to trifluoroacetic acid at room temperature smoothly furnished the desired intermediates **11** and **12** in high yields (Scheme **9**).

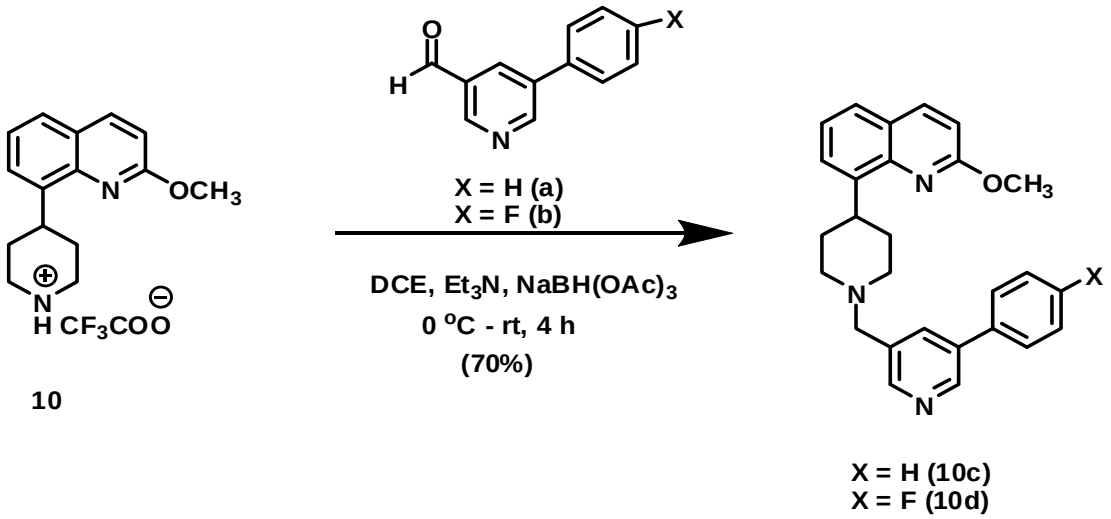


Scheme 9 : Synthesis of arylpiperidines 11 and 12 (an alternate route).

Having the desired arylpiperidines (**10-12**) and biarylaldehdyes **(b-f)** in hands, we next performed the reductive amination of arylpiperidines and aldehydes in 1,2-dichloroethane, using $NaBH(OAc)_3$as reducing agent to accomplish the final ligands**(10a-10f)(**Schemes: **10**, **11**and **12)**. In the similar fashion compounds **11a-11f** and **12a-12f**were synthesized from the reductive amination of the arylpiperidines **11** and **12** with the corresponding aldehydes **a-f**.



Scheme 10 : Synthesis of 1-aryl-4-(biarylmethylene) piperidines 10a&10b



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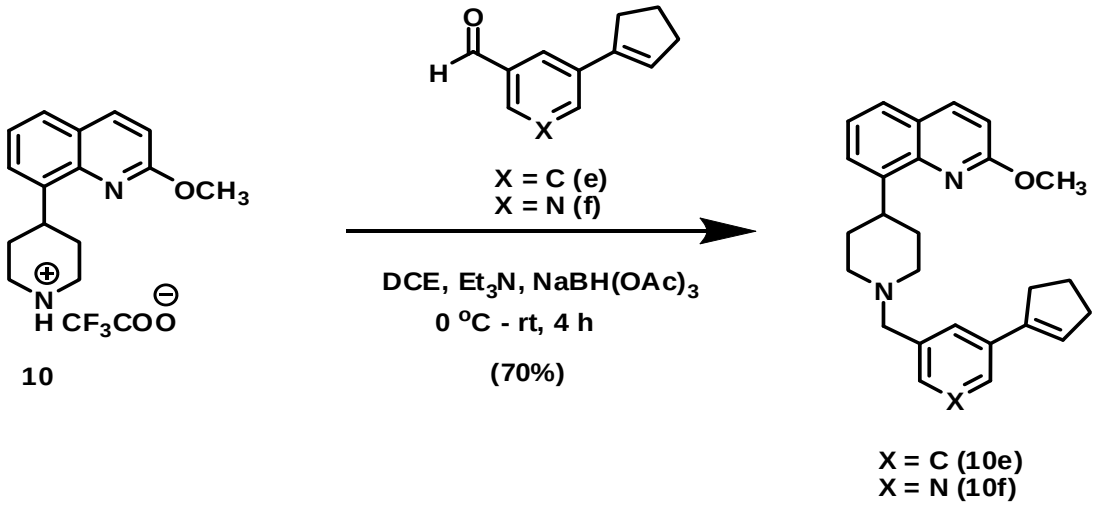
Scheme 11 : Synthesis of 1-aryl-4-(biarylmethylene) piperidines 10c& 10d



Scheme 12 : Synthesis of 1-aryl-4-(biarylmethylene) piperidines 10e& 10f

CHAPTER 3

EXPERIMENTAL WORK

3.1. INSTRUMENTATION AND CHEMICALS

^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL Lambda 500 and 400 MHz spectrometer. Chemical shifts were reported in ppm (δ) relative to tetramethyl silane (TMS) by using ($CDCl_3$), (DMSO) or methanol as deuterated solvents. Multiplicities were reported as singlet (s), doublet (d), triplet (t), quartet (q) or multiplet (m), and coupling constants (J) were reported in hertz (Hz). IR Spectra were recorded on a NicoletTM 6700 FT-IR spectrometer from a thermo-electron by using a smart orbit for net samples, and they were reported in wave numbers (cm^{-1}) (Spectral resolution, 4 cm^{-1}; Number of scans, 4). Mass was determined by using Agilent 7000A Triple Quadrupole GC/MS.

Elemental analysis was carried out on a EuroVector Elemental Analyzer Model EA3000. All mps are uncorrected. Thin layer chromatography (TLC) was frequently used to monitor reactions and to give qualitative determination of sample purity. TLC analyses were performed on silica gel Merck 60 F254 plates, and spots were visualized under a spectroline UV lamp operating at short and long wavelength ranges. Visualization was improved by dipping plates into a phosphomolybdic acid solution, and

then by drying in a blast of hot air. Purification of the products was carried out either by recrystallization or by flash column chromatography. The column was packed with silica gel 100 from Fluka Chemie AG (Buchs, Switzerland). Ethyl acetate, petroleum ether (boiling fraction 60-80) and hexane were used as eluting solvents, in volume-by-volume ratios as stated.

Chemicals were purchased from commercial sources, and they were used without any further purification unless otherwise specified. All solvents were of reagent grade, and dichloromethane was passed through alumina before use. Specially dried 53 (anhydrous) solvents were used where necessary. Glassware for moisture-sensitive reactions were oven dried at 120-140 °C for at least three hours and cooled in a desiccators prior to use. Some of the reactions were run in an inert atmosphere of nitrogen as stated.

3.2. SYNTHESIS OF NEW 4-ARYL-1-(BIARYLMETHYLENE) PIPERIDINES

3.2.1. Synthesis of compound 4'-fluorobiphenyl-4-carbaldehyde (b)

4-bromobenzaldehyde (2.76 g, 14.92 mmol) was dissolved in toluene (100 mL), an aqueous 2.0 M Na_2CO_3 solution (47 mL) and an ethanolic solution (47 mL) of the corresponding boronic acid (2.5 g, 17.86 mmol) were added. The mixture was deoxygenated under reduced pressure and flushed with nitrogen. After repeating this cycle several times $Pd(PPh_3)_4$ (4 mol%) was added and the resulting suspension was heated under reflux for 8 h. After cooling ethyl acetate (20 mL) and water (20 mL) were added and the organic phase was separated. The water phase was extracted with ethyl acetate (2 x 20 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered over a short plug of celite and evaporated under reduced pressure. The compounds were purified by flash chromatography on silica gel, eluting with CH_2Cl_2:hexanes (8:2) to obtained the title compound as a light yellow solid (2.88 g, 95%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.18-7.14 (m, 2H), 7.61-7.58 (m, 2H), 7.71-7.69 (m, 2H), 7.95-7.93 (m, 2H), 10.05 (s, 1H, CHO). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 116.08, 116.25, 127.74, 129.25, 129.31, 130.54, 135.44, 146.42, 162.53, 164.52, 192.36.

3.2.2. Synthesis of compound 5-bromonicotinaldehyde (16)

A 1-l three-neck flask was charged with glacial acetic acid (300 ml) and 3-pyridinecarboxaldehyde (30 g, 0.278 mmol). To this solution, bromine (90 g, 0.5 mmol) was added dropwise over 30 min at room temperature. The reaction mixture was heated under reflux for 2 h while fumes of HBr were exhausted. The mixture was cooled, poured into 600 ml of H_2O, and extracted 3 times with 200 ml each of CH_2Cl_2. The combined organic layers were washed with brine, and then with 2N NaOH, before being dried over $MgSO_4$. Removal of the solvent produced a dark brown product which was purified by column chromatography on a silica gel column, eluted first with CH2Cl2, then with CH_2Cl_2:EtOAc (9:1) to give 5-bromo-3-pyridinecarboxaldehyde (14.8 g, 28%) as light yellow crystals, mp 95–96 ^oC. ^1H NMR ($CDCl_3$, 500 MHz) δ: 8.29–8.33 (m, 1H), 8.92 (d, 1H, J = 2.6 Hz), 8.99 (d, 1H, J = 1.94 Hz), 10.10 (s, 1H).

3.2.3. Synthesis of compound (c) and (d)

According to the procedures of compound **(b)**, the suzuki coupling of **16** with phenyl boronic acid and 4-fluorophenyl boronic acid produced the desired (c**)** (82%) and **(d)** (86%).

Compound5-phenylnicotinaldehyde (c):

Light yellow thick oil, 82% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.30 (m, 1H), 7.47-7.43 (m, 2H), 7.60 (d, 2H, J = 8.0 Hz), 9.05 (d, 2H, J = 2.6 Hz), 10.18 (s, 1H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 127.28, 128.98, 129.44, 131.48, 133.78, 136.38, 137.38, 150.86, 153.41, 191.23.

Compound5-(4-fluorophenyl) nicotinaldehyde (d):

Light yellow solid, 86% yield.^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.18-7.23 (m, 2H), 7.55-7.62 (m, 2H), 8.31 (s, 1H), 9.05 (s, 2H), 10.20 (s, 1H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 115.90, 129.24, 131.48, 136.65, 137.38, 151.01, 153.32, 191.19.

3.2.4. Synthesis of compound 2-(3-bromophenyl)-1, 3-dioxolane (20)

3-bromobenzaldehyde (**19**, 27.9 g, 151 mmol) and ethylene glycol (13.8 g, 222 mmol) were dissolved in 120 mL of benzene. After the addition of 45 mg of 4-toluenesulfonic acid, the mixture was refluxed in a Dean-Stark apparatus until no more water was produced. The reaction mixture was washed with $NaHCO_3$ solution, and the organic layer was then separated and dried over anhydrous Na_2SO_4. After the evaporation of benzene and distillation under vacuum, 2-(3-bromophenyl)-1,3-dioxolane was obtained as a colorless liquid. Yield: 25 g, 72%. ^{1}H NMR (400 MHz, $CDCl_3$)

δ: 7.64 (t, 1H, 2-H), 7.49 (m, 1H, 6-H), 7.40 (m, 1H, 4-H), 7.26 (t, 1H, 5-H), 5.77 (s, 1H, C*H*(OCH_2)$_2$), 4.14-3.99 (m, 4H, CH(OC*H*$_2$)$_2$.

3.2.5. Synthesis of compound 1-(3-(1, 3-dioxolan-2-yl) phenyl) cyclopentanol (21)

n-Butyllithium (2.5M in THF, 10 mL, 25 mmol) is slowly added to a flask containing THF (60 mL) at -78 ^{o}C, followed by the dropwise addition of compound **20** (5.20 g, 22.72 mmol) in dry THF (20 mL). After being stirred the mixture for 0.5 h at -78 ^{o}C, a solution of cyclopentanone (3 mL, 34 mmol) was added dropwise. The temperature of the reaction was allowed to come back up to ambient temperature over two hours. The solution is treated with H_2O (15 mL), diluted with EtOAc (100 mL) and washed with water and finally with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography over silica eluting with EtOAc:hexanes (4:6) and then changing to (7:3) afforded the product as light yellow thick oil (3.38 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.61 (s, 1H), 1.86 (m, 2H), 1.99 (m, 6H), 4.04 (m, 2H), 4.13 (m, 2H), 5.81 (s, 1H), 7.36 (m, 2H), 7.49 (m, 1H), 7.61 (m, 1H).

3.2.6. Synthesis of compound 3-cyclopentenylbenzaldehyde (e) from (21)

To a solution of compound **21** (3 g, 12.82 mmol) in acetonitrile (50 mL) at 0 ^{o}C was added 6M HCl (15 mL) and the reaction mixture was heated to 80 ^{o}C for 12 hours. The mixture was cooled to room temperature, neutralized with saturated Na_2CO_3 and concentrated under reduced pressure to evaporate acetonitrile. The residue were taken in EtOAc (100 mL) and washed with water, brine, dried over Na_2SO_4 and evaporated. Column chromatography over silica eluting with EtOAc:hexanes (3:7) afforded the product as a light yellow thick oil (1.24 g, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.06 (m, 2H), 2.57 (m, 2H), 2.72 (m, 2H), 6.30 (s, 1H), 7.49 (t, 1H), 7.71 (m, 2H), 7.61 (m, 1H), 7.91 (s, 1H0, 10.02 (s, 1H).

3.2.7. Synthesis of compound 1-(5-bromopyridin-3-yl) cyclopentanol (23)

To a suspension of 2.25 g of magnesium (92.6 mmol) in THF (25 mL) was added a crystal of iodine and a few drops of 1,4-dibromobutane. The mixture was heated at 65 °C until it turned colorless, then a solution of 1,4-dibromobutane (10 g, 46.3 mmol) in THF (50 mL) was added dropwise while maintaining the reaction at 65 °C. The reaction mixture was then stirred at this temperature for 4 hours and cooled to 0 °C. A solution of ethyl 5-bromo-3-pyridinecarboxylate (**22**, 10 g, 46.3 mmol) in 60 mL of THF was added

dropwise. The mixture was slowly brought to room and stirred for 16 hours. The reaction was poured in a cold, saturated aqueous solution of ammonium chloride and extracted with ethyl acetate. The combined organic layer was washed with water, brine dried over sodium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, cyclohexane-ethyl acetate, 70:30) to give 2.70 g (24%) of the product as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.74-1.77 (m, 2H), 1.85-1.88 (m, 6H), 2.70-2.73 (m, 2H), 3.93 (s, 1H), 7.15 (d, J = 5.0 Hz, 1H), 8.38 (d, J = 5.0 Hz, 1H), 8.64 (s, 1H).

3.2.8. Synthesis of compound 3-bromo-5-cyclopentenylpyridine (24)

A solution of 1-(5-bromo-pyridin-3-yl)-cyclopentanol **23**(1.70 g, 11.3 mmol) in 50 mL of toluene and containing 5 mL of concentrated HCl was heated at 120 °C for 12 hours with continuous removal of the water formed. The reaction mixture was cooled to room temperature and poured into a saturated aqueous solution of sodium bicarbonate, extracted with ethyl acetate and the combined organic layer washed with water and brine. The organic solution was dried over sodium sulfate, filtered and the solvent removed in vacuo. The residue was purified by flash column chromatography (silica gel, cyclohexane-ethyl acetate, 60:40) to give V (1.52 g, 60%) as an off-white solid. mp = 43 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.03-2.06 (m, 2H), 2.55-2.58 (m, 2H), 2.70-2.73 (m, 2H), 6.31 (s, 1H), 7.80-7.82 (m, 1H), 8.49 (d, J = 2.0 Hz, 1H), 8.59 (d, J = 2.0 Hz, 1H).

3.2.9. Synthesis of compound 5-cyclopentenylnicotinaldehyde (f) from (24)

A solution of 3-bromo-5-cyclopenten-1-yl-pyridine **24**(1 g, 4.46 mmol) in 25 mL of diethyl ether was added to a solution of n-butyl lithium (1.6 M in hexane, 4.20 mL, 6.68 mmol) in 25 mL of diethyl ether at -60 °C. The reaction mixture was stirred for 2 h at -60 °C, and then 4-morpholinecarboxaldehyde (1.40 mL, 13.38 mmol) was added. The reaction mixture was stirred for 1 h at -60 °C and then quenched with water, washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, cyclohexane/ethyl acetate, 80:20) to afford **(f)** (0.35 g, 45%) as an off-white solid, mp = 50 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.09-2.11 (m, 2H), 2.60-2.62 (m, 2H), 2.70-2.73 (m, 2H), 6.49 (s, 1H), 8.32 (s, 1H), 8.89 (s, 1H), 8.93 (s, 1H), 10.10 (s, 1H).

3.2.10. Synthesis of compound 3-bromo-5-(dimethoxymethyl) pyridine (25)

p-Toluenesulfonic acid (2.7 g, 143 mmol) and trimethyl orthoformate (1.6 mL, 143 mmol) were added to a stirred solution of compound **16** (2.42 g, 13 mmol) in MeOH (50 mL). The mixture was heated at reflux for 18 hours and then cooled to room temperature. Aqueous Na_2CO_3 was added to attain pH 8 and the mixture was concentrated by evaporation. H_2O was added and the mixture extracted with EtOAc. The

extract was washed with brine, dried over Na_2SO_4 and evaporated. Column chromatography over silica eluting with EtOAc:hexanes (3:7) afforded the product as a yellow oil (2.1 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.34 (s, 6H), 5.44 (s, 1H), 7.94 (d, 1H), 8.59 (d, 1H), 8.64 (d, 1H).

3.2.11. Synthesis of compound 1-(5-(dimethoxymethyl) pyridin-3 yl) cyclopentanol (26)

n-Butyllithium (2.5M in THF, 5 mL, 12.5 mmol) is slowly added to a flask containing THF (30 mL) at -78 ^{o}C, followed by the dropwise addition of compound **25** (2.57 g, 11.4 mmol) in dry THF (10 mL). After being stirred the mixture for 0.5 h at -78 ^{o}C, a solution of cyclopentanone (1.5 mL, 17.1 mmol) was added dropwise. The temperature of the reaction was allowed to come back up to ambient temperature over two hours. The solution is treated with H_2O (10 mL), diluted with EtOAc (50 mL) and washed with water and finally with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography over silica eluting with EtOAc:hexanes (4:6) and then changing to (7:3) afforded the product as light yellow thick oil (1.68 g, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.86 (m, 2H), 2.02 (m, 6H), 3.32 (s, 6H), 5.42 (s, 1H), 7.88 (s, 1H), 8.48 (s, 1H), 8.646 (s, 1H).

3.2.12. Synthesis of compound 5-cyclopentenylnicotinaldehyde (f) from (26)

To a solution of compound **26** (1.5 g, 5.33 mmol) in acetonitrile (15 mL) at 0 ^{o}C was added 6M HCl (5 mL) and the reaction mixture was heated to 80 ^{o}C for 12 hours. The mixture was cooled to room temperature, neutralized with saturated Na_2CO_3 and concentrated under reduced pressure to evaporate acetonitrile. The residue were taken in EtOAc (50 mL) and washed with water, brine, dried over Na_2SO_4 and evaporated. Column chromatography over silica eluting with EtOAc:hexanes (4:6) afforded the product as off white solid (0.60 g, 65%).

3.2.13. Synthesis of compoundtert-butyl 4(trifluoromethylsulfonyloxy)-5, 6-dihydropyridine-1(2H)-carboxylate (28)

To a stirred solution of **27** (10 g, 50.2 mmol) in dry THF (200 mL) at -78 ^{o}C was added 1M solution of lithium bis(trimethylsilyl) amide in THF (60.2 mL, 60.2 mmol) over 10 min under N_2. The reaction mixture was stirred for 1 h and N-phenyltrifluoromethanesulfonimide (21.73 g, 60.2 mmol) was added in one portion. The reaction mixture was allowed to warm to 0 ^{o}C and stirred for 4 h. The solvent was removed in vacuo and the residue was dissolved in EtOAc (200 mL), and washed successively with 2M NaOH, H_2O and brine. Drying over $Na_2SO_4$and evaporation under vaccuo yielded a brown oily material. The later was chromatographed on basic alumina,

eluting with EtOAc:hexanes (1:9), to obtain compound **28** as light yellow oil (13.64 g, 82%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: ^{1}H NMR (400 MHz, $CDCl_3$) 1.47 (s, 9H), 2.44 (s, 2H), 3.63 (m, 2H), 4.04 (m, 2H), 5.72 (br. s, 1H).

3.2.14. Synthesis of compound tert-butyl 4-(4, 4, 5, 5-tetramethyl 1, 3, 2-dioxaborolan-2-yl)-5, 6-dihydropyridine-1(2H)carboxylate (30)

To a flask were added bis(pinacolato)diboron (2.92 g, 11.5 mmol), KOAc (3.1 g, 31.4 mmol), $PdCl_2$dppf (0.22 g, 0.31 mmol), dppf (0.17 g, 0.31 mmol) and the contents flushed with nitrogen. A solution of the triflate (3.44 g, 10.4 mmol) in 1,4-dioxane (60 mL) was added and the mixture was stirred at 80°C overnight. After work-up, flash chromatography (SiO_2, Pentane/EtOAc) gave the boronate **30** as white solids (2.32 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) 1.25 (s, 12H), 1.45 (s, 9H), 2.20 (m, 2H), 3.43 (m, 2H), 3.95 (m, 2H), 6.45 (br. s, 1H).

3.2.15. Synthesis of compound N-(2-bromophenyl) cinnamamide (33)

A mixture of cinnamoyl chloride (84 g, 0.50 mol), 2-bromoaniline (86 g, 0.50 mol), and potassium carbonate (0.10 kg, 0.75 mol) in water (0.25 L) and acetone (0.20 L) was kept for 2 h at 0 °C before being poured into ice-water (0.50 L). The precipitate formed was collected and crystallized from hexanes to afford compound **33**; colorless prisms; m.p. 151-152 °C; yield: 133 g (88%). The spectral data coincided to the literature reported values[56]^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.60 (d, *J* = 15.9 Hz, 1 H),

6.99 (t, *J* = 7.9 Hz, 1 H), 7.34 (t, *J* = 7.9 Hz, 1 H), 7.59-7.38 (m, 6 H), 7.77 (d, *J* = 15.9 Hz, 1 H), 7.81 (s, 1 H), 8.51 (d, *J* = 8.2 Hz, 1 H).

3.2.16. Synthesis of compound 8-bromoquinolin-2(1H)-one (34)

A solution of 2-bromocinnamanilide (0.12 kg, 0.40mol) and aluminium chloride (0.32 kg, 2.4 mol) in chlorobenzene (0.40 L) was heated to 125 °C for 2 h. At 50 °C, it was then poured onto ice, and the resulting precipitate was filtered and crystallized from ethanol; colorless needles; m.p. 197-198 °C; yield: 43.0 g (48%). The spectral data coincided to the literature reported values [56]. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.68 (d, *J* = 9.4 Hz, 1 H), 7.80 (t, *J* = 7.8 Hz, 1 H), 7.53 (dd, *J* = 7.8, 1.1 Hz, 1 H), 7.71 (d, *J* = 9.4 Hz, 1 H), 8.11 (s, 1 H).

3.2.17. Synthesis of compound (35)

Phosphorus oxychloride (37 mL, 61 g, 0.40 mol) and **34** (45 g, 0.20 mol) were heated to 125 °C for 2 h before being poured onto ice. The resulting precipitate was filtered and crystallized from methanol; colorless prisms; m.p. 114-115 °C; yield: 39.33 g (81%). The spectral data coincided to the literature reported values [56]. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.49-7.39 (m, 2 H), 7.78 (d, *J* = 7.8 Hz, 1 H), 8.05 (d, *J* = 7.8 Hz, 1 H), 8.10 (d, *J* = 8.3 Hz, 1 H).

3.2.18. Synthesis of compound 8-bromo-2-methoxyquinoline (36)

To a solution of **35** (4.85 g, 20 mmol) in methanol (90 mL) was added NaOMe (2.4 g, 100 mmol) and refluxed for 5 h. The solvent was evaporated under reduced pressure, and ethyl acetate (150 mL) was added and washed with H_2O and brine, dried over Na_2SO_4 and evaporated to obtain compound **36** as a light violet solid (4.33 g, 91%).^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.14 (m, 3 H), 6.94 (d, *J* = 8.8 Hz, 1 H), 7.22 (m, 1 H), 7.68 (d, *J* = 8.8 Hz, 1 H), 7.95 (m, 2 H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 53.35, 113.75, 122.51, 124.38, 126.17, 127.10, 133.11, 139.20, 143.83, 163.08.

3.2.19. Synthesis of compound tert-Butyl 4-(2-methoxyquinolin-8-yl)-5, 6-dihydropyridine-1(2H)-carboxylate (37)

Following the same procedure adopted for the synthesis of **42**, the title compound was obtained from Suzuki reaction of boronate **30** and bromoquinoline **36** as dark brown gum, (0.64 g, yield 42 %). M.p. 132-133 ^{o}C. – IR (neat): ν = 3037, 2978, 1677, 1604, 1486, 1176 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.49 (s, 9H, OC*(CH$_3$)$_3$*), 2.85 (br. s, 2 H, piperidine H), 3.70 (m, 2 H, piperidine H), 4.02 (s, 3 H, OCH_3), 4.13 (br. s, 2 H, piperidine H), 5.86 (br. s, 1 H, piperidine H), 6.90 (d, *J* = 8.5 Hz, 1 H, 3-H), 7.32 (t, *J* = 7.6 Hz, 1 H, aromatic H), 7.48 (dd, *J* = 1.5, 7.3 Hz, 1 H, aromatic H), 7.63 (dd, *J* = 1.2, 7.8 Hz, 1 H, aromatic H), 7.97 (d, *J* = 8.8 Hz, 1 H, aromatic H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 24.54 (C_{piper}), 28.51 (OC*(CH$_3$)$_3$*), 29.84, 42.32 (all C_{piper}), 53.37

(OCH_3), 79.52 ($OC(CH_3)_3$), 112.71, 123.80, 125.13, 126.99, 128.81, 139.06, 139.74, 144.03, 161.37 (all C_{arom}). – $C_{20}H_{24}N_2O_3$ (340.42): calcd. C 70.56, H 7.11, N 8.23, found C 70.50, H 7.16, N 8.17.

3.2.20. Synthesis of tert-Butyl 4-(2-methoxyquinolin-8-yl) piperidine-1-carboxylate (38)

To a solution of compound **37** (0.6 g, 1.76 mmol) in a mixture of THF (5 mL) and EtOH (10 mL) was added Pd-C (10% wet basis, 0.4 g) and the mixture was subjected to hydrogenation in Parr apparatus at 60 psi for 7 hours. After filtering over the pad of celite, the solution was concentrated and chromatographed on silica column, eluting with ethyl acetate:hexanes (20:80) to get the title compound as off-white solid (0.57 g, yield 94 %). M.p. 72-73 ^oC. – IR (neat): ν = 3031, 2935, 1675, 1608, 1484 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.42 (s, 9 H, $OC(CH_3)_3$), 1.71 (m, 2 H, piperidine H), 1.95 (m, 2 H, piperidine H), 2.88 (m, 2 H, piperidine H), 3.82 (m, 1 H, piperidine H), 3.99 (s, 3 H, OCH_3), 4.22 (br. s, 2 H, piperidine H), 6.84 (d, J = 8.5 Hz, 1 H, 3-H), 7.28 (m, 1 H, aromatic H), 7.38 (m, 1 H, aromatic H), 7.51 (m, 1 H, aromatic H), 7.97 (d, J = 8.8 Hz, 1 H, aromatic H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 28.48 ($OC(CH_3)_3$), 32.15, 36.84, 42.84 (all C_{piper}), 53.23 (OCH_3), 79.30 ($OC(CH_3)_3$), 112.38, 123.89, 124.96, 125.64, 126.04, 139.40, 143.93 (all C_{arom}), 155.21 (C=O), 161.67 (C_{arom}). – $C_{20}H_{26}N_2O_3$ (342.43): calcd. C 70.15, H 7.65, N 8.18; found C 70.10, H 7.70, N, 8.11.

3.2.21. Synthesis of ynt2-Methoxy-8-(piperidin-4-yl) quinoline (10)

The title compound **10** was obtained from compound **37** as an off-white solid (0.46 g, yield 92 %). M.p. 142-144 ^{o}C. – IR (neat): ν = 3031, 2982, 1612, 1441, 1213 cm^{-1}. – ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.99 (m, 2 H, piperidine H), 2.14 (m, 2 H, piperidine H), 3.16 (m, 2 H, piperidine H), 3.45 (m, 2 H, piperidine H), 4.01 (s, 3 H, OCH_3), 7.01 (d, J = 8.2 Hz, 1 H, 3-H), 7.41 (m, 1 H, aromatic H), 7.51 (m, 1 H, aromatic H), 7.92 (d, J = 8.3 Hz, 1 H, aromatic H). ^{13}C NMR (125.7 MHz, [D$_6$]DMSO): δ = 28.72, 31.00, 34.40, 36.02, 44.33 (all C_{piper}), 53.28 (OCH_3), 112.76, 114.52, 116.83, 124.23, 126.19, 126.48, 140.10, 158.76, 161.23 (all C_{arom}). – $C_{17}H_{19}F_3N_2O_3$ (356.34): calcd. C 57.30, H 5.37, N 7.86; found C 57.24, H 5.42, N 7.80.

3.2.22. Synthesis of 2-(benzyloxy)-8-bromoquinoline (39)

To a solution of benzyl alcohol (3.57 g, 33.0 mmol) in DMF (30 mL) at 0 ^{o}C was added NaH (0.95 g, 39.6 mmol) and after being stirred for 10 minutes at room temperature, compound **22** (4 g, 16.53 mmol) was added and the mixture was stirred at 60 ^{o}C for 5 h. The reaction was diluted with ethyl acetate (100 mL) and washed with H2O (20 mL), brine (3 x 20 mL), dried over Na_2SO_4 and evaporated. Column chromatography on silica column eluting with hexanes:ethyl acetate (1:1) yielded compound **39** as a white crystalline solid (4.67 g, 90%).^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.63 (s, 2H), 6.96 (d, 1H), 7.24 (m, 1H), 7.32 (m, 1H), 7.37-7.40 (m, 2H), 7.62 (m, 2H),

7.67 (dd, 2H), 7.93-7.97 (m, 2H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 68.0, 114.05, 122.56, 124.47, 126.29, 127.10, 128.01, 128.41, 128.89, 133.10, 137.10, 139.29, 143.63, 162.25.

3.2.23. Synthesis of compound 1-Benzyl-4-(2-(benzyloxy) quinolin-8-yl) piperidin-4-ol (40)

A solution of 2-(benzyloxy)-8-bromoquinoline **39**(2.0 g, 6.4 mmol) in THF (20 mL) was added dropwise over 10 min to a solution of n-BuLi (2.5 M, 2.8 mL, 7 mmol) in hexane cooled to -78 °C. The mixture was stirred for 1 h at -78 °C, and a solution of 1-benzylpiperidone **39** (1.21 g, 6.4 mmol) in THF (10 mL) was added dropwise over a period of 10 min, maintaining the reaction temperature at -78 °C. The resulting mixture was stirred at -78 °C for 0.5 h and at -10 °C for 1.5 h whereupon a saturated solution of ammonium chloride (4 mL) was added. The reaction mixture was stirred and warmed to room temperature. Water (50 mL) was added to the reaction mixture and extracted with dichloromethane (3 x 30 mL). The combined organic extracts were washed with water, dried with Na_2SO_4, and filtered. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (1M NH_3 in MeOH/dichloromethane, 2:98 to 7:93) to afford the title compound **40** as dark brown thick oil (1.84 g 68 %). – IR (neat): ν = 3365, 3042, 3032, 2971, 1607, 1485, 1260, 1192 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.15 (br. s, 4 H, piperidine H), 2.73-2.78 (m, 5

H, piperidine H, OH), 3.62 (s, 2 H, NCH_2), 5.43 (s, 2 H, O*C*H_2), 6.99 (d, J = 9.0 Hz, 1 H, 3-H), 7.23-7.47 (m, 11 H, aromatic H), 7.60 (m, 2 H, aromatic H), 8.04 (d, J = 8.5 Hz, 1 H, 4-H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 37.26, 49.46 (all C_{piper}), 53.02 (O*C*H_2), 63.52 (NCH_2), 68.48 (C_{piper}), 113.21 (C-3), 124.75, 126.30, 127.48, 127.80, 128.05, 128.54, 128.70, 128.87, 129.08, 129.39, 129.93, 136.84, 141.18, 142.25, 144.64 (all C_{arom}), 160.31 (C-2). – $C_{42}H_{44}N_4O_3$ (652.82): calcd. C 77.27, H 6.79, N 8.58; found C 77.20, H 6.84, N 8.51.

3.2.24. Synthesis of compound 8-(1-Benzyl-1, 2, 3, 6-tetrahydropyridin-4-yl) quinolin-2(1H)-one (41)

A solution of compound **40** (1.5 g, 5.35 mmol) in a mixture of methanol (15 mL) and concentrated HCl (15 mL) was heated at reflux temperature for 5 h. The reaction mixture was cooled and the solvent was removed under reduced pressure to give crude product as a hydrochloride salt, which was converted to the free base (aq NaOH/ethyl acetate) and purified by column chromatography eluting with ethyl acetate/hexane (20:80 to 40:60) to afford the title compound **41** as a light yellow gum (0.95 g, 56 %). – IR (neat): ν = 3182, 3054, 3022, 2978, 1638, 1610, 1465 cm^{-1}.– ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.15 (br. s, 2 H, piperidine H), 2.97 (t, J = 5.5 Hz, 2 H, piperidine H), 3.34 (br. s, 2 H, piperidine H), 3.87 (s, 2 H, NCH_2Ph), 5.79 (br. s, 1 H, piperidine H), 6.62 (d, J = 9.5 Hz, 1 H, 3-H), 7.18 (t, J = 7.5 Hz, 1 H, aromatic H), 7.28-7.47 (m, 8 H, aromatic H), 7.76 (d, J = 9.5 Hz, 1 H, 4-H), 10.17 (br. s, 1 H, NHCO). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 31.52, 48.1, 51.9, 115.82 (all C_{piper}), 120.93, 123.73, 124.66, 127.58, 128.07, 128.66, 128.88, 129.49, 129.99, 134.85, 136.44, 141.10, 141.85 (all C_{arom}), 160.32 (C-2). – $C_{21}H_{20}N_2O$ (316.40): calcd. C 79.72, H 6.37, N 8.85; found C 79.66, H 6.41, N 8.80.

3.2.25. Synthesis of compound tert-Butyl 4-(2-(benzyloxy) quinolin-8-yl)-5,6-dihydropyridine-1(2H)-carboxylate (42)

Nitrogen was flushed for 3 minutes in a flask containing a solution of the boronate **30** (1.39 g, 4.5 mmol), K_2CO_3 (1.86 g, 13.5 mmol) and bromide **10** (1.49 g, 4.74 mmol) in DMF (30 mL), followed by the addition of $PdCl_2$dppf (0.23 g, 0.28 mmol). The reaction mixture was heated to 80 °C and stirred under N_2 overnight, cool to room temperature and filtered through a pad of celite. The filtrate was added ethyl acetate (50 mL) and washed successively with water (20 mL), brine (3 x 15 mL), dried over Na_2SO_4 and evaporated. Column chromatography of the brown oily material on silica gel, eluting with ethyl acetate:hexanes (10:90) and then changing to (25:75) gave the title compound **41** as light yellow amorphous solid (0.97 g, 52 %). – IR (neat): ν = 3043, 3021, 2978, 1681, 1607, 1442, 1175 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.49 (s, 9 H, OC*(CH$_3$)$_3$*), 2.76 (br. s, 2 H, piperidine H), 3.68 (br. s, 2 H, piperidine H), 4.13 (br. s, 2 H, piperidine H), 5.49 (s, 2 H, O*C*H$_2$Ph), 5.85 (br. s, 1 H, piperidine H), 6.95 (d, *J* = 8.8 Hz, 1 H, aromatic H), 7.30-7.38 (m, 4 H, aromatic H), 7.46-7.48 (m, 3 H, aromatic H), 7.63 (dd, *J* = 1.5, 7.9 Hz, 1 H, aromatic H), 7.99 (d, *J* = 8.8 Hz, 1 H, aromatic H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 28.77 (OC*(CH$_3$)$_3$*), 30.18, 44.32, 67.73 (all C_{piper}), 79.74 (O*C*$(CH_3)_3$), 113.18, 124.14, 125.55, 127.22, 128.04, 128.20, 128.66, 129.12, 137.51, 139.51, 140.12, 144.24 (all C_{arom}), 155.60 (C=O), 161.02 (C_{arom}). – $C_{26}H_{28}N_2O_3$ (416.51): calcd. C 74.97, H 6.78, N 6.73; found C 74.91, H 6.83, N 6.67.

3.2.26. Synthesis of tert-Butyl 4-(2-oxo-1, 2, 3, 4-tetrahydroquinolin-8-yl) piperidine-1-carboxylate (43)

To a solution of compound **42** (0.7 g, 1.68 mmol) in a mixture of THF (5 mL) and EtOH (10 mL) was added Pd-C (10% wet basis, 0.5 g) and the mixture was subjected to hydrogenation in Parr apparatus at 50 psi for 6 hours. After being filtered through a pad of celite, the solution was concentrated to get brown oily material, which was resolved over silica column eluting with ethyl acetate:hexanes (30:70) and then changing to (60:40) to get compound **43** as an off-white solid (0.15 g, 27 %). M.p. 132-134 ^{o}C. – IR (neat): ν = 3245, 3019, 2971, 1668, 1603, 1472 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.49 (s, 9 H, OC*(CH$_3$)$_3$*), 1.61 (m, 2 H, piperidine H), 1.69 (m, 2 H, piperidine H), 2.61 (m, 2 H, 4-H), 2.79 (m, 1 H, piperidine H), 2.85 (br. s, 2 H, piperidine H), 2.93 (m, 2 H, 3-H), 4.28 (br. s, 2 H, piperidine H), 6.97 (t, J = 7.6 Hz, 1 H, aromatic H), 7.04-7.09 (m, 2 H, aromatic H), 8.30 (br. s, 1 H, NHCO). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 26.00 (C-4), 28.45 (OC*(CH$_3$)$_3$*), 30.68 (C-3), 32.13, 35.62 (all C_{piper}), 79.56 (O*C*$(CH_3)_3$), 123.18, 124.48, 124.75, 126.02, 130.65, 134.23 (all C_{arom}), 154.75 (C=O), 172.03 (C-2). – $C_{19}H_{26}N_2O_3$ (330.42): calcd. C 69.06, H 7.93, N 8.48; found C 69.00, H 7.98, N 8.41.

3.2.27. Synthesis of tert-Butyl 4-(2-oxo-1, 2-dihydroquinolin-yl) piperidine-1-carboxylate(44)

The title compound **44** was obtained from the reaction described for compound **43** as a light yellow solid (0.36 g, yield 65 %). M.p. 101-103 ^{o}C. – IR (neat): ν = 3172, 3031, 2965, 1645, 1603, 1461, 1112 cm^{-1}.– ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.50 (s, 9 H, OC*(CH$_3$)$_3$*), 1.69 (m, 2 H, piperidine H), 1.91 (m, 2 H, piperidine H), 3.10 (br. s, 2 H, piperidine H), 3.42 (m, 1 H, piperidine H), 4.30 (br. s, 2 H, piperidine H), 6.67 (d, J = 9.5 Hz, 1 H, 3-H), 7.20 (t, J = 7.6 Hz, 1 H, aromatic H), 7.40-7.45 (m, 2 H, aromatic H), 7.78 (t, J = 7.6 Hz, 1 H, 4-H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 28.48 (OC*(CH$_3$)$_3$*), 30.29, 32.33, 34.70 (all C_{piper}), 79.49 (O*C*$(CH_3)_3$), 120.20, 121.24, 122.54, 123.84, 126.41, 127.76, 131.38, 135.78, 141.74 (all C_{arom}), 154.83 (C=O), 163.99 (C_{arom}), 172.58 (C=O). – $C_{19}H_{24}N_2O_3$ (328.41): calcd. C 69.49, H 7.37, N 8.53; found C 69.45, H 7.43, N 8.46.

3.2.28. Synthesis of 8-(Piperidin-4-yl) quinolin-2(1H)-one (11)

To a solution of **44** (0.5 g, 1.52 mmol) in CH_2Cl_2 (15 mL) was added trifluoroacetic acid (3 mL) at 0 ^{o}C and the reaction mixture was stirred for 6 h at room temperature. Solvents were evaporated under reduced pressure and triturating with diethyl ether gave the title compound **11** as trifluoroacetic acid salt as an off-white solid (0.45 g, 90 %). M.p. 256-258 ^{o}C. – IR (neat): ν = 3266, 3031, 3011, 2990, 1672, 1618,

1445 cm^{-1}.– ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 1.86 (br. s, 4 H, piperidine H), 3.08 (m, 2 H, piperidine H), 3.42 (m, 2 H, piperidine H), 3.48 (m, 1 H, piperidine H), 6.51 (d, J = 9.4 Hz, 1 H, 3-H), 7.19 (t, J = 8.1 Hz, 1 H, aromatic H), 7.37 (d, J = 8.0 Hz, 1 H, aromatic H), 7.54 (d, J = 7.9 Hz, 1 H, aromatic H H), 7.91 (d, J = 9.5 Hz, 1 H, 4-H), 8.49 (br. s, 1 H, NHCO).– ^{13}C NMR (125.7 MHz, [D_6]DMSO): δ = 28.91, 31.68, 44.05 (all C_{piper}), 119.91, 121.60, 122.31, 127.09, 127.56, 129.40, 136.09, 141.55 (all C_{arom}), 162.92 (C=O).– $C_{16}H_{17}F_3N_2O_3$ (342.31): calcd. C 56.14, H 5.01, N 8.18; found C 56.08, H 5.06, N 8.11.

3.2.29. Synthesis of 8-(Piperidin-4-yl)-3, 4-dihydroquinolin-2(1H)-one (12)

Following the same procedure adopted for the synthesis of **11**, the title compound was obtained from compound **43** as off-white solid (0.70 g, yield 89 %). M.p. 247-248 ^{o}C. – IR (neat): ν = 3221, 3021, 2988, 1660, 1603, 1445, 1186 cm^{-1}.– ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 1.79 (m, 4 H, piperidine H), 2.51 (m, 2 H, 2-H), 2.85 (m, 2 H, 3-H), 2.99-3.06 (m, 3 H, piperidine H), 3.34 (m, 2 H, piperidine H), 6.96 (m, 1 H, aromatic H), 7.07 (m, 1 H, aromatic H), 9.63 (s, 1 H, NHCO). – ^{13}C NMR (125.7 MHz, [D_6]DMSO): δ = 25.88 (C-4), 29.22 (C_{piper}), 30.88 (C-3), 32.29, 44.82 (all C_{piper}), 123.05, 124.68, 125.63, 126.62, 130.45, 135.37 (all C_{arom}), 170.02 (C=O).– $C_{16}H_{19}F_3N_2O_3$ (344.33): calcd. C 55.81, H 5.56, N 8.14; found C 55.74, H 5.62, N 8.08.

3.2.30. Synthesis of 8-(1-(Biphenyl-4-ylmethyl) piperidin-4-yl)-2-methoxyquinoline (10a)

To a solution of compound **10** (0.15 g, 0.42 mmol) and biphenyl-4-carbaldehyde**a** (0.1 g, 0.55 mmol) in 1,2-dichloroethane (5 mL) at 0 ^{o}C was added Et_3N (0.13 mL, 0.97 mmol). After being stirred for 10 min at room temperature, $NaBH(OAc)_3$(0.11 g, 0.53 mmol) was added and reaction mixture was stirred for 6 h. The reaction was added sat. $NaHCO_3$ solution (10 mL) and stirred for 15 min, followed by the addition of ethyl acetate (30 mL). The organic layer was separated and washed with sat. $NaHCO_3$, brine, and dried over Na_2SO_4. Purification of the brown oily material on silica column, eluting with ethyl acetate:hexanes (70:30) and then changing to ethyl acetate (100%) yielded the titled compound **10a** as a light yellow solid 0.126 g, yield 45 %). M.p. 84-85 ^{o}C. – IR (neat): ν = 3031, 3021, 2936, 1609, 1444, 1186, 1120 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.15 (m, 2 H, piperidine H), 2.36 (m, 2 H, piperidine H), 2.85 (br. s, 2 H, piperidine H), 3.64 (m, 2 H, piperidine H), 4.03 (s, 3 H, OCH_3), 4.20 (s, 2 H, NCH_2), 6.88 (d, J = 8.8 Hz, 1 H, 3-H), 7.32-7.38 (m, 2 H, aromatic H), 7.45 (t, J = 7.3 Hz, 2 H, aromatic H), 7.51 (d, J = 7.3 Hz, 1 H, aromatic H), 7.56-7.59 (m, 4 H, aromatic H), 7.63 (m, 2 H, aromatic H), 7.95 (d, J = 8.5 Hz, 1 H, aromatic H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 29.47, 34.92 (all C_{piper}), 53.14 (OCH_3), 61.71 (NCH_2), 112.62 (C-3), 123.98, 124.98, 126.21, 127.06, 127.72, 128.85, 131.30, 139.31, 139.55, 140.02, 142.37, 143.86 (all C_{arom}), 161.44 (C-2). – $C_{28}H_{28}N_2O$ (408.53): calcd. C 82.32, H 6.91, N 6.86; found C 82.25, H 6.96, N 6.79.

3.2.31. Synthesis of 8-(4-((4'-Fluorobiphenyl-4-yl) methyl) piperazin-1-yl)-2-methoxyquinoline (10b)

Following the same procedure adopted for the synthesis of **10a**, the title compound was obtained by reductive amination of compound **10** and **b** as an off-white solid (yield 37 %). M.p. 94-95 ^{o}C. – IR (neat): ν = 3042, 3011, 2926, 1603, 1440, 1183, 1132 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.92 (m, 2 H, piperidine H), 2.02 (m, 2 H, piperidine H), 2.30 (m, 2 H, piperidine H), 3.18 (m, 2 H, piperidine e H), 3.70 (s, 2 H, NCH_2), 3.83 (m, 1 H, piperidine H), 4.05 (s, 3 H, OCH_3), 6.88 (d, J = 8.5 Hz, 1 H, 3-H), 7.09-7.12 (m, 2 H, aromatic H), 7.32 (t, J = 7.6 Hz, 1 H, aromatic H), 7.45-7.56 (m, 8 H, aromatic H), 7.94 (d, J = 8.8 Hz, 1 H, aromatic H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 32.03, 36.07 (all C_{piper}), 53.07 (OCH_3), 54.66 (C_{piper}), 62.95 (NCH_2), 112.36 (C-3), 115.49, 115.66, 123.85, 124.91, 125.41, 125.81, 126.84, 128.52, 128.57, 129.97, 136.71, 136.98, 139.17, 142.32, 144.13 (all C_{arom}), 161.20 (C-2). – $C_{28}H_{27}FN_2O$ (426.53): calcd. C 78.85, H 6.38, N 6.57; found C 78.79, H 6.44, N, 6.50.

3.2.32. Synthesis of 2-Methoxy-8-(4-((5-phenylpyridin-3-yl)methyl) piperazin-1-yl)quinoline (10c)

Following the same procedure adopted for the synthesis of **10a**, the title compound was obtained by reductive amination of compound **10** and **c** as an off white solid (yield 35 %). M.p. 135-137 ^{o}C. – IR (neat): ν = 3021, 2945, 1601, 1433, 1263,

1228 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.90 (m, 2 H, piperidine H), 2.02 (m, 2 H, piperidine H), 2.30 (m, 2 H, piperidine H), 3.09 (m, 2 H, piperidine H), 3.67 (s, 2 H, NCH_2), 3.82 (m, 1 H, piperidine H), 4.07 (s, 3 H, OCH_3), 6.88 (d, *J* = 8.8 Hz, 1 H, 3-H), 7.33 (t, *J* = 7.6 Hz, 1 H, aromatic H), 7.41 (d, *J* = 7.3 Hz, 1 H, aromatic H), 7.47-7.53 (m, 3 H, aromatic H), 7.64 (m, 2 H, aromatic H), 7.94 (m, 2 H, aromatic H), 8.59 (d, *J* = 1.8 Hz, 1 H, aromatic H), 8.77 (d, *J* = 2.1 Hz, 1 H, aromatic H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 32.33, 36.36 (all C_{piper}), 53.05 (OCH_3), 54.79 (C_{piper}), 60.65 (NCH_2), 112.32 (C-3), 124.88, 125.33, 125.77, 127.16, 127.98, 128.97, 134.08, 135.05, 136.23, 137.81, 139.11, 142.49, 144.13, 146.95, 149.17 (all C_{arom}), 161.13 (C-2). – $C_{27}H_{27}N_3O$ (409.52): calcd. C 79.19, H 6.65, N 10.26; found C 79.12, H 6.71, N 10.19.

3.2.33. Synthesis of 8-(4-((5-(4-Fluorophenyl) pyridin-3-yl) methyl) piperazin-1-yl)-2-methoxyquinoline (10d)

Following the same procedure adopted for the synthesis of **10a**, the title compound was obtained by reductive amination of compound **10** and **d** as a light brown solid (yield 32 %). M.p. 156-158 ^oC. – IR (neat): ν = 3025, 2931, 1607, 1431, 1266 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.89 (m, 2 H, piperidine H), 2.01 (m, 2 H, piperidine H), 2.28 (m, 2 H, piperidine H), 3.05 (m, 2 H, piperidine H), 3.65 (s, 2 H, NCH_2), 3.81 (m, 1 H, piperidine H), 4.06 (s, 3 H, OCH_3), 6.88 (d, *J* = 8.5 Hz, 1 H, 3-H), 7.16 (m, 2 H, aromatic H), 7.33 (t, *J* = 7.6, 1 H, aromatic H), 7.51 (dd, *J* = 1.2, 7.3 Hz, 1 H, aromatic H), 7.54-7.59 (m, 3 H, aromatic H), 7.89 (m, 1 H, aromatic H), 7.94 (d, *J* = 8.8 Hz , 1 H,

aromatic H), 8.59 (d, J = 1.5 Hz, 1 H, aromatic H), 8.77 (d, J = 2.1 Hz, 1 H, aromatic H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 32.33, 36.35 (all C_{piper}), 53.04 (OCH_3), 54.82 (C_{piper}), 60.62 (NCH_2), 112.34 (C-3), 115.86, 116.03, 123.78, 124.90, 125.36, 125.77, 128.80, 128.85, 133.92, 134.22, 134.89, 135.33, 139.12, 142.47, 144.13, 146.76, 149.17, 161.13, 163.82 (all C_{arom}). – $C_{27}H_{26}FN_3O$ (427.51): calcd. C 75.85, H 6.13, N 9.83; found C 75.79, H 6.19, N 9.76.

3.2.34. Synthesis of 8-(4-(3-Cyclopentenylbenzyl) piperazin-1-yl)-2-methoxyquinoline (10e)

Following the same procedure adopted for the synthesis of **10a**, the title compound was obtained by reductive amination of compound**10** and **e** as a light yellow solid (yield 46 %). M.p. 125-126 ^{o}C. – IR (neat): ν = 3028, 2982, 2898, 1605, 1472, 1445, 1263, 1258 cm^{-1}.– ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.85-192 (m, 2 H, piperidine H), 1.98-2.04 (m, 4 H, piperidine H, cyclopent H), 2.24 (m, 2 H, cyclopent H), 2.72 (m, 2 H, cyclopent H), 3.05 (m, 2 H, piperidine H), 3.60 (s, 2 H, NCH_2), 3.79 (m, 1 H, piperidine H), 4.05 (s, 3H, OCH_3), 6.20 (s, 1 H, cyclopent H), 6.85 (d, J = 8.8 Hz, 1 H, 3-H), 7.24-7.34 (m, 4 H, aromatic H), 7.45-7.54 (m, 3 H, aromatic H), 7.91 (d, J = 8.8 Hz, 1 H, aromatic H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 23.33 ($C_{cyclopent}$), 32.33 (C_{piper}), 33.22, 33.30 (all $C_{cyclopent}$), 36.32 (C_{piper}), 53.05 (OCH_3), 54.74 (C_{piper}), 63.62 (NCH_2), 112.34 ($C_{cyclopent}$), 123.80, 124.27, 124.87, 125.28, 125.80, 126.12, 126.46, 127.88,

128.10, 136.67, 138.29, 139.11, 142.41, 142.67, 144.13, 161.12 (all C_{arom}). − $C_{27}H_{30}N_2O$ (398.54): calcd. C 81.37, H 7.59, N 7.03; found C 81.31, H 7.64, N 6.97.

3.2.35. Synthesis of S8-(4-((5-Cyclopentenylpyridin-3-yl) methyl) piperazin-1-yl)-2-methoxyquinoline (10f)

Following the same procedure adopted for the synthesis of **10a**, the title compound was obtained by reductive amination of compound **10**and **f** as a light yellow amorphous solid (yield 39 %). M.p. 85-86 ^{o}C. – IR (neat): ν = 3021, 2992, 2828, 1601, 1472, 1445, 1255 cm^{-1}. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.89-194 (m, 2 H, piperidine H), 2.02-2.09 (m, 4 H, piperidine H, cyclopent H), 2.26-2.31 (m, 2 H, cyclopent H), 2.73 (m, 2 H, cyclopent H), 3.09 (m, 2 H, piperidine H), 3.61 (s, 2 H, NCH_2), 3.80 (m, 1 H, piperidine H), 4.05 (s, 3 H, OCH_3), 6.30 (s, 1 H, cyclopent H), 6.87 (d, J = 8.5 Hz, 1 H, 3-H), 7.32 (m, 1 H, aromatic H), 7.49 (d, J = 7.3 Hz, 1 H, aromatic H), 7.55 (d, J = 7.9 Hz, 1 H, aromatic H), 7.76 (s, 1 H, aromatic H), 7.95 (d, J = 8.8 Hz, 1 H, aromatic H), 8.42 (s, 1 H, aromatic H), 8.59 (s, 1 H, aromatic H). − ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 23.16 ($C_{cyclopent}$), 32.09 (C_{piper}), 32.88, 33.36 (all $C_{cyclopent}$), 36.24 (C_{piper}), 53.03 (OCH_3), 54.57 (C_{piper}), 60.46 (NCH_2), 112.32 ($C_{cyclopent}$), 123.77, 124.87, 125.36, 125.78, 128.35, 132.04, 133.14, 133.59, 139.10, 139.38, 142.34, 144.10, 145.74, 148.46 (all C_{arom}), 161.14 (C-2). − $C_{26}H_{29}N_3O$ (399.53): calcd. C 78.16, H 7.32, N 10.52; found C 78.10, H 7.38, N 10.45.

3.2.36. Synthesis of 8-(4-(Biphenyl-4-ylmethyl) piperazin-1-yl) quinolin-2(1H)-one (11a)

Following the same procedure adopted for the synthesis of **10a**, the title compound was obtained by reductive amination of compound **11** and **a** as a light yellow solid (yield 45 %). M.p. 146-148 ^{o}C. – IR (neat): ν = 3193, 3038, 3021, 2938, 1641, 1601, 1437, 1218 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.81 (m, 4 H, piperidine H), 2.26 (m, 2 H, piperidine H), 3.00 (br. s, 3 H, piperidine H), 3.60 (s, 2 H, NCH_2), 6.65 (d, J = 9.4 Hz, 1 H, 3-H), 7.10 (t, J = 8.7 Hz, 1 H, aromatic H), 7.34-7.55 (m, 5 H, aromatic H), 7.61 (d, J = 9.4 Hz, 1 H, 4-H), 10.12 (br. s, 1 H, NHCO).– ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 32.41, 34.93, 53.83 (all C_{piper}), 63.03 (NCH_2), 119.99, 121.17, 122.47, 126.18, 126.92, 127.03, 127.16, 127.78, 128.73, 129.75, 131.41, 135.71, 137.02, 139.95, 140.92, 141.61 (all C_{arom}), 163.46 (C=O). – $C_{27}H_{26}N_2O$ (394.51): calcd. C 82.20, H 6.64, N 7.10; found C 82.14, H 6.70, N 7.03.

3.2.37. Synthesis of 8-(4-((4'-Fluorobiphenyl-4-yl) methyl) piperazin-1-yl) quinolin-2(1H)-one (11b)

Following the same procedure adopted for the synthesis of **10a**, the title compound was obtained by reductive amination of compound **11** and **b** as an off white solid (yield 41 %). M.p. 159-161 ^{o}C. – IR (neat): ν = 3213, 3028, 2928, 1637, 1609, 1447, 1171 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.88 (m, 4 H, piperidine H), 2.24

(m, 2 H, piperidine H), 2.90 (m, 1 H, piperidine H), 3.08 (m, 2 H, piperidine H), 3.65 (s, 2 H, NCH_2), 6.62 (d, J = 9.4 Hz, 1 H, 3-H), 7.12 (t, J = 8.7 Hz, 1 H, aromatic H), 7.20 (t, J = 8.5 Hz, 1 H, aromatic H), 7.41-7.44 (m, 4 H, aromatic H), 7.52-7.58 (m, 5 H, aromatic H), 7.73 (d, J = 9.4 Hz, 1 H, 4-H), 9.55 (br. s, 1 H, NHCO).– ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 32.32, 35.36, 54.03 (all C_{piper}), 63.02 (NCH_2), 115.52, 115.73, 120.06, 121.21, 122.62, 126.32, 126.86, 127.82, 128.56, 128.64, 129.77, 130.08, 135.66, 137.05, 137.07, 139.03, 141.70 (all C_{arom}), 161.32 (C=O), 163.11 (C_{arom}). – $C_{27}H_{25}FN_2O$ (412.50): calcd. C 78.62, H 6.11, N 6.79; found C 78.56, H 6.16, N 6.72.

3.2.38. Synthesis of 8-(4-((5-Phenylpyridin-3-yl) methyl) piperazin-1-yl) quinolin-2(1H)-one (11c)

Following the same procedure adopted for the synthesis of **10a**, the title compound was obtained by reductive amination of compound **11** and **c** as a light yellow solid (yield 38 %). M.p. 158-160 ^{o}C. – IR (neat): ν = 3363, 3051, 3018, 2932, 1643, 1600, 1433, 1208 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.90 (m, 4 H, piperidine H), 2.17 (m, 2 H, piperidine H), 3.07 (m, 3 H, piperidine H), 3.71 (s, 2 H, NCH_2), 6.59 (d, J = 9.5 Hz, 1 H, 3-H), 7.21 (t, J = 7.6 Hz, 1 H, aromatic H), 7.41-7.43 (m, 2 H, aromatic H), 7.47-7.51 (m, 4 H, aromatic H), 7.64 (m, 2 H, aromatic H), 7.7 (d, J = 9.4 Hz, 1 H, 4-H) 7.92 (s, 1 H, aromatic H), 8.57 (d, J = 1.8 Hz, 1 H, aromatic H), 8.78 (d, J = 1.6 Hz, 1 H, aromatic H), 10.52 (br. s, 1 H, NHCO).– ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 32.28, 34.67, 53.84 (all C_{piper}), 60.47 (NCH_2), 120.03, 121.06, 122.55, 126.26, 127.19, 127.81, 128.07,

129.02, 131.34, 133.55, 135.16, 135.69, 136.31, 137.71, 141.73, 147.06, 149.16 (all C_{arom}), 163.65 (C=O). Anal. Calcd for $C_{26}H_{25}N_3O$ (395.50): C, 78.96; H, 6.37; N, 10.62%. Found: C, 78.90; H, 6.43; N, 10.57%.

3.2.39. Synthesis of 8-(4-((5-(4-Fluorophenyl) pyridin-3-yl) methyl) piperazin-1-yl)quinolin-2(1H)-one (11d)

Following the same procedure adopted for the synthesis of **10a**, the title compound was obtained by reductive amination of compound **11** and **d** as a light yellow solid (yield 34 %). M.p. 161-163 ^{o}C. – IR (neat): ν = 3373, 3058, 3040, 2928, 1640, 1602, 1430, 1228 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.91 (m, 4 H, piperidine H), 2.39 (m, 2 H, piperidine H), 3.09 (m, 3 H, piperidine H), 3.71 (s, 2 H, NCH_2), 6.62 (d, J = 11.8 Hz, 1 H, 3-H), 7.18-7.22 (m, 4 H, aromatic H), 7.44-7.48 (m, 2 H, aromatic H), 7.59-7.62 (m, 2 H, aromatic H), 7.80 (d, J = 11.2 Hz, 1 H, 4-H), 7.91 (br. s, 1 H, NH), 8.59 (d, J = 1.8 Hz, 1 H, aromatic H), 8.75 (d, J = 1.8 Hz, 1 H, aromatic H), 10.20 (br. s, 1 H, NHCO).– ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 32.26, 34.89, 53.99 (all C_{piper}), 60.46 (NCH_2), 115.97, 116.18, 120.07, 121.15, 123.63, 126.38, 127.85, 128.89, 131.10, 133.87, 135.03, 135.48, 141.77, 147.01, 149.24, 163.50, 164.36 (all C_{arom}). − $C_{26}H_{24}FN_3O$ (413.49): calcd. C 75.52, H 5.85, N 10.16; found C 75.46, H 5.91, N 10.09.

3.2.40. Synthesis of 8-(4-(3-Cyclopentenylbenzyl) piperazin-1-yl) quinolin-2(1H)-one (11e)

Following the same procedure adopted for the synthesis of **10a**, the title compound was obtained by reductive amination of compound **11**and **e** as a white solid (yield 42 %). M.p. 123-125 ^{o}C. – IR (neat): ν = 3164, 3110, 3022, 3011, 2936, 2886, 1639, 1599, 1471, 1116 cm^{-1}.– ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.83-191 (m, 6 H, piperidine H, cyclopent H), 2.21-2.29 (m, 2 H, cyclopent H), 2.51-2.59 (m, 2 H, piperidine H), 2.73 (m, 2 H, cyclopent H), 2.83 (m, 1 H, piperidine H), 3.08 (m, 2 H, piperidine H), 3.60 (s, 2 H, NCH_2), 6.22 (s, 1 H, cyclopent H), 6.60 (d, J = 9.4 Hz, 1 H, 3-H), 7.11-7.28 (m, 2 H, aromatic H), 7.29 (t, J = 7.8 Hz, 1 H, aromatic H), 7.33 (m, 1 H, aromatic H), 7.42 (m, 2 H, aromatic H), 7.52 (m, 1 H, aromatic H), 7.75 (d, J = 9.4 Hz, 1 H, 4-H), 9.36 (br. s, 1 H, NHCO). − ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 23.37 ($C_{cyclopent}$), 32.27 (C_{piper}), 33.28, 33.34 (all $C_{cyclopent}$), 35.47, 53.99 (all C_{piper}), 63.44 (NCH_2), 119.94, 121.21, 122.58, 124.37, 126.26, 126.43, 127.81, 128.18, 130.84, 135.47, 136.77, 137.01, 141.64, 142.42 (all C_{arom}), 162.98 (C=O). − $C_{26}H_{28}N_2O$ (384.51): calcd. C 81.21, H 7.34, N 7.29; found C 81.15, H 7.40, N 7.22.

3.2.41. Synthesis of 8-(4-((5-Cyclopentenylpyridin-3-yl) methyl) piperazin-1-yl)quinolin-2(1H)-one (11f)

Following the same procedure adopted for the synthesis of **10a**, the title compound was obtained by reductive amination of compound **11** and **f** as an off white solid (yield 31 %). M.p. 133-135 ^{o}C. – IR (neat): ν = 3169, 3026, 2934, 1639, 1601, 1411, 1190, 1127 cm^{-1}.– ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.81-191 (m, 4 H, piperidine H), 1.98-2.10 (m, 2 H, cyclopent H), 2.25-2.36 (m, 2 H, cyclopent H), 2.52-2.59 (m, 2 H, piperidine H), 2.72 (m, 2 H, cyclopent H), 3.00 (m, 3 H, piperidine H), 3.59 (s, 2 H, NCH_2), 6.30 (s, 1 H, cyclopent H), 6.57 (d, J = 9.4 Hz, 1 H, 3-H), 7.18 (t, J = 8.8 Hz, 1 H, aromatic H), 7.41 (m, 2 H, aromatic H), 7.68 (s, 1 H, aromatic H), 7.76 (d, J = 9.4 Hz, 1 H, 4-H), 8.40 (s, 1 H, aromatic H), 8.59 (s, 1 H, aromatic H), 10.18 (br. s, 1 H, NHCO). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 23.33 ($C_{cyclopent}$), 32.33 (C_{piper}), 33.22, 33.30 (all $C_{cyclopent}$), 36.32 (C_{piper}), 53.05 (OCH_3), 54.74 (C_{piper}), 63.62 (NCH_2), 113.98 ($C_{cyclopent}$), 120.14 (Ar-C), 122.26, 122.41, 124.11, 128.50, 132.05, 132.59, 133.36, 133.58, 138.80, 139.29, 140.65, 145.98, 148.45 (all C_{arom}), 162.28 (C-2). – $C_{25}H_{27}N_3O$ (385.50): calcd. C 77.89, H 7.06, N 10.90; found C 77.83, H 7.12, N 10.83.

3.2.42. Synthesis of 8-(4-(Biphenyl-4-ylmethyl) piperazin-1-yl)-3, 4-dihydroquinolin-2(1H)-one (12a)

Following the same procedure adopted for the synthesis of **10a**, the title compound was obtained by reductive amination of compound **12** and **a** as an off white solid (yield 41 %). M.p. 116-118 ^{o}C. – IR (neat): ν = 3217, 3053, 2912, 2872, 1668, 1601, 1482, 1211 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ =1.76-184 (m, 4 H, piperidine H), 2.15 (m, 4 H, piperidine H), 2.53 (m, 1 H, piperidine H), 2.59 (t, J = 7.6, 2 H, 4-H), 2.94 (t, J = 6.7, 2 H, 3-H), 3.05 (m, 2 H, piperidine H), 3.60 (s, 2 H, NCH_2), 6.97-7.03 (m, 2 H, aromatic H), 7.15 (m, 1 H, aromatic H), 7.34 (m, 1 H, aromatic H), 7.41-7.45 (m, 4 H, aromatic H), 7.55 (d, J = 7.3, 1 H, aromatic H), 7.60 (d, J = 7.3, 1 H, aromatic H), 7.87 (br. s, 1 H, NHCO). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 25.95 (C-4), 30.62 (C-3), 32.24, 35.82, 54.07 (all C_{piper}), 63.00 (NCH_2), 123.09, 124.21, 124.80, 125.69, 126.92, 127.01, 127.12, 128.69, 129.62, 130.91, 134.20, 137.22, 139.95, 140.91 (all C_{arom}), 171.68 (C-2). – $C_{27}H_{28}N_2O$ (396.52): calcd. C 81.78, H 7.12, N 7.06; found C 81.72, H 7.17, N 7.00.

3.2.43. Synthesis of 8-(4-((4'-Fluorobiphenyl-4-yl) methyl) piperazin-1-yl)-3, 4-dihydroquinolin-2(1H)-one (12b)

Following the same procedure adopted for the synthesis of **10a**, the title compound was obtained by reductive amination of compound **12** and **b** as an light yellow solid

(yield 33 %). M.p. 132-134 ^{o}C. – IR (neat): ν = 3223, 3050, 2902, 2862, 1667, 1600, 1489, 1231 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ =1.67-173 (m, 4 H, piperidine H), 2.07 (m, 2 H, piperidine H), 2.50 (m, 3 H, piperidine H, 4-H), 2.83 (t, J = 7.6, 2 H, 3-H), 2.96 (m, 2 H, piperidine H), 3.51 (s, 2 H, NCH_2), 6.88-6.94 ((m, 2 H, aromatic H), 7.01-7.12 ((m, 3 H, aromatic H), 7.32 (d, J = 7.6 Hz, 2 H, aromatic H), 7.39-7.49 ((m, 4 H, aromatic H), 7.94 (br. s, 1 H, NHCO). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 26.02 (C-4), 30.71 (C-3), 32.30, 35.78, 54.10 (all C_{piper}), 63.02 (NCH_2), 115.52, 115.73, 123.16, 124.31, 124.87, 125.87, 126.84, 128.56, 129.78, 131.05, 134.31, 137.08, 137.24, 139.04, 161.32, 163.62 (all C_{arom}), 170.87 (C=O). – $C_{27}H_{27}FN_2O$ (414.51): calcd. C 78.23, H 6.57, N 6.76; found C 78.26, H 6.62, N 6.69.

3.2.44. Synthesis of 8-(4-((5-Phenylpyridin-3-yl) methyl) piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (12c)

Following the same procedure adopted for the synthesis of **10a**, the title compound was obtained by reductive amination of compound **12** and **c** as a light yellow gum (yield 34 %). – IR (neat): ν =3213, 3032, 2922, 1662, 1608, 1472, 1201 cm^{-1}.– ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.76-189 (m, 4 H, piperidine H), 2.27 (m, 2 H, piperidine H), 2.56-2.66 (m, 3 H, piperidine H, 4-H), 2.93 (m, 2 H, 3-H), 3.05 (m, 2 H, piperidine H), 3.67 (s, 2 H, NCH_2), 6.97 (m, 2 H, aromatic H), 7.07 (m, 1 H, aromatic H), 7.43 (m, 1 H, aromatic H), 7.50 (t, J = 7.5 Hz, 2 H, aromatic H), 7.89 (s, 1 H, aromatic H), 8.41 (s, 1 H, aromatic H), 8.54 (s, 1 H, NHCO), 8.72 (s, 1 H, aromatic H).– ^{13}C NMR (125.7

MHz, $CDCl_3$): δ =25.93 (C-4), 30.63 (C-3), 31.93, 35.26, 53.85 (all C_{piper}), 60.13 (s, 2 H, NCH_2), 115.99, 116.20, 123.34, 124.43, 124.91, 125.96, 128.87, 128.95, 130.99, 133.68, 134.21, 135.43, 146.80, 148.93, 161.76, 164.22 (all C_{arom}), 172.50 (C=O). − $C_{26}H_{27}N_3O$ (397.51): calcd. C 78.56, H 6.85, N 10.57; found C 78.50, H 6.91, N 10.50.

3.2.45. Synthesis of 8-(4-((5-(4-Fluorophenyl) pyridin-3-yl) methyl) piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (12d)

Following the same procedure adopted for the synthesis of **10a**, the title compound was obtained by reductive amination of compound **12** and **d** as a light yellow solid (yield 30 %). M.p. 136-138 ^oC. – IR (neat): ν =3198, 3051, 2931, 1660, 1608, 1468, 1186 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 1.74-189 (m, 4 H, piperidine H), 2.31 (m, 2 H, piperidine H), 2.56 (m, 2 H, 4-H), 2.72 (m, 1 H, piperidine H), 2.89 (m, 2 H, 3-H), 3.07 (m, 2 H, piperidine H), 3.70 (s, 2 H, NCH_2), 6.93-7.06 (m, 2 H, aromatic H), 7.13 (d, J = 8.2 Hz, 1 H, aromatic H), 7.35-7.55 (t, J = 9.0 Hz, 3 H, aromatic H), 7.62 (m, 2 H, aromatic H), 7.93 (s, 1 H, aromatic H), 8.54 (s, 1 H, aromatic H), 9.61 (br. s, 1 H, NHCO).− ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 25.95 (C-4), 30.68 (C-3), 31.95, 35.04, 53.69 (all C_{piper}), 60.07 (NCH_2), 123.30, 124.46, 124.93, 125.90, 127.20, 128.23, 129.10, 131.25, 133.00, 134.37, 135.69, 136.55, 137.51, 146.91, 148.90 (all C_{arom}), 172.66 (C=O). – $C_{26}H_{26}FN_3O$ (415.50): calcd. C 75.16, H 6.31, N 10.11; found C 75.10, H 6.37, N 10.03.

3.2.46. Synthesis of 8-(4-(3-Cyclopentenylbenzyl) piperazin-1-yl)-3, 4-dihydroquinolin-2(1H)-one (12e)

Following the same procedure adopted for the synthesis of **10a**, the title compound was obtained by reductive amination of compound **12** and **e** as a light green solid (yield 45 %). M.p. 115-117 ^{o}C. – IR (neat): ν = 3191, 3067, 2922, 2842, 1665, 1603, 1431, 1188 cm^{-1}.– ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.71-189 (m, 4 H, piperidine H), 1.98-2.08 (m, 2 H, cyclopent H), 2.11-2.18 (m, 2 H, cyclopent H), 2.48-2.56 (m, 5 H, piperidine H, 4-H), 2.74 (m, 2 H, cyclopent H), 2.95 (m, 2 H, 3-H), 3.03 (m, 2 H, piperidine H), 3.57 (s, 2 H, NCH_2), 6.22 (br. s, 1 H, cyclopent H), 6.94-7.13 (m, 2 H, aromatic H), 7.16 (d, J = 7.7 Hz, 1 H, aromatic H), 7.23 (d, J = 7.6 Hz, 1 H, aromatic H), 7.25-7.32 (m, 2 H, aromatic H), 7.41 (s, 1 H, aromatic H), 7.98 (br. s, 1 H, NHCO). − ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 23.40 ($C_{cyclopent}$), 26.04 (C-4), 30.71 (C-3), 32.31 (C_{piper}), 33.29, 33.37 (all $C_{cyclopent}$), 35.83, 54.07 (all C_{piper}), 63.49 (NCH_2), 123.13 ($C_{cyclopent}$), 124.28, 124.37, 124.88, 125.83, 126.27, 126.26, 127.88, 128.18, 131.11, 134.30, 136.82, 137.04, 142.42 (all C_{arom}), 171.82 (C=O). − $C_{26}H_{30}N_2O$ (386.53): calcd. C 80.79, H 7.82, N 7.25; found C 80.73, H 7.88, N 7.18.

3.2.47. Synthesis of 8-(4-((5-cyclopentenylpyridin-3-yl) methyl) piperazin-1-yl)-3, 4-dihydroquinolin-2(1H)-one (12f)

Following the same procedure adopted for the synthesis of **10a**, the title compound was obtained by reductive amination of compound **12** and **f** as a light yellow solid (yield 39 %). M.p. 123-125 ^{o}C. – IR (neat): ν = 3195, 3057, 2932, 2832, 1667, 1600, 1437, 1182 cm^{-1}.– ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.73-188 (m, 4 H, piperidine H), 2.00-2.11 (m, 2 H, cyclopent H), 2.12-2.16 (m, 2 H, cyclopent H), 2.51-2.66 (m, 4 H, piperidine H, 4-H), 2.69-2.76 (m, 2 H, cyclopent H), 2.92-3.06 (m, 4 H, piperidine H, 3-H), 3.57 (s, 2 H, NCH_2), 6.31 (br. s, 1 H, cyclopent H), 6.92-7.12 (m, 2 H, aromatic H), 7.16 (d, J = 7.7 Hz, 1 H, aromatic H), 7.69 (s, 1 H, aromatic H), 8.12 (br. s, 1 H, NHCO), 8.41 (s, 1 H, aromatic H), 8.59 (s, 1 H, aromatic H). − ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 23.25 ($C_{cyclopent}$), 26.03 (C-4), 30.71 (C-3), 32.25 (C_{piper}), 32.99, 33.44 (all $C_{cyclopent}$), 35.62, 54.04 (all C_{piper}), 60.57 (NCH_2), 123.13 ($C_{cyclopent}$), 124.34, 124.84, 125.88, 128.35, 130.98, 132.02, 133.07, 133.31, 134.33, 139.49, 146.02, 148.68 (all C_{arom}), 171.87 (C=O). − $C_{25}H_{29}N_3O$ (387.52): calcd. C 77.48, H 7.54, N 10.84; found C 77.42, H 7.60, N 10.77.

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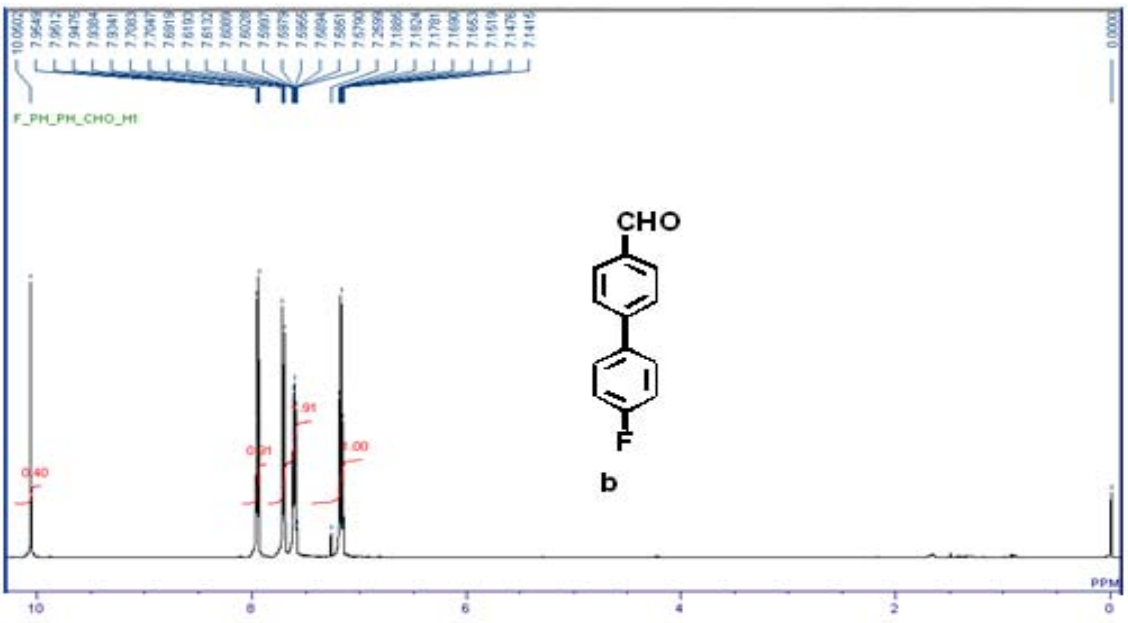
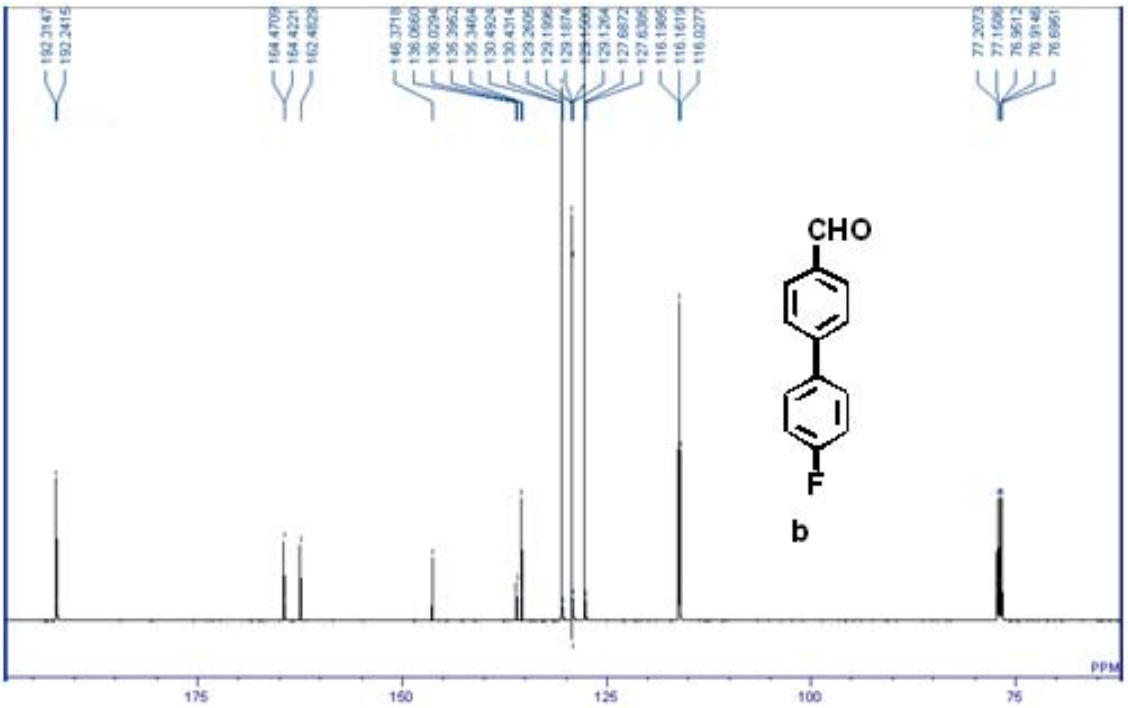
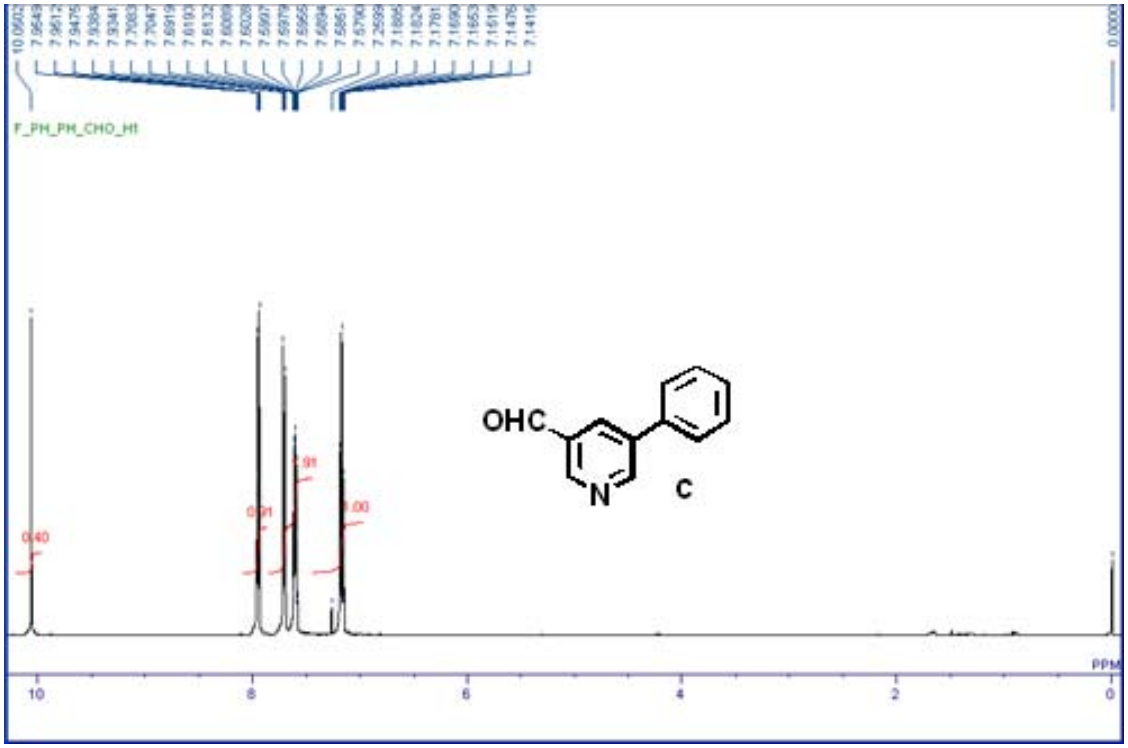
APPENDICES



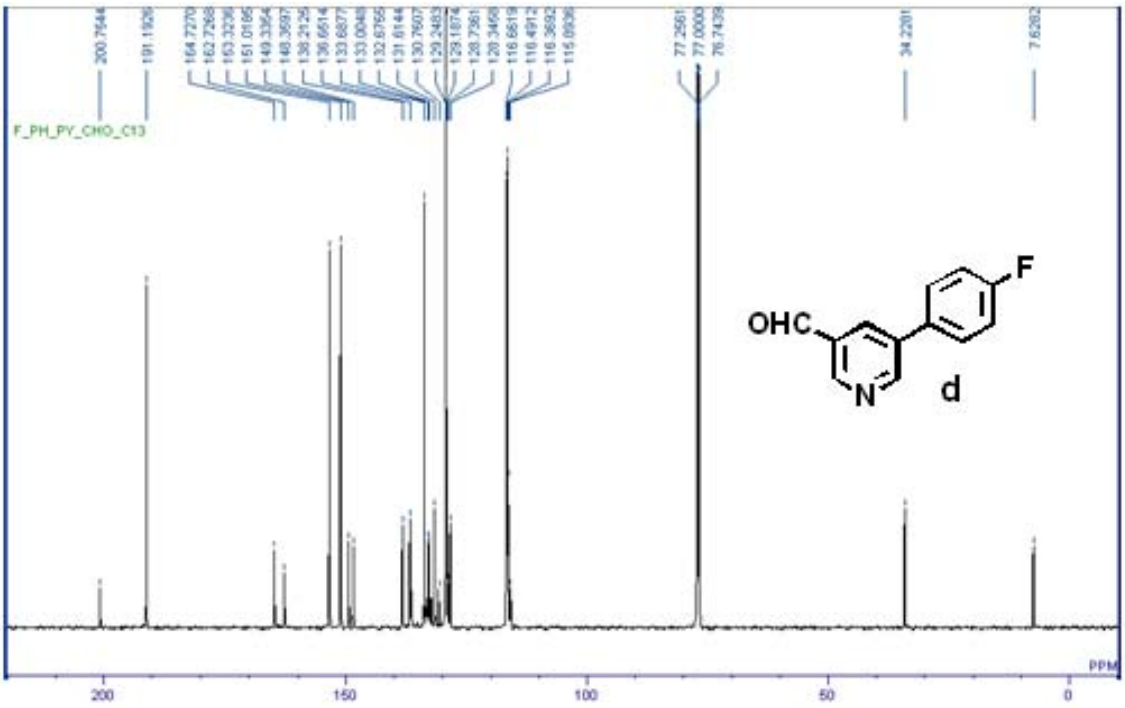
Appendix 1:H^1 of 4'-fluorobiphenyl-4-carbaldehyde (b)



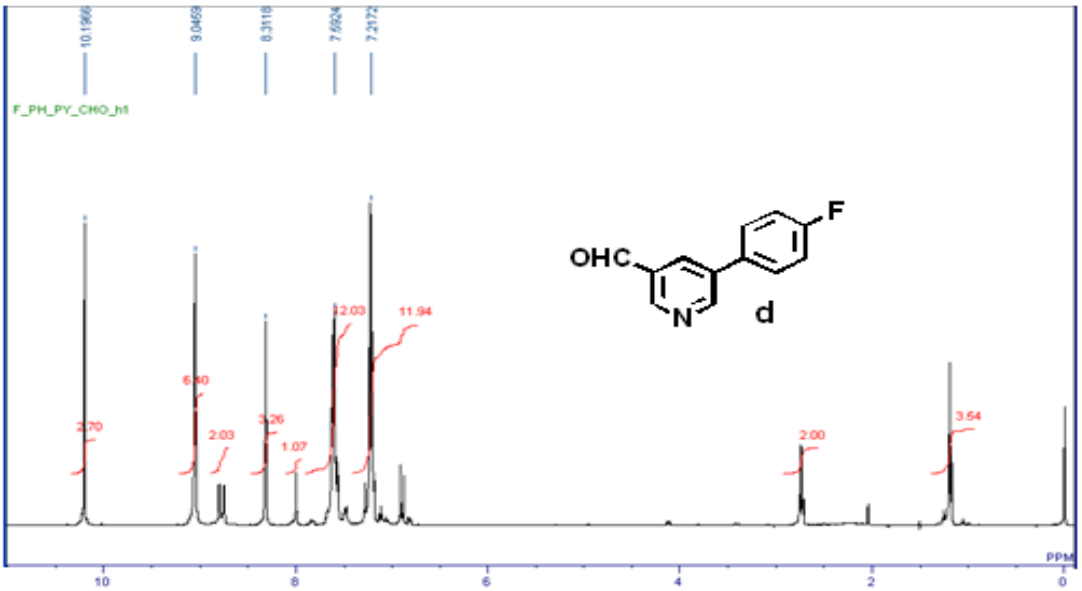
Appendix 2: C^{13} of 4'-fluorobiphenyl-4-carbaldehyde (b)



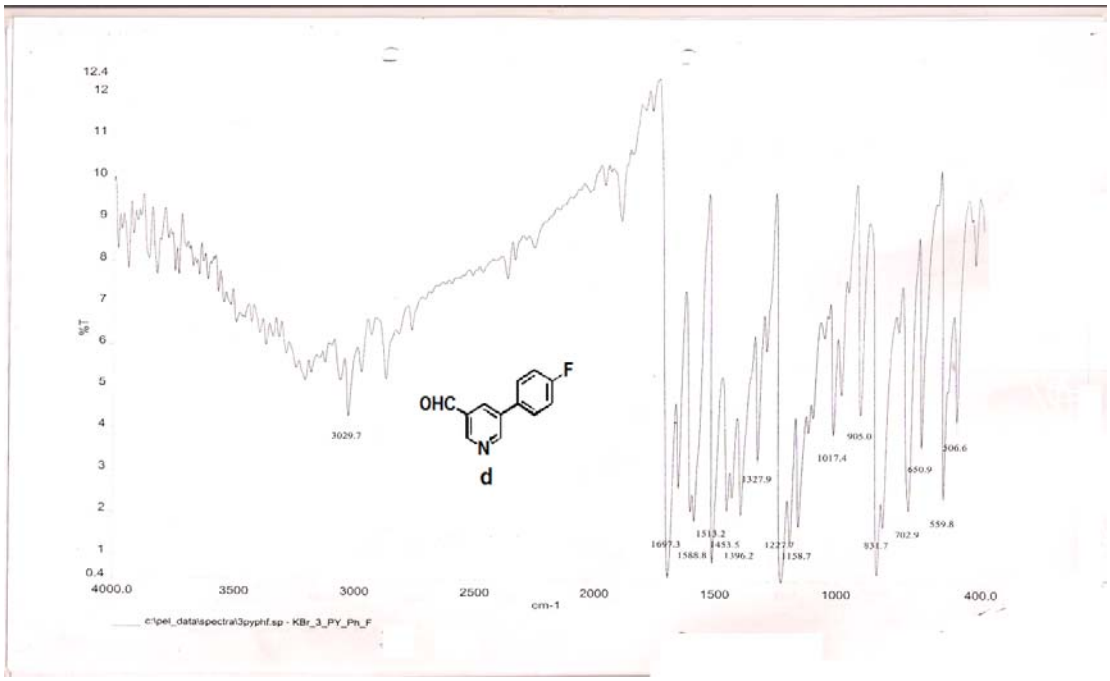
Appendix 3:H[1] of 5-phenylnicotinaldehyde (c)



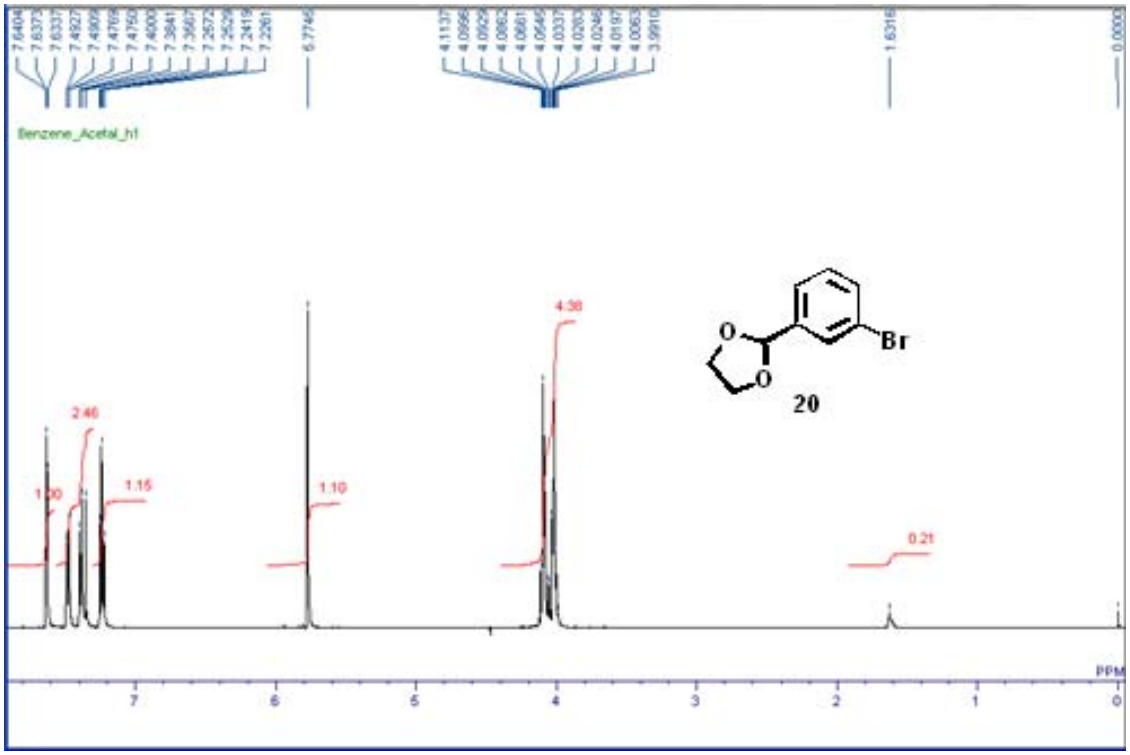
Appendix 4:C^{13} of 5-(4-fluorophenyl)nicotinaldehyde (d)



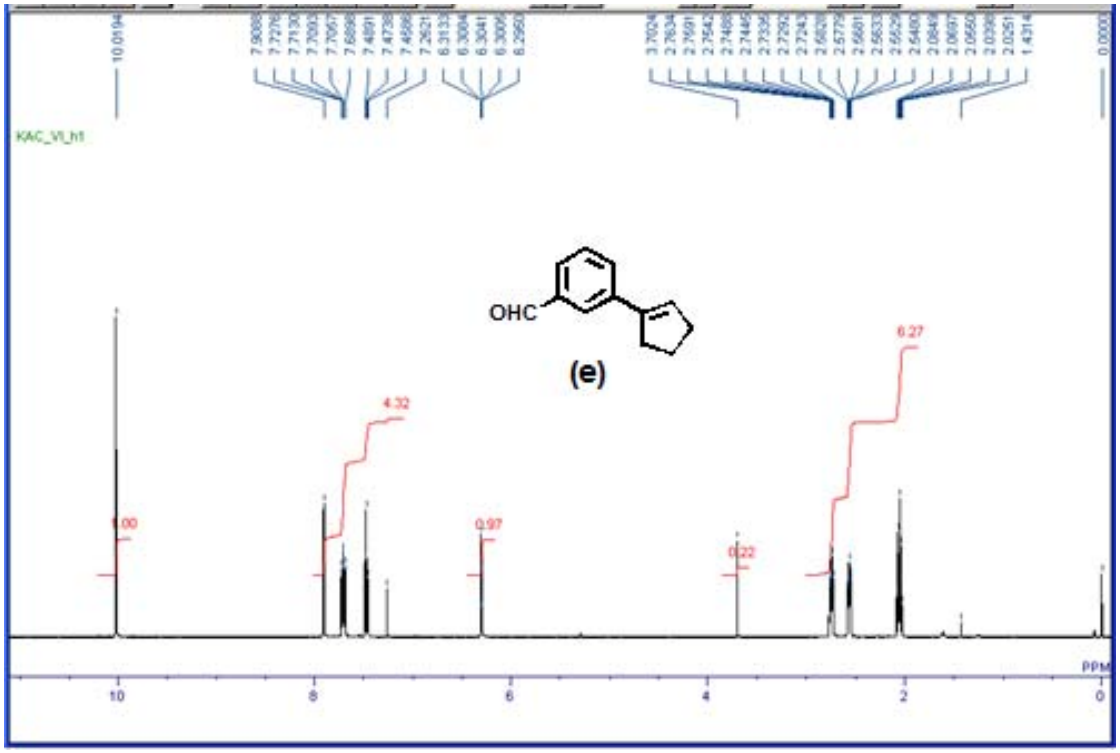
Appendix 5: H^1 of 5-(4-fluorophenyl)nicotinaldehyde (d)



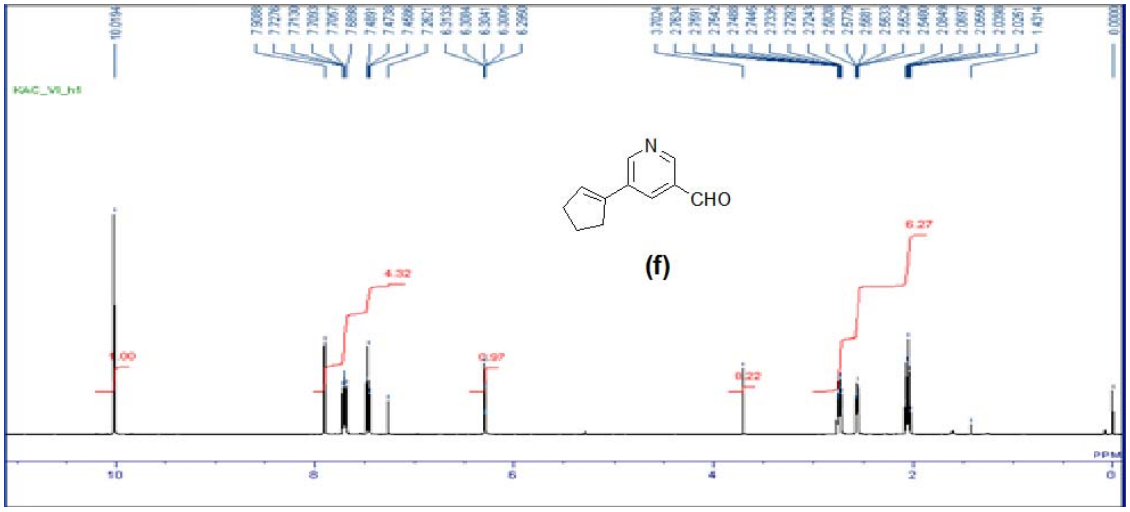
Appendix 6: IR of 5-(4-fluorophenyl)nicotinaldehyde (d)



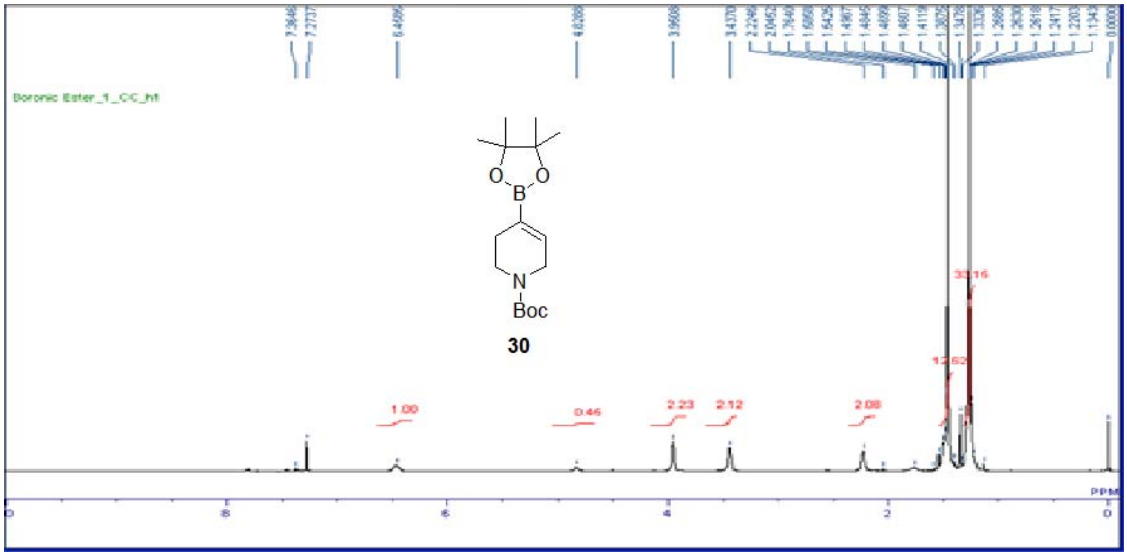
Appendix 7: H^1 of 2-(3-bromophenyl)-1,3-dioxolane 20



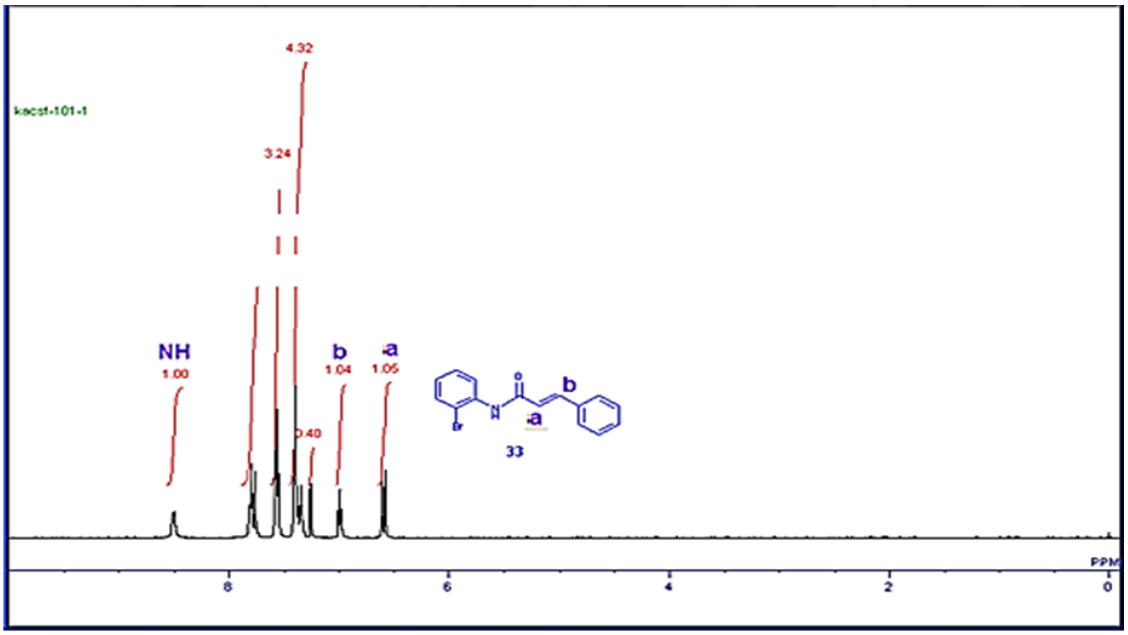
Appendix 8: H^1 of 3-cyclopentenylbenzaldehyde (e)



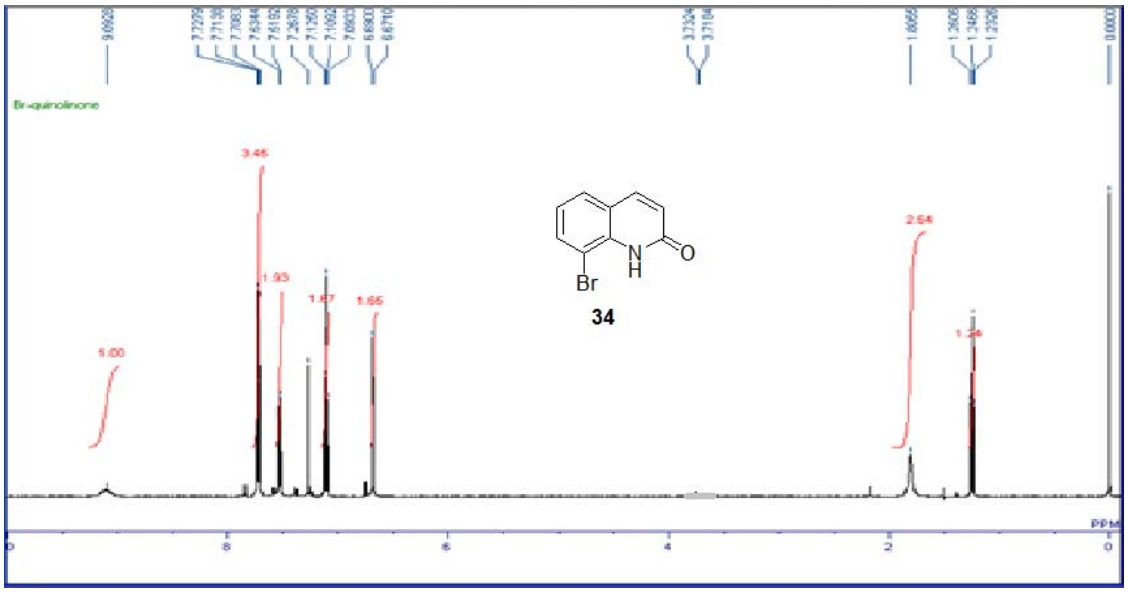
Appendix 9: H^1 of 5-cyclopentenylnicotinaldehyde (f)



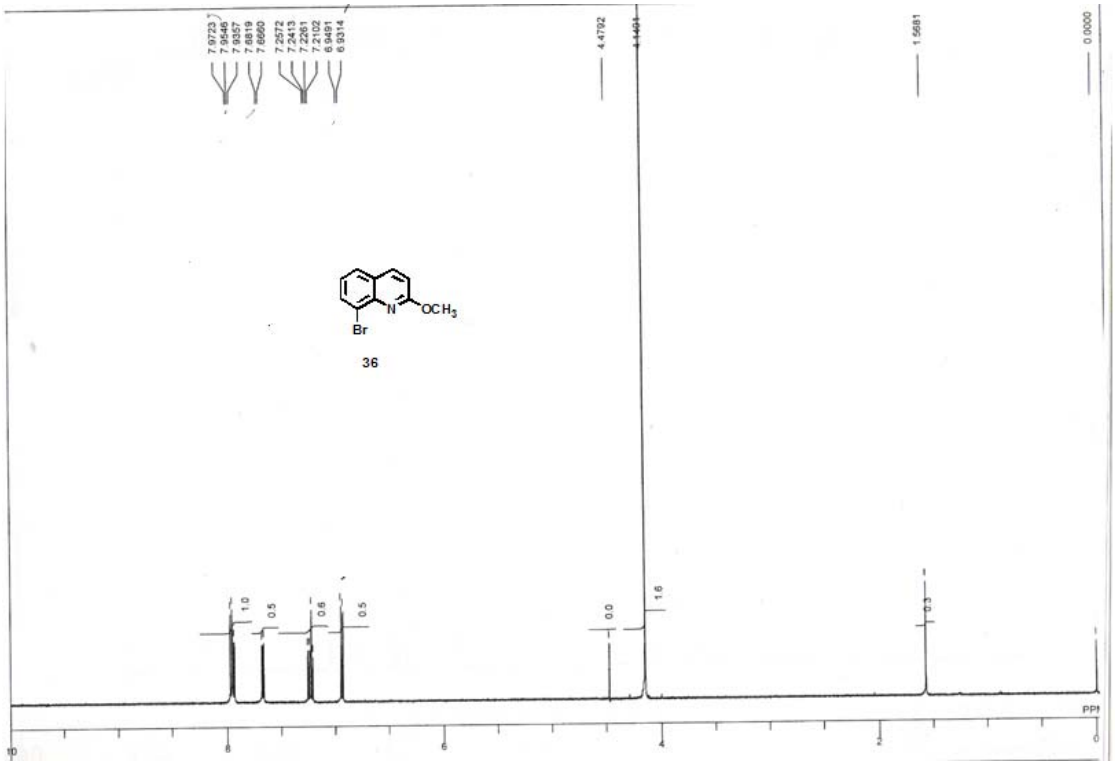
Appendix 10: H^1 of tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate(30)



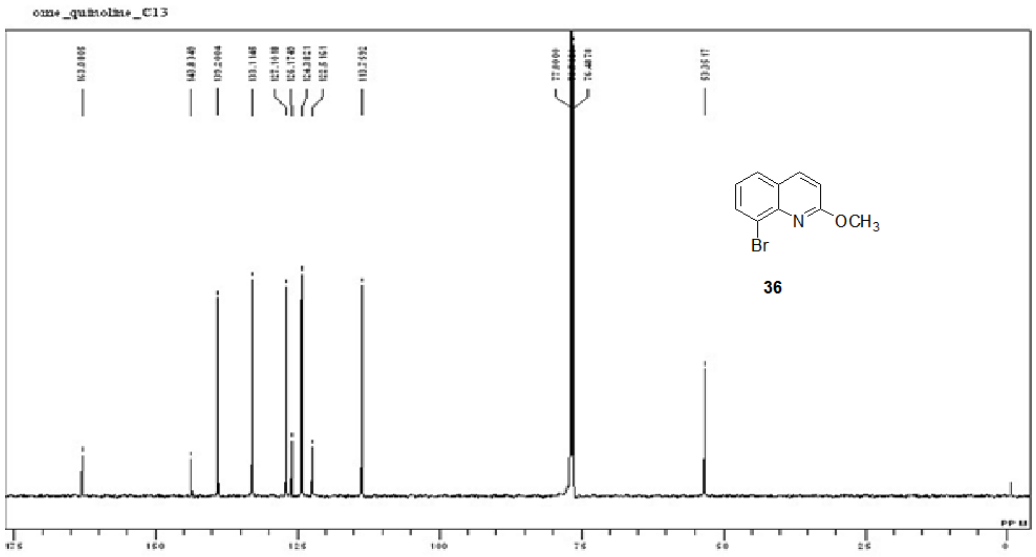
Appendix 11: H^1 of N-(2-bromophenyl)cinnamamide(33)



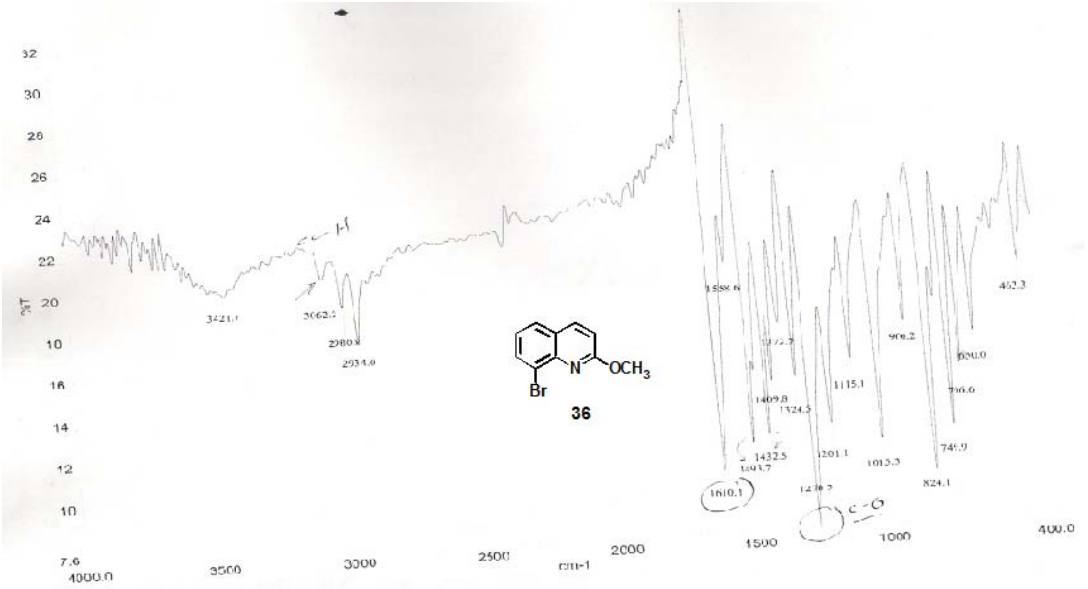
Appendix 12: H^1 of 8-bromoquinolin-2(1H)-one (34)



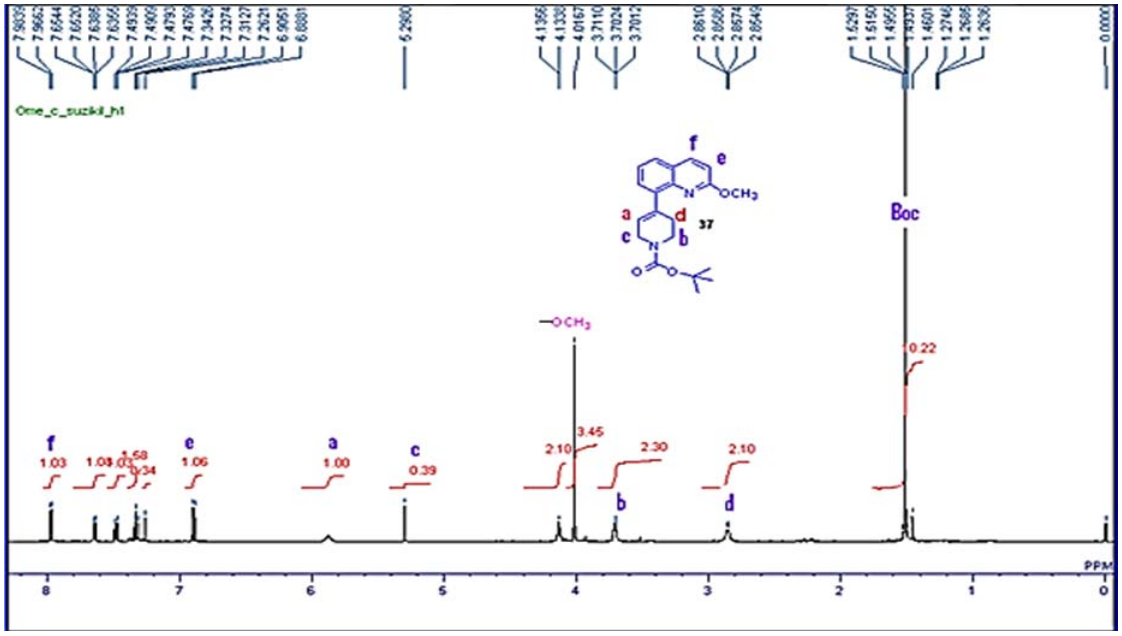
Appendix 13: H^1 of 8-bromo-2-methoxyquinoline (36)



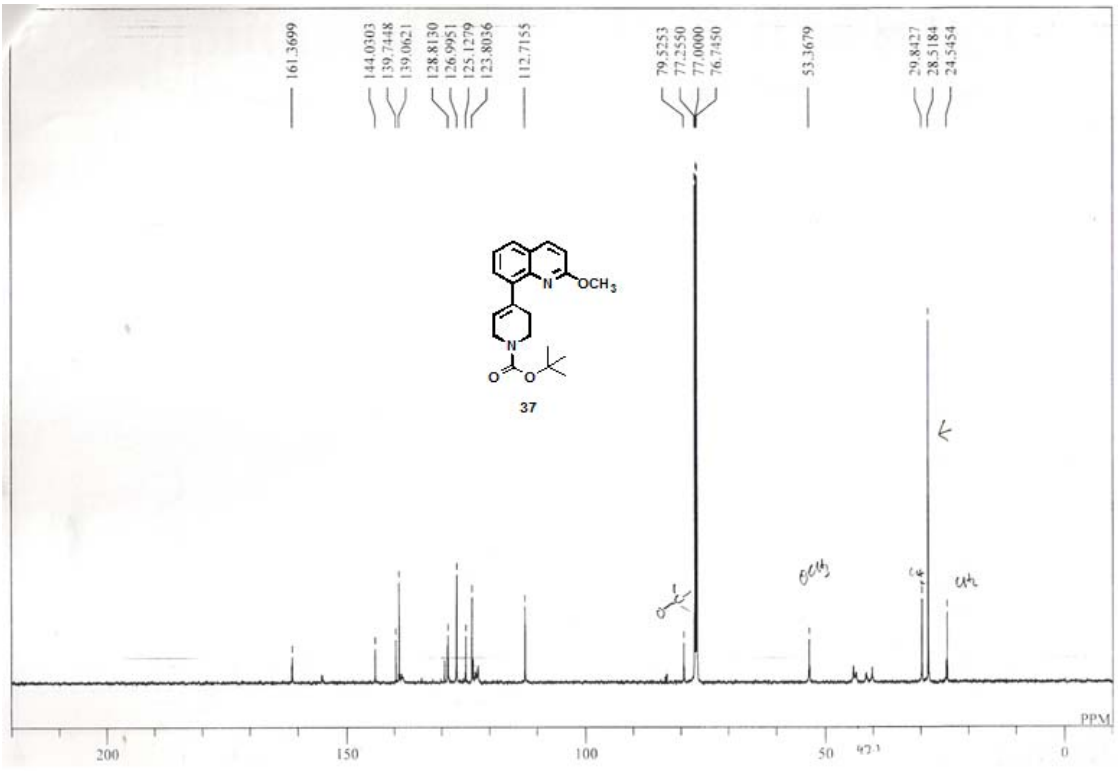
Appendix 14: C^{13} of 8-bromo-2-methoxyquinoline (36)



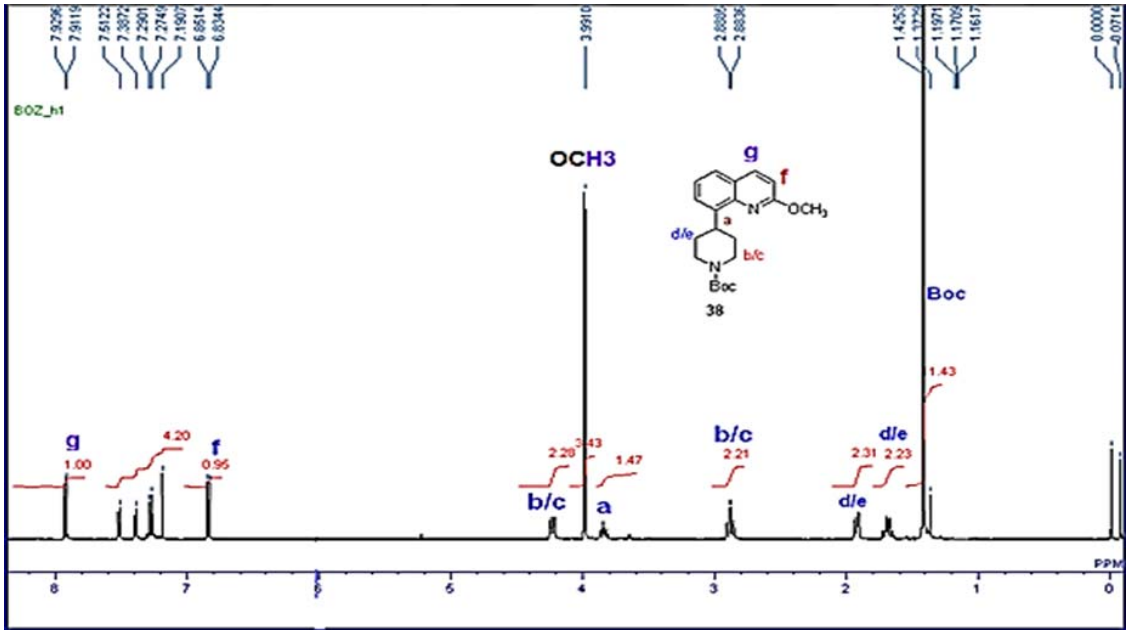
Appendix 15: IR of 8-bromo-2-methoxyquinoline (36)



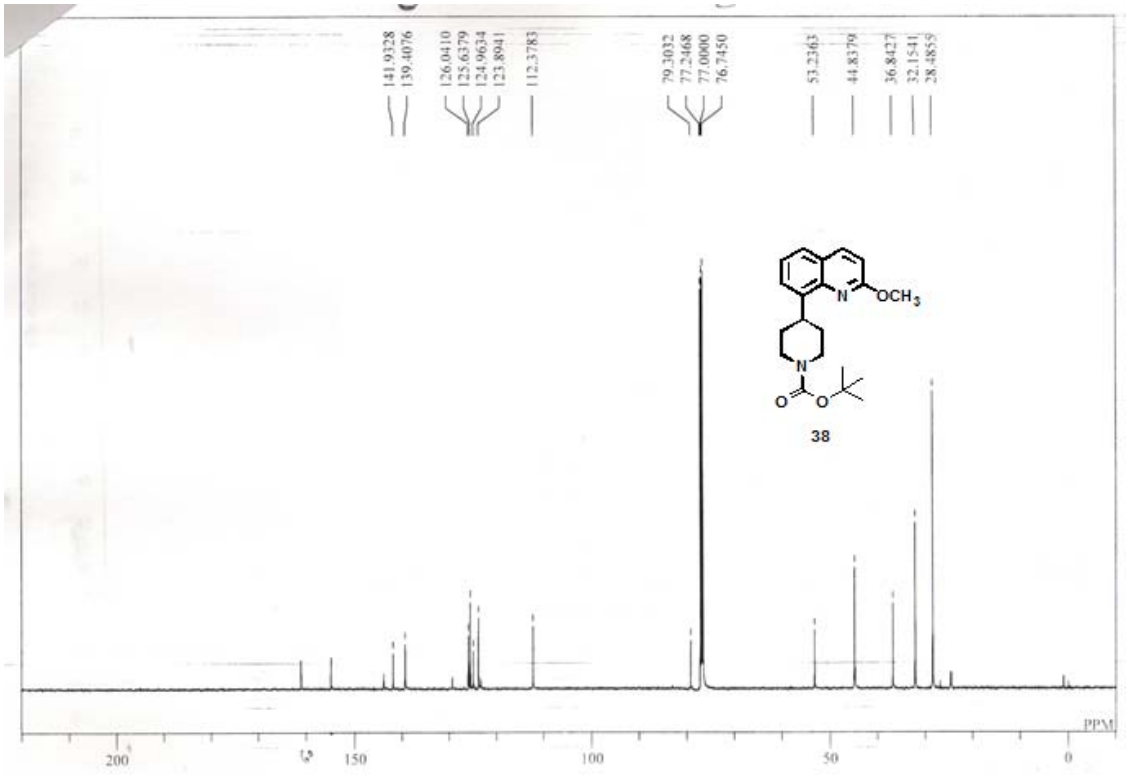
Appendix 16: H^1 of tert-Butyl 4-(2-methoxyquinolin-8-yl)-5,6-dihydropyridine-1(2H)-carboxylate (37)



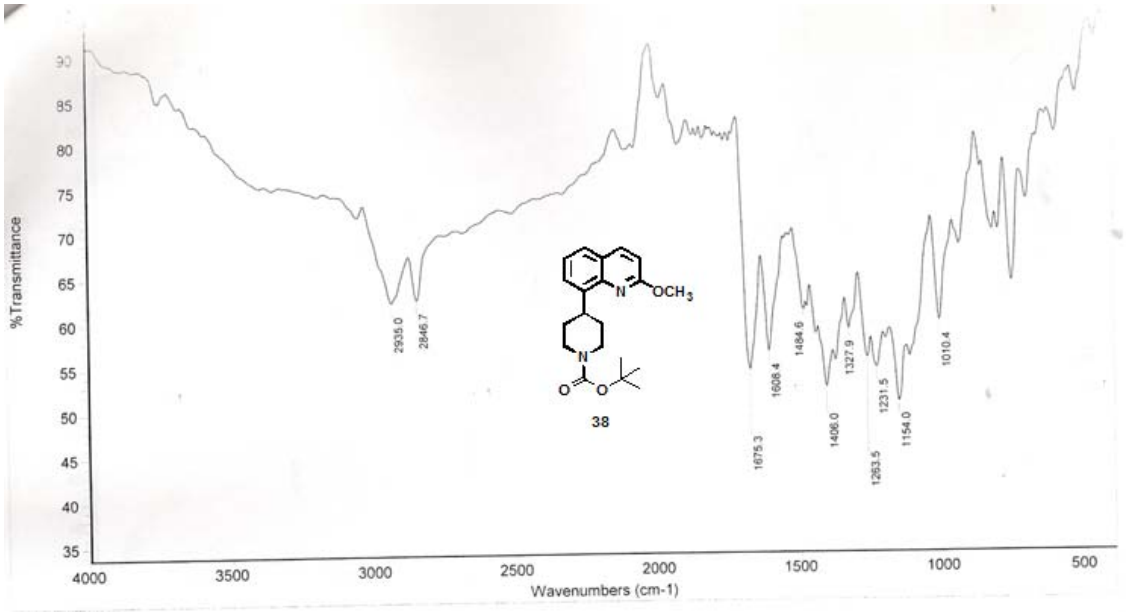
Appendix 17: C^{13} of of tert-Butyl 4-(2-methoxyquinolin-8-yl)-5,6-dihydropyridine-1(2H)-carboxylate (37)



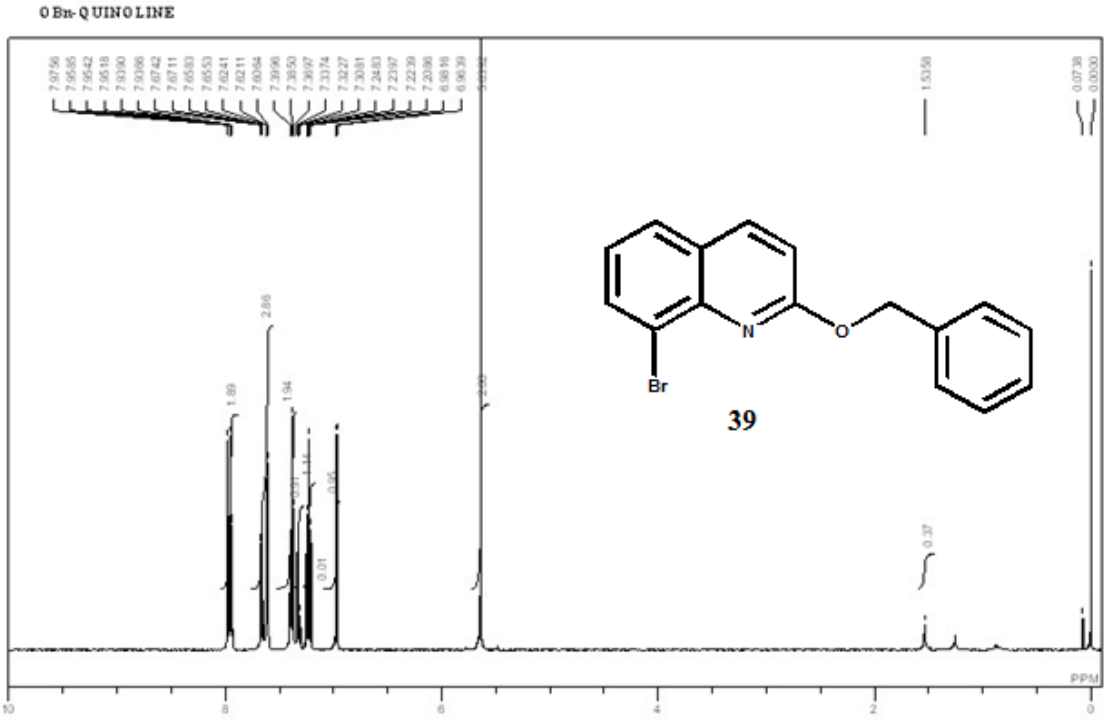
Appendix 18: H^1 of tert-Butyl 4-(2-methoxyquinolin-8-yl)piperidine-1-carboxylate (38)



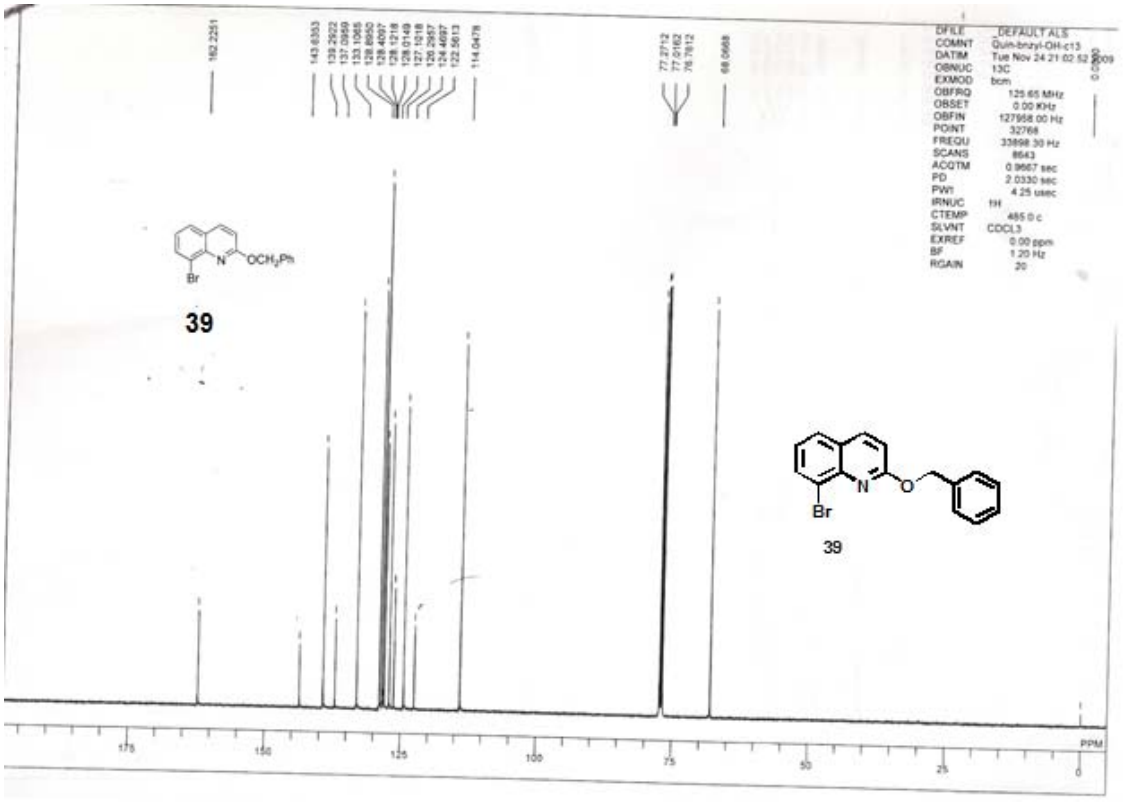
Appendix 19:C^{13} of tert-Butyl 4-(2-methoxyquinolin-8-yl)piperidine-1-carboxylate (38)



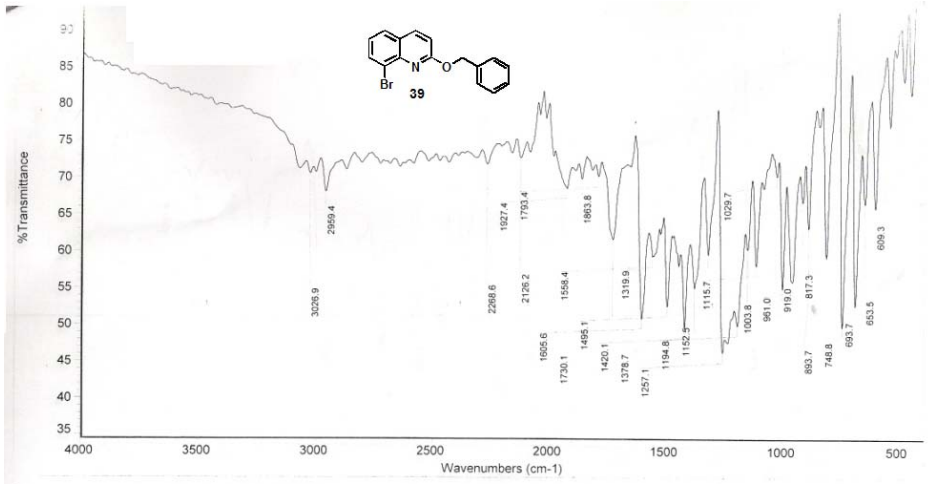
Appendix 20: IR of tert-Butyl 4-(2-methoxyquinolin-8-yl)piperidine-1-carboxylate (38)



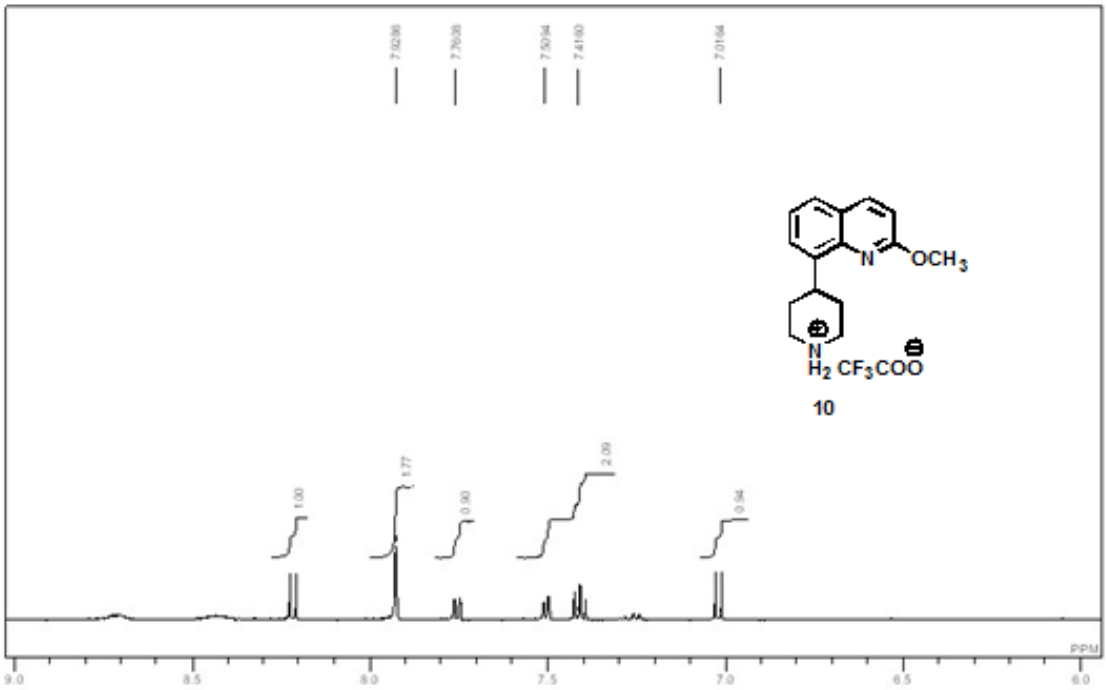
Appendix 21: H^1 of 2-(benzyloxy)-8-bromoquinoline(39)



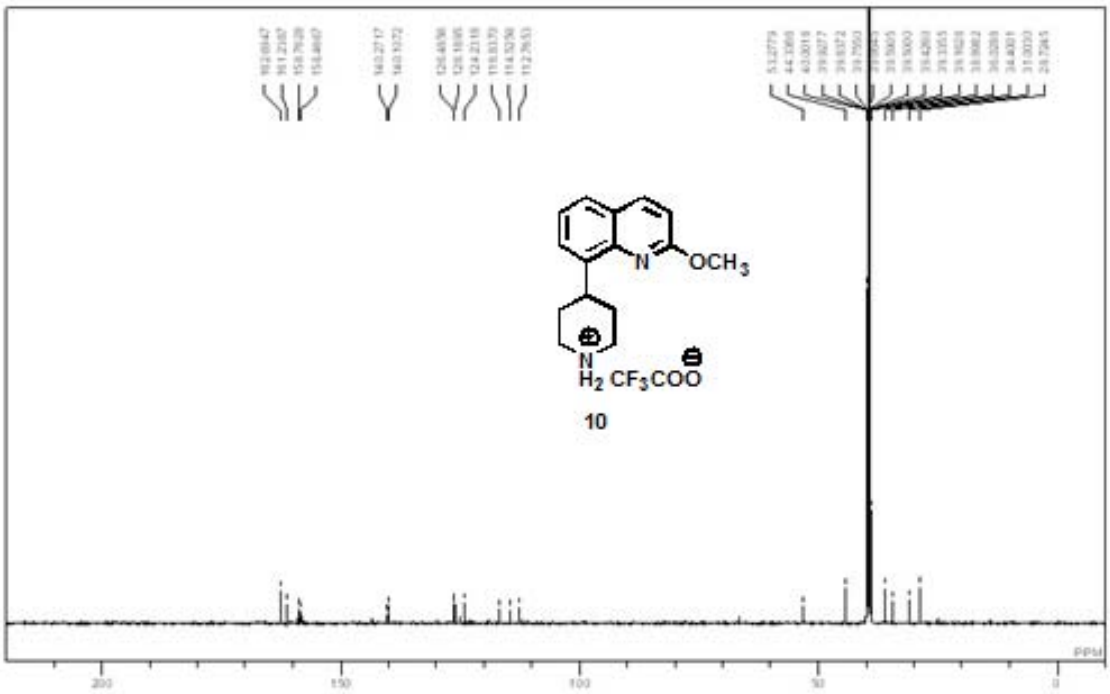
Appendix 22: C^{13} of 2-(benzyloxy)-8-bromoquinoline (39)



Appendix 23: IR of 2-(benzyloxy)-8-bromoquinoline(39)



Appendix 24: H^1 of ynt2-Methoxy-8-(piperidin-4-yl)quinoline(10)



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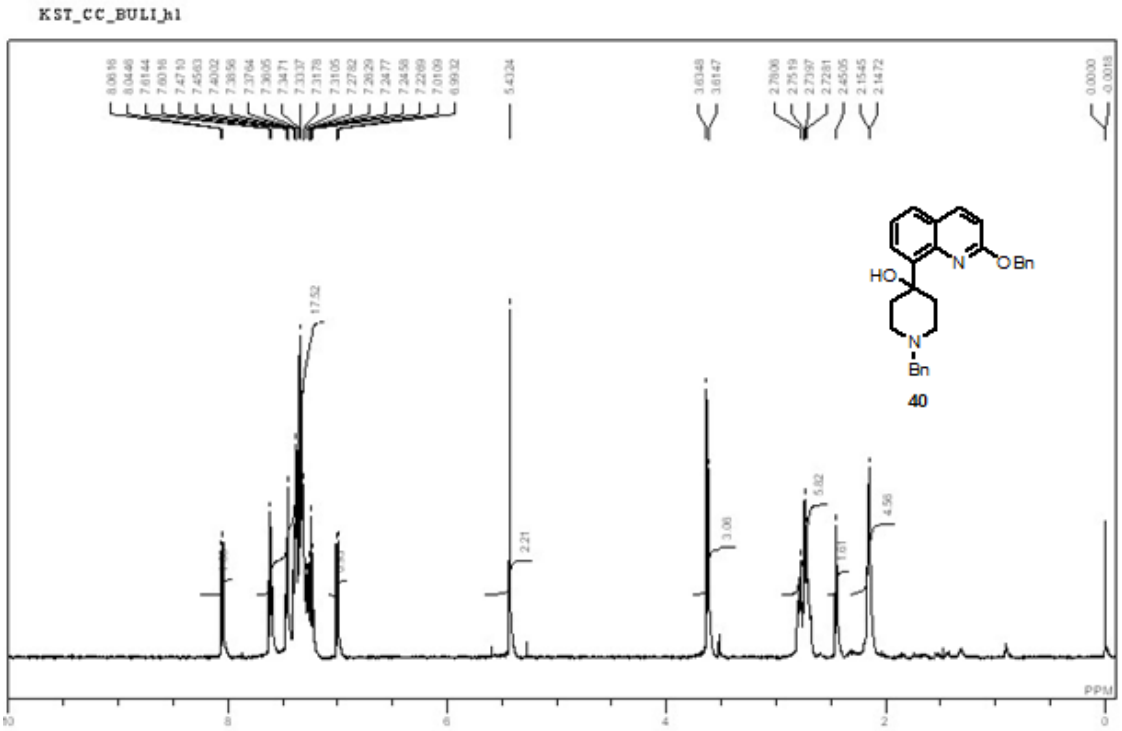
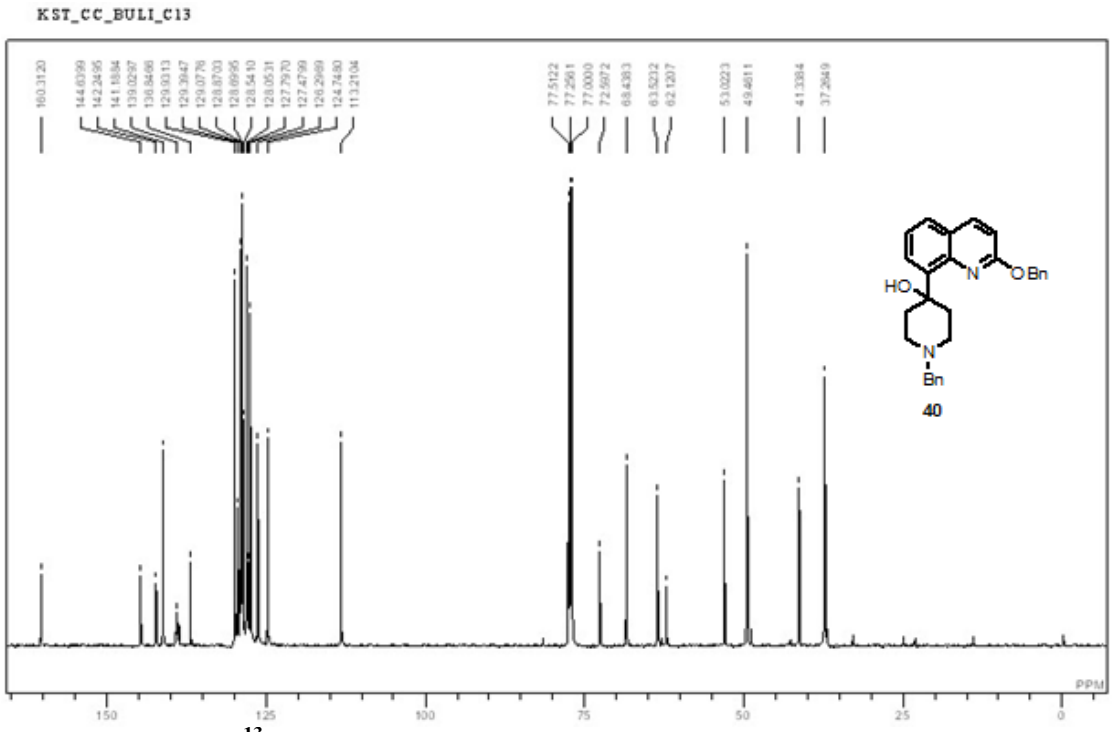
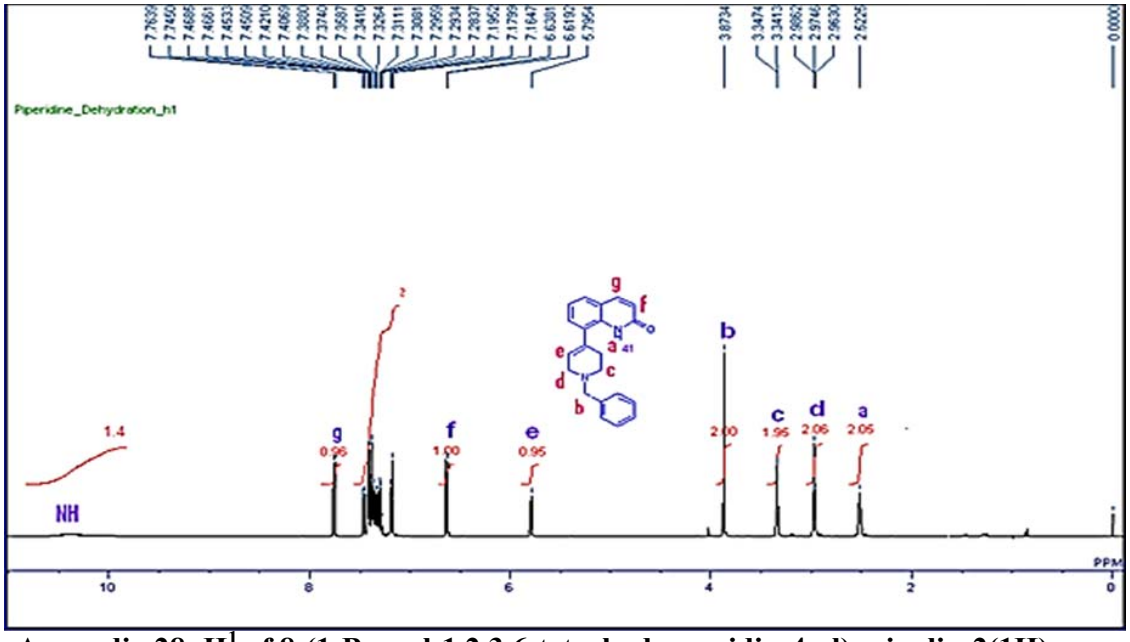


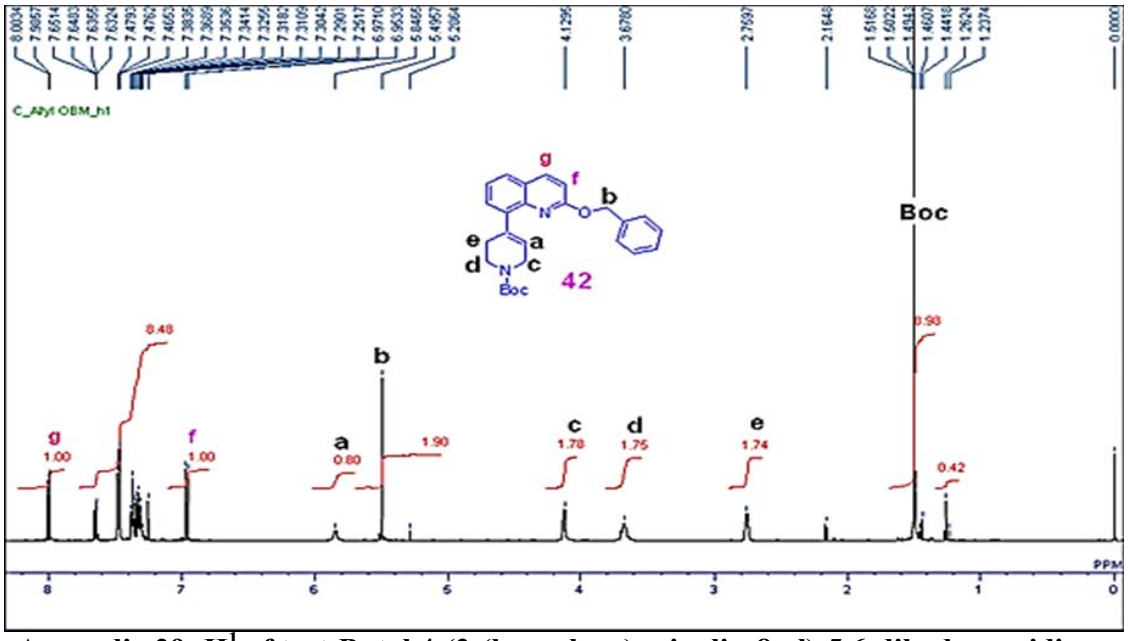
Appendix 26: H^1 of 1-Benzyl-4-(2-(benzyloxy)quinolin-8-yl)piperidin-4-ol (40)



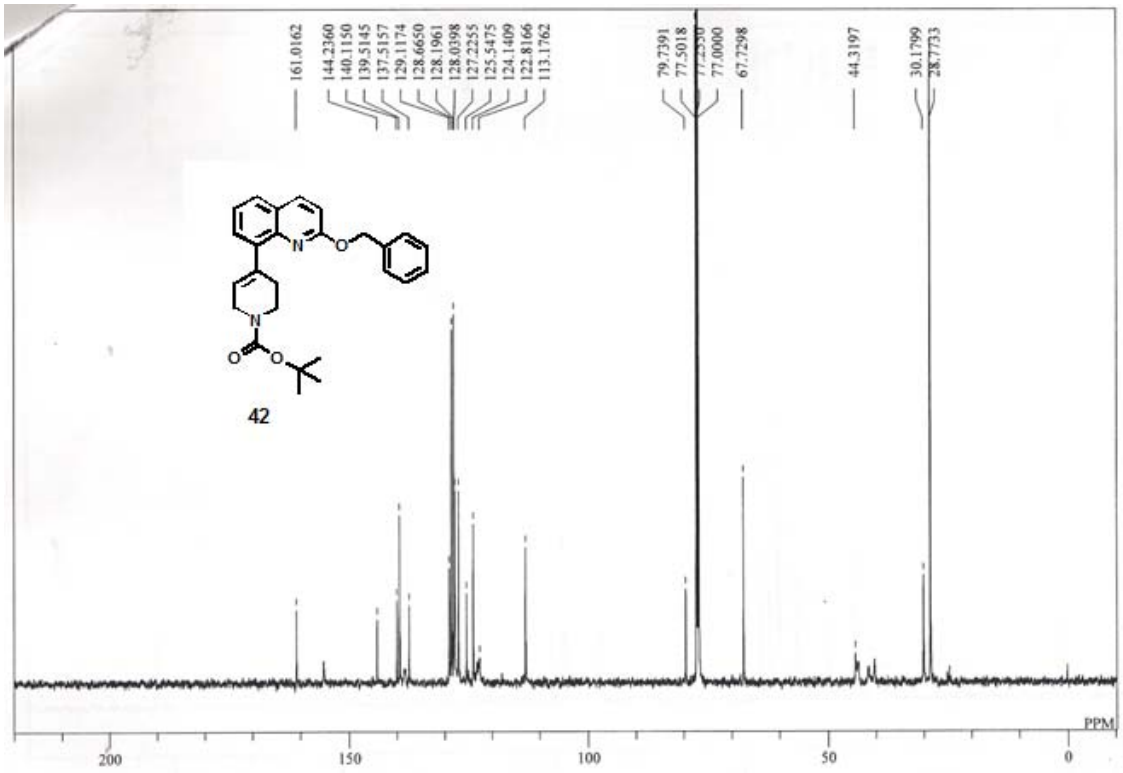
Appendix 27: C^{13} of 1-Benzyl-4-(2-(benzyloxy)quinolin-8-yl)piperidin-4-ol (40)



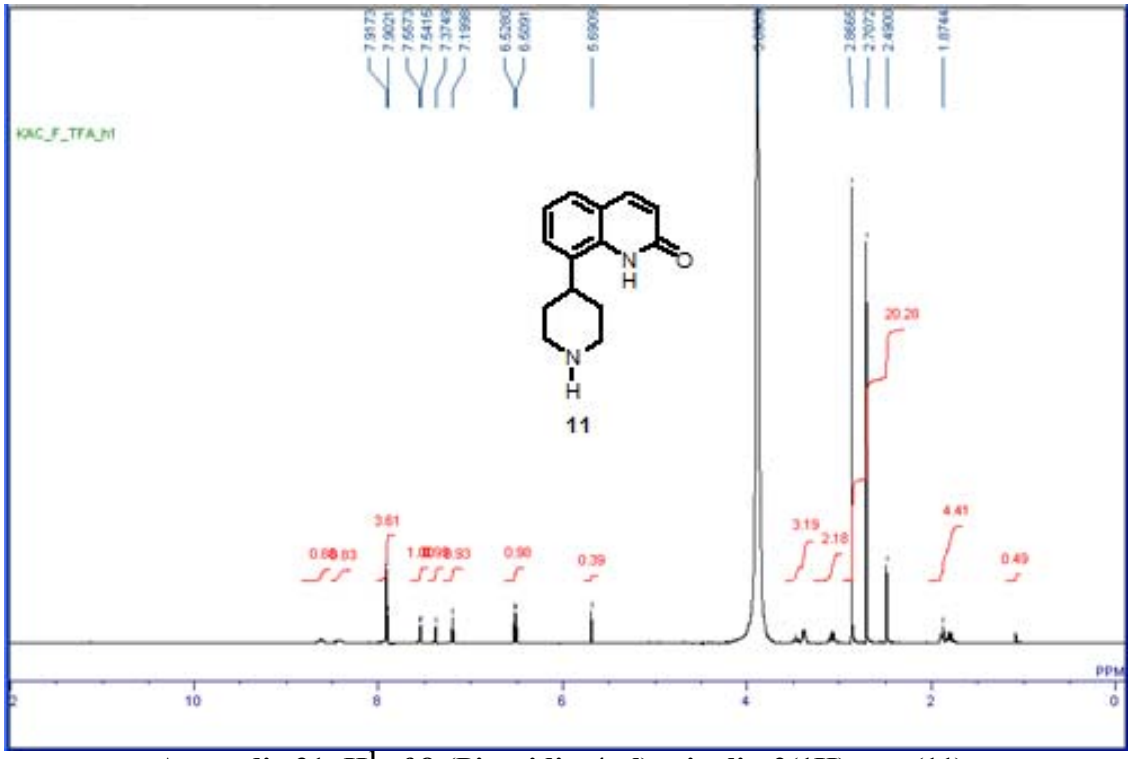
Appendix 28: H^{1} of 8-(1-Benzyl-1,2,3,6-tetrahydropyridin-4-yl)quinolin-2(1H)-one (41)



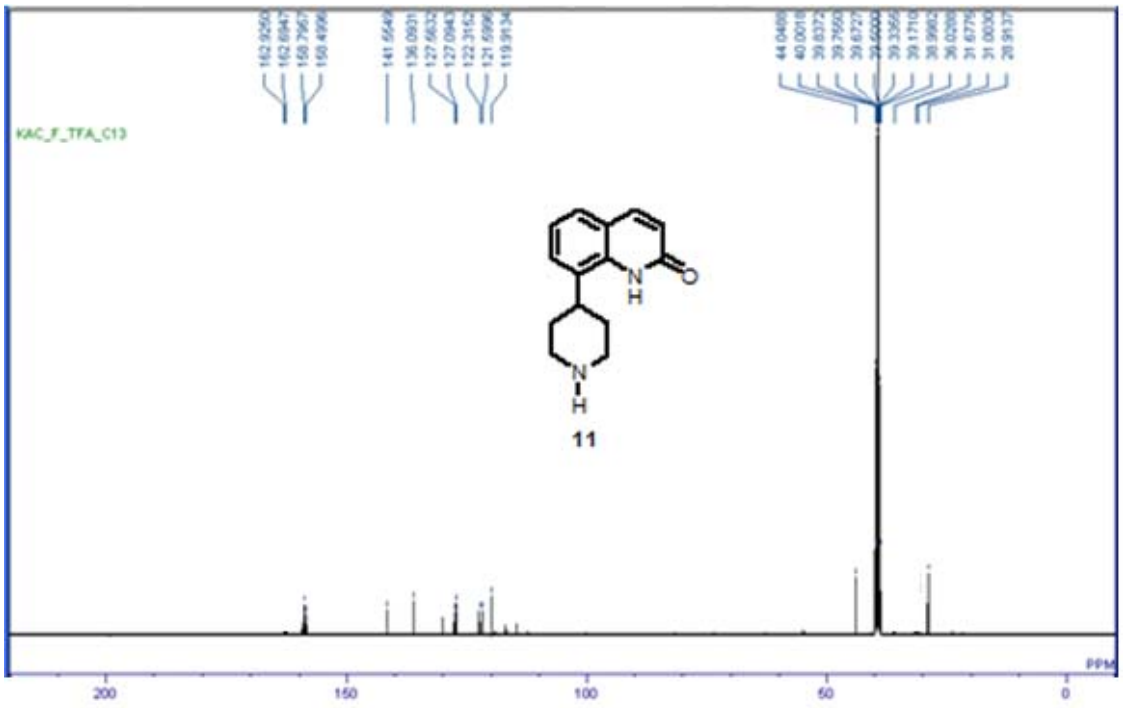
Appendix 29: H^1 of tert-Butyl 4-(2-(benzyloxy)quinolin-8-yl)-5,6-dihydropyridine-1(2H)-carboxylate (42)



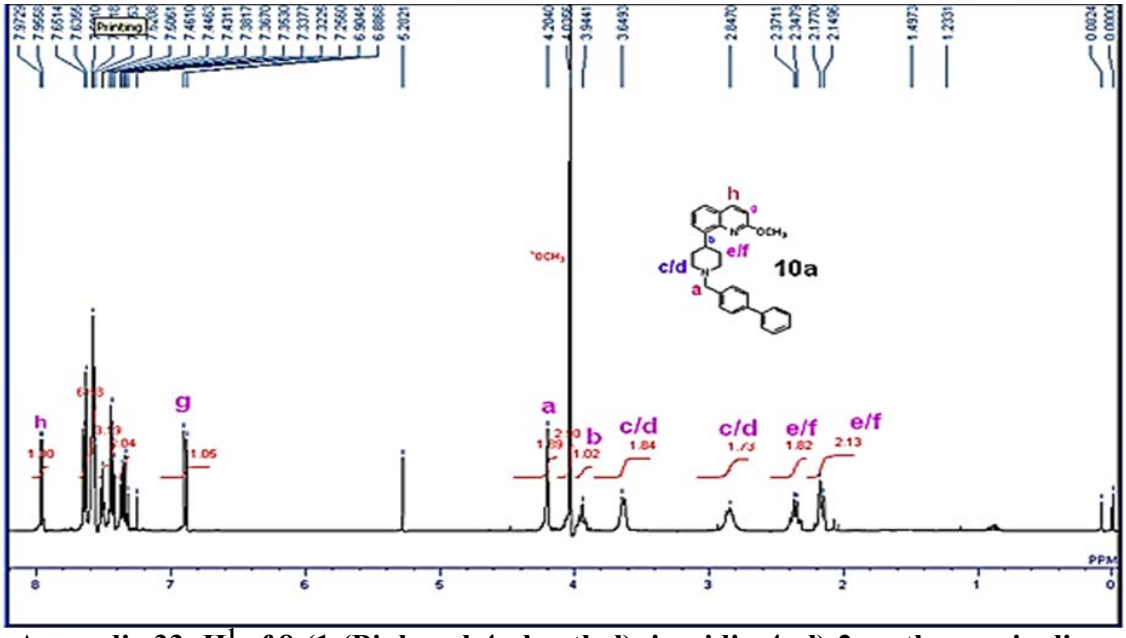
Appendix 30: C^{13} of tert-Butyl 4-(2-(benzyloxy)quinolin-8-yl)-5,6-dihydropyridine-1(2H)-carboxylate (42)



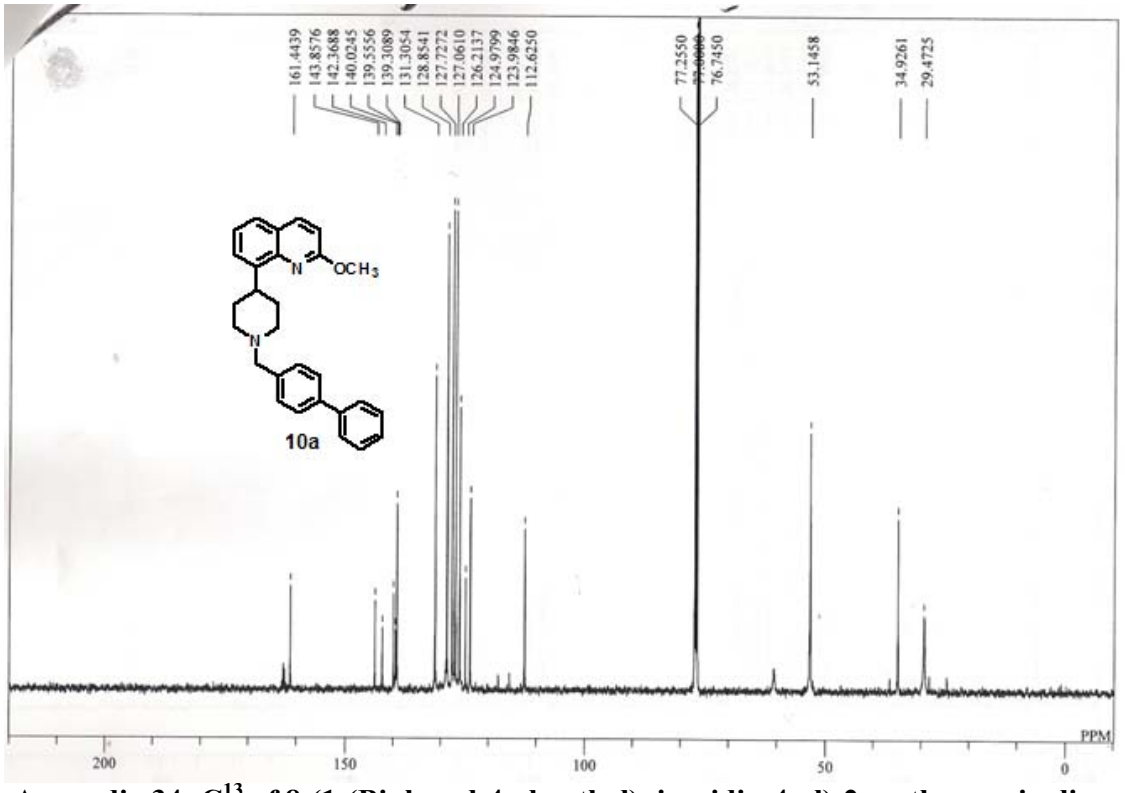
Appendix 31: H^1 of 8-(Piperidin-4-yl)quinolin-2(1H)-one (11)



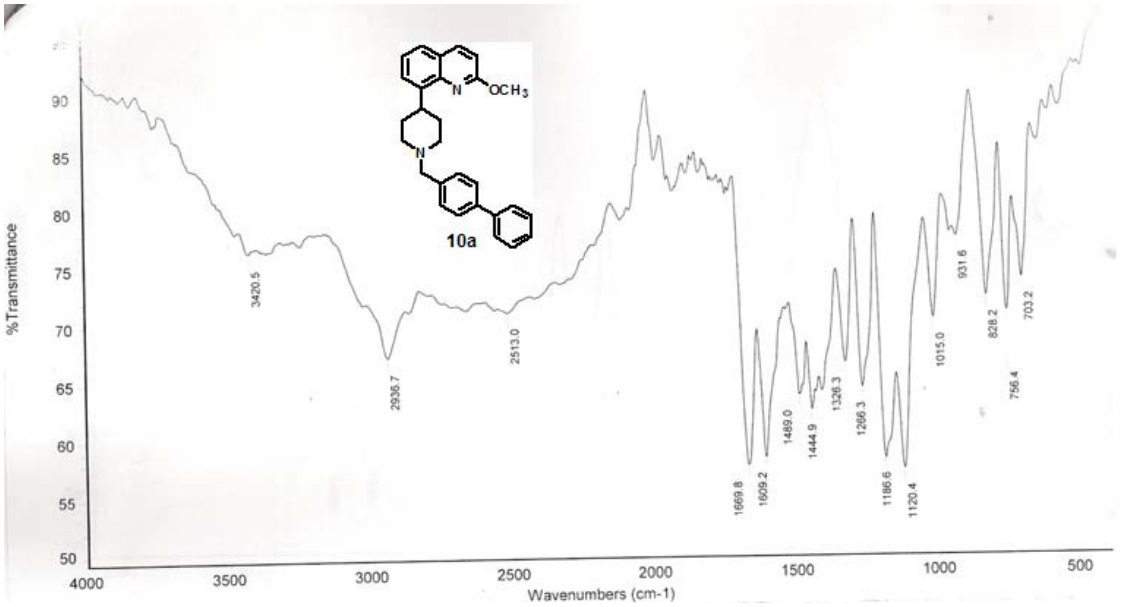
Appendix 32: C^{13} of 8-(Piperidin-4-yl)quinolin-2(1H)-one (11)



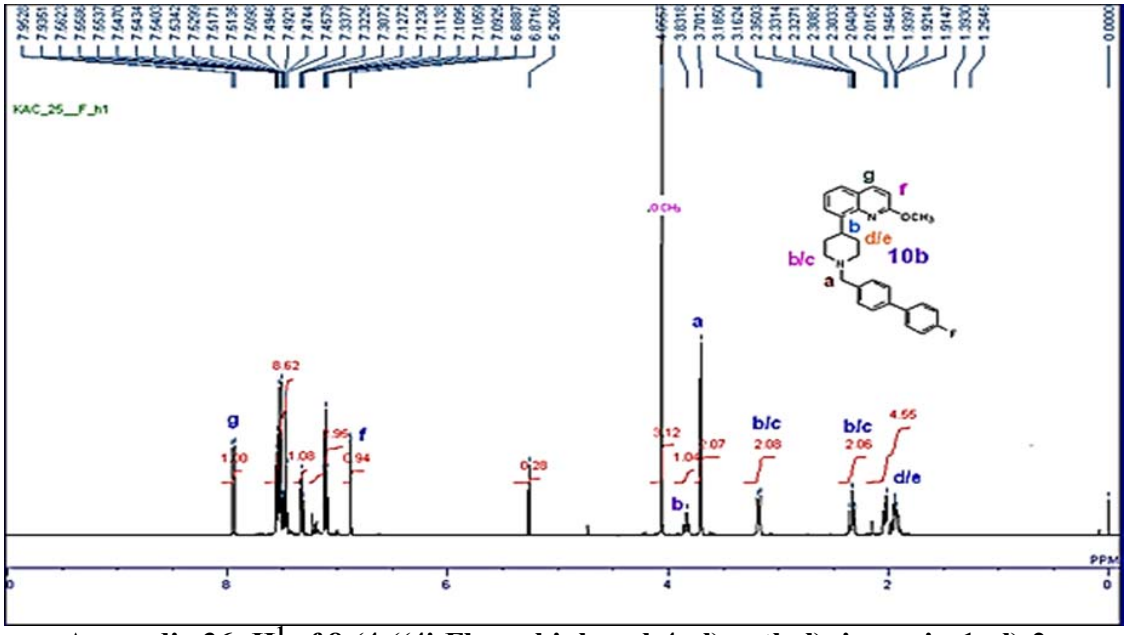
Appendix 33: H^1 of 8-(1-(Biphenyl-4-ylmethyl)piperidin-4-yl)-2-methoxyquinoline (10a)



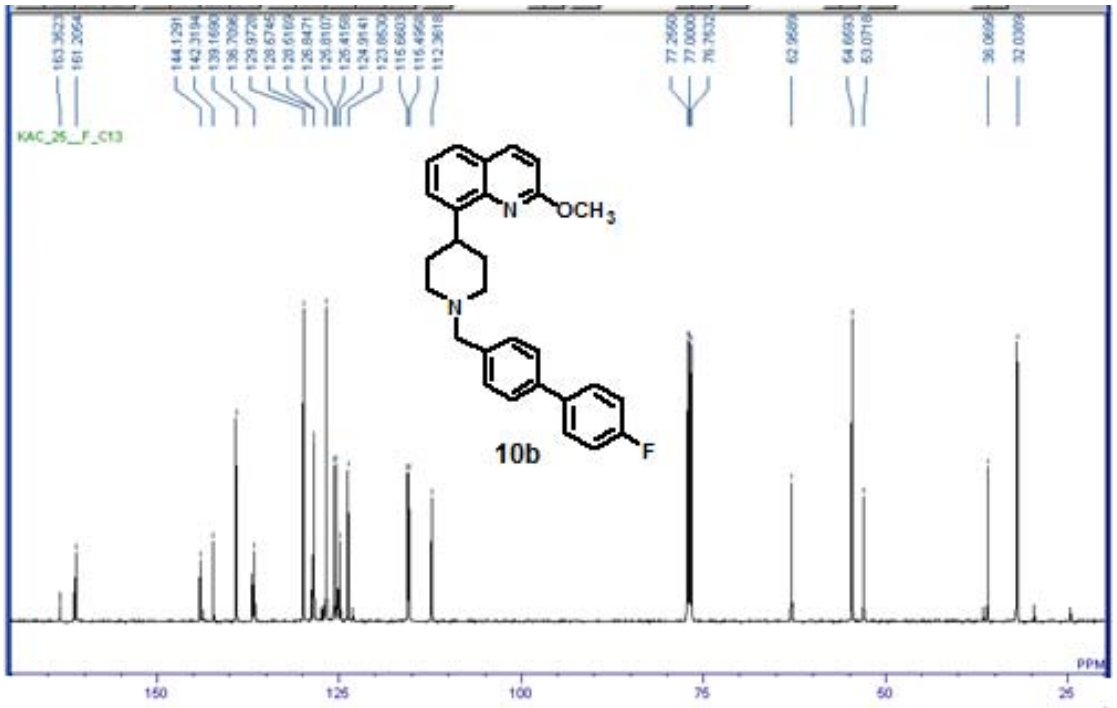
Appendix 34: C^{13} of 8-(1-(Biphenyl-4-ylmethyl)piperidin-4-yl)-2-methoxyquinoline (10a)



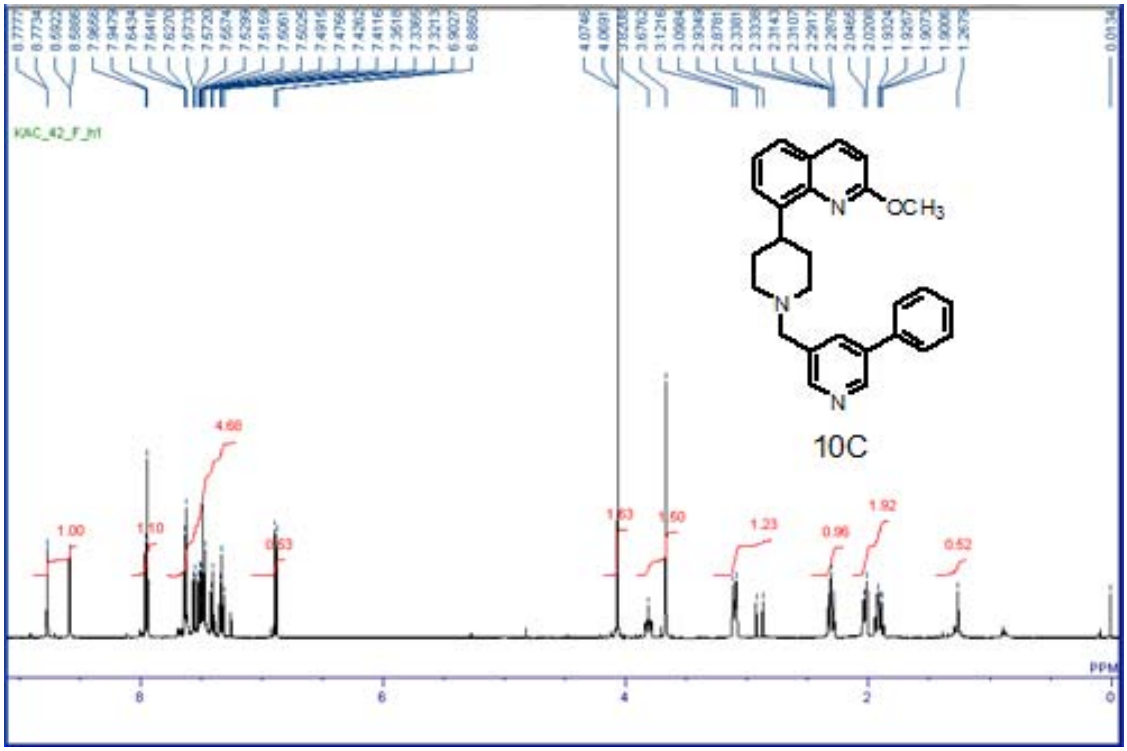
Appendix 35: IR of 8-(1-(Biphenyl-4-ylmethyl)piperidin-4-yl)-2-methoxyquinoline (10a)



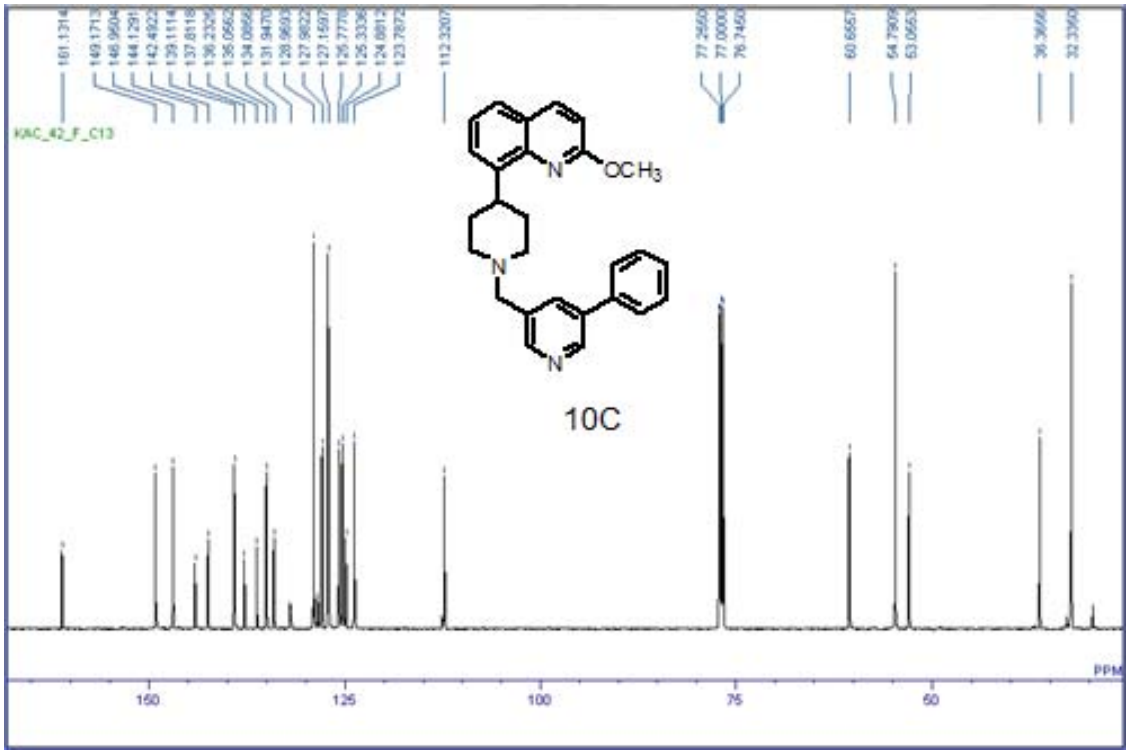
Appendix 36: H^1 of 8-(4-((4'-Fluorobiphenyl-4-yl)methyl)piperazin-1-yl)-2-methoxyquinoline (10b)



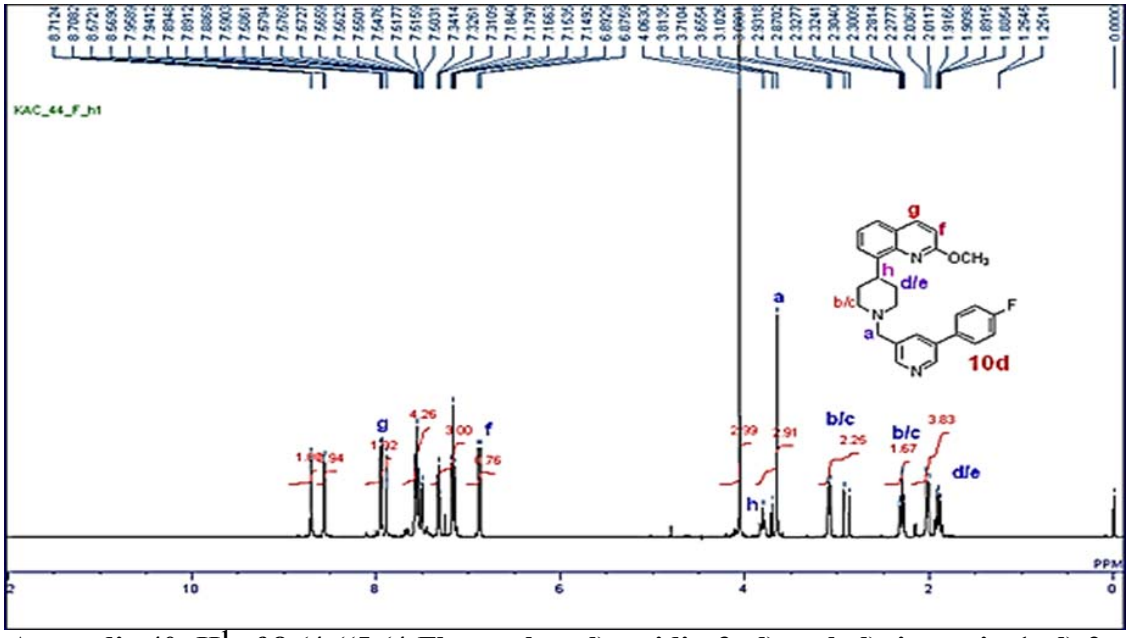
Appendix 37: C^{13} of 8-(4-((4'-Fluorobiphenyl-4-yl)methyl)piperazin-1-yl)-2-methoxyquinoline (10b)



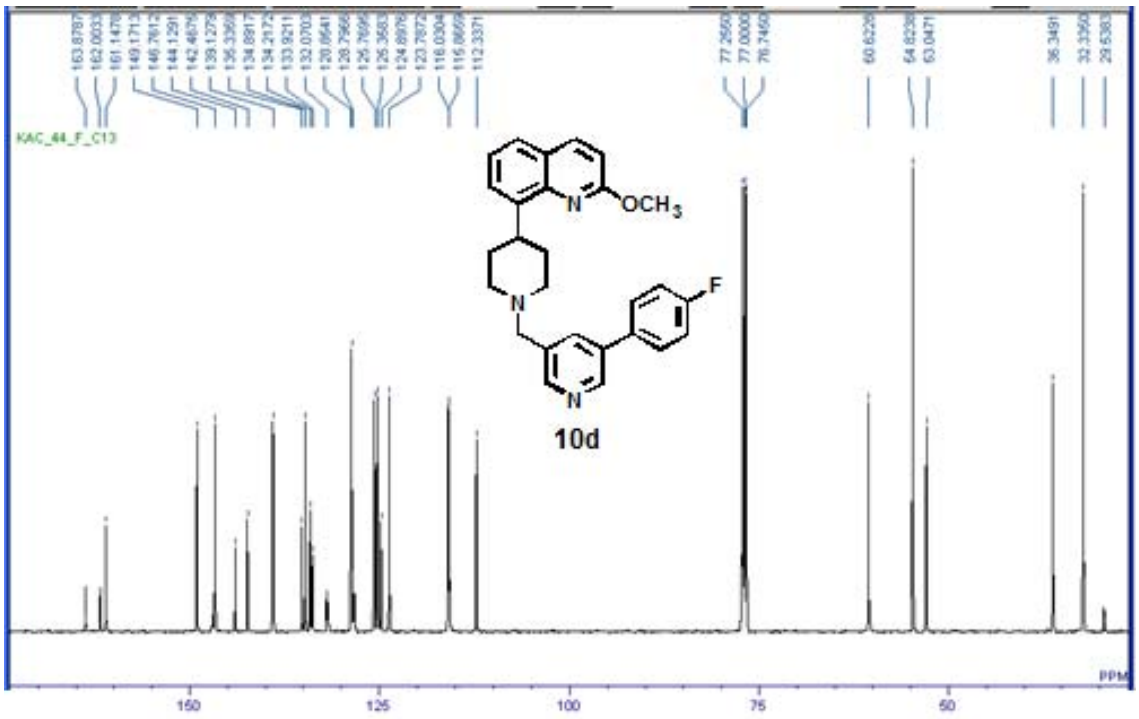
Appendix 38: H^1 of 2-Methoxy-8-(4-((5-phenylpyridin-3-yl)methyl)piperazin-1-yl)quinoline (10c)



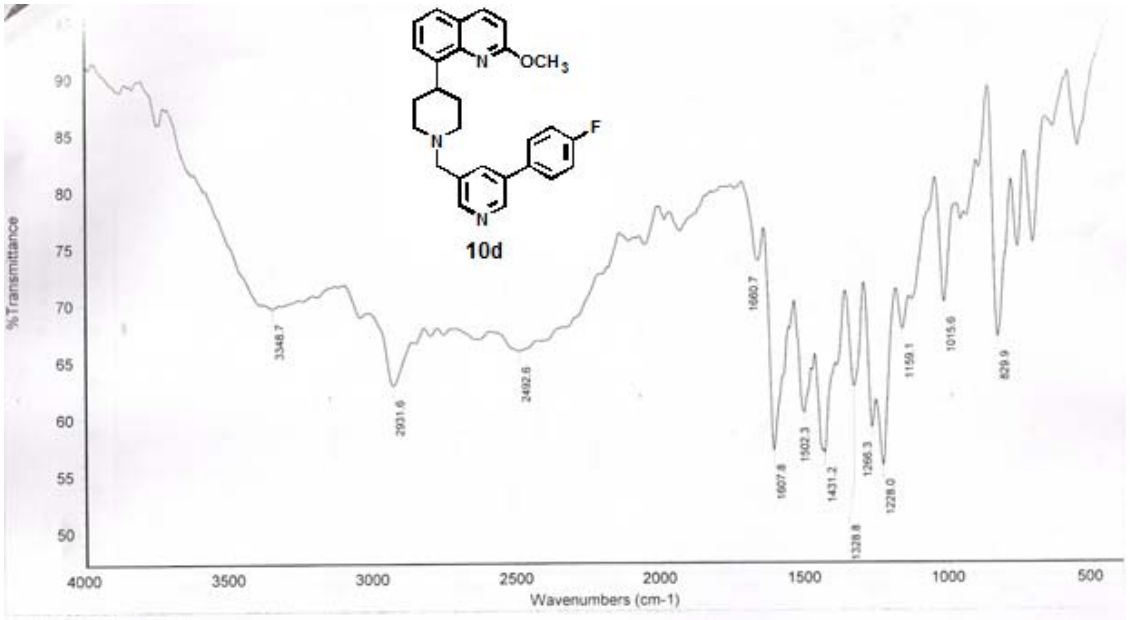
Appendix 39: C^{13} of 2-Methoxy-8-(4-((5-phenylpyridin-3-yl)methyl)piperazin-1-yl)quinoline (10c)



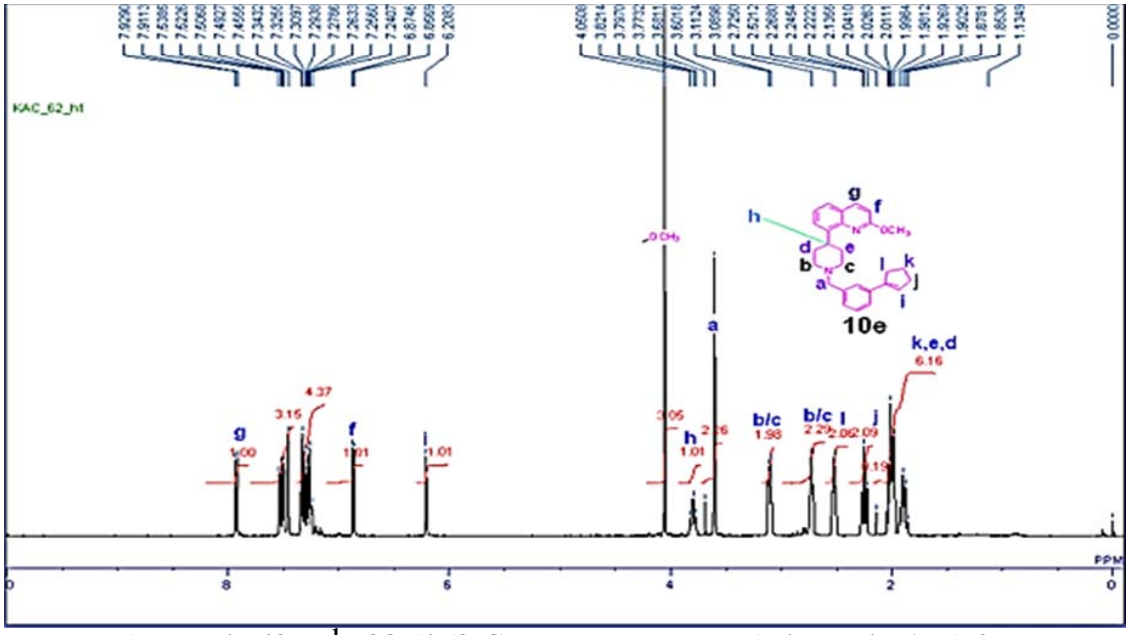
Appendix 40: H^1 of 8-(4-((5-(4-Fluorophenyl)pyridin-3-yl)methyl)piperazin-1-yl)-2-methoxyquinoline (10d)



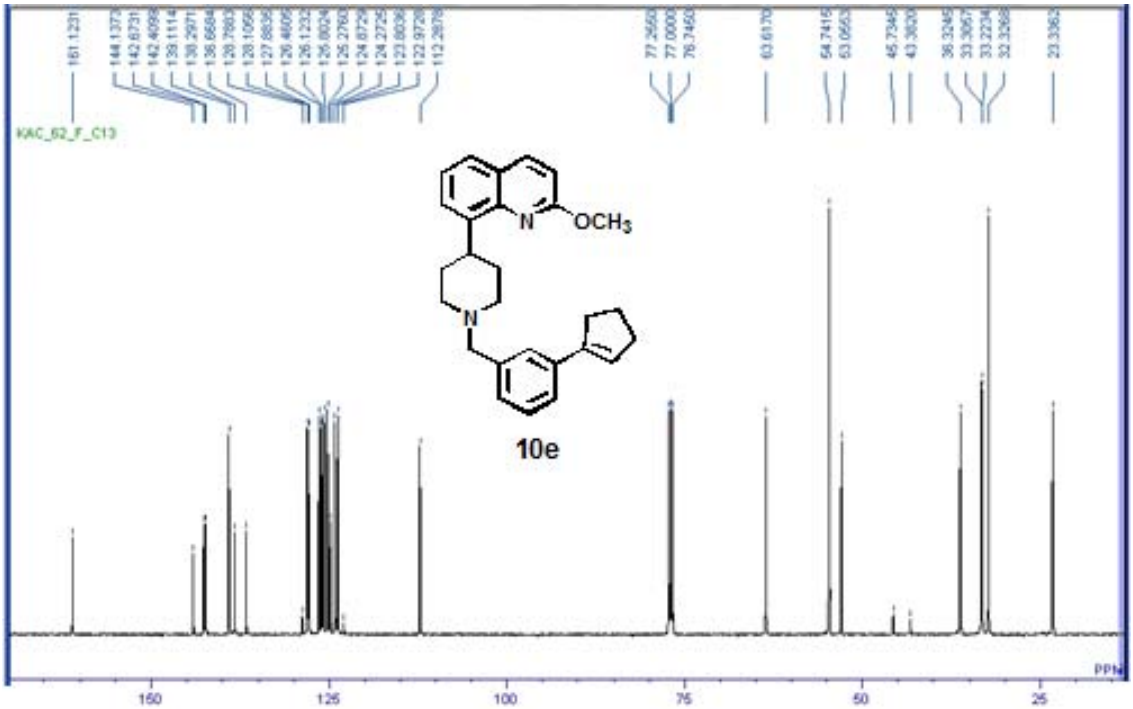
Appendix 41: C^{13} of 8-(4-((5-(4-Fluorophenyl)pyridin-3-yl)methyl)piperazin-1-yl)-2-methoxyquinoline (10d)



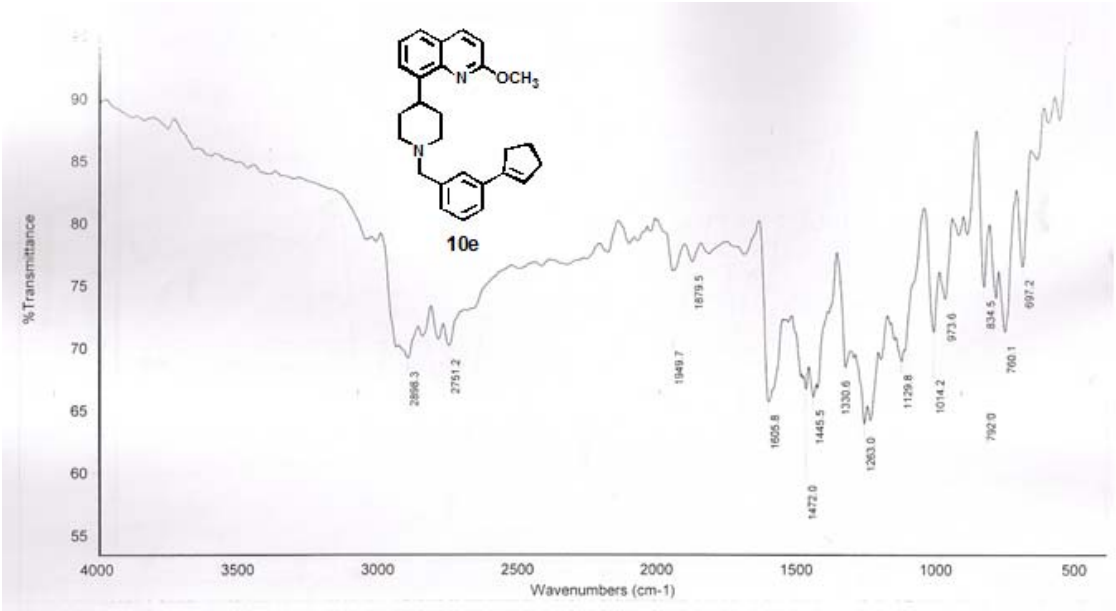
Appendix 42: IR of 8-(4-((5-(4-Fluorophenyl)pyridin-3-yl)methyl)piperazin-1-yl)-2-methoxyquinoline (10d)



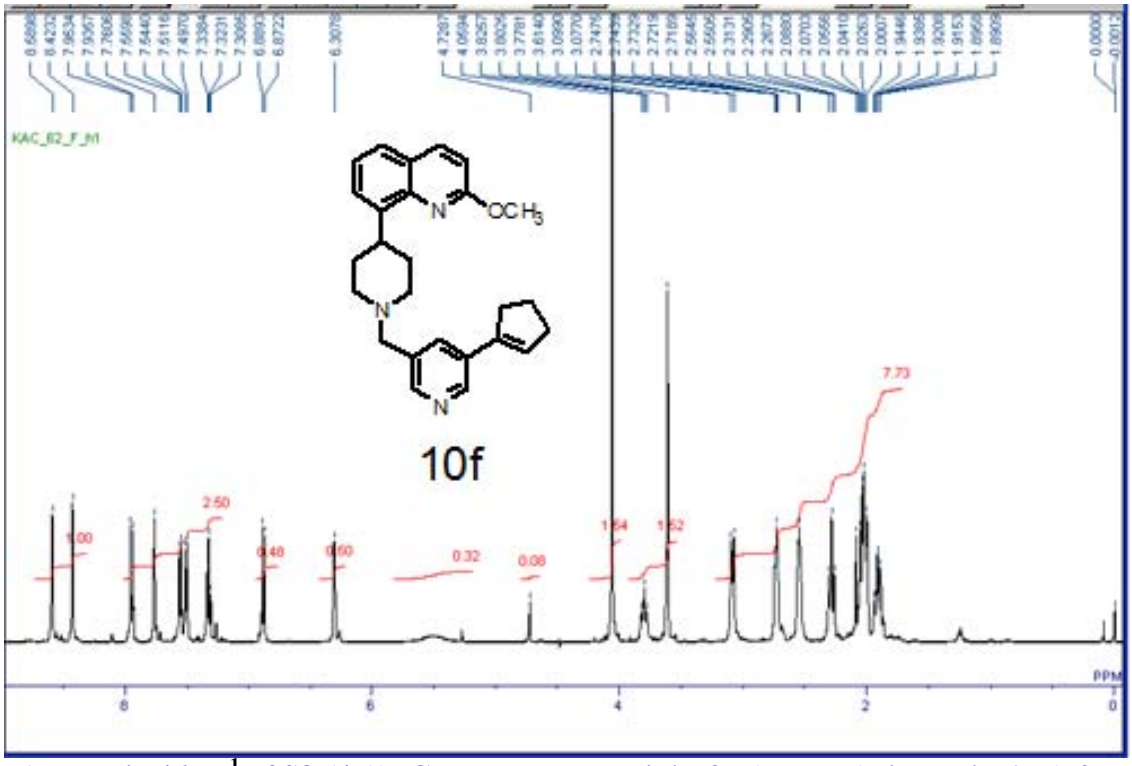
Appendix 43: H^1 of 8-(4-(3-Cyclopentenylbenzyl)piperazin-1-yl)-2-methoxyquinoline(10e)



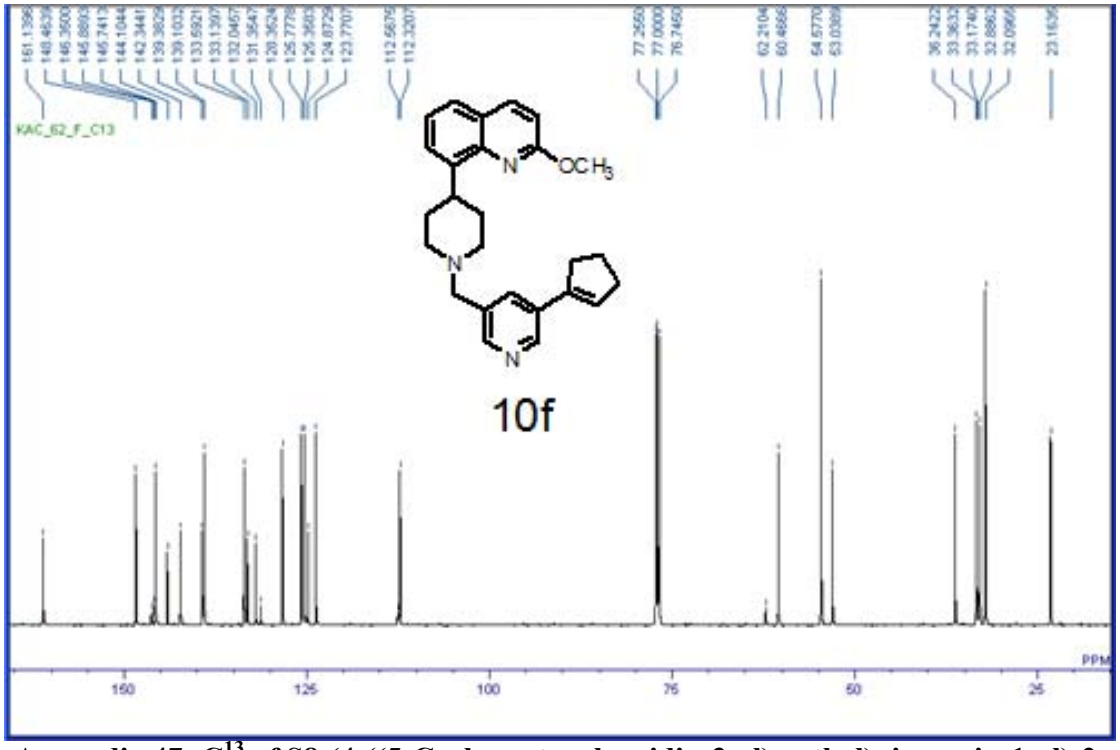
Appendix 44: C^{13} of 8-(4-(3-Cyclopentenylbenzyl)piperazin-1-yl)-2-methoxyquinoline (10e)



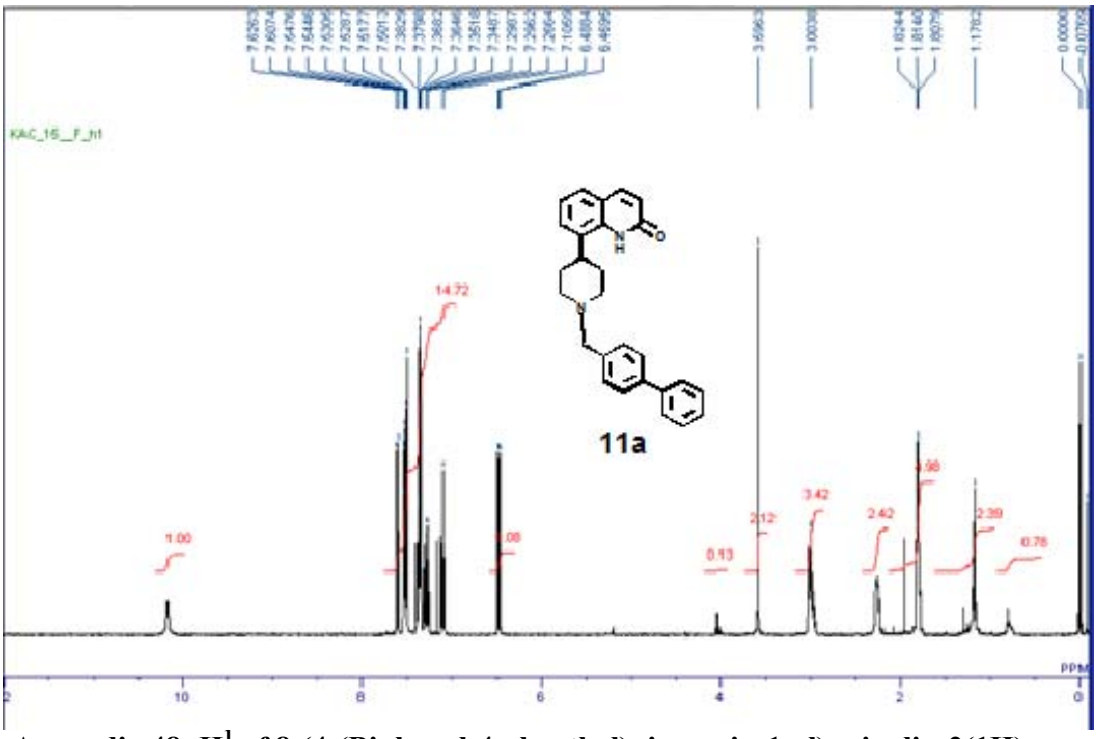
Appendix 45: IR of 8-(4-(3-Cyclopentenylbenzyl)piperazin-1-yl)-2-methoxyquinoline (10e)



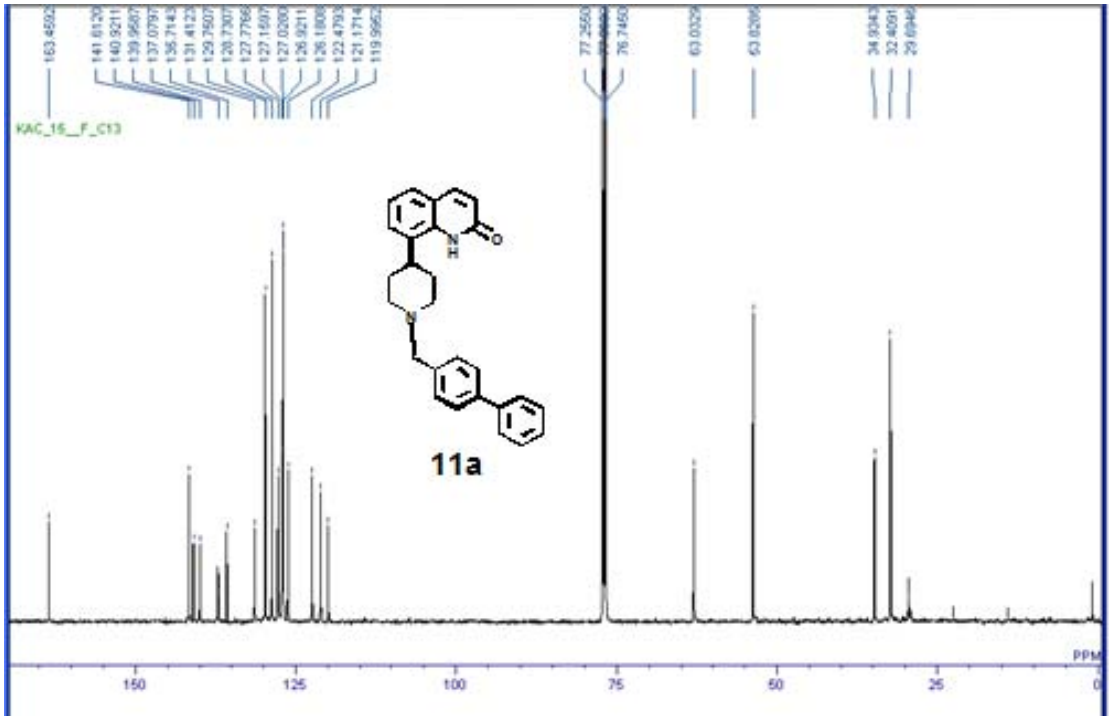
Appendix 46: H^1 of S8-(4-((5-Cyclopentenylpyridin-3-yl)methyl)piperazin-1-yl)-2-methoxyquinoline (10f)



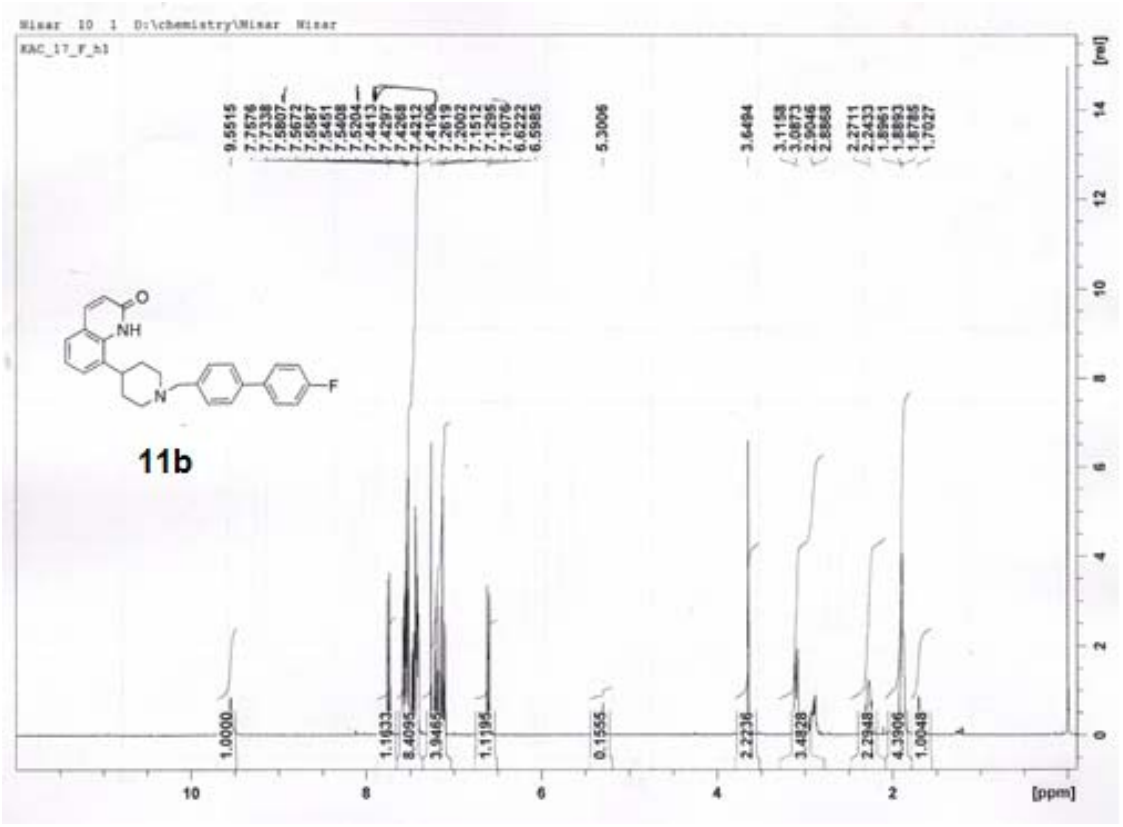
Appendix 47: C^{13} of S8-(4-((5-Cyclopentenylpyridin-3-yl)methyl)piperazin-1-yl)-2-methoxyquinoline (10f)



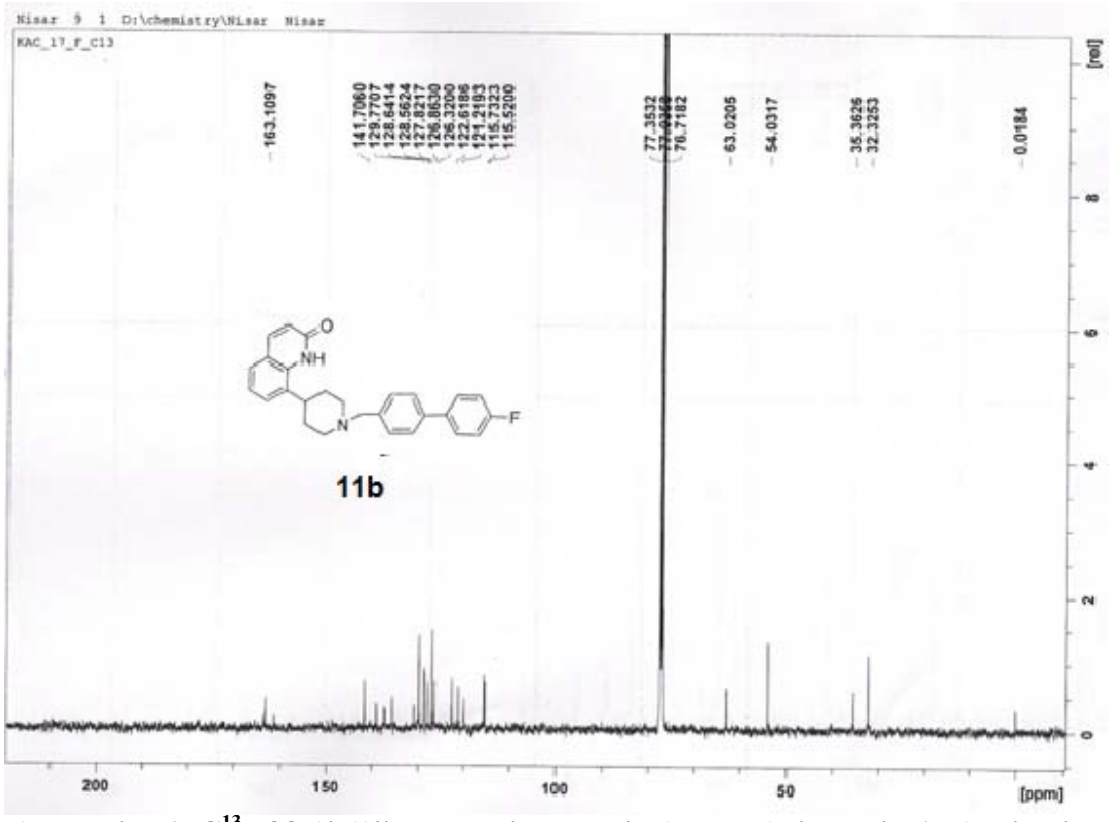
Appendix 48: H^1 of 8-(4-(Biphenyl-4-ylmethyl)piperazin-1-yl)quinolin-2(1H)-one (11a)



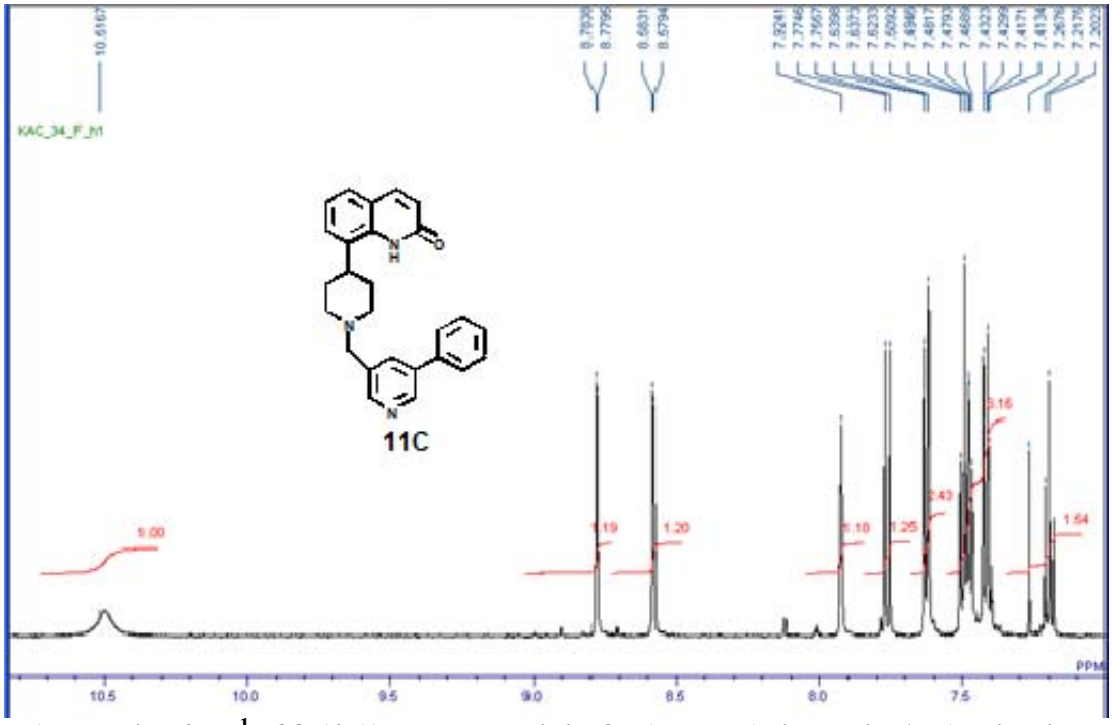
Appendix 49: C^{13} of 8-(4-(Biphenyl-4-ylmethyl)piperazin-1-yl)quinolin-2(1H)-one (11a)



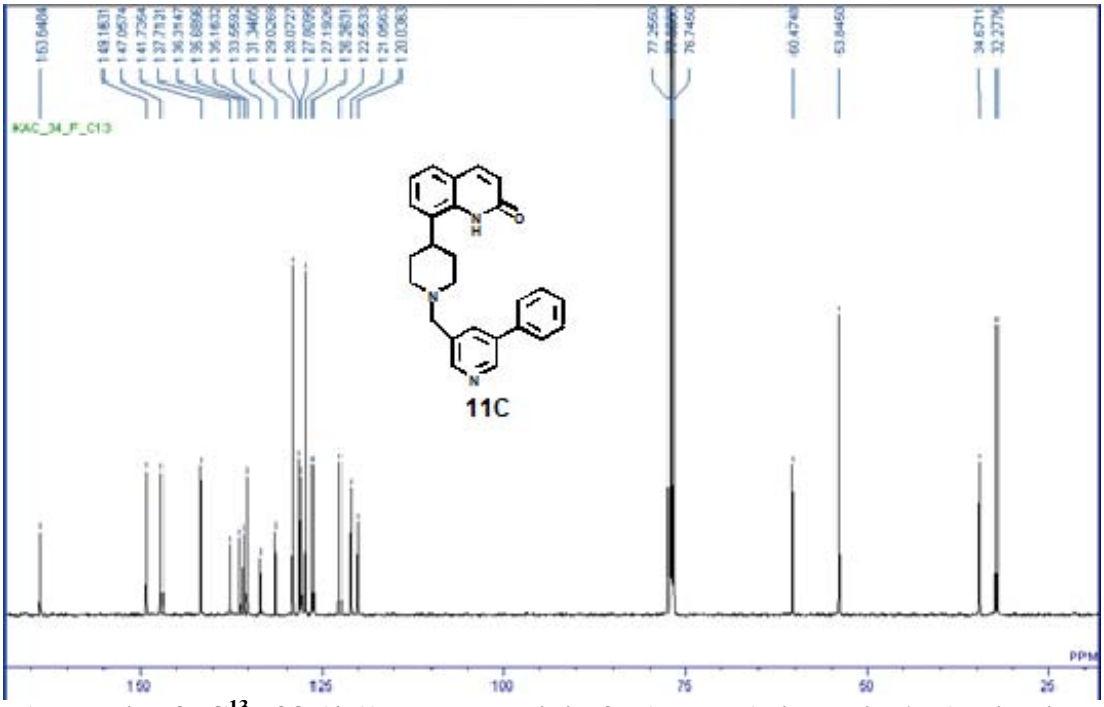
Appendix 50: H^1 of 8-(4-((4'-Fluorobiphenyl-4-yl)methyl)piperazin-1-yl)quinolin-2(1H)-one (11b)



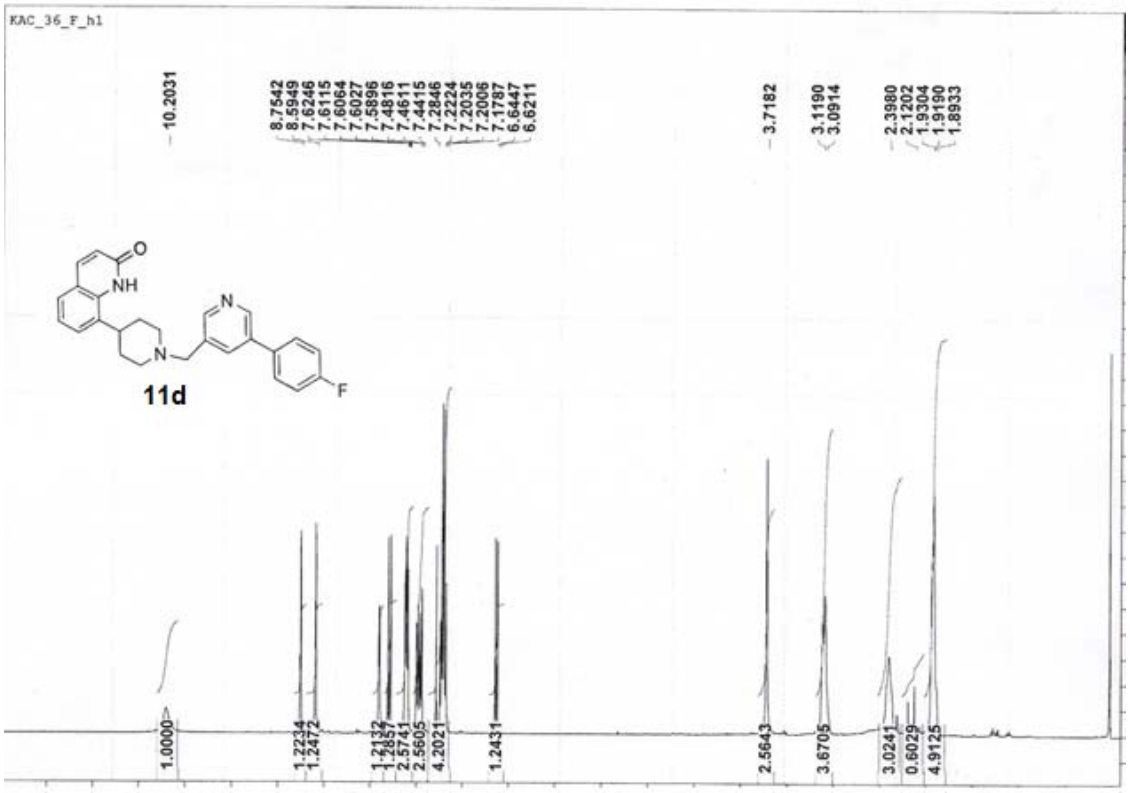
Appendix 51: C^{13} of 8-(4-((4'-Fluorobiphenyl-4-yl)methyl)piperazin-1-yl)quinolin-2(1H)-one (11b)



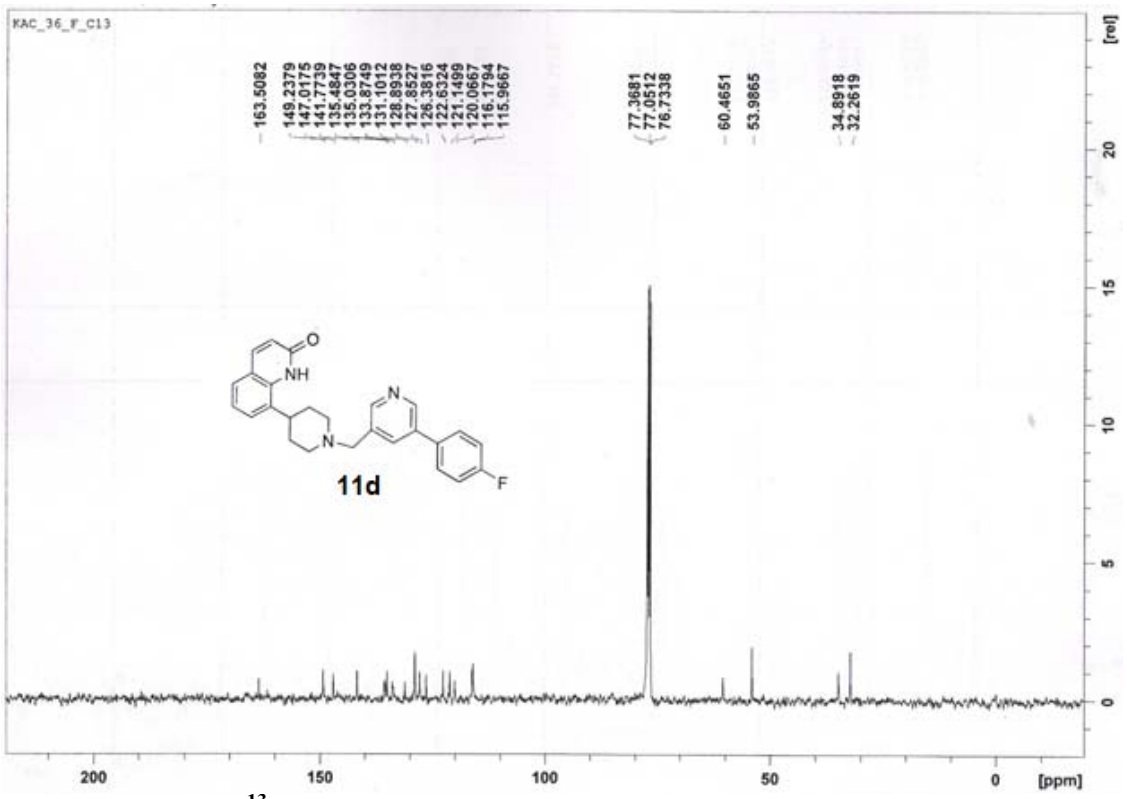
Appendix 52: H^1 of 8-(4-((5-Phenylpyridin-3-yl)methyl)piperazin-1-yl)quinolin-2(1H)-one (11c)



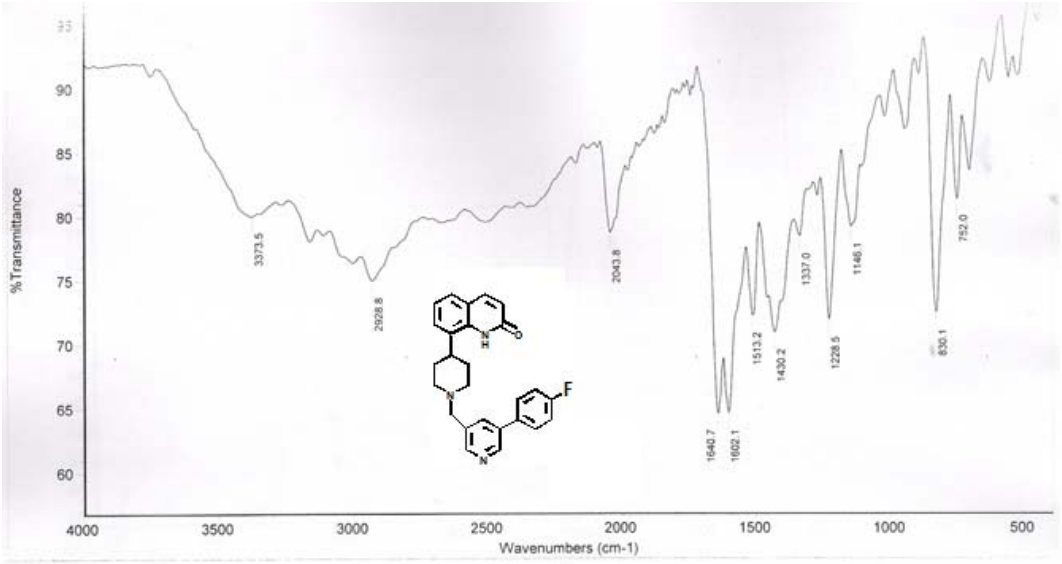
Appendix 53: C^{13} of 8-(4-((5-Phenylpyridin-3-yl)methyl)piperazin-1-yl)quinolin-2(1H)-one (11c)



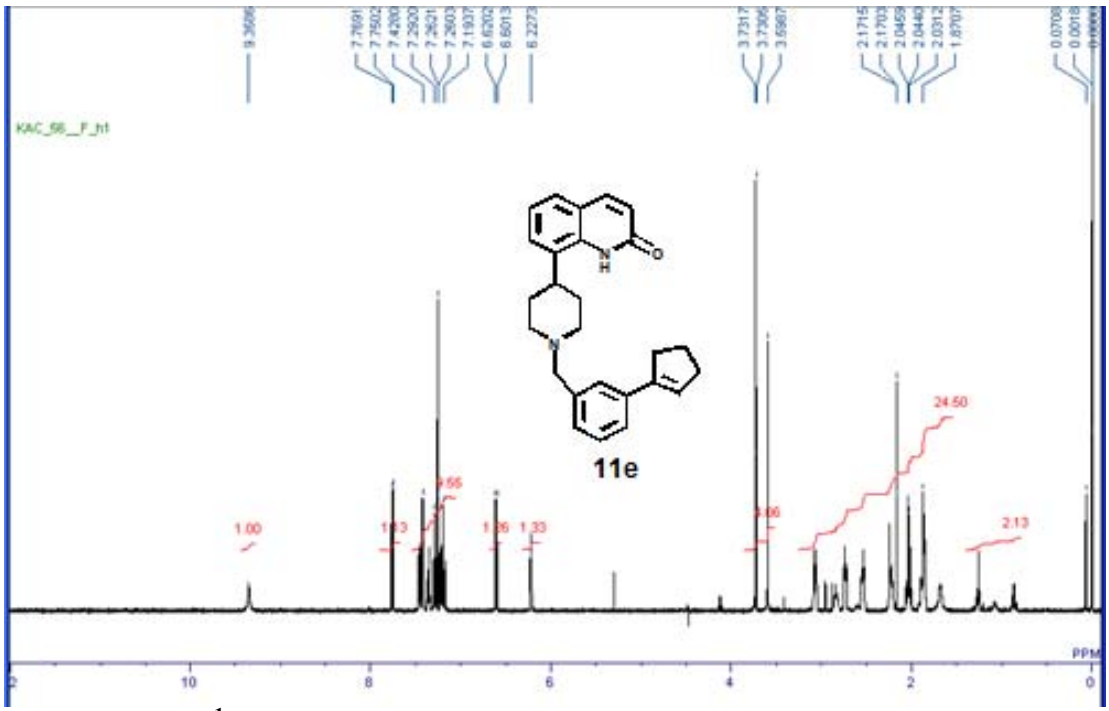
Appendix 54: H^1 of 8-(4-((5-(4-Fluorophenyl)pyridin-3-yl)methyl)piperazin-1-yl)quinolin-2(1H)-one (11d)



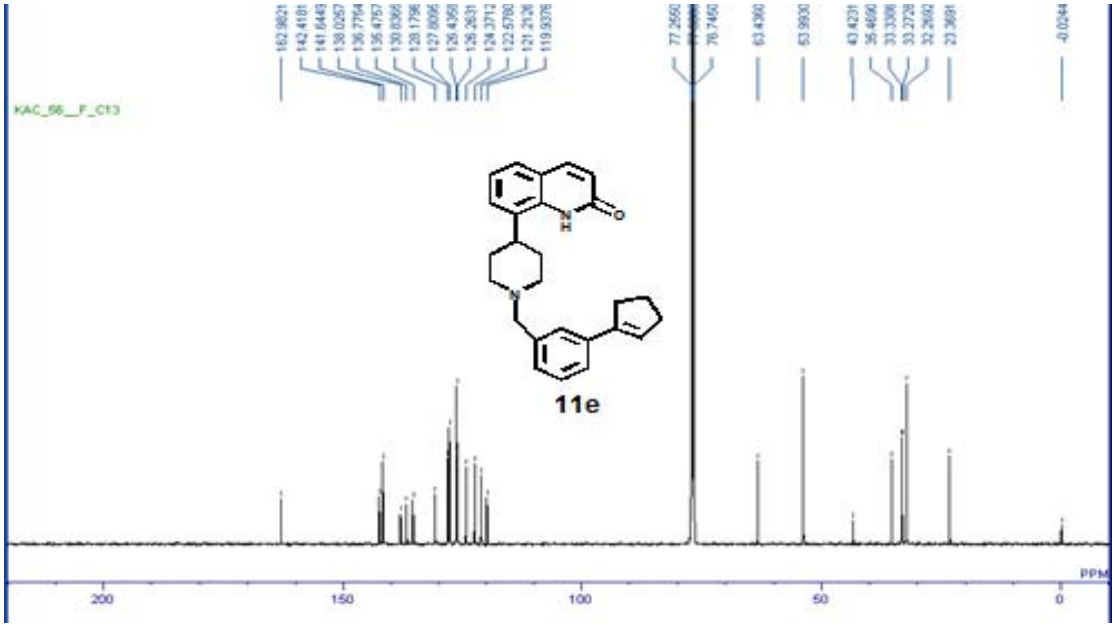
Appendix 55: C^{13} of 8-(4-((5-(4-Fluorophenyl)pyridin-3-yl)methyl)piperazin-1-yl)quinolin-2(1H)-one (11d)



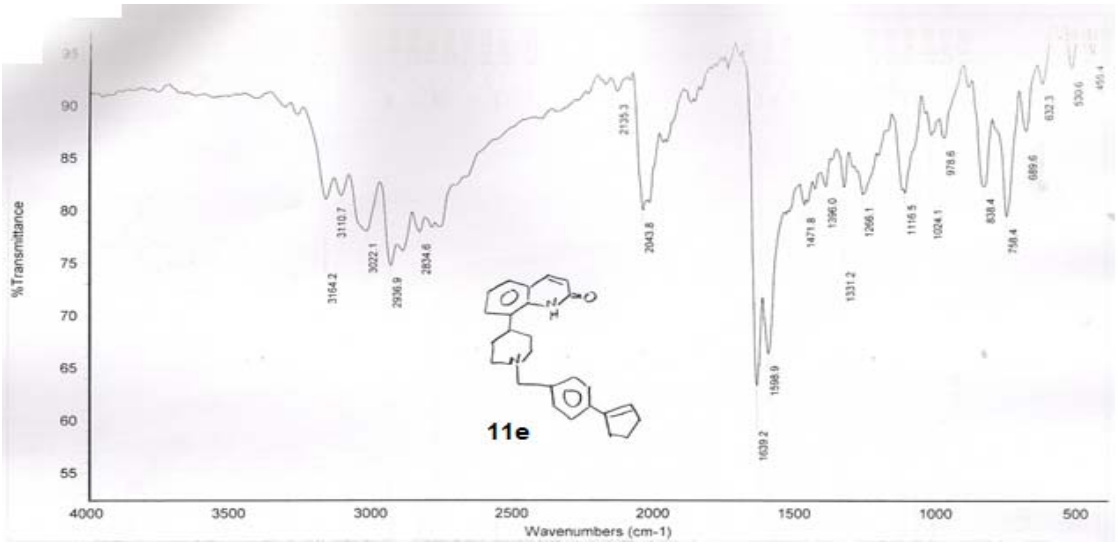
Appendix 56: IR of 8-(4-((5-(4-Fluorophenyl) pyridin-3-yl) methyl) piperazin-1-yl) quinolin-2(1H)-one (11d)



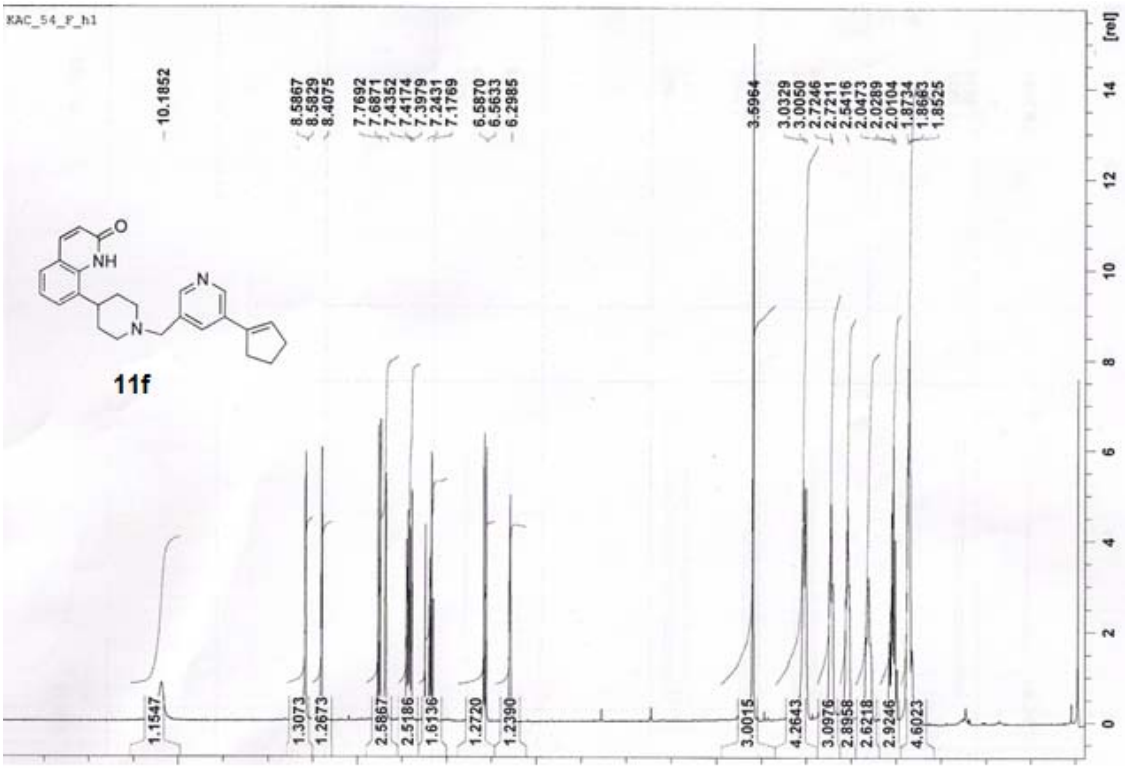
Appendix 57: H^1 of 8-(4-(3-Cyclopentenylbenzyl)piperazin-1-yl)quinolin-2(1H)-one (11e)



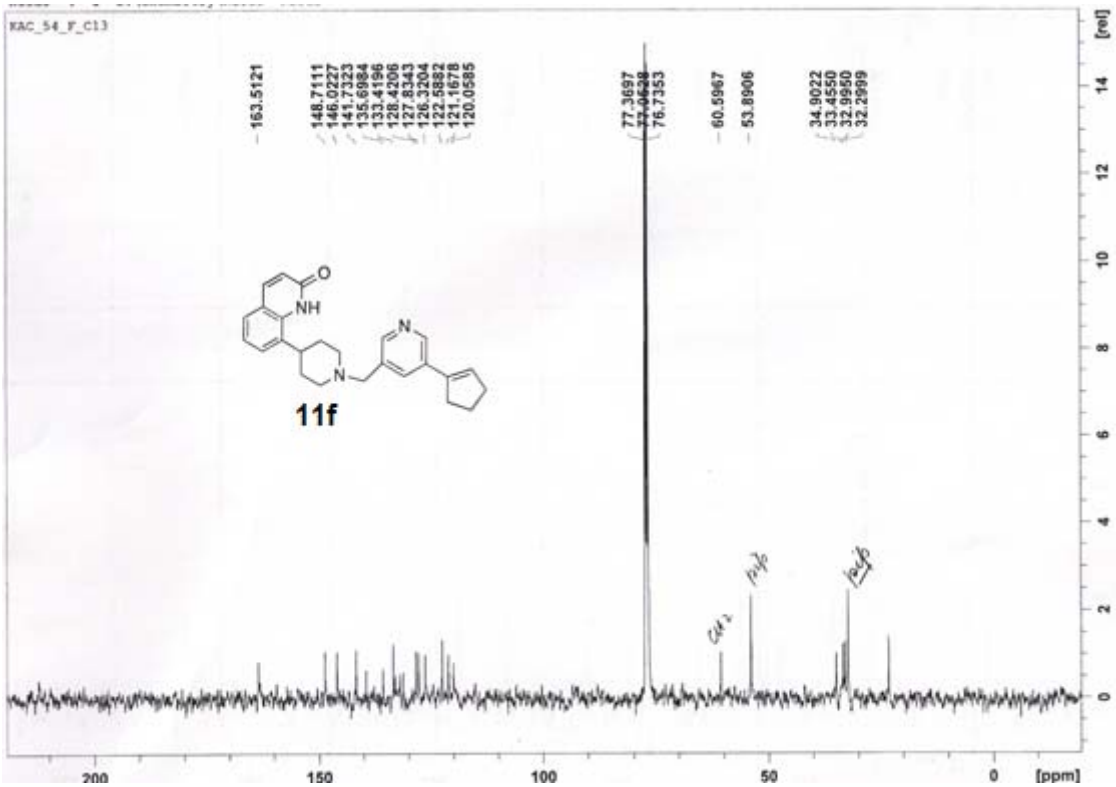
Appendix 58: C^{13} of 8-(4-(3-Cyclopentenylbenzyl)piperazin-1-yl)quinolin-2(1H)-one (11e)



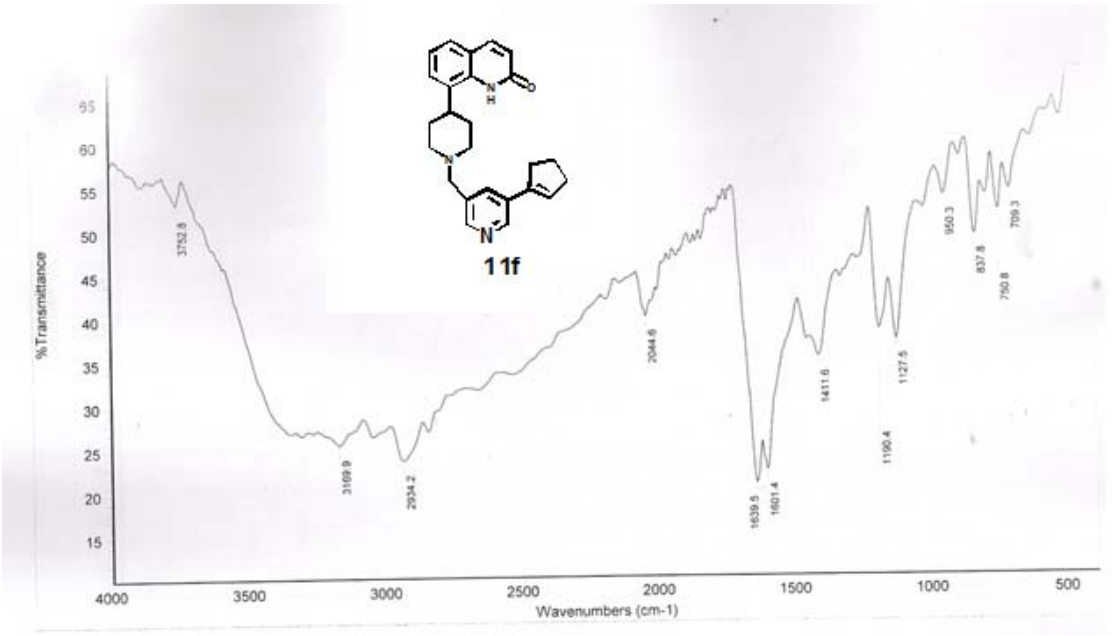
Appendix 59: IR of 8-(4-(3-Cyclopentenylbenzyl)piperazin-1-yl)quinolin-2(1H)-one (11e)



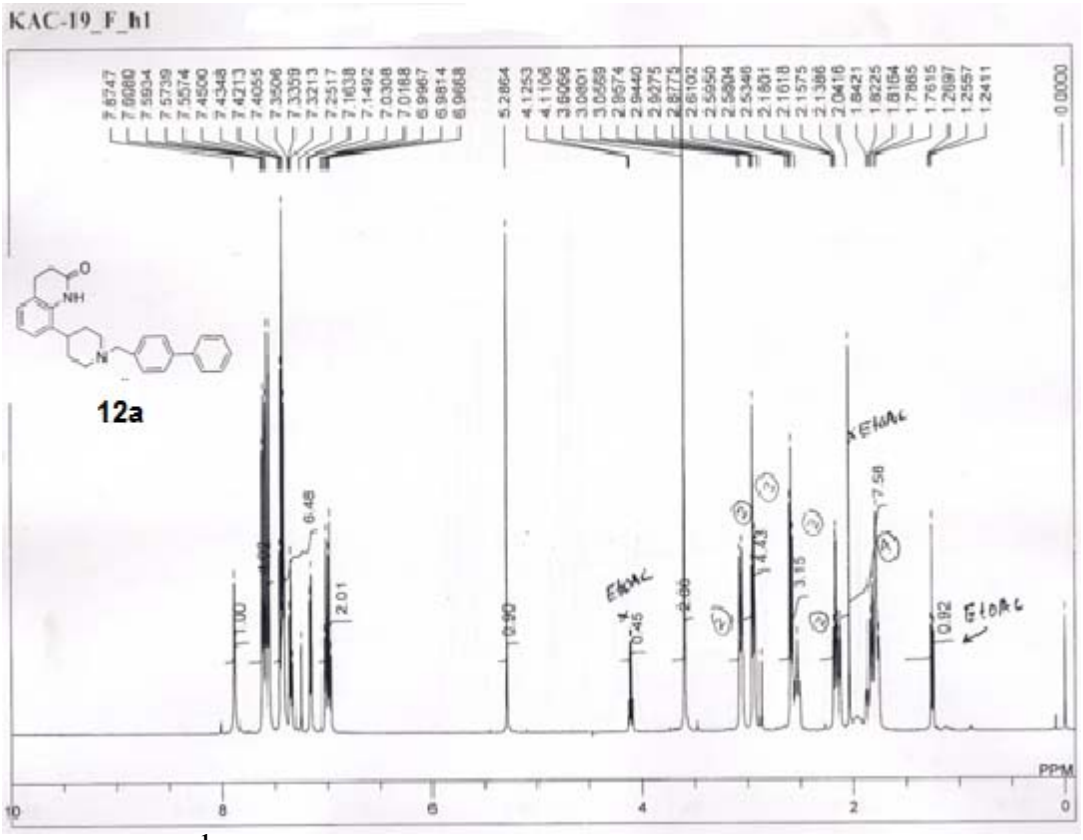
Appendix 60: H^1 of 8-(4-((5-Cyclopentenylpyridin-3-yl)methyl)piperazin-1-yl)quinolin-2(1H)-one (11f)



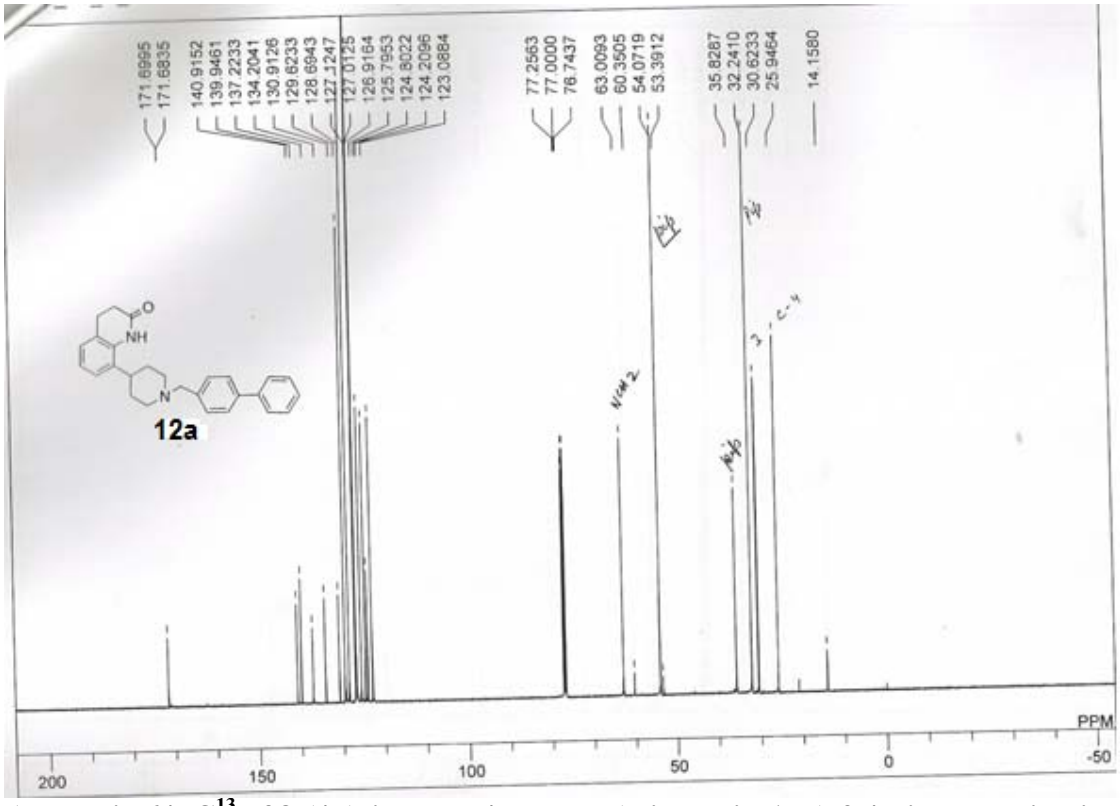
Appendix 61: C^{13} of 8-(4-((5-Cyclopentenylpyridin-3-yl)methyl)piperazin-1-yl)quinolin-2(1H)-one (11f)



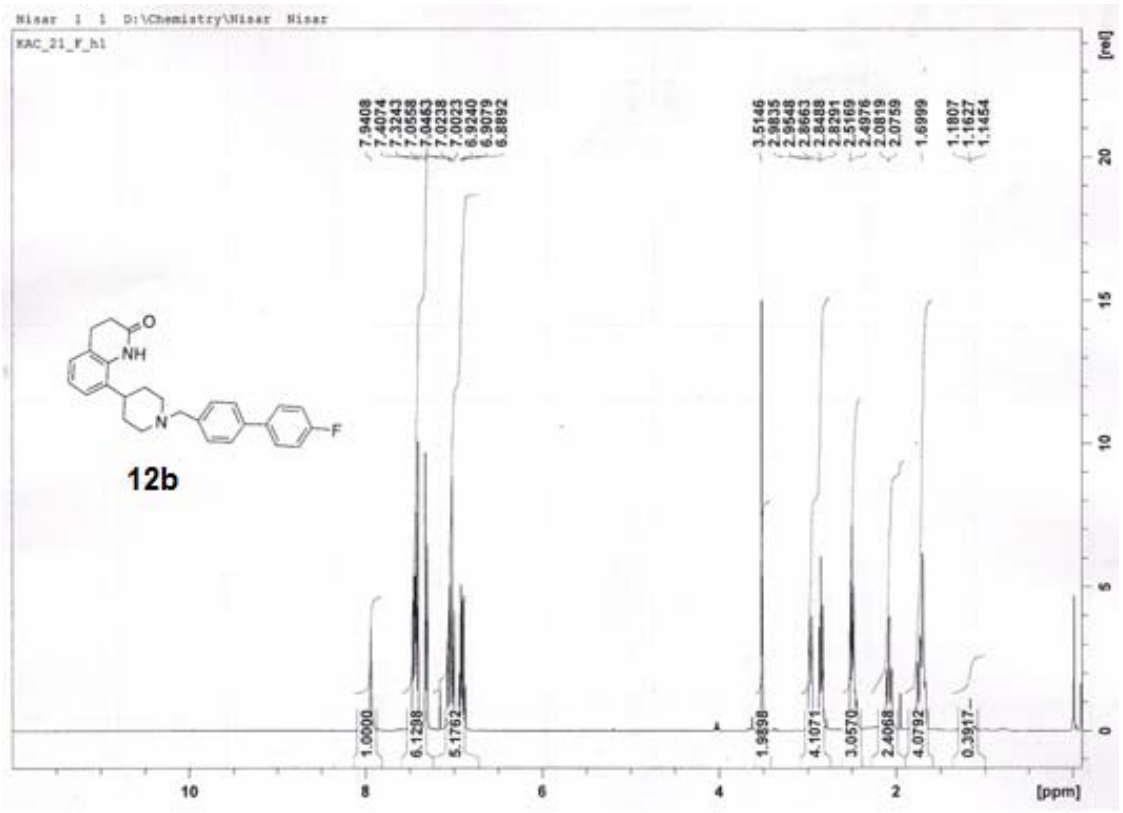
Appendix 62: IR of 8-(4-((5-Cyclopentenylpyridin-3-yl)methyl)piperazin-1-yl)quinolin-2(1H)-one (11f)



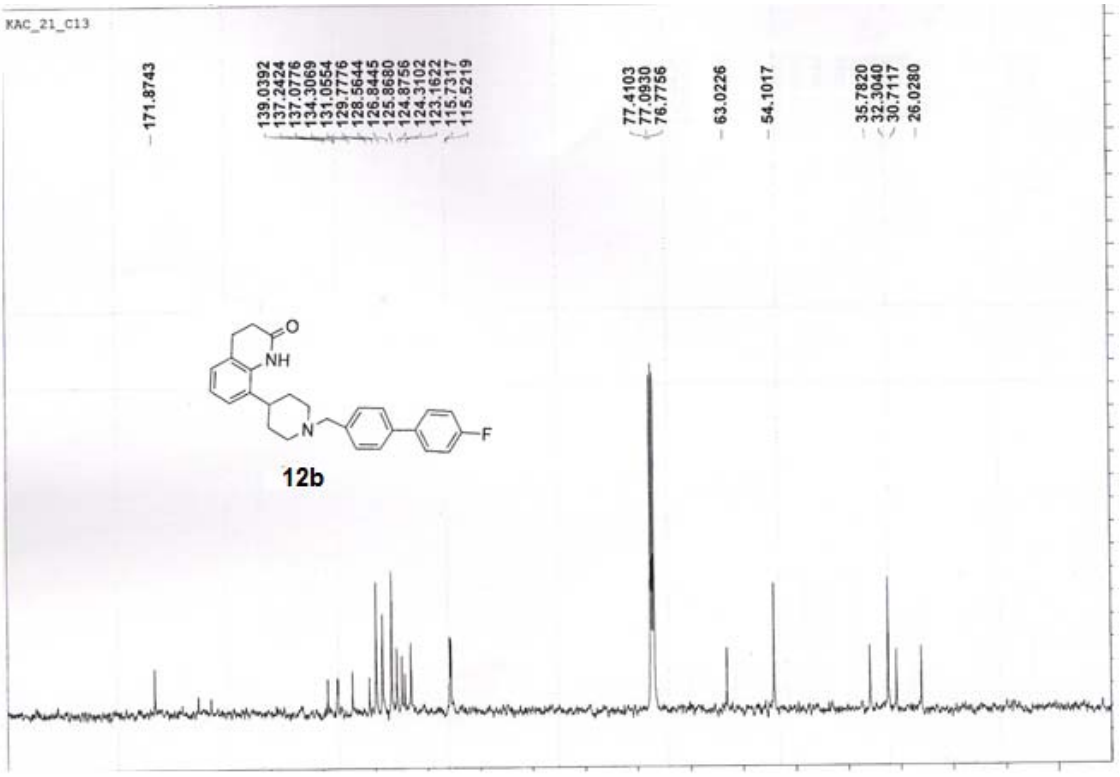
Appendix 63: H^1 of 8-(4-(Biphenyl-4-ylmethyl)piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (12a)



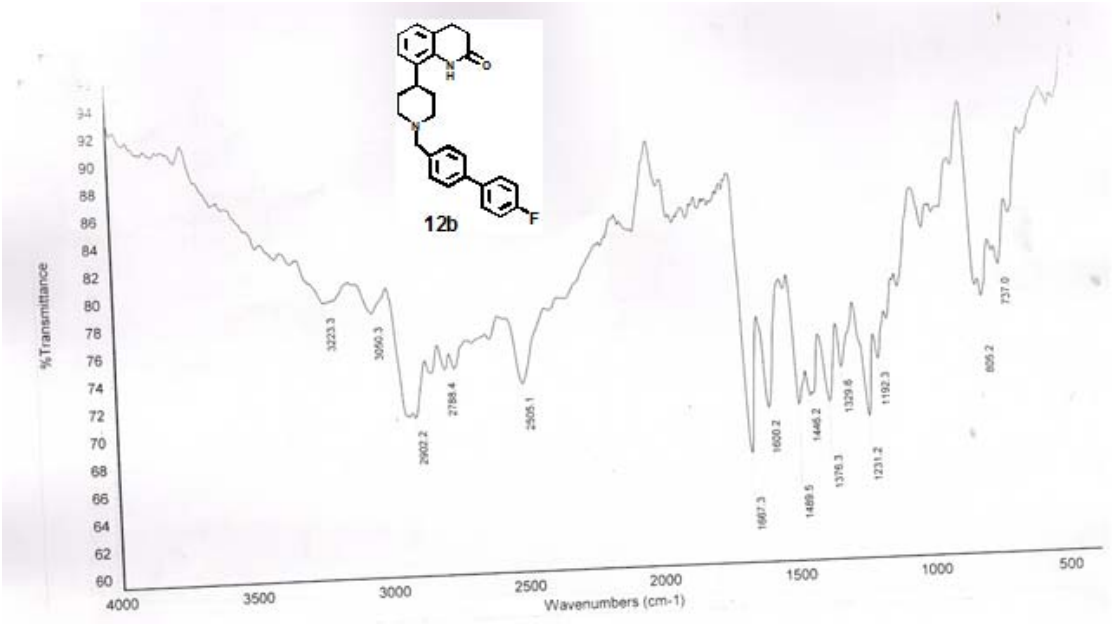
Appendix 64: C^{13} of 8-(4-(Biphenyl-4-ylmethyl)piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (12a)



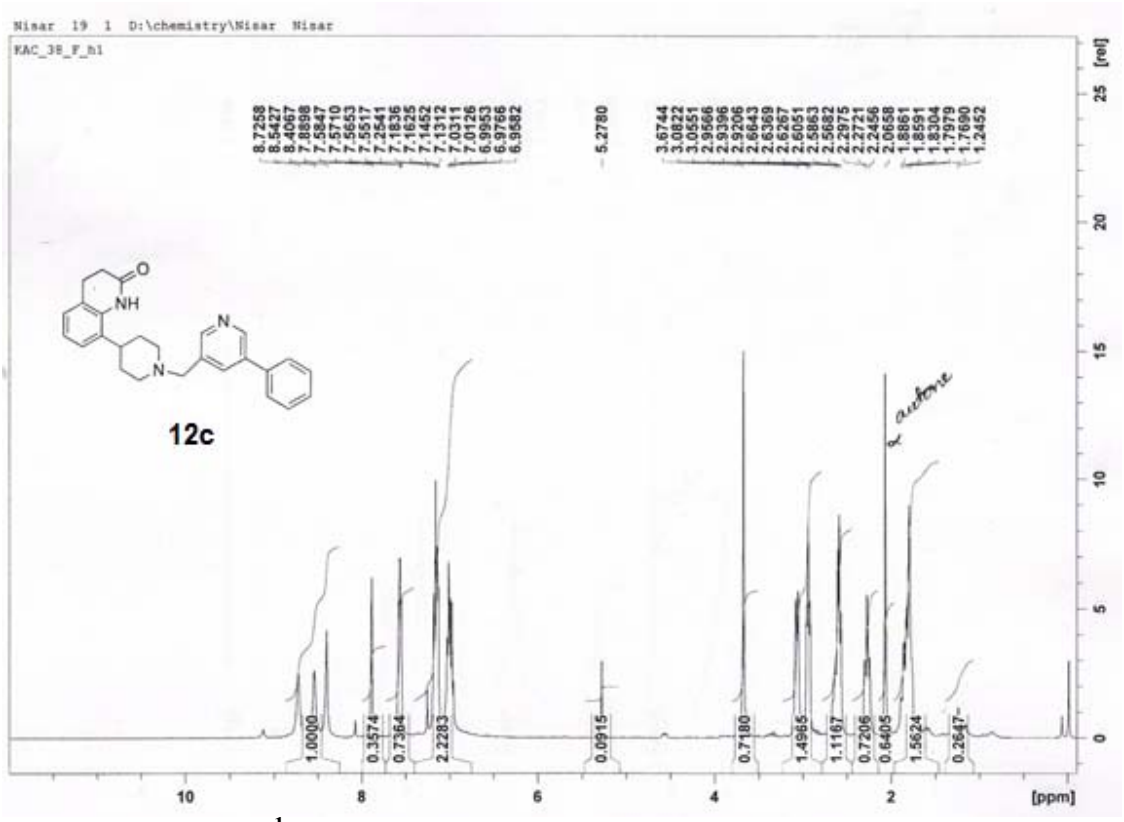
Appendix 65: H^1 of 8-(4-((4'-Fluorobiphenyl-4-yl)methyl)piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (12b)



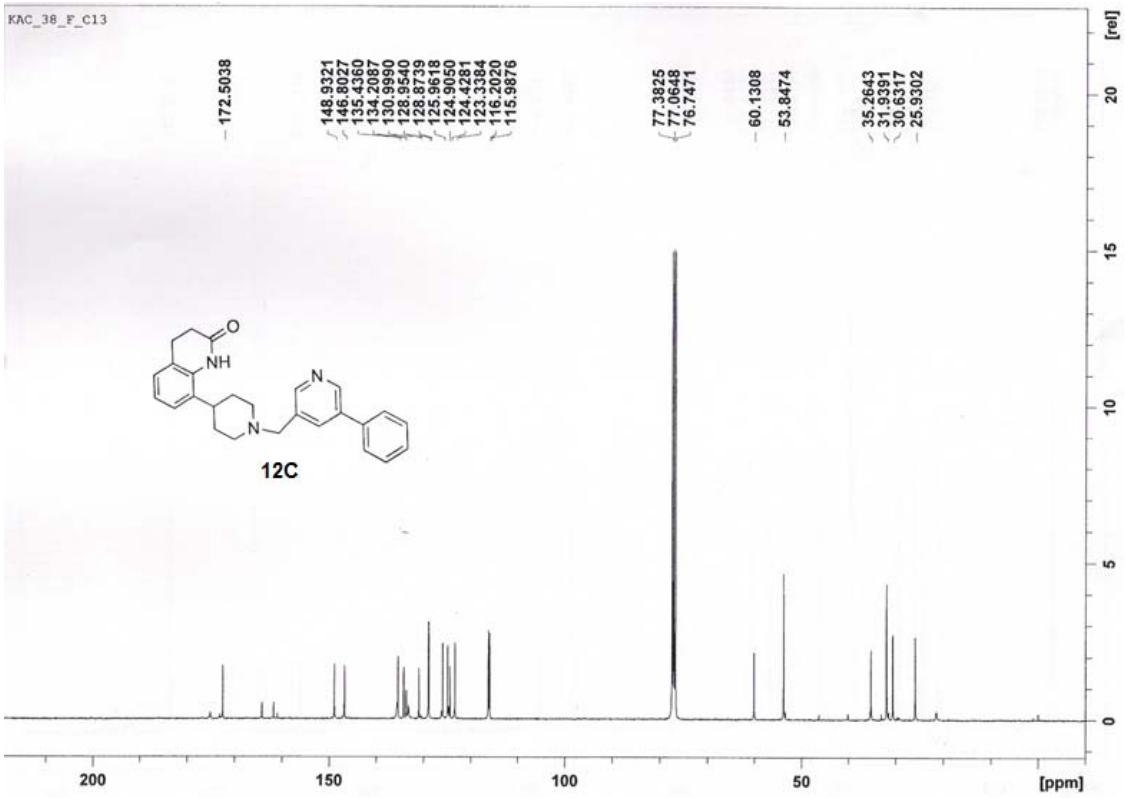
Appendix 66: C^{13} of 8-(4-((4'-Fluorobiphenyl-4-yl)methyl)piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (12b)



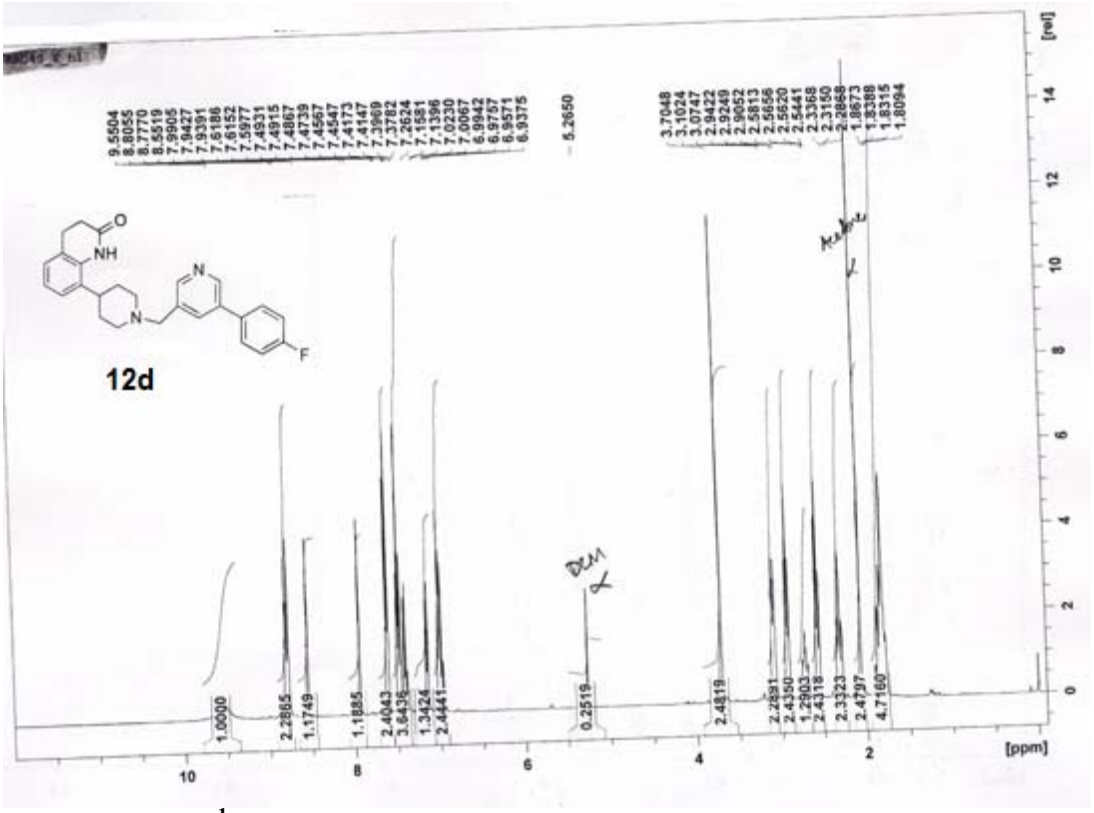
Appendix 67: IR of 8-(4-((4'-Fluorobiphenyl-4-yl)methyl)piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (12b)



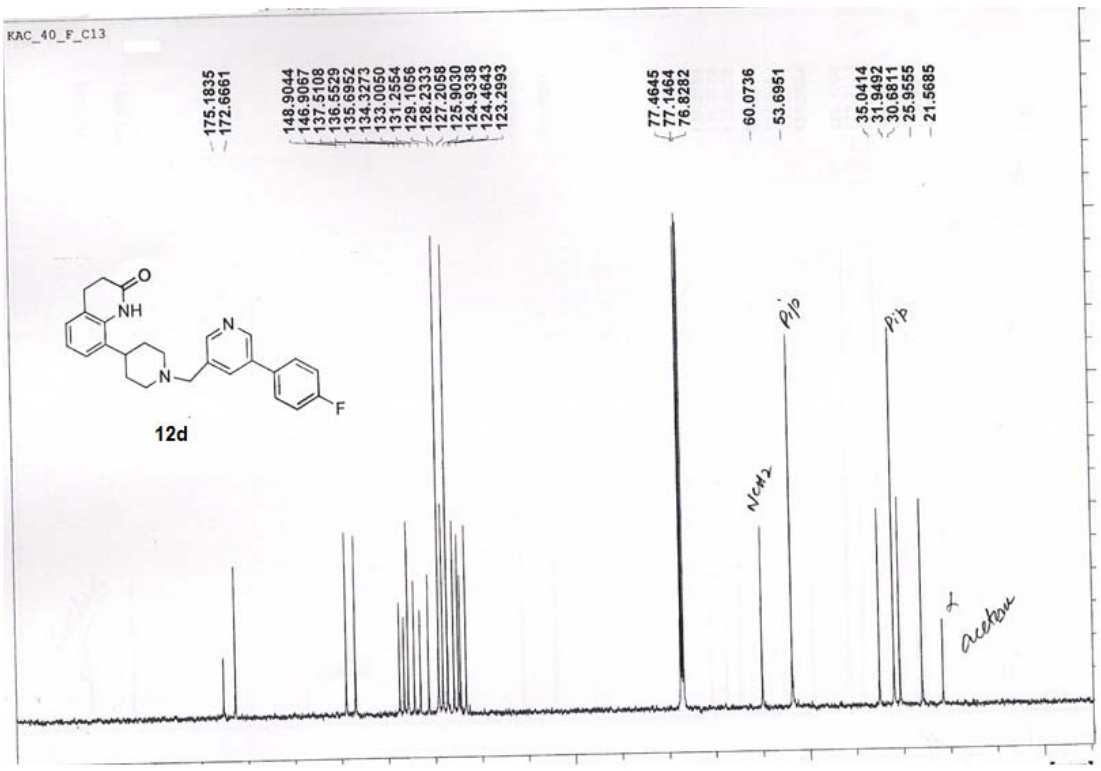
Appendix 68: H^1 of 8-(4-((5-Phenylpyridin-3-yl)methyl)piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (12c)



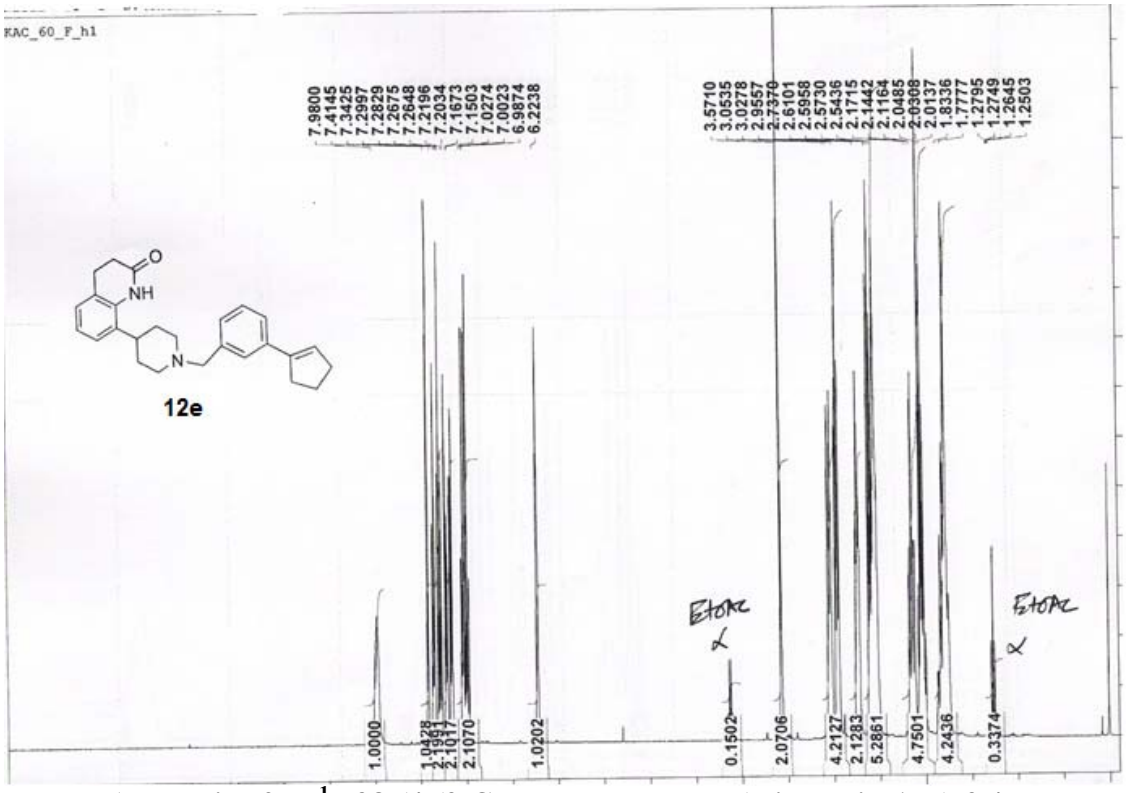
Appendix 69: C^{13} of 8-(4-((5-Phenylpyridin-3-yl)methyl)piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (12c)



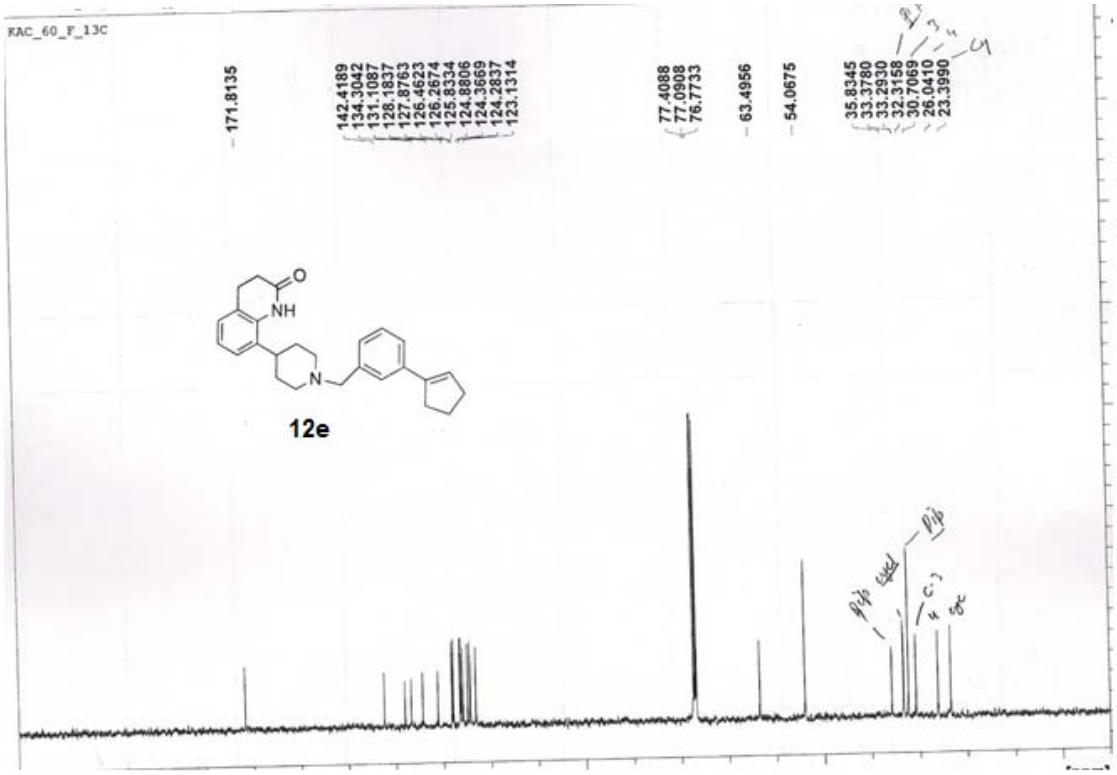
Appendix 70: H^1 of 8-(4-((5-(4-Fluorophenyl)pyridin-3-yl)methyl)piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (12d)



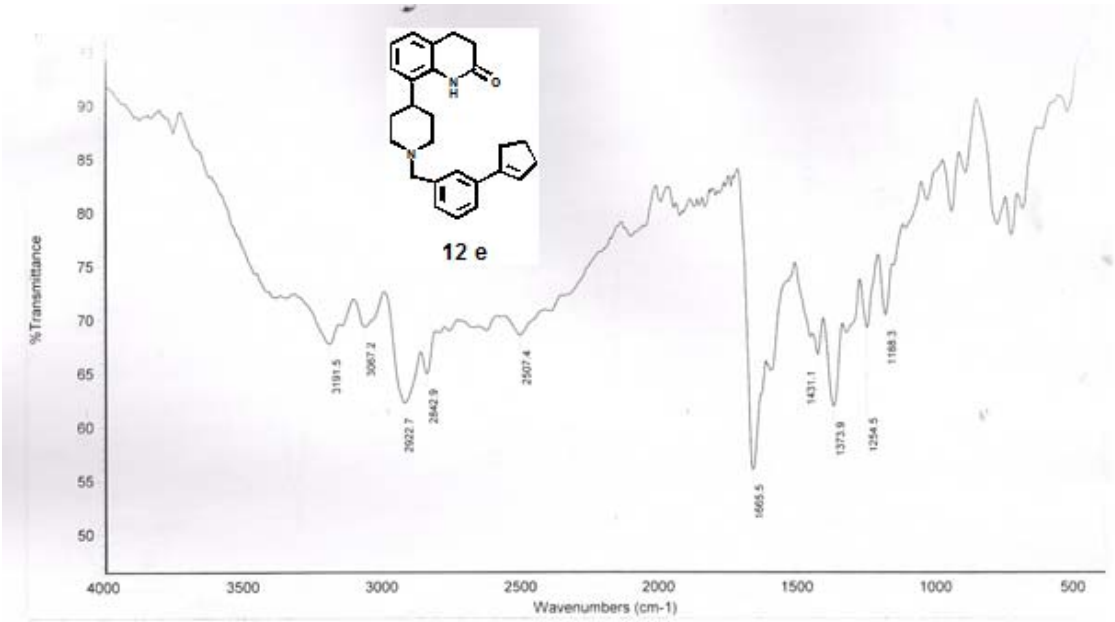
Appendix 71: C^{13} of 8-(4-((5-(4-Fluorophenyl)pyridin-3-yl)methyl)piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (12d)



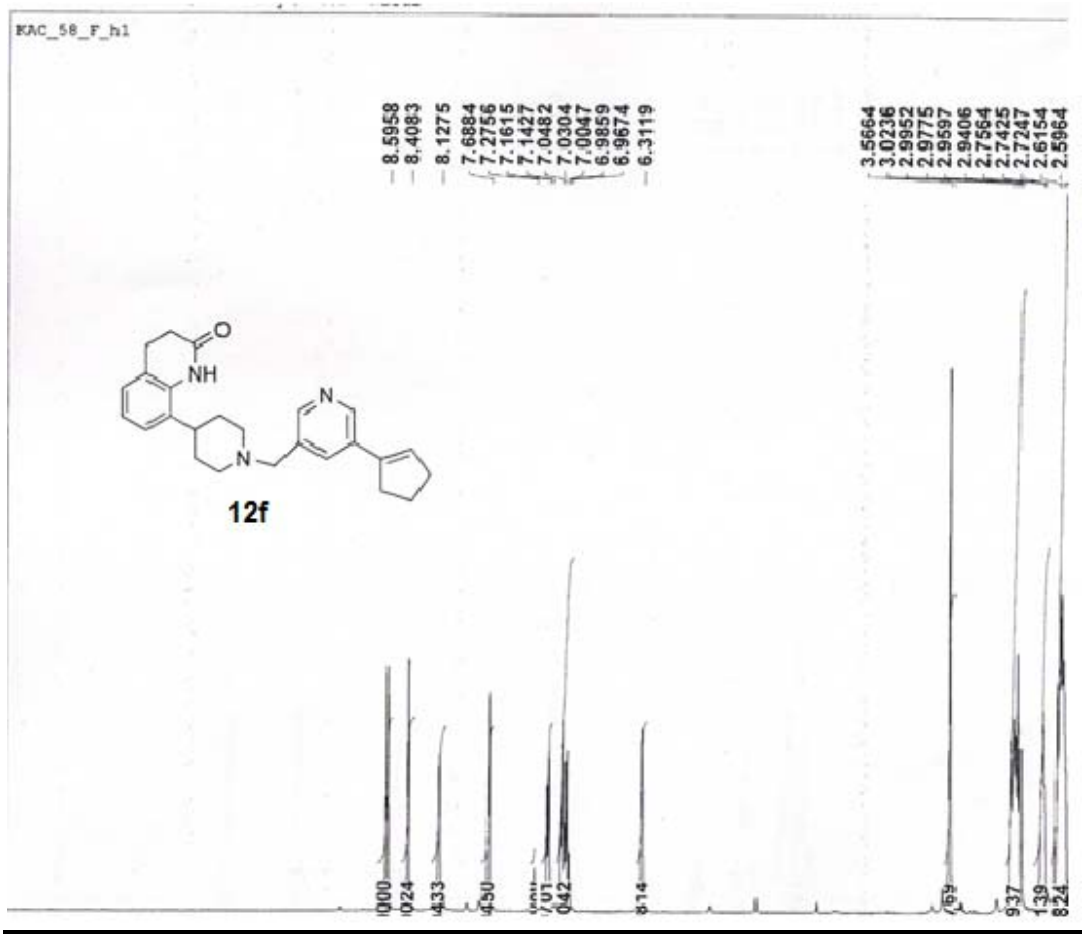
Appendix 72: H^1 of 8-(4-(3-Cyclopentenylbenzyl)piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (12e)



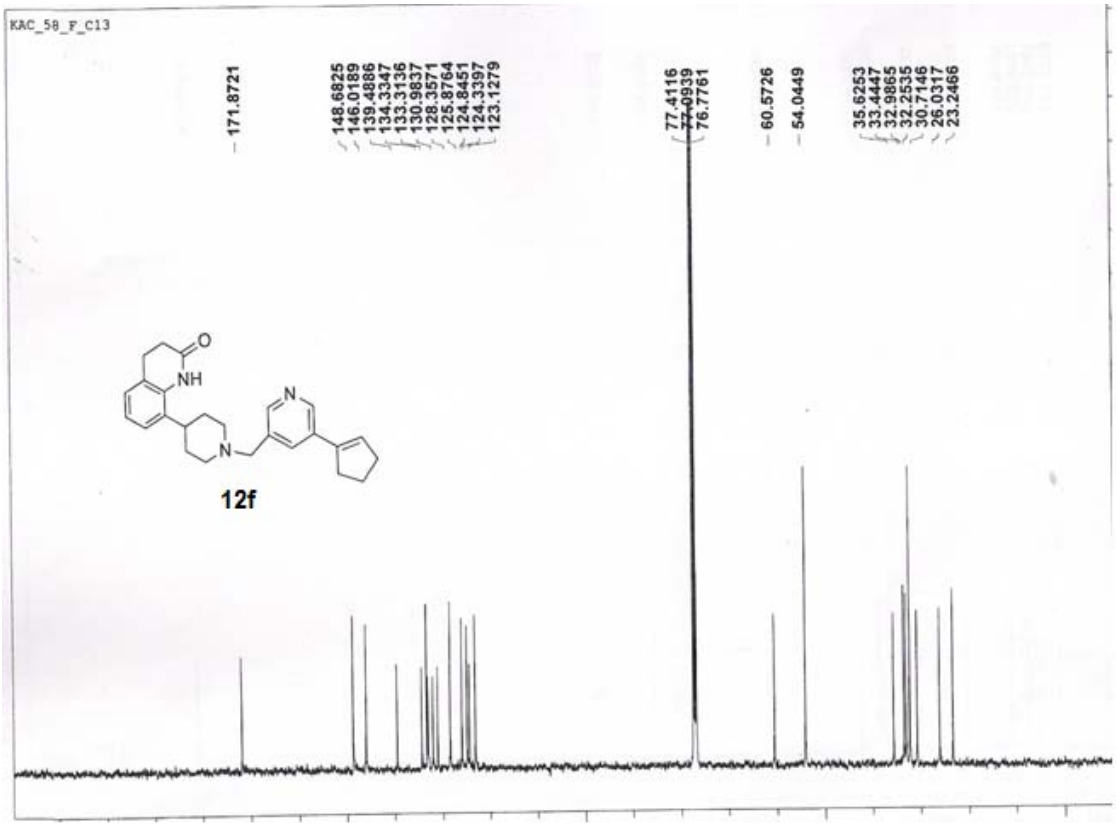
Appendix 73: C^{13} of 8-(4-(3-Cyclopentenylbenzyl)piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (12e)



Appendix 74: IR of 8-(4-(3-Cyclopentenylbenzyl)piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (12e)



Appendix 75: H^1 of 8-(4-((5-cyclopentenylpyridin-3-yl)methyl)piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (12f)



Appendix 76: C^{13} of 8-(4-((5-cyclopentenylpyridin-3-yl)methyl)piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (12f)

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