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Microwave-assisted synthesis of heterocycles from aryldiazoacetates

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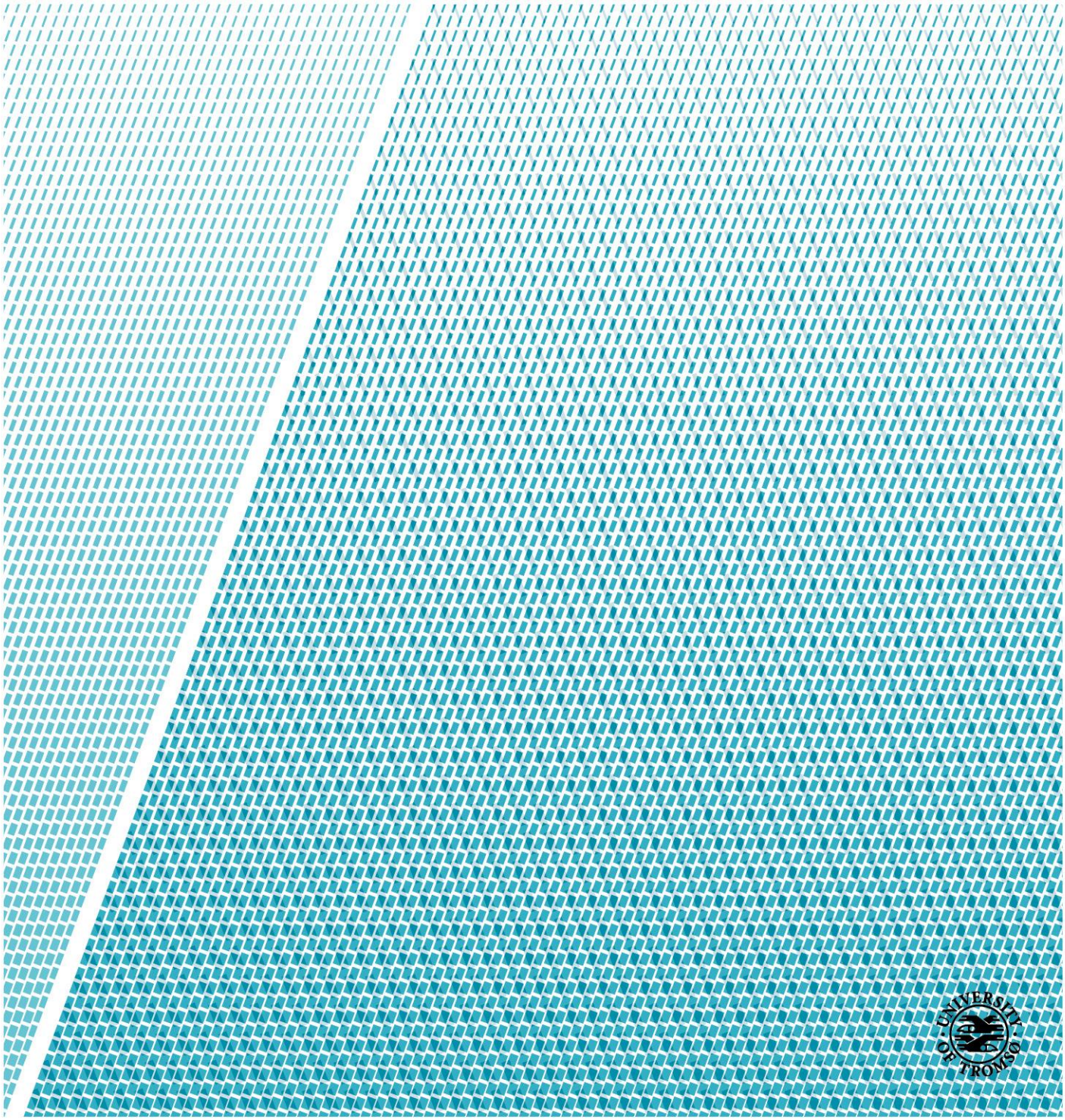
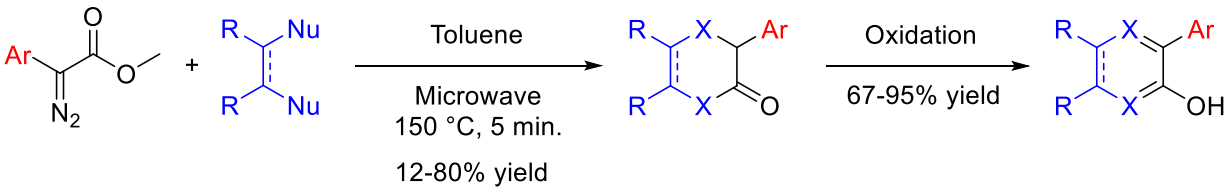
KJE-3900 Master's thesis in Organic Chemistry, November 2017



Abstract



A novel microwave-assisted method for generation of heterocycles have been explored. A range of 3,4-dihydroquinoxalin-2-ones have been prepared via an N-H insertion/cyclization cascade of dinucleophiles and aryldiazoacetates in moderate to good yields (12 - 80%). Reactions of aryldiazoacetates with *o*-phenylenediamine generated the best yields, while reactions with aliphatic and benzylic dinucleophiles resulted products in lower yields. Oxidation of 3,4-dihydroquinoxalin-2-one products afforded quinoxaline-2-ol derivatives in good to excellent yields (67 – 95 %).

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Table of Contents

List of Figures, Tables and Schemes

Abbreviations

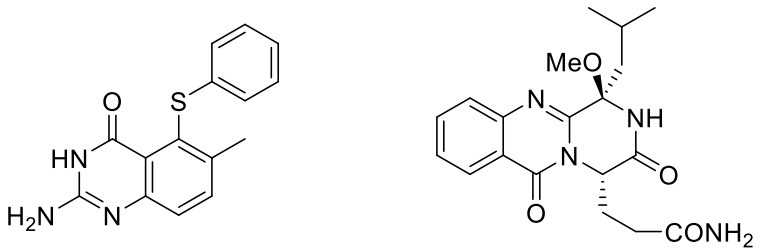
^{1}H-NMR	Proton nuclear magnetic resonance
^{13}C-NMR	Carbon nuclear magnetic resonance
COSY	Correlation spectroscopy
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIPEA	N,N-Diisopropylethylamine
DMSO	Dimethylsulfoxide
EAS	Electrophilic aromatic substitution
EtOAc	Ethyl acetate
EtOH	Etanol
GC-MS	Gas chromatography – Mass Spectrometry
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear single-quantum correlation spectroscopy
IR	Infrared (spectroscopy)
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
MeCN	Acetonitrile
MeOH	Methanol
TFA	Trifluoroacetic acid
TFT	Trifluorotoluene

THF	Tetrahydrofuran
TLC	Thin layer chromatography
p-ABSA	*para*-acetamidobenzenesulfonyl azide
ROESY	Rotating frame nuclear Overhauser effect spectroscopy

1 Introduction

1.1 Relevance

In the search of compounds with desirable medicinal or material properties, the development of synthetic methodologies to access functionalized compounds is essential. As compounds are to be tested to serve as ligands of various drug targets, synthetic methods to produce compounds that explore the chemical space is highly advantageous[1]. In particular, heterocycles serve an important role in modern chemistry. Heterocyclic structures are abundant motifs found both in nature, and a majority of drugs on the market are made up of heterocyclic small molecule structural elements. A common approach in drug discovery is to synthesise compounds that have similar structural elements to natural products, in which heterocycles play a major role.[2] In the late 1980's, Evans et al. coined the term "privileged scaffold" for structural elements showing broad biological activity[3]. Since then, the term includes bioactive structural elements found both in natural products, and synthetically derived drugs, a majority of which, are heterocyclic structures. This is exemplified by quinazolinone (Figure 1). The heterocycle has several targets of interaction, and may be found as a natural product, or be produced synthetically. Today, medicinal chemists often use privileged scaffolds in their drug design process.[4] A central topic of this thesis is the development of a practical synthetic methodology for generating valuable heterocycles that could become privileged scaffolds.



Nolatrexed
Antineoplastic

Aurantiamide A
Cytotoxic to tumor cell lines
(Natural product)

Figure 1: A privileged scaffold: Quinazolinone.

1.2 Quinoxalinone

The quinoxaline-2-one heterocycles are bicyclic benzene-fused ketopiperazines with a carbonyl group in the second position. The nomenclature of quinoxaline-2-one compounds and their derivatives, are derived from the amide nitrogen, which is given the highest priority (Figure 2).

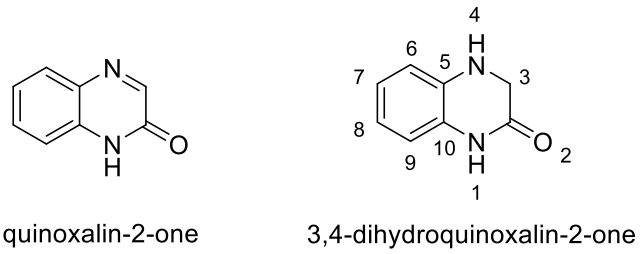


Figure 2: The quinoxalin-2-one scaffold. Numbering system shown

The quinoxaline-2-one heterocycles have been of high interest for several decades due to their high potential to serve as medicinal agents. Quinoxalin-2-one derivatives have shown a variety of potential pharmaceutical applications as several studies on this scaffold have demonstrated a range of biological activities. For example: antibacterial, antifungal, anticancer, antitubercular, antimalarial, and antidepressant activities have been described in the literature.[5-8] In addition, quinoxalines have been used as metal-complex ligands for platinum drugs[9], in iridium complexes for organic-, and polymer light emitting diodes[10], and used as Schiff base transition metal ligands.[11]

A major advantage of the quinoxalinone scaffold is the broad range of diversification strategies that can be applied (Figure 3). The basic scaffold can be modified by electrophilic aromatic substitution on the aryl portion, alkylation chemistry at the NH sites, carbonyl oxygen and α-site, as well as other carbonyl transformations. Thus, this represents a powerful scaffold for diversity-oriented library design for small molecule development.[12-13]

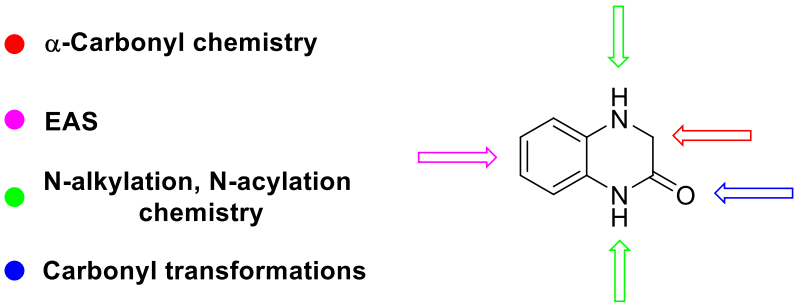


Figure 3: Various diversification possibilities of the quinoxalinone scaffold.

1.2.1 Examples of biological activity

This section will highlight some examples of biologically active quinoxalinones to emphasize why this scaffold is of interest to generate.

A recent study by Liu and co-workers found BH6870 (Figure 4a) compound containing the quinoxaline-2-one scaffold, to be a potent antiviral agent against the Hepatitis C virus by structure activity relationship studies on quinoxalinone derivatives.[14]

A quinolinone derivative, TKI258 (Figure 4b) has shown potent antitumor activities, as a multitargeted receptor tyrosine kinase inhibitor (RTK). In clinical trials, phase 1, TKI258 showed antitumor activity against several tumour types.[15]

Based on the promising results of TKI258, Faquing Ye et al. designed and studied a range of quinoxaline-2-one derivatives.[16] Their study found that a range of aryl-substituted 3-vinyl-quinoxalin-2(*1H*)-one derivatives (Figure 4c) showed promising antitumor activities as fibroblast growth factor receptor inhibitor (FGFRI), as well as cytotoxicity in in vitro cell lines.

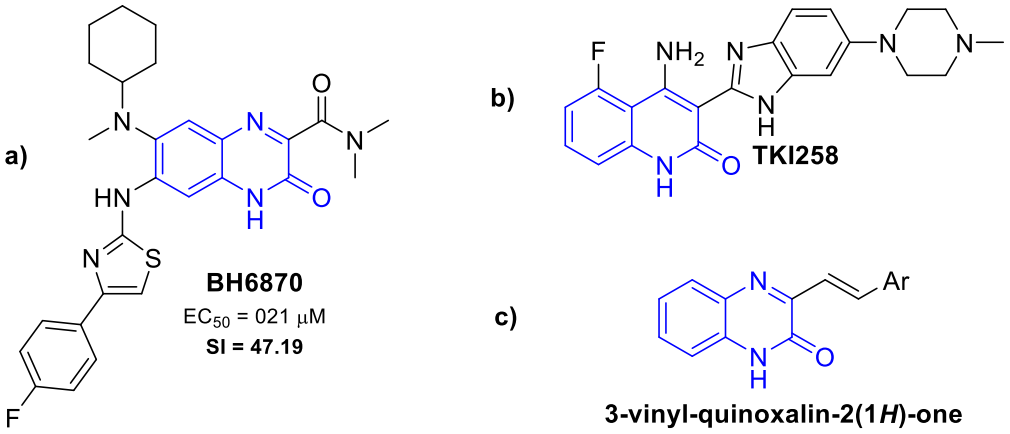
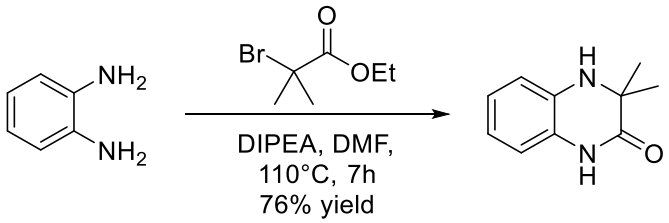


Figure 4: Quinoxalin-2-one derivatives shown to have potent biological activity.

1.2.2 Quinoxalinone synthesis

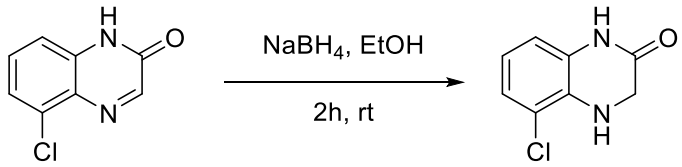
In the interest of obtaining the quinoxaline-2-one scaffolds, various methods have been reported. However, one of the oldest and more widely used methods of precuring the quinoxaline-2-one scaffold is by condensation reactions between *o*-phenylenediamines with electrophilic two-carbon unit suppliers, such pyruvate derivatives and α-haloacetates.[17-18]

Tenbrink, et al. used this method in the synthesis of 3,3,-dimethyl-1,2,3,4-tetrahydroquinoxalin-2-one as an intermediate to develop imidazo[1,5-*a*]quinoxaline derivatives.[6] In the synthesis of their quinoxalin-2-one derivative, they reacted *o*-phenylenediamine with an α-bromoester in the presence of base, to result 3,3-dimethyl-1,2,3,4-tetrahydroquinoxalin-2-one in good yield.



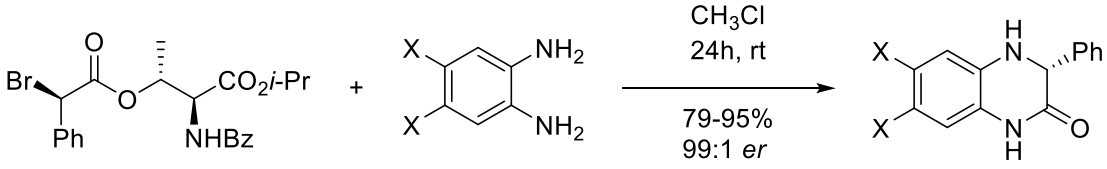
Scheme 1: Synthesis of 3,3-disubstituted quinoxalin-2-one derivative from reactions of o-phenylenediamine with α-bromoester.

In a later study Jacobsen et. al. demonstrated how the quinoxaline-2-one scaffold can be transformed to the 3,4-dihydroquinoxalin-2-one (Scheme 2). As they obtained a mixture of the two in their synthesis of 3,4-dihydroquinoxalin-2-one, quinoxaline-2-one was transformed into 3,4-dihydroquinoxalin-2-one by reduction with sodium borohydride.[19]



Scheme 2: Transformation of quinoxaline-2-one to 3,4-dihydroquinoxalin-2-one.

Park et. al. recently reported a high yielding, stereoselective, asymmetric synthesis of substituted 3,4-dihydroqionoxalin-2-ones, from enantiopure α-bromophenylacetates in reactions with o-phenylenediamines (Scheme 3). The reactions resulted in 3-substituted quinoxaline-2-ones with high enantiomeric excess.[20]



Scheme 3: Stereoselective synthesis of 3-substituted 3,4-dihydroquinoxalin-2-one. X = H, Cl, Me

1.3 Microwave in synthesis

In the search of novel high-speed methods of producing compounds in organic synthesis, the use of microwave-assisted organic synthesis, has become commonplace both in academia and industry. Since the initial reports of using microwave-assisted organic synthesis in 1986, it has emerged as a highly valuable synthetic tool, particularly for accelerating the synthetic process. For decades reports have been made demonstrating microwave heating as beneficial in synthesis for various reactions. Examples include: alkylation, acylation, substitution, cross coupling, and peptide synthesis; the benefits are mainly due to reduced reaction times, but also because of improved and purity.[21-25] This section will highlight some synthetic applications of microwave techniques.

Microwaves are part of the electromagnetic spectrum, located between infrared and radio radiation, with frequencies ranging from 0,3 GHz to 300 GHz, corresponding to wavelengths of 1 mm to 1 m. Modern domestic household microwaves, as well as specialized microwave reactors for synthesis, are set to operate at a frequency of 2,45 GHz, to avoid interference with RADAR and other telecommunication service technologies which also utilizes microwave frequencies (Figure 5).[26]

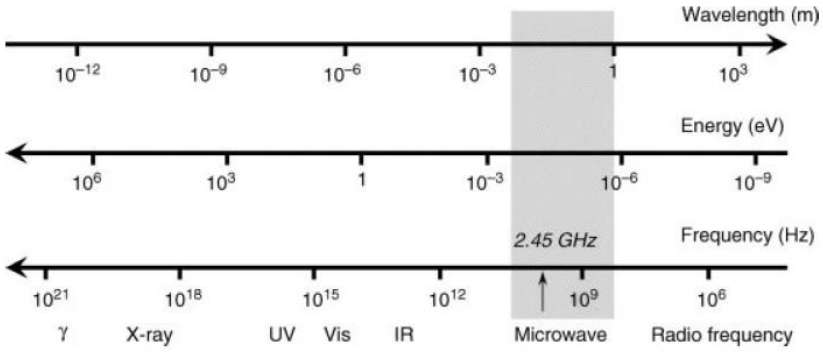


Figure 5: Microwaves are located in the lower frequency range of the electromagnetic spectrum. Microwave frequencies used in synthesis correspond to 2,45 GHz. (figure from [26])

Microwaves heat materials by microwave dielectric heating, and is dependent on the material's dielectric properties - the material's ability to absorb microwave energy and convert it to heat. Depending on the material irradiated, heating occurs by way of two mechanisms: dipolar polarization for dipolar materials such as water, and ionic conduction for ionic materials. When a sample is exposed to microwaves, the dipoles (or ions) in the sample attempt to adjust themselves along with the applied electric field. As the applied electric field oscillates, the

dipoles attempt to adjust themselves accordingly. The electrical energy applied is converted into thermal energy by molecular friction from the movement of the dipoles. Increased reaction rates by microwave heating may be rationalized by the Arrhenius equation; as temperature is increased, the rate of the reaction increases.[26-27]

The benefits of using microwave-assisted synthesis in the drug discovery process were investigated in an experiment performed by Sarko and co. workers. Two researchers were given the same task of generating the same compound library, independent, and unaware of each other's progress. While one researcher was constructing the library using conventional heating methods, the other was given access to a microwave reactor. Independently, both researchers surveyed the current literature, and used the same strategy for constructing their library. While library construction by conventional heating method required 37 days, the microwave-assisted course was completed after 2 days with remarkably improved yields (Figure 6). The difference can be explained by the major difference in heating time. While several of the reactions done using conventional methods, were heated over several hours (and up to 24 hours), the microwave assisted were greatly shorter, with reaction times spanning from 5 min. to 1 hour.[27-28] The unique experiment greatly illustrates the immense benefits of microwave use, contributing to chemical synthesis, and the drug discovery process.

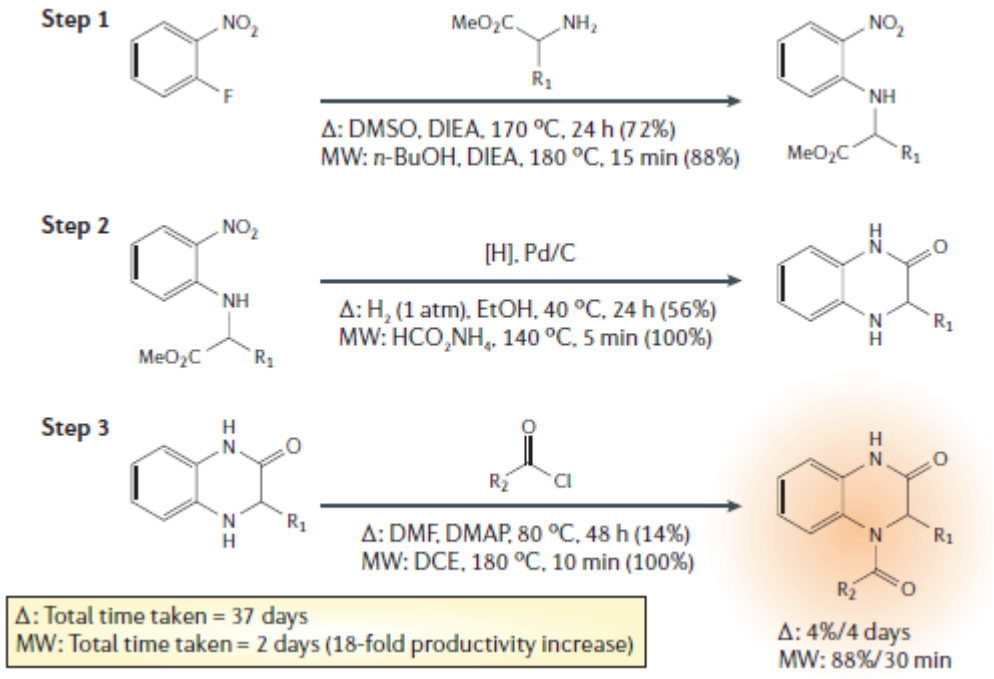
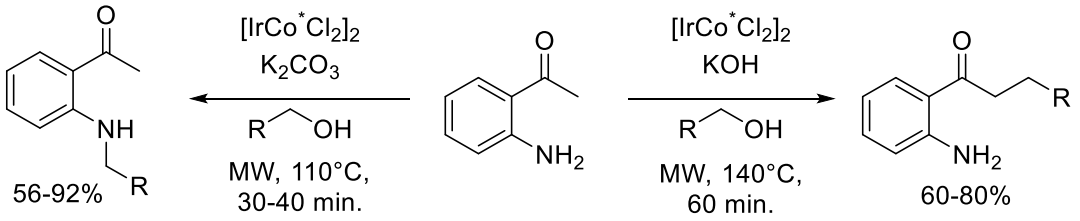


Figure 6: Comparison of library construction using conventional-, and microwave-assisted heating methods (figure from [27]).

In 2012, Sridharan et al. reported chemoselective *N*-, and *C*- alkylation of 2-aminoacetophenone with primary benzyl alcohols under microwave conditions (Scheme 4).[29] The iridium catalyzed reaction, using K_2CO_3 as base, resulted in the corresponding *N*-alkylated products in good to excellent yields, while when using KOH as base, afforded the corresponding *C*-alkylated products in good yields.



Scheme 4: Iridium catalyzed N-, and C- alkylations of 2-aminoacetophenone.

Gaonkar and co-workers described a simple, effective, and high yielding, microwave-assisted method for the synthesis the antihyperglycemic drug rosiglitazone (Figure 7).[30] Their synthesis utilized microwave irradiation in 4 out of 5 reaction steps to obtain the desired product. The method required no distillations or column chromatography for purifications of intermediates. In addition, they demonstrated further how the microwave assisted synthesis lowered the total reaction time from days to hours, in comparison to conventional heating (Figure 8).

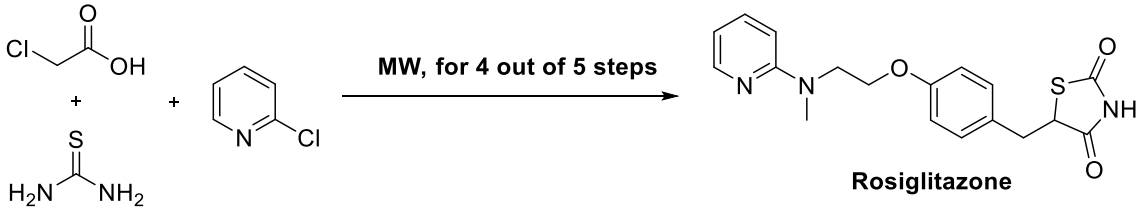
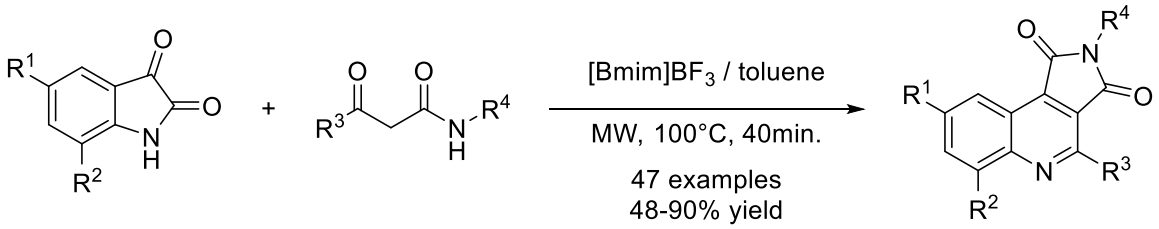


Figure 7: Multi-step microwave-assisted synthesis of Rosiglitazone

Reaction	By microwave heating			By conventional heating		
	Conditions	Time	Yield %	Conditions	Time	Yield %
(a)	H_2O 140 °C	10 min	90	H_2O 100 °C	12 h	82
(b)	Solvent free 140 °C	20 min	92	Solvent free 140 °C	15 h	85
(c)	KOH, water, toluene, TBAHS, 85 °C	20 min	90	DMF, NaH 80 °C	8 h	80
(d)	Toluene, piperidine, CH_3COOH, SiO_2, 130 °C	10 min	93	Toluene, piperidine, CH_3COOH, reflux	15 h	85

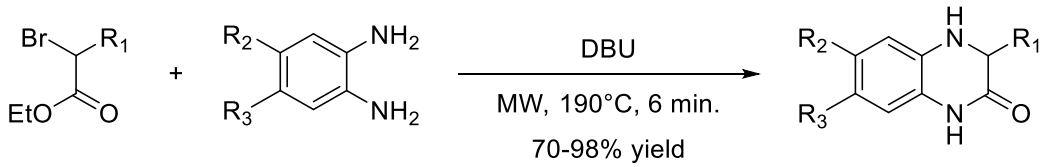
Figure 8: Synthesis steps of total synthesis of rosiglitazone using microwave, in comparison to conventional heating (figure from [30]).

Wee et. al. demonstrated a microwave assisted synthesis of pyrrolo[3,4-*c*]quinoline-1,3-diones from cascade reactions of *β*-ketoamides and istatines (Scheme 5).[31] The reaction was demonstrated to generate 47 examples in good to excellent yields.



Scheme 5: Lewis acid catalyzed, microwave-assisted synthesis of pyrrolo[3,4-c]quinoline-1,3-diones.

Biehl et. al. demonstrated a microwave-assisted, high yielding, solvent free synthesis of 3,4-dihydroquinoxalin-2-ones from *o*-phenylenediamines and α-bromoesters (Scheme 6). The reactions were complete without the use of any solvent, or solid support. However it was dependent on DBU as quenching agent, as free HBr from the reaction protonated the nucleophile.[32]



Scheme 6: Solvent free, microwave-assisted synthesis of 3,4-digydrowuinoxalin-2-one.

1.4 Carbenes and N-H insertion

Carbenes are neutral, six electron carbon species, where the carbene carbon has four bonding electrons, and two non-bonding electrons surrounding it. Carbenes can either be in a triplet or a singlet carbene state, depending on the carbene structure and conditions, where they differ in the electron spin configuration in the orbitals (Figure 9).[33]

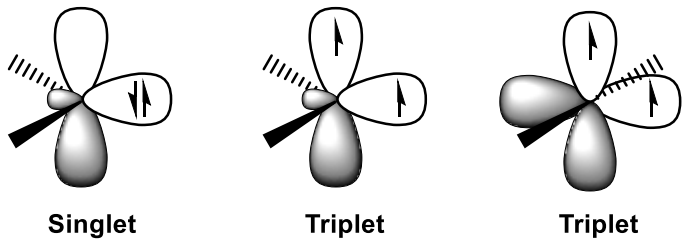
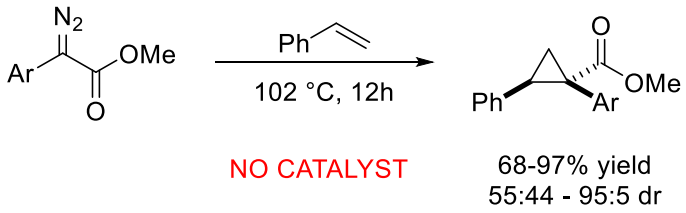


Figure 9: Singlet and triplet carbene.

The singlet carbene electronic configuration makes its reactivity both electrophilic, and nucleophilic, depending on substituents of the carbene and the nature of the reagent. The singlet carbene non-bonding electrons are of opposite spins, both of which occupy an sp^2 hybrid orbital. As the sp^2 hybrid orbital (HOMO) is filled, the singlet carbene may react as a nucleophile. On the other hand, its empty-p orbital (LUMO) is accessible to nucleophilic attack, making the species electrophilic. The triplet carbene non-bonding electrons are of the same spin. Consistent with Hunds rule of maximum multiplicity, the electrons of the triplet carbene are distributed in two separate orbitals. Depending on the substituents, the electrons can occupy one of each in a sp^2 and sp^3 hybrid orbital, in a triplet carbene of bent shape, or both can occupy two separate p orbitals in triplet carbenes of linear shape. Due to triplet carbenes having two singly occupied orbitals, their reactivity is usually of a radical nature. As carbenes have both electrophilic, nucleophilic and radical properties depending on their substituents, carbene reactivity may be fine-tuned to obtain a desired effect.[33-34]

Various methods using carbenes have been reported. Carbenes are generally highly reactive and have the capability of contributing in various reactions. Carbenes are often utilized in cyclopropane formation in Simmons-Smith type reactions, in addition to their heavy use as metallocarbenoid species in C-H functionalization reactions.[33, 35-36]

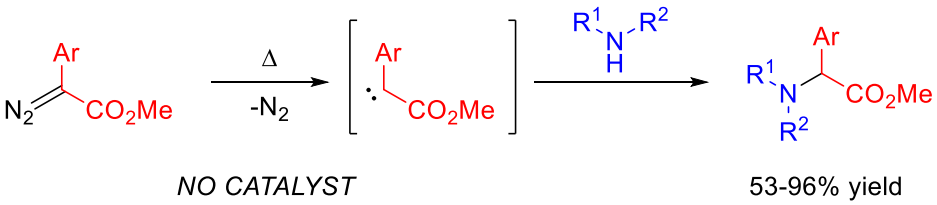
In 2011, Davies et al. reported highly selective cycloaddition reactions with alkenes and aryldiazo compounds (Scheme 7).[37] Their study found that donor/acceptor carbenes, derived from thermal decomposition of aryldiazo compounds, generated cyclopropanes, without the use of a metal catalyst.



Scheme 7: Cyclopropanation reaction of alkenes and carbenes thermally generated from aryldiazo compounds.

Expanding on these findings, they later reported metal free N-H insertions of thermally generated donor/acceptor carbenes from aryldiazoacetates (Scheme 8).[38] Their study found that

primary-, secondary-, aryl- and heteroarylamines would undergo N-H insertions of the carbene to generate α-amino-esters in high yields.



Scheme 8: α-amino-ester synthesis from N-H-insertions to carbenes thermally generated from aryldiazo compounds.

Through kinetic studies of the decomposition of diazoesters, it was found that the rate of decomposition is highly dependent on the aryl substituent (Figure 10). While diazoesters containing the electron-donating methoxy-substituted aryl substituent decomposed with a half-life of only a few minutes, electron-withdrawing, nitro-substituted aryl substituent had a half-life of over five hours. Their study showed that as aryl donor substituent stabilize the diazo compounds, they decomposed in a controlled manner, with first order-kinetics.[37]

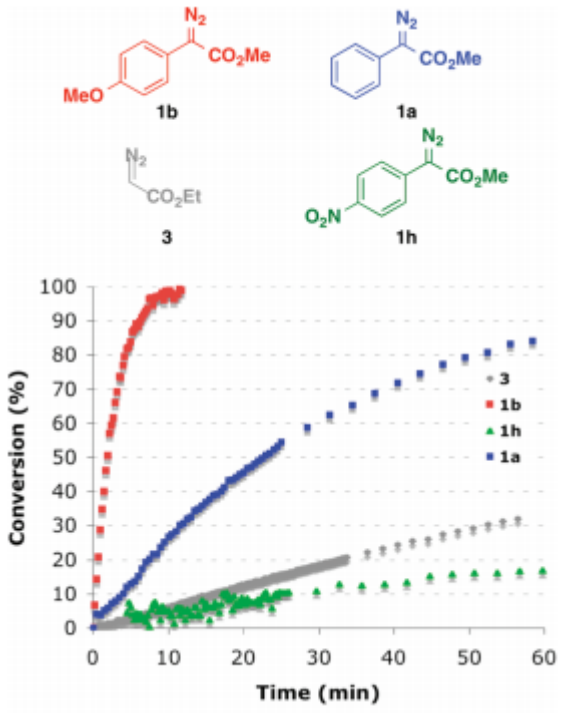
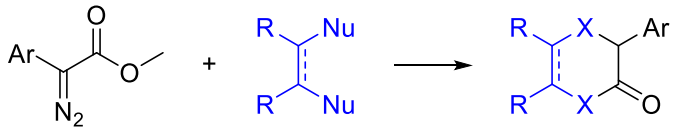


Figure 10: Kinetic studies on thermal decomposition of diazo compounds (figure from [37]).

1.5 Hypothesis and aims of study.

The literature reports of N-H insertions of carbenes and our expansion of those ideas, led to the following formulation of a hypothesis for this work:

α-aryldiazoacetates can undergo a N-H insertion/cyclization cascade with 1,2-dinucleophiles to generate a range of 6-membered heterocycles with the potential for further diversification. The principle is illustrated in Scheme 6.



Scheme 9: Hypothesized reaction outline.

To explore the hypothesis, the following partial aims were set for this study:

1) Perform chemical synthesis of a range of aryldiazoacetates to explore the proposed reaction.
2) Test microwave conditions in contrast to previous results with conventional heating.
3) Find high- yielding and practical reaction conditions using microwaves.
4) Explore the scope and limitations of α-aryldiazo compound and dinucleophile structures.
5) Explore further transformations of the initial products.

1.6 Previous works

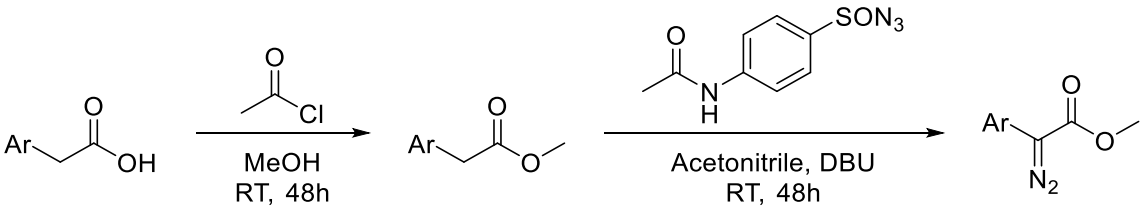
Previously there have been several attempts at this reaction using thermal conditions. This work was done by exchange students visiting the Hansen group.

Several attempts at reacting methyl-phenyldiazoacetate with several o-phenylenediamines using conventional heating were performed, including attempts to catalyze the reaction using Lewis acids. These reactions typically led to black/tarry crude reaction mixtures, which were challenging to purify. Attempts at optimizing the conventional heated reaction found that the reaction was favored by higher diamine:diazo ratio (2 equiv. or higher), 10 ml/mmol (or more) solvent, and reaction times of 6 hours or less. In any case, the complex reaction mixtures, problematic purifications and poor yields halted further developments of the conventional heating approach.

2 Results and discussion

2.1 Synthesis of aryldiazoacetates

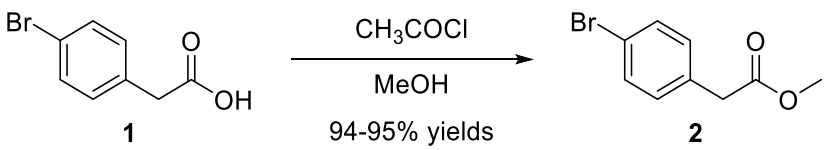
Aryldiazoacetates are precursors to stable donor/acceptor carbene intermediates. This section describes the efforts made to obtain the aryldiazoacetates starting material used in the microwave reactions. The general outline for the synthesis of aryldiazoacetates is shown in Scheme 10.



Scheme 10: Synthesis of aryl diazoacetates outline.

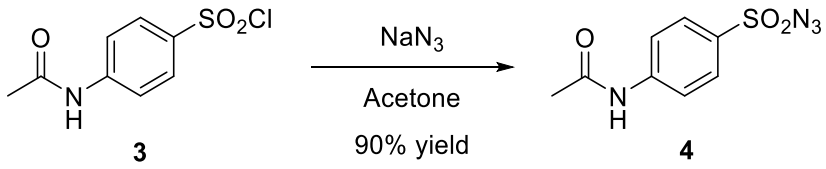
Aryl diazoacetates are commonly made by reacting 2-arylacetates with a diazo transfer reagent such as benzenesulfonyl azide. The diazo-transfer reaction is carried out under basic conditions, and therefore cannot be done on carboxylic acids; Carboxylic acid groups need to be transformed to their corresponding ester before diazo transfer is performed.

A fisher esterification reaction was carried out on commercially available *para*-bromophenylacetic acid **1** to obtain the corresponding methyl ester, methyl (*para*-bromophenyl) acetate **2** (Scheme 11). The esterification was performed according to literature procedures, using acetyl chloride as a catalyst, methanol as both the solvent and nucleophile[39]. The ester product was obtained in two separate batches in excellent 94% and 95% yields, and used in subsequent reactions without further purification.



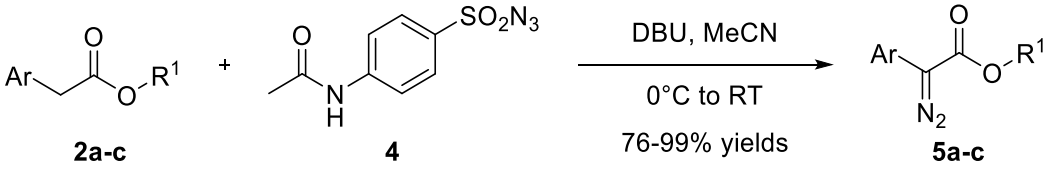
Scheme 11: Fisher esterification of carboxylic acid to generate ester.

The diazo-transfer reagent *para*-acetamidobenzenesulfonyl azide (*p*-ABSA) is used to add the diazo functional group, and is commonly made by reacting sulfonyl chlorides with sodium azides in a substitution reaction (Scheme 12). Unlike many other diazo-transfer reagents, *p*-ABSA is stable, safe to handle and easy to prepare. Because of the high toxicity of sodium azides, extreme caution is necessary during this reaction. The *p*-ABSA synthesis was prepared in accordance with literature procedures.[40-41] *para*-acetamidobenzenesulfonyl chloride suspended in acetone, was treated with aqueous sodium azide on an 80 g scale to afford the desired product in 90 % yield.



Scheme 12: Substitution reaction to generate p-ABSA

Diazo transfer is a method of adding the diazonium functional group to a scaffold. In the reaction, an -N_2 from an azide source, such as R-sulfonyl azide, is displacing two hydrogens on a methylene group (Scheme 13).[42]



Scheme 13: Synthesis of aryl diazoacetate by diazo transfer reaction.

The reaction is base catalyzed by a non-nucleophilic base such as DBU. The base deprotonates the α-carbonyl carbon, which yields an ester enolate. The nucleophilic enolate attacks the terminal nitrogen of the sulfonyl azide, giving the α-nitrogen to the sulfonyl a negative charge. This enables the α-nitrogen to deprotonate the second α-proton of the carbonyl in an intramolecular reaction, that goes through a 5-membered ring transition state, resulting in sulfonyl amine departure (Figure 11).[43-44]

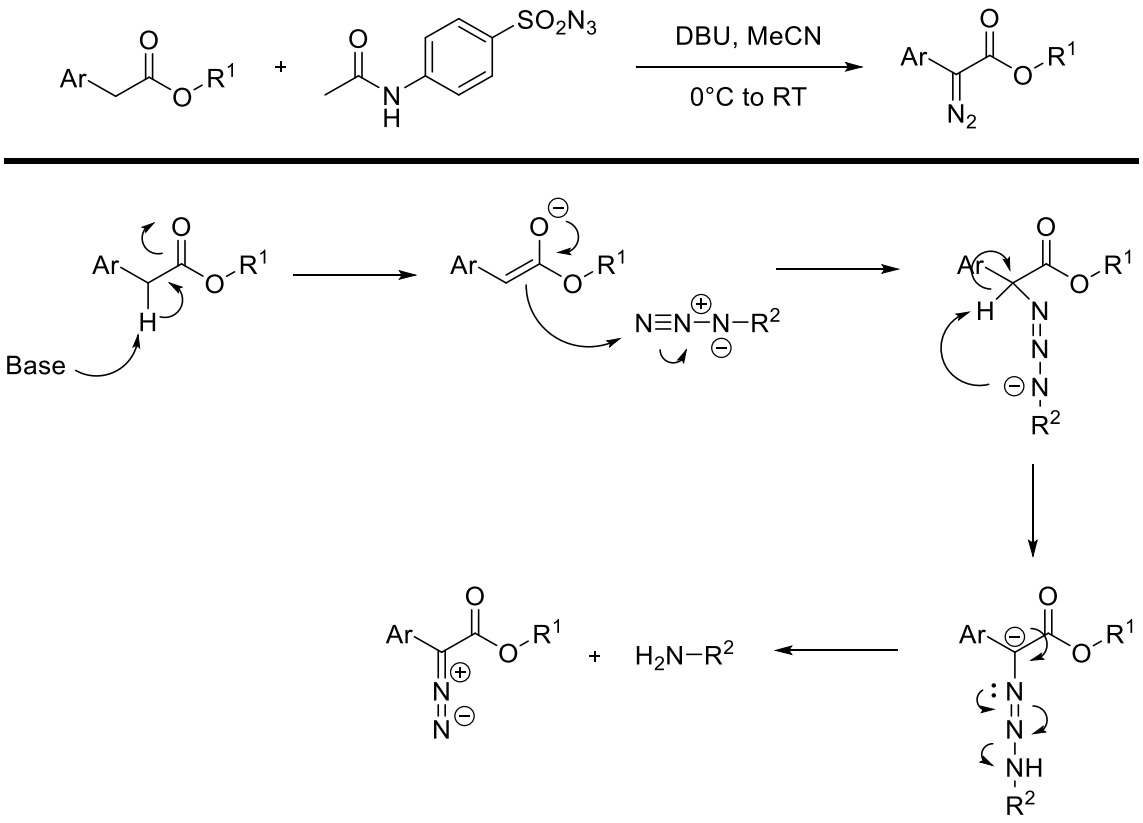
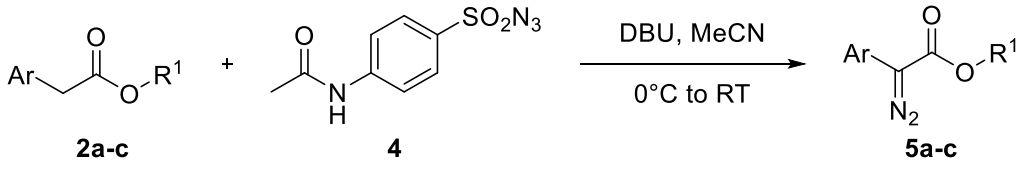


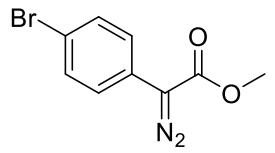
Figure 11: Reaction mechanism of diazo transfer reaction. R^1=Me, Et, R^2=C_2H_4ON-C_6H_4-SO_2

Yields from diazo transfer reactions to generate diazoacetates **5a-c** are shown in Table 1. The reactions were performed by adapted methods from literature procedures[45-46].

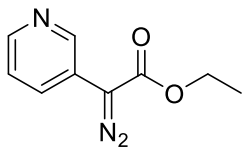
Methyl *p*-bromophenyldiazoacetate was chosen as the model diazo compound to study the microwave reaction, because it is a solid and known to be very stable. Moreover, it is likely to yield solid products because of the heavy Br-substituent. **5a** was prepared in two batches 76% and 86% yields. The yields are slightly lower in comparison to what has been presented in recent literature[47]. In our study, it was desired to introduce heterocyclic substituents such as pyridines, to generate diversity. Therefore, compounds **5b** and **5c** were synthesized in 99% and 95% yields respectively, from commercially available ethyl esters. Other diazo compounds employed in this study, were supplied by Dr. Stephanie Hansen.

*Table 1: Aryl diazoacetates **5a-5c** obtained by diazo transfer reactions.*

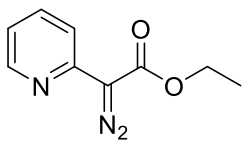




5a
76, 86% yield



5b
99% yield



5c
94% yield

2.2 Microwave-assisted synthesis of 3,4-dihydroquinoxalin-2-ones

In this, and the upcoming sections, the microwave-assisted synthesis of 3,4-dihydroquinoxalin-2-one heterocycles will be discussed.

Because of their interest in the carbene intermediate, Davies et al. performed a mechanistic study of the thermal N-H insertion of the thermally induced carbene intermediate[38]. Upon heating, the loss of nitrogen gas generates the highly reactive and electrophilic carbene intermediate. A nucleophile (*o*-phenylenediamine as shown in Figure 12) attacks the carbene by adding its lone pair electrons to the empty p- orbital (unfilled LUMO) of the singlet carbene, which leads to an ylide. Proton transfer leads to an ester enol which tautomerizes to the ester; which is susceptible to substitution by the second nucleophilic amine and yields a ketopiperazine-like heterocycle.

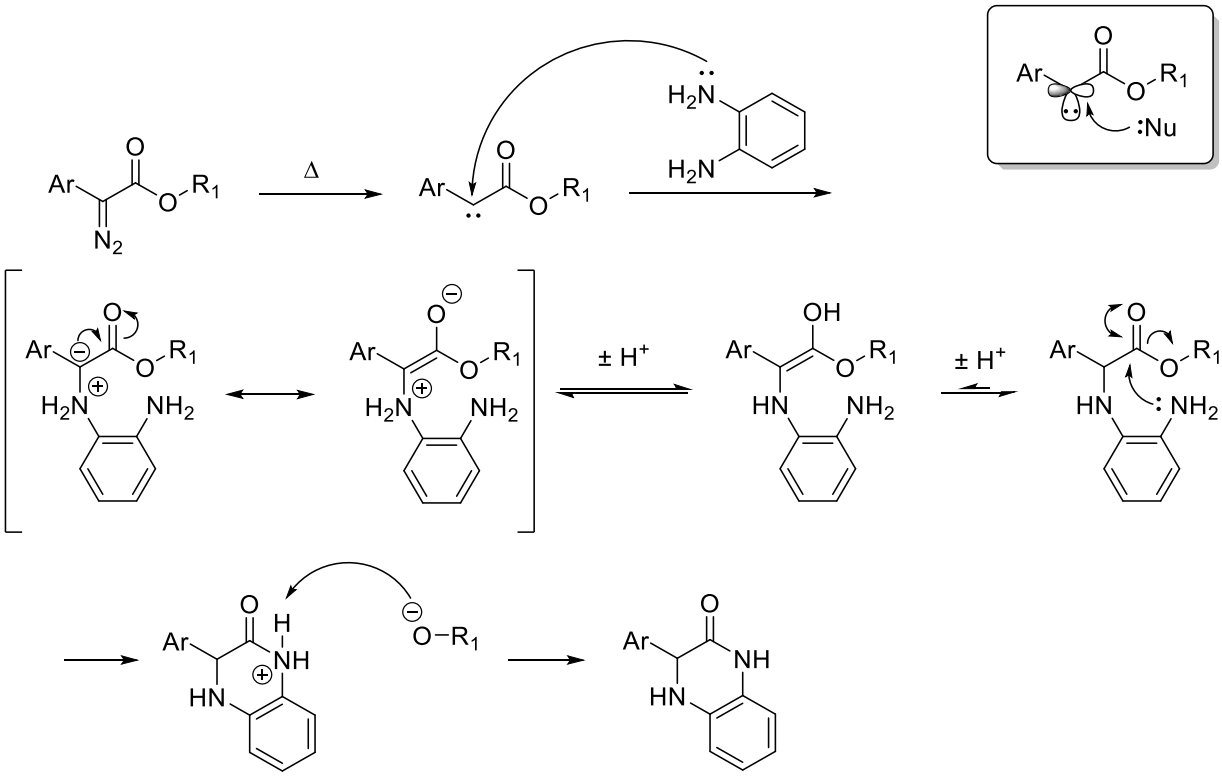
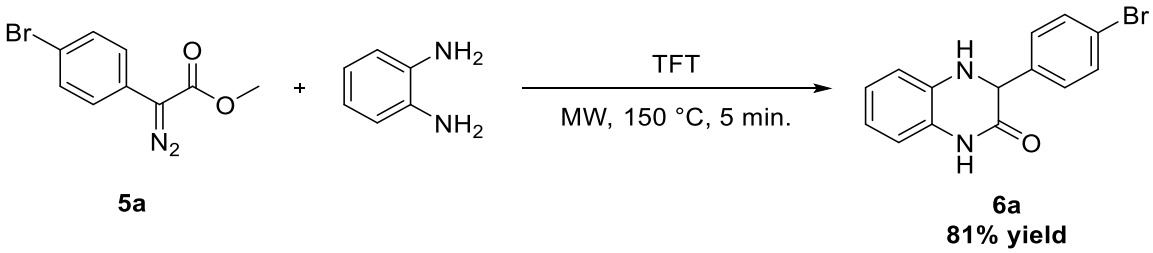


Figure 12: N-H insertion – cyclization reaction mechanism.

Based upon previous work done in Hansen group (section 1.6), exploring the possibility of a thermal N-H insertion – cyclization cascade reaction, initial experiments of a microwave-assisted synthesis of 3-aryl-3,4-dihydroquinoxalin-2-ones were conducted (Scheme 14). These experiments indicated that the reaction worked in the microwave with acceptable yields, and improved purity in comparison to conventional heating methods, and the completed reaction resulted in a product that had precipitated and could be isolated by filtration. The microwave settings used during the tests were used in further exploration of the reaction.



5a **6a**
81% yield

Scheme 14: Inital experiments of microwave-assisted synthesis of 3-aryl-3,4-dihydroquinoxalin-2-one.

para-bromophenyldiazoacetate **5a** (0,5 M) was reacted with *o*-phenylenediamine (1,7 eq.) and used Trifluorotoluene (TFT) (2 ml) as solvent in the microwave. TFT was chosen as solvent, as it had been used in N-H insertion to carbene reactions done by the Davies group[38]. The microwave settings used in the initial tests were used and held constant. Figure 13 displays the

microwave program table which is presenting the microwave settings used. The temperature was set to reach 150 °C as fast as possible, and hold the temperature at 150 °C for 5 minutes, before cooling to 55 °C. The stirring rate was set to 900 rpm.

Step	Program	Temperature	Time	Cooling	Stirrer Speed
		°C	hh:mm:ss		rpm
1	Heat as fast as possible	150	-	On	900
2	Hold	-	00:05:00	On	900
3	Cool down	55	-	On	900

Figure 13: Microwave program settings used during N-H insertion – cyclization reaction.

Figure 14 demonstrates how power input in the beginning of the reaction quickly raises the temperature, and holds 150 °C until cooling starts. As the solvent refluxes and N_2 is released from the reaction, pressure builds up to 5 bar; well below the 30 bar limit of the microwave reactor.

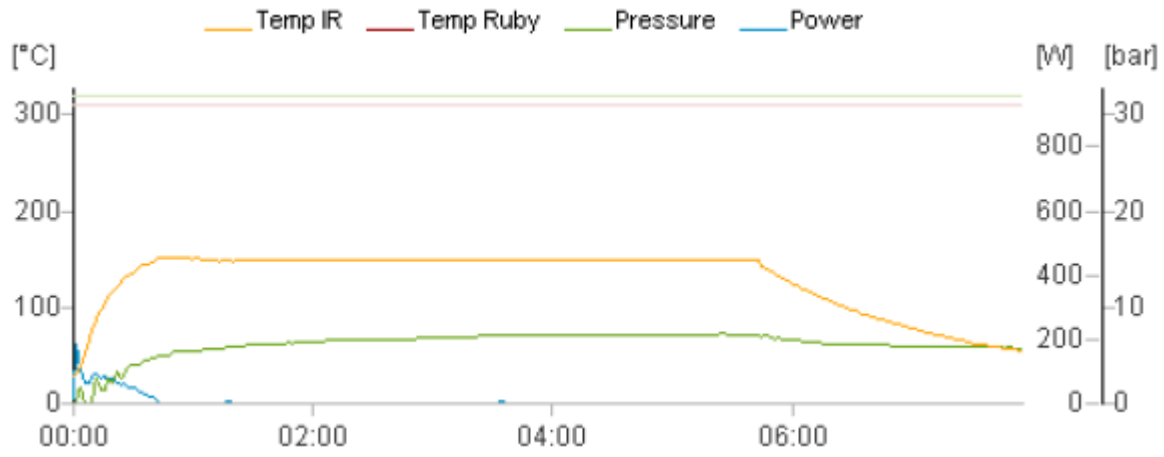


Figure 14: Microwave reaction progression over time (X-axis).

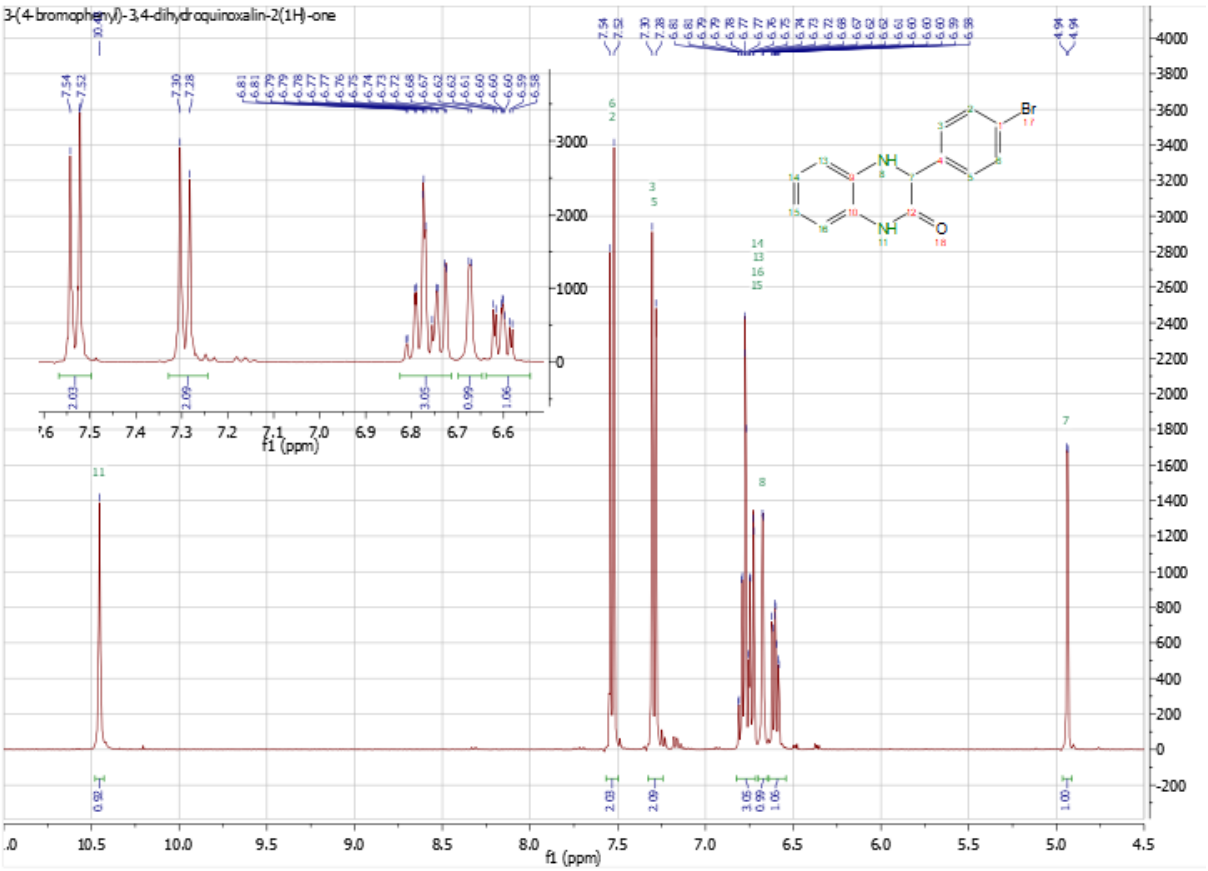


Figure 15: NMR of product isolated by filtration.

Figure 15 shows the ^{1}H-NMR of **6a**, and the characteristic features of the para-substituted-aryl-3,4-dihydroquinoxalin-2-one is expressed. The para-bromo-aryl protons (**H 6,2, 3,5**) displays two doublets at 7,53 and 7,29 ppm. The methine proton **(H7)** is a doublet at 4,95 ppm, coupling to the amine proton (**NH8**) which appears as a doublet at 6,67 ppm. The amide proton (**NH11**) shows up in the spectrum as a singlet at 10,45 ppm, and aromatic protons on of the quinoxaline-ring displays as multiplets between 6,5 – 6,8 ppm.

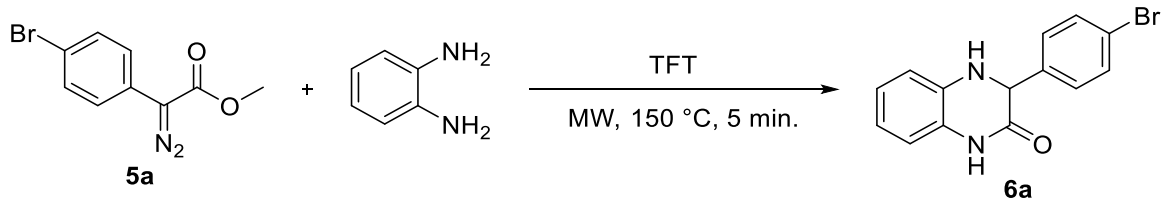
The 3,4-dihydroquinoxalin-2-one products oxidize slowly in air. This process is observed when samples of the product is left in ambient atmosphere and can be seen as peaks at 8,25 ppm and 7,75 ppm that appear in the spectrum over time. These signals come from the para-bromo aryl protons upshifted in the oxidized 3-aryl quinoxaline-2-ol. When oxidized, the aromatic protons (**H13-16**) are shifted up-field as well. In addition, as the product oxidizes, the phenol proton quinoxaline-2-ol appears at 12,5 ppm, and the amine and amide protons disappears.

2.3 Improving reaction conditions.

To improve the reaction yield, the variables of concentration of aryldiazo compound, equivalency (equiv.) of diamine, solvent, and potential additives were studied. The microwave settings used in the initial tests were used and remained unchanged.

2.3.1 Comparing mass of precipitated product

The initial efforts of the study focused on improving the reaction conditions to obtain high yields, starting with the conditions used during the initial tests.



Scheme 15: Outline of microwave reaction.

As previously mentioned, the product precipitates out after the reaction and may be isolated by filtration to yield crude product with few impurities. Because of the low occurrence of impurities, the simplest way to obtain a yield table, was to compare the mass of the precipitated products.

After the reactions, the precipitated products were filtrated in a pre-weighted glass sintered funnel, washed and dried by the vacuum of the water pump, followed by drying over P_2O_5 overnight.

In total 14 reactions were run with different conditions, varying the solvent, concentration of *p*-bromophenyldiazo acetate, equivalents of *o*-phenylenediamine, and DIPEA as additive was tested to determine if addition of base would be beneficial to the reaction (Table 2). ^{1}H-NMR spectra were obtained, as well as GCMS-analysis of the products and their filtrates were conducted.

Table 2: Yields from study if reaction conditions, determined by mass of collected precipitate of product.

Entry	Solvent	Additive	Equiv. of diamine	Conc. of diazo	Yield	Observation
1	TFT	-	1,7	0,5	**81**	
2	TFT	-	1,7	0,5	**78**	
3	PhMe	-	1,7	0,5	55	
4	PhMe – TFT[b]	-	1,7	0,5	72	No precipitation[a]
5	PhMe – TFT[b]	-	1,7	0,5	-	
6	PhMe	-	1,7	0,5	77	
7	MeCN	-	1,7	0,5	28	No precipitation[a]
8	MeCN – TFT[b]	-	1,7	0,5	68	No precipitation[a]
9	PhMe	1,1 equiv. DIPEA	1,7	0,5	55	
10	PhMe	1,1 equiv. DIPEA	1,1	0,5	40	
11	PhMe	3 equiv. DIPEA	1,7	0,5	61	No precipitation[a]
12	PhMe – TFT[b]	3 equiv. DIPEA	1,7	0,5	**78**	
13	PhMe	-	1,7	0,75	64	
14	PhMe	-	0,8	0,5	25	No precipitation[a]

a) Product was not precipitated after the reactions. Product precipitation were observed in varying rates.
b) As product had not precipitated, the reaction solvent was removed and TFT was added, the mixtures were heated to reflux. Product precipitated in the new solvent, and collected by filtration.

The precipitation of the product was not consistent across all conditions. For some conditions no precipitation was observed, or precipitation occurred some time after the reaction was complete at differing rates. GCMS analysis showed that some product remained in the filtrate. A solution to the poor precipitation of the product was found by using a second solvent; after removal of the reaction solvent, the crude mixture was dissolved in TFT. The mixture was heated to yield the precipitated product during cooling. This allowed the product to be isolated by filtration while still a bit warm.

While most conditions resulted in pure products, others resulted in larger amounts of diamine collected, as in the case of entry 11 (Figure 16). In addition, several conditions resulted in larger amount of product loss to the filtrate. Large amount of product can be seen in the GCMS spectra of the filtrate of entry 7 (Figure 17).

Due to the inconsistency in both purity, and the amount of product collected by the method, it was concluded that another method of determining the yields for the reactions was necessary.

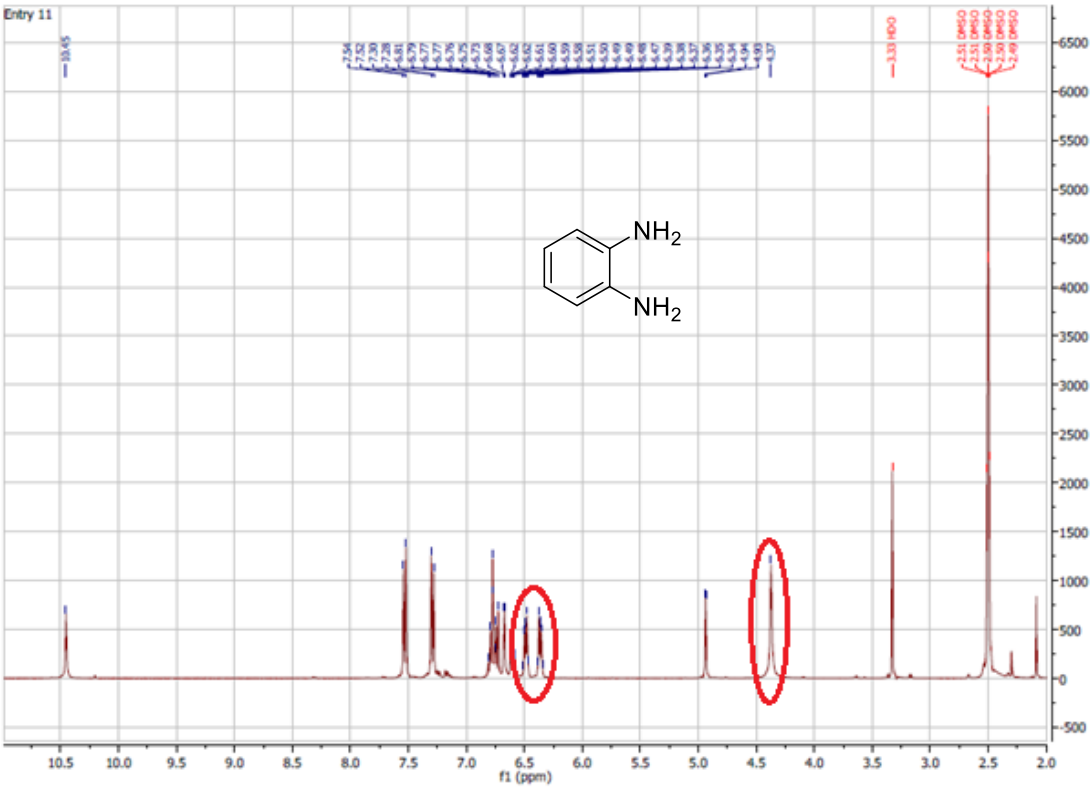


Figure 16: Collected product of entry 11 containing large amount of diamine circled in red.

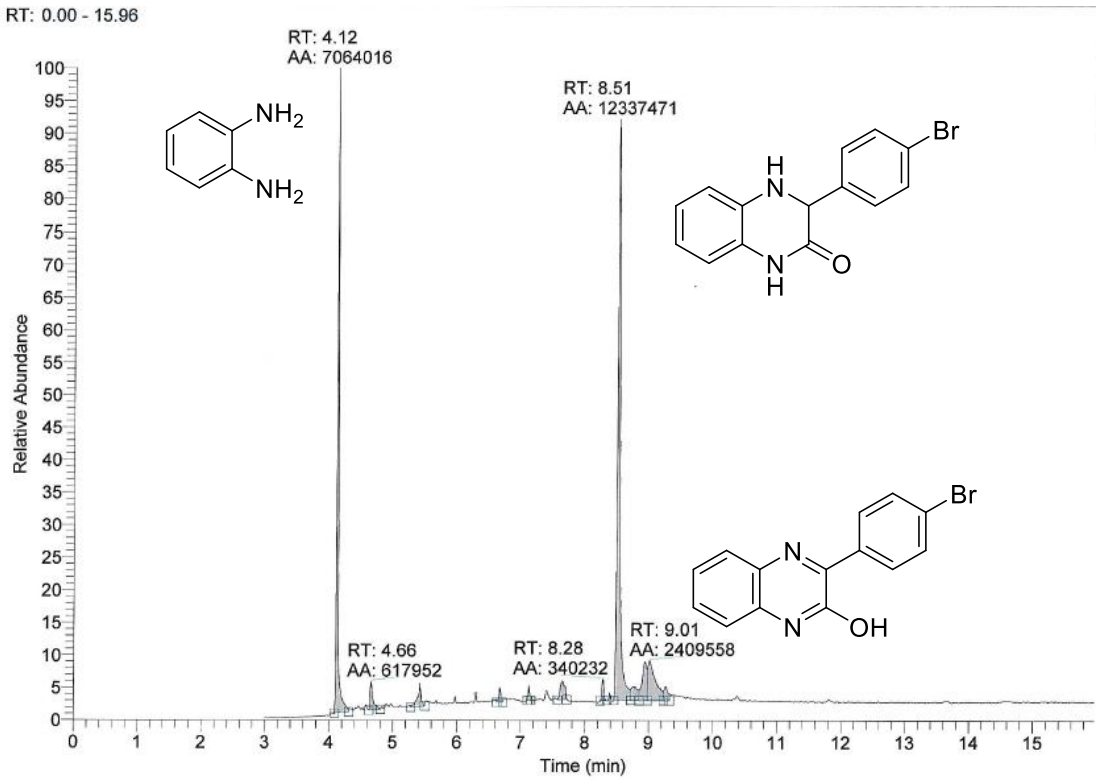


Figure 17: GCMS chromatogram of filtrate of entry 7 containing large amount of product at 8,51 minutes retention time (RT)

While working to improve the yield, several attempts were made to recrystallize the product in various solvents (Table 3). Although some product was obtained and purified, none of the solvents tested were good choices for purification by recrystallization.

Table 3: Attempts at recrystallization.

Attempt #	Solvent	Result
1	EtOH	Low product precipitation, dissolved product too well, 3 % yield
2	EtOH / Heptane mixtures	Did not fully dissolve crude
3	EtOAc / Heptane mixtures	Did not fully dissolve crude
4	MeCN	Low product precipitation
5	THF	Did not dissolve crude
6	Chloroform	Did not dissolve crude
7	Diethyl ether	Did not dissolve crude

As crude product would either not dissolve completely, or not completely precipitate during recrystallization attempts other purification methods were explored.

An attempt at an acidic work-up of the crude product was made with the intention to remove any unreacted diamine that remained after the reaction. The crude product was dissolved in ethyl acetate and washed with aqueous hydrochloric acid solution (pH 1-2). After drying and removal of the organic solvent, the diamine was no longer present. Figure 18 illustrates that the method was successful in removing excess diamine, as the diamine is present before (left), and is removed by acidic work-up (right).

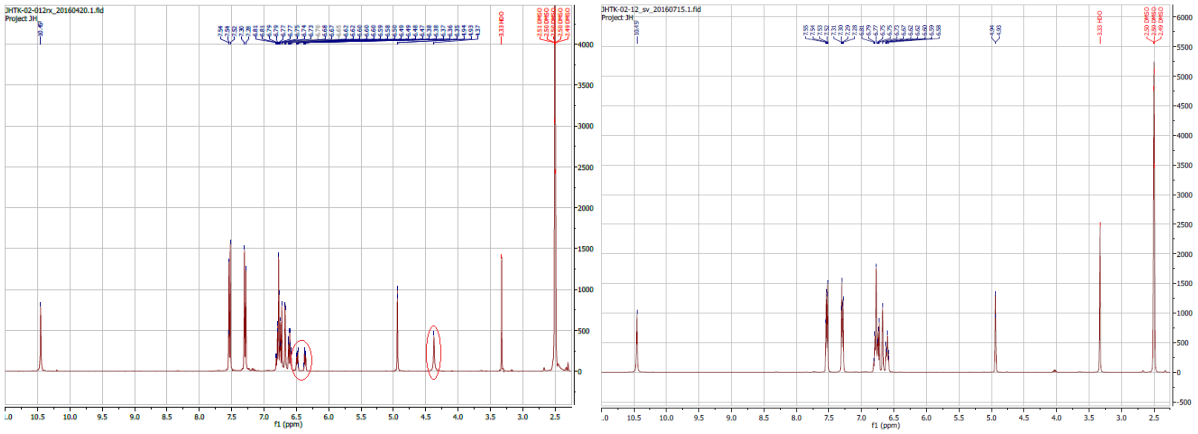


Figure 18: Product crude containing diamine residues marked in red before acidic work-up (left). Diamine residues removed by acidic work-up (right).

2.3.2 Determining yield by NMR

Due to the time requirement of purifying each entry, the decision was made to use NMR to determine the yield by way of an internal standard. The method is based on comparing the integral of the compound of interest to an added internal standard. A specific amount of the internal standard is used in order to be comparable to the compound of interest. Methyl benzoate was chosen as internal standard, as its methoxy protons signal at 3,85 ppm in DMSO-d_6, is distinct, and does not interferre with crude product signals.

After the microwave reactions, the reaction solvent was removed and the solid residue was dissolved in DMSO-d_6. The solution was added 0,5 mmol methyl benzoate and ^{1}H-NMR spectrum of this mixture was obtained. The integral of the methyl protons of the standard was compared to the integral of the methine proton of the quinoxalinone, and from the comparison, the yield was back calculated, and determined (Figure 19).

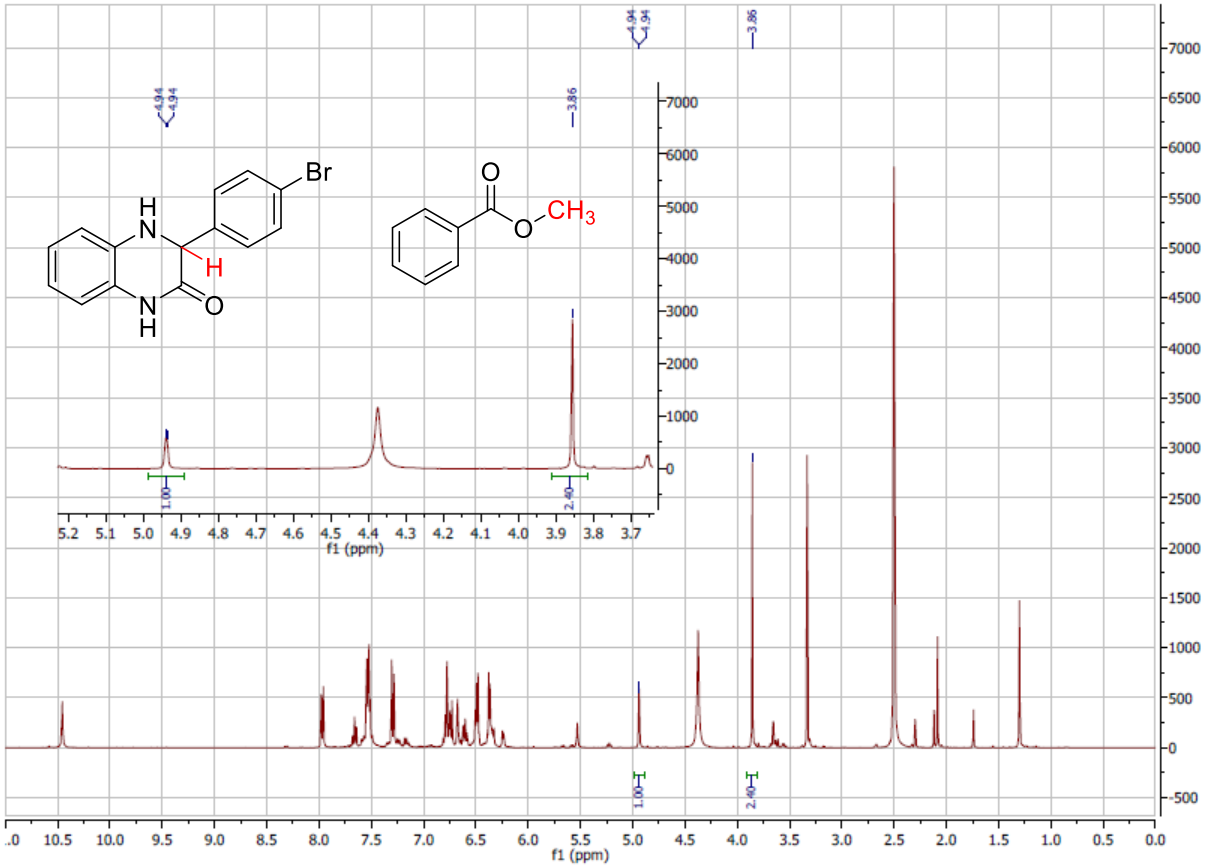


Figure 19: Comparison of the methine proton signal integral (4,94 ppm) and methoxy protons integral (3,86 ppm) to determine the NMR-yield.

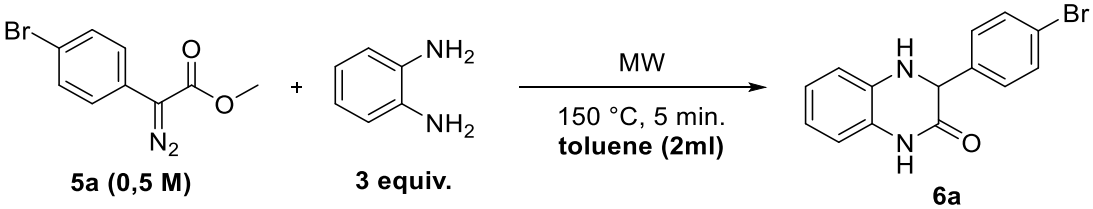
To confirm that the NMR-yields would correspond to isolated yields, the products of entry 1 and 13 were isolated by flash chromatography.

As Table 4 indicates, lower equivalence of *o*-phenylenediamine resulted in lower yields, while higher equivalence generated higher yields. DBU and TFA additives were tested in order to investigate whether the reaction was enhanced by basic or acidic conditions, but both lowered the yield dramatically. Increasing the concentration of diazo compound resulted in similar, but slightly lowered yields.

Table 4: NMR-yields obtained from reactions of varying reaction conditions is shown.

Entry	Solvent	Additive	Equiv. of diamine	Conc. of diazo	Yield by NMR	Isolated yield
1	TFT	-	1,7	0,5	66%	64%
2	PhMe	-	1,7	0,5	63%	-
3	PhMe	-	0,9	0,5	52%	-
4	PhMe	-	1,2	0,5	59%	-
5	PhMe	-	1,5	0,5	66%	-
6	PhMe	-	2	0,5	71%	-
7	**PhMe**	**-**	**3**	**0,5**	**80%**	**-**
8	PhMe	-	4	0,5	81%	-
9	PhMe	DBU	2	0,5	45%	-
10	PhMe	TFA	2	0,5	32%	-
11	PhMe	-	2	0,75	69%	-
12	**PhMe**	**-**	**3**	**0,5**	**80%, 88%**	**77%**

Both yield tables indicate slightly higher yields when TFT is used as the solvent, instead of toluene. However, because TFT is less common and more expensive compared to toluene, toluene was chosen as the better solvent for the reaction as the product was formed in satisfactory yields. Entry 8 shows the highest yield was obtained from using 4 equivalents of diamine, however, the increase from 3 equivalents was negligible and the latter was therefore found to be optimal. The determined reaction conditions illustrated in Scheme 16 was used in subsequent exploration of the reaction.

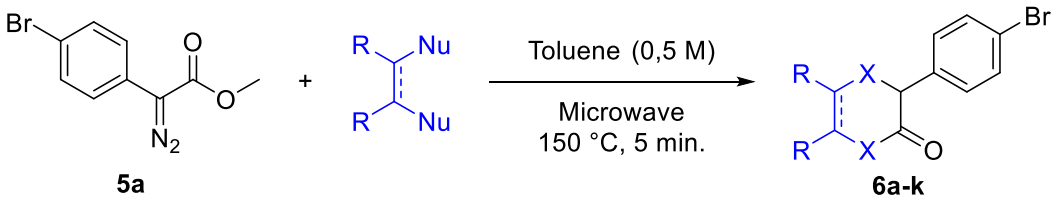


Scheme 16:Reaction conditions determined from NMR-yield study.

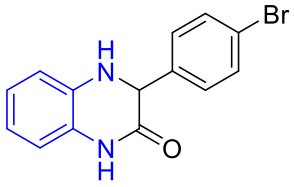
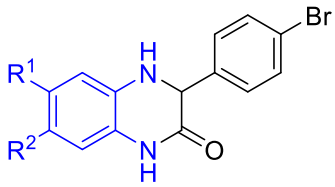
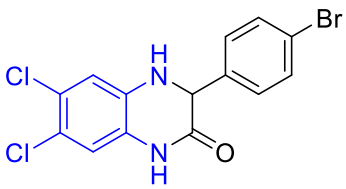
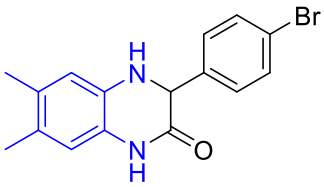
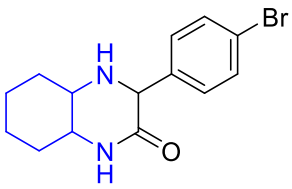
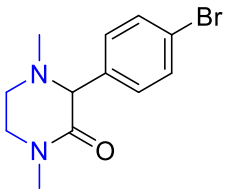
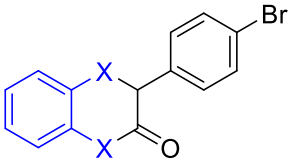
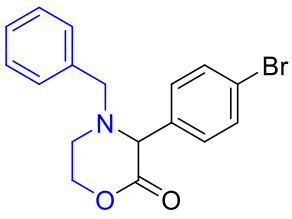
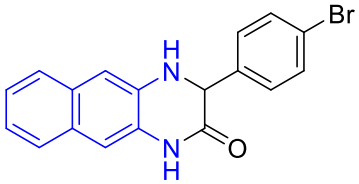
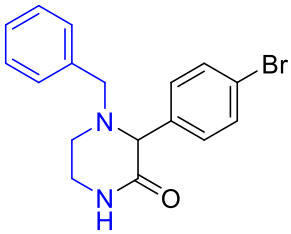
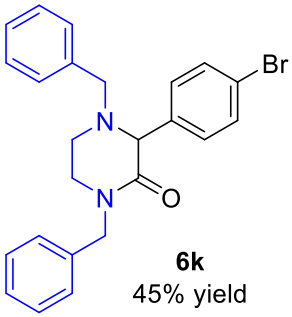
2.4 3-(4-bromophenyl)-3,4-dihydroquinoxalin-2(1*H*)-one derivatives

To investigate the scope of diamines or dinucleophiles in the reaction and, potential selectivity, reactions were carried out using a selection of different dinucleophiles. Table 5 summarizes the findings in these reactions.

Table 5: Products of microwave-assisted synthesis of para-bromophenyl-quinoxalin-2-one derivatives.



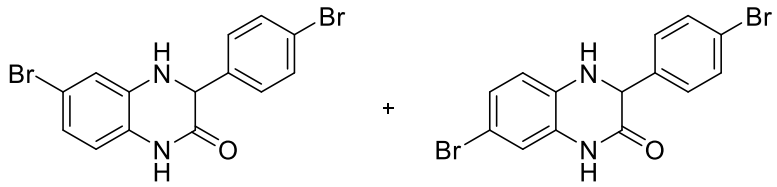
5a **6a-k**

 **6a** 80% yield	 **6b** 67% yield	 **6c** 69% yield
 **6d** 78% yield	 **6e** 26% yield	 **6f** 57% yield
 **6g** -	 **6h** 35% yield	 **6i** 67% yield
 **6j** 12% yield	 **6k** 45% yield	

R^1= H, Br, R^2= H, Br, X= N, O. 6g not fully isolated, yield not determined.

The microwave reaction resulted in the desired products in moderate to good yields for a range of diamines. Both symmetrical and unsymmetrical diamines as well as dinucleophiles were tolerated. Aliphatic diamines resulted in lower yields, however alternative work-up procedures might result in higher yields. Exploration of the selectivity of a secondary amine versus primary amine or hydroxy, suggested the more sterically hindered secondary amine reacts as the initial nucleophile in the reaction. However, reactions of secondary, non-aromatic amine, resulted in lower yields, in comparison to aromatic primary diamines.

As new products displayed varying properties of solubility, and R_f values, a trial and error purification process occurred for most new products. This section will describe the efforts made in obtaining the products presented in Table 5 (Compound **6a** is described in the previous section).



6b[1] **6b[2]**

*Figure 20: Compound **6b[1]** and **6b[2].***

To explore potential selectivity of unsymmetrical diamines, **5a** was reacted with the 4-bromobenzene-1,2-diamine to obtain product **6b** (Figure 20).

The reaction resulted in a black suspension crude mixture. Product did not precipitate out and both the black particulate diamine and crude were poorly soluble in toluene and most other solvents tested. As the *o*-phenylenediamine was possible to remove by acid work-up of product **6a**, the same was performed in this case. After acidic work-up of the crude mixture, the product was purified by flash chromatography to afford **6b** in 64 % yield.

The product was mainly isolated as mixtures of the two isomers, however some fractions indicated separate isomers. Figure 21 displays one isomer on the left, and a mixture on the right.

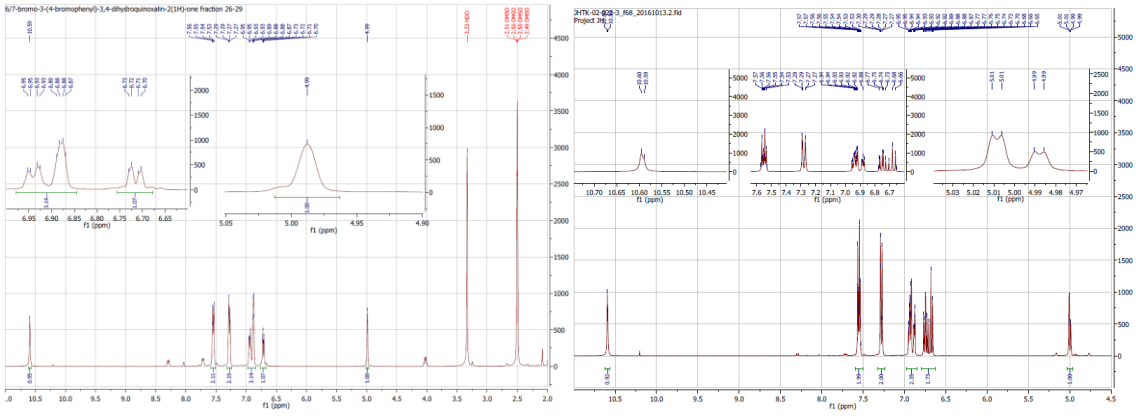
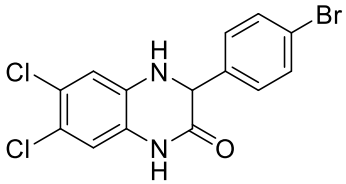


Figure 21: NMR of isolated isomer fraction (left), and isomer mixture (right)

Characterization was obtained from the isolated isomer fraction shown in Figure 21. Both carbon and proton NMR spectra indicate that product has been formed, as the proton integrals, and number of carbons fits to the expected product. The product is also found by HRMS. Elucidation of the product by NMR (COSY, HSQC and HMBC) was attempted, however was not successful, and we are not able to distinguish between the two isomers. Several attempts at separating both isomers completely were made, however these were unsuccessful.

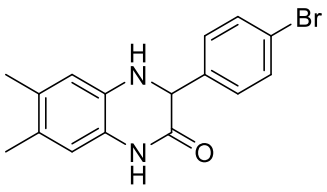


6c

*Figure 22: Compound **6c.***

To explore the reaction using electron withdrawing groups, **5a** was reacted with the dichloro-substituted, symmetrical 4,5-dichloro-o-phenylenediamine, to obtain the **6c** product (Figure 22). Since an initial attempt at acidic work-up to remove the diamine was not successful, a small-scale test was carried out, to see if the crude mixture could be purified by automatic flash chromatography, which resulted in isolated pure product.

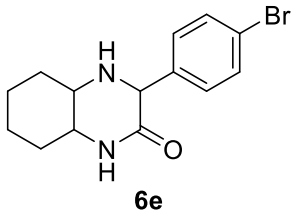
The reaction was carried out again, and the crude was directly transferred to the pre-column, using THF as solvent, and was purified by automated flash chromatography. Despite some fractions collected contained pure product, several fractions were collected as mixtures of both product and diamine. Impure product fractions were combined and purified on a second column, and this process yielded 69 % desired product overall.



6d

*Figure 23: Compound **6d**.*

5a was reacted with dimethyl substituted, symmetrical 4,5-dichloro-o-phenylenediamine to obtain product **6d** (Figure 23). Since purification by automatic flash chromatography had worked well for **6c**, the same method was attempted here. As TLC of the crude showed nine separate spots, isolation by chromatography was difficult and resulted in only mixed fractions. In addition, the crude had not been completely absorbed by the precolumn, and the product was poorly soluble in THF. The reaction was performed again. The crude product was suspended in THF and filtrated, which resulted in 52 % pure product. The filtrate was concentrated, and purified by automatic flash chromatography to yield 26 % more product. Impure product fractions were collected and purified in an additional column to yield 78 % isolated **6d** product in total.

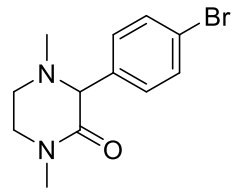


6e

*Figure 24: Compound **6e**.*

In order to investigate if the reaction would work with non-aromatic diamines, **5a** was reacted with non-aromatic (±)-trans-1,2-diaminocyclohexane to yield the **6e** product (Figure 24). Product precipitate was filtrated and washed with toluene, to yield 27 % white solid product. The product had low UV activity, and analysis by TLC was troublesome. Stains tested did not help visualize the product. However, when leaving the TLC for days, product spot appeared, likely due to product oxidation in air.

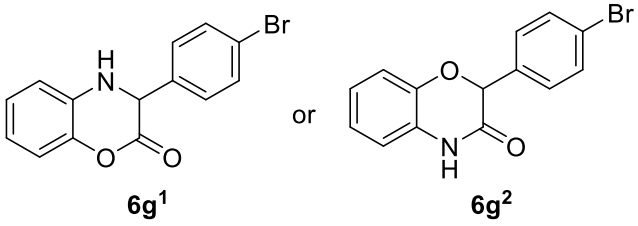
An attempt at purification by automated flash chromatography of the crude mixture directly following the reaction was made. Fractions was collected as impure mixtures. Due to challenges localizing product fractions, further isolation and purification efforts was not pursued. As product was observed by TLC in the filtrate, the actual yield is expected to be higher, and work-up procedures should be explored further.



6f

*Figure 25: compound **6f**.*

To explore the reaction using secondary amines, **5a** was reacted with N1,N2-dimethylethane-1,2-diamine to yield the 3-(4-bromophenyl)-1,4-dimethylpiperazin-2-one product (Figure 25). Crude product was purified directly following the reaction by automatic flash chromatography, to isolate the product in 57 % yield.



6g^1 **6g^2**

*Figure 26: Compound **6g**.*

5a was reacted with N1,N2-dimethylethane-1,2-diamine to yield **6g** (Figure 26), in order to investigate potential selectivity of the primary amine versus phenol in the carbene addition step .Several attempts at the reaction followed by flash chromatographic purification was done, however mainly mixed product fractions were collected.

TLC of the crude shows 11 different spots, which indicates the possibility of several by-products from the reaction. Both **6g^1** and **6g^2** product may be made, and both uncyclized intermediates may be present. Investigations using HRMS and GCMS indicted the both uncyclized intermediates, and expected product (Figure 27).

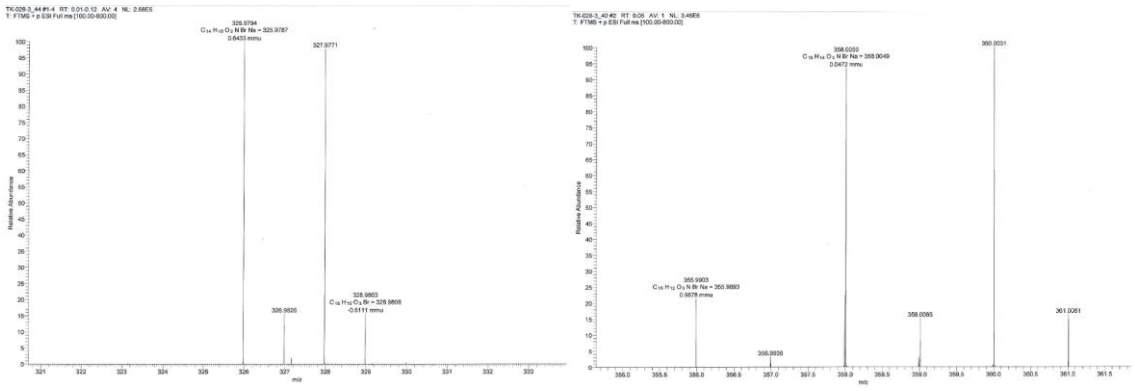


Figure 27: HRMS spectrum showing product mass of product (left), and uncyclized intermediate (right).

Although attempts at purification did not isolate the product completely, a fraction was pure enough to study by NMR. Illustrated by Figure 28, signal pattern and the number of protons and carbons is consistent with the expected product. The high proton shift at 10,98 ppm (Figure 28, left), indicates product **6g²** as the amide N-H proton is expected to be found in this range, while amine N-H, is typically found at a lower shift. In addition, the methine proton can be seen as a singlet at 5,78 ppm, indicating that it do not couple with amine proton, suggest **6g²** to be the isolated product.

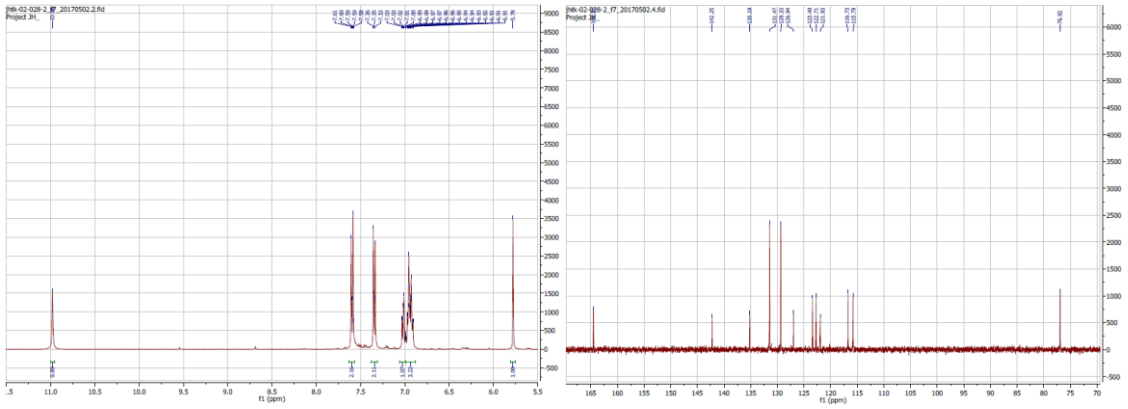
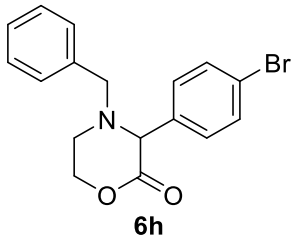


*Figure 28: NMR of pure 6g fraction is displayed: Proton NMR (left), and carbon NMR (right). High shift of proton at 11 ppm, indicate product **6g²**.*

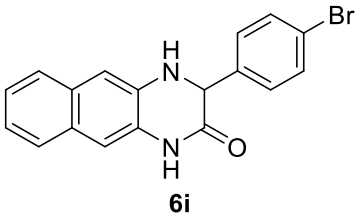
Isolated **6g²** fraction indicates the that the phenol has reacted as the initial nucleophile rather than the amine. As only one fraction was isolated the ratio of **6g²** and potential other products is not known. Attempts at further isolation of product(s) was not successful.



6h

*Figure 29: Compound **6h**.*

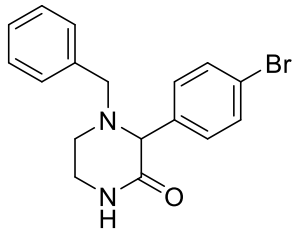
5a was reacted with 2-Benzylaminoethanol to yield **6h** product (Figure 29), and to further investigate potential amine versus hydroxy selectivity of the reaction. An initial attempt at isolation and purification by automatic flash chromatography directly following the reaction was made. However, product fractions collected contained several impurities. To obtain NMR-yield, the reaction was carried out again. NMR-yield was obtained using $CDCl_3$ instead of DMSO-d_6 as previously, since the methine proton signal overlapped with aliphatic ring protons in DMSO. NMR-yield was determined to be 37 %. NMR solvent was removed by evaporation and the solid residue purified by automatic flash column using a slower solvent gradient, than the first attempt. Pure **6h** product was obtained as a clear oil in 35 % yield. The observation of product **6h** suggests a selectivity for the secondary amine as the initial nucleophile rather than the hydroxy group. As NMR of **6h** crude indicated only one product present (only one methine proton peak), it appears the amide isomer did not form in detectable amounts in the reaction.



6i

*Figure 30: Compound **6i**.*

To explore the reaction using diamines with extended pi-systems, **5a** was reacted with 1,2-diaminonaphthalene to yield benzoquinoxalin-2-one **6i** (Figure 30). NMR yield was determined to be 69 %. After aqueous, acidic workup, the residue crude was purified by automatic flash chromatography to yield 58 % product. Impure product fractions were collected and purified by an additional column, to obtain product **6i** in 67 % yield total.



6j

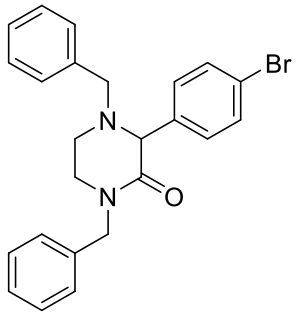
*Figure 31: Compound **6j**.*

para-bromophenyldiazoacetate **5a** was reacted with *N*-benzylethylenediamine to yield **6j** (Figure 31) and explore potential selectivity of the less nucleophilic primary amine, versus more sterically hindered secondary amine. NMR yield was pursued, but due to overlap of the internal standard and product crude, it was not possible to obtained this. The crude product mixture was subjected to flash chromatography (3%-30% ethyl acetate in heptane), in an attempt of product isolation. None of the resulting fractions contained product, and it was discovered that none of the five spots on the TLC were product, but that the product was stuck on the baseline (40 % EtOAc/Heptane). The reaction was performed again, and the resulting crude mixture was purified by automatic flash chromatography. Product was completely isolated, and fractions containing product were collected and subjected to an additional column. Product fractions were not completely isolated from the diamine, but it was discovered that the product crashed out in ethyl acetate. Product fractions were collected and recrystallized from ethyl acetate to yield 12 % **6j** product as a white crystalline solid.

The isolated product suggest that although sterically hindered, the secondary amine is the stronger nucleophile, and reacts with the electrophilic carbene intermediate initially, and the primary amine cyclizes the intermediate to yield the **6j** product. Isolated yield was low; however, as the workup method was not ideal, and TLC of the filtrate from recrystallisation filtration contained product, the actual yield is expected to be higher.

Crude NMR indicates the possibility of an isomer of the product is formed, as it contains two singlets in the region where the methine proton signal is expected. GCMS of the crude mixture was recorded, but the chromatogram was of to poor quality to discern potential product.

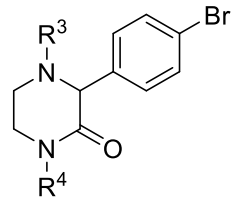
As there is a possibility of a second product, and not all of the product was collected, the reaction needs further exploration to investigate the potential second isomer product, and obtain the entire yield of **6j.**



6k

*Figure 31: Compound **6k**.*

To explore the reaction using two sterically hindered secondary amines, **5a** was reacted with N,N'-Dibenzylethylenediamine1,2-diaminonaphthalene to obtain product **6k** as seen in Figure 32. After the reaction, solvent was evaporated, and the crude solid was purified by automatic flash chromatography. Product was isolated as a clear oil in 45 % yield. NMR yield was determined to be 50 %.



6x

*Figure 32: Compound **6x***

Attempts were made at reacting methyl *para*-bromophenyldiazoacetate, **5a** with triethylenetetraamine, in the interest of exploring the potential product selectivity (Figure 33). As the diamine has four nucleophiles sites, pairwise chemically inequivalent, several product options are present, including double carbene additions. The reaction was performed twice. Once with standard 3 equivalents of the amine, and once using only 0,5 equivalents of amine to increase the chance of two **5a** molecules reacting with one triethylenetetraamine.

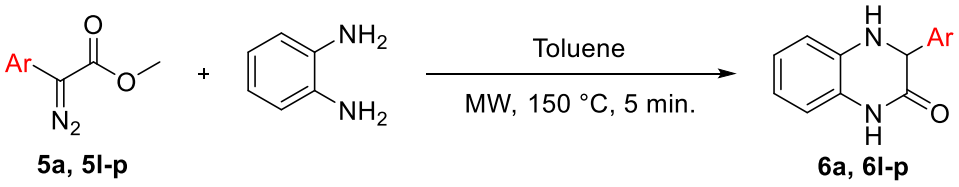
Investigations of the resulting crude mixture by TLC were problematic, as both potential product and triethylenetetramine would not move from the baseline. Severall solvent mixtures was tested with increasing polarity, but none would move the components form the baseline. Tests on deactivated silica plates, reverse phase TLC, and neutral aluminium TLC plates were also unsuccessful. An attempt at basic work up was performed, however it was not successful in separating potential product from amine. NMR of the crude mixture displays what might be the methine proton signal expected from a product, however, due to difficulties of work-ups, further isolation attempts were not pursued.

2.5 Exploring the scope of aryldiazo compounds

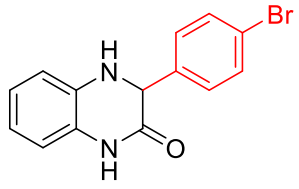
A selection of aryldiazoacetates were tested in the microwave reaction as reagents to investigate the scope of the aryl-substituent of the aryldiazoacetate. The aryldiazoacetates were reacted using the standard conditions found in section 2.3.2, and *o*-phenylenediamine as the test substrate. The resulting products and yields are displayed in Table 6. The resultant crude mixtures of **6l-o** were acid washed to remove excess diamine, and the products were purified by flash chromatography. The crude mixture of **6p** was not subjected to acidic work-up as the pKa value (5,3) of protonated pyridine would suggest it to be protonated by acidic work-up; and hence, would not be separated from the diamine. Instead the product precipitate was filtrated, and the isolated product, and the resultant filtrate, were purified separately by flash chromatography.

All aryldiazoacetates tested performed well in for the reaction, and resulted in good yields in general. Electron donating groups such as *p*-methoxyphenyl, and 3,4-dichlorophenyl, extended pi-system of naphthalene, and electron deficient pyridine aryl groups, all resulted in similar good yields. Electron withdrawing trifluoromethyl phenyl resulted in slightly lower yield (**6n**), however, increasing the reaction time **6n** from 5 to 25 minutes, increased the yield from 55 % to 68 %. The cause of this was the slower rate of nitrogen extrusion from the trifluoromethyl diazo compound.

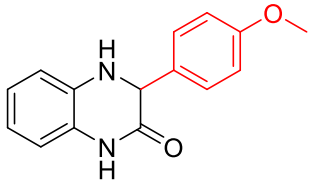
Table 6: Products of microwave-assisted synthesis of aryl-quinoxalin-2-on derivatives.



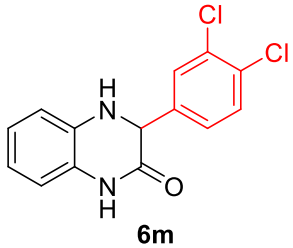
5a, 5l-p → **6a, 6l-p**



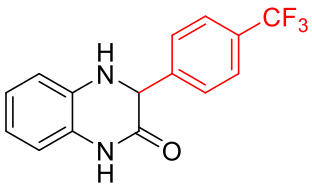
6a
80% yield



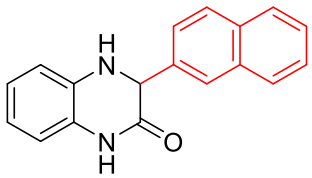
6l
64% yield



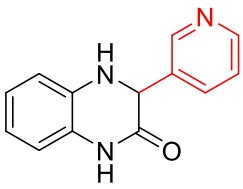
6m
67% yield



6n
55% yield



6o
68% yield



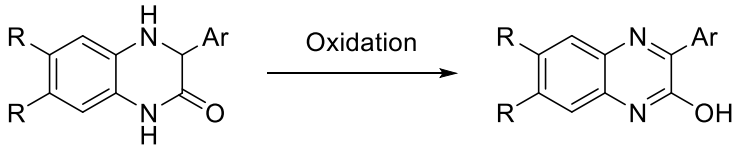
6p
66% yield

Products **6l-p** were made by visiting exchange student Eliot Starck, under supervision by the author.

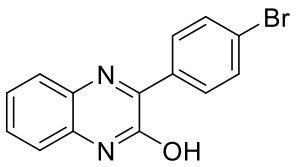
2.6 Transformation to quinoxalin-2-ols by oxidation

A major advantage of the products formed in the microwave reaction, is that they are readily transformed into 3-arylquinoxalin-2-ols by straight-straight forward oxidation. As such, our microwave protocol can be used for the synthesis of such aromatic heterocycles as well; products **6a**, **6d** and **6l-m** were oxidized to the corresponding 3-arylquinoxaline-2-ol products (Table 7). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) is a strong dehydrogenation agent, used in various chemical transformations.[48-49] Chloranil is a milder, less toxic benzoquinone, as it is chloro-, instead of cyano-substituted. These reagents are commonly used as oxidizing reagents for aromatization.[48]

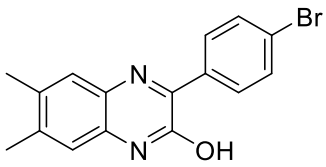
Table 7: Products of oxidation reactions.



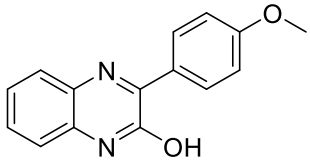
6a, 6d, 6l-p **7a, 7d, 7l-p**



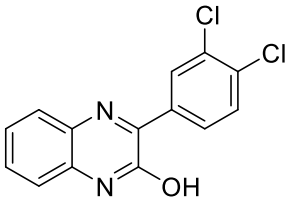
7a[a]
85% yield



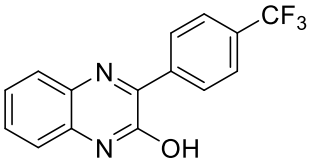
7d[a]
79% yield



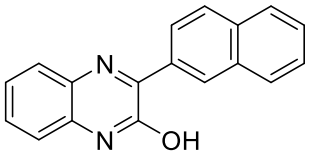
7l[b]
76% yield



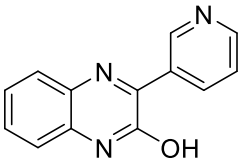
7m[b]
67% yield



7n[b]
95% yield



7o[b]
96% yield



7p[b]
68% yield

R = H, Me. a) DDQ (1,1 equiv.) THF (20ml), 1h, room temperature b) Chloranil (1,1 equiv.) THF (20 ml), 1-24 h, room temperature. Products **7l-7p** were made by visiting exchange student Eliot Starck, under supervision by the author.

All oxidation reactions showed 100 % conversion by TLC. The 3-arylquinoxaline-2-ol products tended to be poorly soluble in common solvents, and some seemed to crystallize during column chromatography. Pure products **7a**, **7d**, **7l-p** were obtained in good to excellent yields.

6a, and **6d** were reacted with DDQ in oxidation reactions. The reactions were monitored by TLC. Within an hour, the starting material was consumed. Water was added the crude mixture of **7a**, which led to product precipitation. The product was isolated by filtration to give 85 % of **7a**. The same strategy of work up was intended for product **7d**, however addition of water led to heavy product precipitation, trapping impurities. The suspension was extracted with ethyl acetate and the residue was purified by automatic flash chromatography. Pure product was obtained in 38 %. Poor solubility of the product in methanol was observed. Most of the solvent was removed from impure product fractions, and methanol was added to induce product precipitation. Precipitated product was filtrated and washed with methanol to a total yield 79 % of **7b**.

Quinoxalin-2-ones **6l-6p** were reacted with chloranil in oxidation reactions to obtain quinoxaline-2-ol products. The reactions were monitored by TLC. While the starting material of **7a** was consumed after one hour, **7m, 7o** and **7p** needed 4 to 5 hours to complete. As **7n** was not done after 6 hours, it was left to stir over night. After the reactions had finished, the reaction solvent was removed, and the crude solids were purified by column chromatography to obtain **7l - 7p** products in 67%-96% yields.

2.7 Compound Characterization

Novel structures have been characterized by ^{1}H-NMR, ^{13}C-NMR (supplemented by COSY, HSQC, HMBC, ROESY, NOESY), HRMS, and IR. **6a** is used as an example to demonstrate the typical signals for obtained 3-phenyl-3,4-dihydroquinoxalin-2-one products.

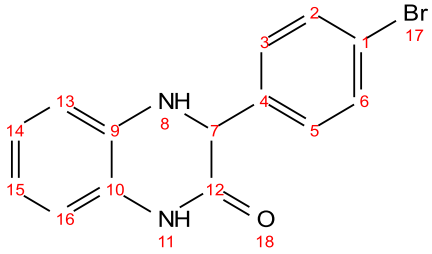


Table 8: Structure elucidation by NMR.

Atom number	C ppm	H ppm	HMBC	ROESY
1	120,81	-	7, 8	-
(2, 6)	131,18	7,53 d, *J* = 8,4 Hz	1, (2,6), 4	(3,5)
(3, 5)	129,20	7,29 d, *J* = 8,4 Hz	1, 7, (3,5)	(2,6)
4	139,51	-	(2,6), 7	-
7	58,72	4,94 d, *J* = 1,9	11, (5,3), 9, 4, 12	(3,5), 8
8	-	10,45 S	10, 12	7,
9	133,60	-	11, 7, (13,14,15,16)	-
10	125,28	-	8, (13,14,15,16)	-
11	-	6,67 d, *J* = 2.0 Hz	7, 9	(13,14,15,16)
12	165,52	-	7, 8	-
(13, 14, 15, 16)	123,08, 117,85, 114,87, 113,40	6,76, m 6,60, ddd, *J* = 8.1, 6.7, 2.1 Hz	10, (13,14,15,16)	11

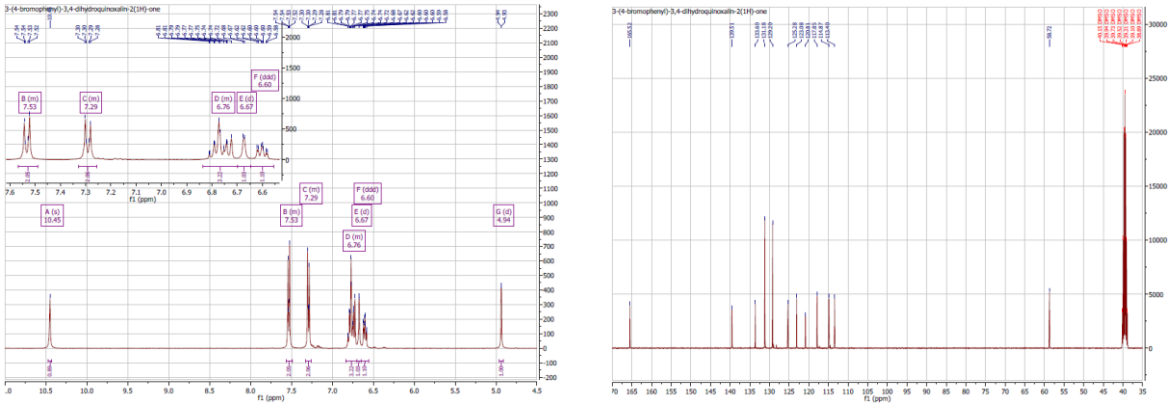


*Figure 33: Proton NMR (left) and carbon NMR (right) of compound **6a***

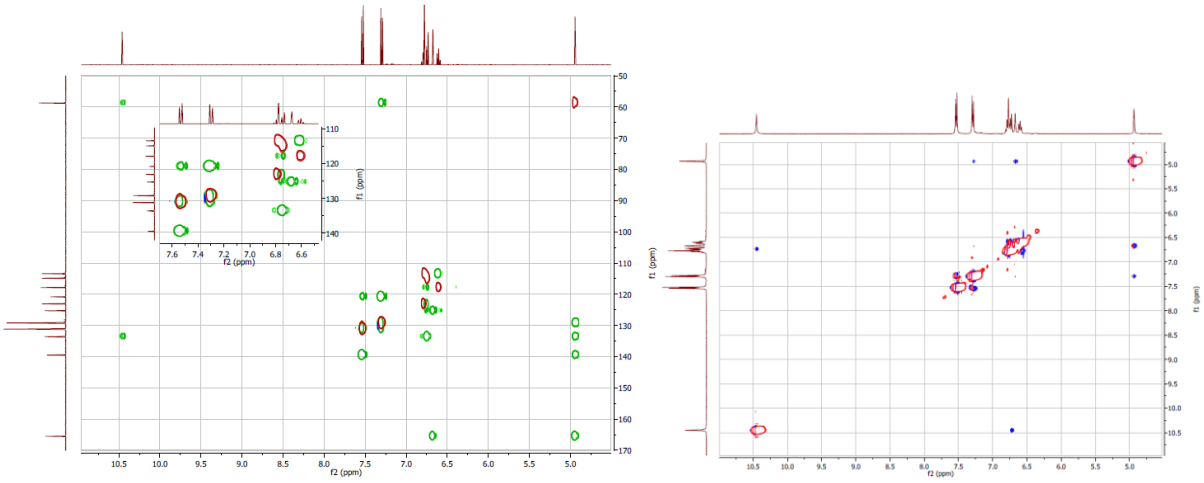


Figure 34: HSQC and HMBC spectra superimposed to visualize proton-carbon single bond correlations, and proton-carbon multiple bond correlations (left). ROESY spectrum displaying through space correlations of protons (right)

Products are found by HRMS in both positive or negative mode.

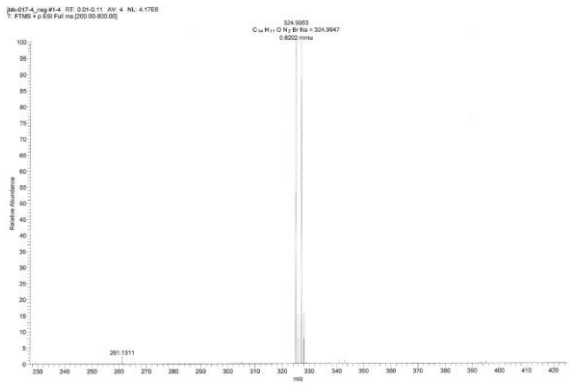


Figure 356: HRMS spectrum of compound 6a.

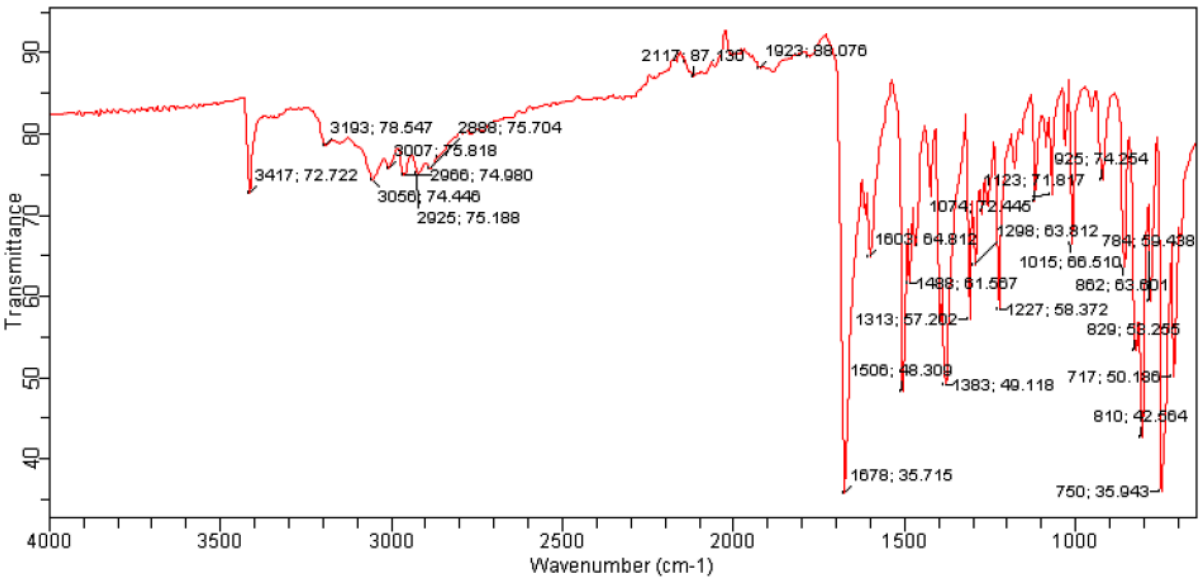
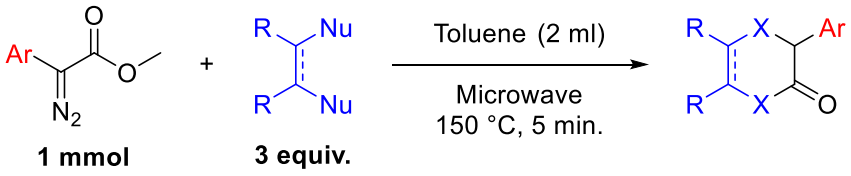


*Figure 37: IR spectrum of compound **6a***

The carbonyl C=O streching signals are commonly found in the 1700 cm^{-1} area. Amides and conjugaton tend to lower the frequency, as can be seen at 1678 cm^{-1} in figure X for compound **6a**, while esters tend to increase the frequency. Amide N-H bending frequency can be seen in the 1640-1550 cm^{-1} range. Secondary amines N-H stretching frequency are found as sharp peaks in the 3500-3300 cm^{-1} range. Both sp^3 and sp^2 hybridized C-H streching frequencies are commonly found in the 3100-2800 cm^{-1} range. The aryl diazoacetate diazonium $C=N_2$ stretch gives rise to a strong peak at 2100 cm^{-1}.

3 Conclusions and future work

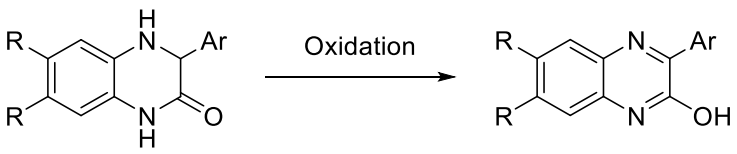
Three aryldiazo compounds have been synthesized to be used in N-H insertion/cyclization reactions with dinucleophiles. The diazocompounds were obtained from diazo transfer reactions in good to excellent yields (76-99%). The synthesis of 3,4-dihydroquinoxalin-2-ones from the hypothesized N-H insertion/cyclization cascade using using microwave-assisted reaction conditions resulted in higher yields and improved purity, compared to conventional heating protocols. High yielding reaction conditions were determined and is summarized in Scheme 17.



Scheme 17: Microwave-assisted synthesis of heterocycles from reaction of aryldiazoacetates and dinucleophiles.

The new microwave-assisted method for preparation of heterocycles has been explored. In the reaction, diamines and some other dinucleophiles were reacted with aryldiazoacetates to afford 3,4-dihydroquinoxalin-2-one or comparable 6-membered heterocycles in moderate to good yields (12-80%). All aryldiazo compounds tested performed well in the reaction. The best yields were obtained from reactions of *o*-phenylenediamine and its substituted analogs, while aliphatic (and benzylic) amines, resulted in lower yields. Exploration of potential selectivity between primary versus secondary amine, suggested that the secondary amine, in spite of beeing more sterically hindered, acts as the initial nucleophile in the reaction.

3,4-dihydroquinoxalin-2-one products **6a**, **6d** and **6l-p** have been transformed to their corresponding quinoxaline-2-ol derivatives through oxidation reactions using DDQ and chloranil, in good to excellent yields (67-95%).



Scheme 18: Oxidation of 3,4-dihyroquinoxalin-2-one to generate quinoxaline-2-ol derivatives. R = H, Me.

Reactions of product **6e**, **6g**, and **6j** should be investigated further. Product **6g**, obtained from exploration of potential selectivity between primary phenylamine versus phenol, indicated the phenol to be the initial nucleophile. However, as the entire yield of the reaction was not isolated, and the reaction should be explored further to determine the yield. Ractions to obtain product **6e** and **6j** should also be explored further, as the yields collected of these two products is not belived to represent the actual yield. In addition, as crude NMR of **6j** indicates a potential second methine proton, the reaction needs to be explored furer to investigate the isomere ratio.

Although the microwave-assisted reaction presented here resulted in the desired products in satisfactory yields, reaction conditions chould be explored further to determine if longer reaction time, or increased temperature would improre product yields further. There was an intention to do so, however there was not enough time to explore this in time before submitting this thesis.

4 References

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51. Hu, X.; Sun, J.; Wang, H.-G.; Manetsch, R., Bcl-XL-Templated Assembly of Its Own Protein−Protein Interaction Modulator from Fragments Decorated with Thio Acids and Sulfonyl Azides. *Journal of the American Chemical Society* **2008,** *130* (42), 13820-13821.

5 Experimental Section

Reagents used during this study were purchased from Sigma Aldrich Co, and used as received. THF was dried on activated molecular sieve (4Å) at minimum 24 hours.

Manual column chromatography was performed using Davisil (35-70 µm) silica gel. Automatic flash column chromatography was performed on Interchim PF-XS420+, or Biotage SP1, using either KP-Sil 10 g or 50 g SNAP Biotage prepacked columns (50µm silica). TLC was run on 60 F254 silica gel plates and visualized by UV and stains.

Microwave reactions were performed using Anton Parr Monowave 300. NMR spectra were recorded on 400 MHz Bruker Avance III HD equipped with a 5 mm SmartProbe BB/1H (BB=19F, 31P-15N). All NMR spectra were processed using Mestrenova version 10.0.2 or 11.0. HRMS spectra were recorded on Thermo scientific LTQ Orbitrap XL using electronspray ionization (ESI). GC-MS spectra were recorded on Thermo Scientific ITQ 1100 detector. IR spectra were recorded on Aglient Cary 630 FTIR.

Compound names were generated by ChemDraw Professional 17.0

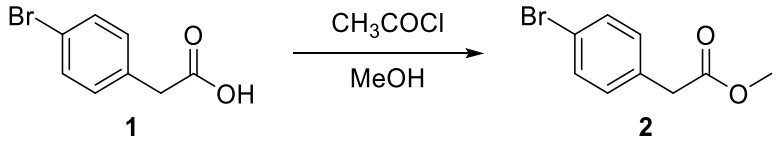
Aryldiazoacetates used to produce compounds **6l-o** were provided by Dr. Stephanie Hansen. Compounds **6l-p** and **7l-p** were made by visiting exchange student Eliot Starck, working under the author's supervision.

General procedure for yield determination by NMR:

After the microwave reaction, the reaction solvent was evaporated. The crude material was dissolved in DMSO-d_6 and added methyl benzoate (62,6 µl, 0,5 mmol). NMR sample was obtained from the mixture.

5.1 Reactions to obtain aryldiazoacetate starting materials

5.1.1 Compound 2 - methyl 2-(4-bromophenyl)acetate

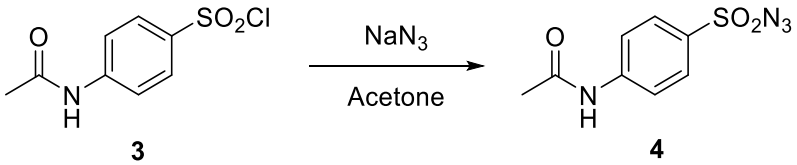


1 2

All glassware was oven dried prior to use, and a drying tube ($CaCl_2$) was used during the reaction. 2-(4-bromophenyl)acetic acid **1** (10 g, 46,5 mmol) was dissolved in Methanol (590 ml), and cooled on an ice bath. Acetyl chloride (3,31 ml, 46,5 mmol, 1 equiv) was added at 0°C and the mixture was left to stir for 48 hours at room temperature. After 48 hours the solvent was removed by rotary evaporation. The solid was dissolved in DCM and washed with sat. $NaHCO_3$, water and brine. The organic phase was dried with Na_2SO_4, filtrated and evaporated to give the clear liquid product. The reaction was conducted twice in 94 % (10 g) and 95 % (10,1 g) yields.

^{1}H-NMR (400 MHz, Chloroform-*d*) δ 7.49 – 7.41 (m, 2H), 7.20 – 7.11 (m, 2H), 3.69 (s, 3H), 3.58 (s, 2H). The data is consistent with published literature[50].

5.1.2 Compound 4 - p-ABSA

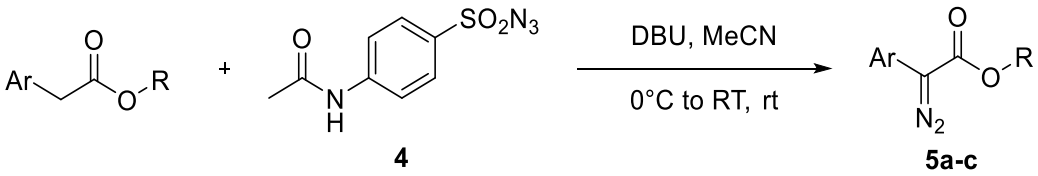


3 4

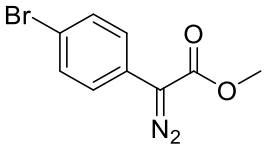
p-Acetamidobenzenesulfonyl chloride **3** (80 g, 340 mmol) was suspended in acetone (687 ml) and a solution of sodium azide (26,7 g, 410 mmol, 1,2 equiv.) in water (205 ml) was added dropwise via an addition funnel. The cloudy white mixture turned clear orange during the addition of the sodium azide. The reaction was stirred at room temperature overnight. After the reaction, product precipitation was induced by addition of ice. The white powdery product was isolated by vacuum filtration and dried on P_2O_5 over several days to give *p*-ABSA as a white powder in 90 % (73 g) yield.

^{1}H-NMR (400 MHz, CD3CN-d_3) δ 8.77 (s, 1H), 7.92 – 7.87 (m, 2H), 7.87 – 7.82 (m, 2H), 2.11 (s, 3H). The data is consistent with published literature[51].

5.2 Diazo compounds



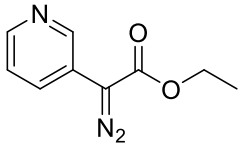
5.2.1 Compound 5a - methyl 2-(4-bromophenyl)-2-diazoacetate



All glassware was oven dried prior to use. Drying tube ($CaCl_2$) was used during the reaction setup, and the reaction proceeded under nitrogen flow. Methyl 2-(4-bromophenyl) acetate (10 g, 44 mmol) and p-ABSA (12,62 g, 52,5 mmol, 1,2 equiv.) was dissolved in acetonitrile (153 ml) and set to stir in an ice bath. At 0 °C DBU (7,84 ml, 52,5 mmol, 1,2 equiv.) was added dropwise via syringe over several minutes. The mixture was then left to stir at ambient temperature. A color change had occurred from clear yellow to orange, after 48 hours. The crude was dissolved in DCM and washed with water brine. The organic phase was dried with Na_2SO_4, filtrated and evaporated. The residue was purified by chromatography on silica gel (10 % diethyl ether in pentane) to give **5a** as an orange solid. The reaction was conducted twice in 76 % (8,5 g), and 86 % (11,6 g) yields.

TLC: 10 % Et_2O/pentane: $\boldsymbol{R_f}$ = 0,83. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 7.64 – 7.55 (m, 2H), 7.50 – 7.41 (m, 2H), 3.79 (s, 3H). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ 164.5, 131.7, 125.6, 125.0, 118.4, 52.1. **HRMS** (ESI) m/z: [M+Na] Calculated for: [$C_9H_7BrN_2O_2Na$] 276,9589; found 276,9583. **IR:** ν/cm^{-1} 3379, 3100, 3078, 3041, 2955, 2091, 1693, 1495, 1436, 1354, 1279, 1249, 1197, 1160, 1078, 1046, 1004

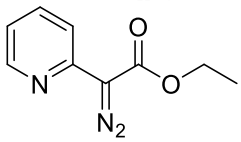
5.2.2 Compound 5b - ethyl 2-diazo-2-(pyridin-3-yl) acetate



All glassware was oven dried prior to use. Drying tube ($CaCl_2$) was used during the reaction setup, and the reaction proceeded under nitrogen flow. p-ABSA (1,75 g, 2,76 mmol, 1,2 equiv.) was dissolved in acetonitrile (22 ml), and added Ethyl-3-pyridylacetate (0,92 ml, 6,1 mmol). The mixture was put on an ice bath to cool. At 0 °C DBU (1,1 ml, 7,26 mmol, 1,2 equiv.) was added dropwise via syringe. The mixture was left to heat up to room temperature, and stir for 12 h. The reaction was monitored by TLC. The mixture was added water and extracted with diethyl ether. The organic layer was washed with brine, dried with Na_2SO_4, and evaporated. The residue was purified by chromatography on silica gel (60 % ethyl acetate in heptane) to give **5b** as an orange solid in 99 % (1,15 g) yield.

TLC: EtOAc: $\boldsymbol{R_f}$ = 0,66. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 8.73 (d, *J* = 2.5 Hz, 1H), 8.39 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.88 (ddd, *J* = 8.2, 2.5, 1.6 Hz, 1H), 7.43 (ddd, *J* = 8.2, 4.7, 0.8 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ 164.2, 146.6, 144.9, 131.1, 123.6, 122.6, 61.1, 14.3. **HRMS** (ESI) m/z: $[M+H]^+$ Calculated for: $[C_{19}H_{10}N_3O_2]$ 192,0773; found 192,0758. **IR:** *v*/cm^{-1} 2985, 2087, 1700, 1488, 1424, 1376, 1343, 1257, 1160, 1063, 1022.

5.2.3 Compound 5c - Ethyl 2-diazo-2-(pyridin-2-yl) acetate

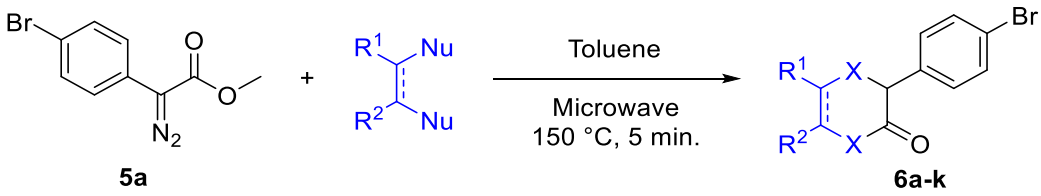


All glassware was oven dried prior to use. Drying tube ($CaCl_2$) was used during the reaction setup, and the reaction proceeded under nitrogen flow. p-ABSA (1,75 g, 7,26 mmol, 1,2 equiv.) added to a dry, nitrogen filled flask, was dissolved in acetonitrile (21 ml), and added Ethyl-2-pyridylacetate (0,92 ml, 6,1 mmol). The mixture was put on an ice bath to cool. At 0 °C DBU (1,1 ml, 7,26 mmol, 1,2 equiv.) was added dropwise via syringe. The mixture was left to heat up to room temperature for 12 h. The reaction was monitored by TLC. The mixture was added water and extracted with diethyl ether. The organic layer was washed with brine and dried with Na_2SO_4, and evaporated. The residue was purified by flash chromatography (50 % ethyl acetate in heptane) to yield 1,1 g (94 %) product **5c** as a white solid.

TLC: EtOAc: $\boldsymbol{R_f}$ = 0,70. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 9.26 (dt, *J* = 7.0, 1.1 Hz, 1H), 8.17 (dt, *J* = 8.9, 1.2 Hz, 1H), 7.75 (ddd, *J* = 8.8, 6.8, 0.9 Hz, 1H), 7.38 (td, *J* = 6.9, 1.3 Hz, 1H),

4.40 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ 160.6, 134.4, 130.6, 128.3, 126.8, 118.3, 117.1, 60.5, 14.2. **HRMS** (ESI) m/z: [M+Na] Calculated for: [$C_9H_9N_3O_2Na$] 214,0592; found 214,0587. **IR:** *ν*/cm^{-1} 3096, 2985, 2914, 1700, 1640, 1525, 1443, 1398, 1272, 1216, 1160, 1071.

5.3 Microwave reaction quinoxaline-2-one derivatives

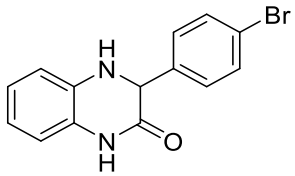


5a **6a-k**

General microwave reaction procedure A (6a-k):

4-Bromo-diazoacetate (1 mmol), dinucleophile (3 eq.), and toluene (2 ml), is mixed in a 10 ml microwave reactor. After addition the mixture is put in an ultrasonic bath for two minutes followed by degassing by bubbling with nitrogen gas. The microwave is set to heat as fast as possible to 150℃, hold for five minutes, and then cool to 55 ℃, with 900 rpm stirring rate. Products were isolated and purified by filtration, acidic work-up, and flash chromatography methods.

5.3.1 Compound 6a - 3-(4-bromophenyl)-3,4-dihydroquinoxalin-2(1*H*)-one

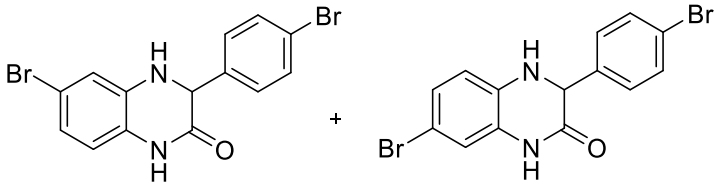


The reaction was performed according to general reaction procedure **A**. The crude mixture was added Ethyl acetate and washed with water and brine. The organic layer was dried with Na_2SO_4, and the solvent was removed. The solid residue was purified by dry loaded flash chromatography on silica gel (10% - 40% ethyl acetate in heptane). Yellow crystalline product was isolated in 80 % (243 mg) yield. ^{1}H-NMR yield: 80 %.

Alternate procedure: Following the microwave reaction the crude was heated quickly by heat gun and filtrated while still a bit warm. The precipitate was washed with toluene. Yellow crystalline product **6a** was isolated in 75 % (228 mg) yield.

TLC: 40 % EtOAc/heptane: R_f = 0,35. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 10.45 (s, 1H), 7.57 – 7.49 (m, 2H), 7.33 – 7.26 (m, 2H), 6.84 – 6.70 (m, 3H), 6.67 (d, *J* = 2.0 Hz, 1H), 6.60 (ddd, *J* = 8.1, 6.7, 2.1 Hz, 1H), 4.94 (d, *J* = 1.9 Hz, 1H). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ 165.5, 139.5, 133.6, 131.2, 129.2, 125.3, 123.1, 120.8, 117.9, 114.9, 113.4, 58.7. **HRMS** (ESI) m/z: [M+Na] Calculated for: [$C_{14}H_{11}BrN_2ONa$] 324.9952; found 324.9953. **IR**: ν/cm^{-1} 3417, 3193, 3056, 2966, 2925, 2888, 1678, 1603, 1506, 1383, 1313, 1227, 1015.

5.3.2 Compound 6b

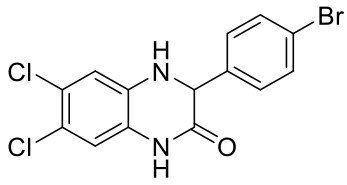


6b^1 **6b^2**

The reaction was performed according to general procedure **A.** The reaction solvent was evaporated, and the crude solid was dissolved in chloroform, and washed with aqueous hydrochloric acid (pH 1-2), then brine. The organic phase was dried with Na_2SO_4 and the solvent was removed. The solid residue was purified by dry-loaded flash chromatography (10% - 40% ethyl acetate in heptane), to yield 245 mg (64 %) orange crystalline product as isomer mixtures. Characterisation obtained from isolated isomer fraction.

TLC: 40 % EtOAc/heptane: R_f = 0,47. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 10.59 (s, 1H), 7.61 – 7.49 (m, 2H), 7.32 – 7.23 (m, 2H), 6.94 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.88 (d, *J* = 2.0 Hz, 1H), 6.87 (d, *J* = 2.3 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 4.99 (d, *J* = 1.9 Hz, 1H). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ 165.3, 139.2, 133.0, 131.3, 129.2, 126.9, 125.3, 121.0, 117.0, 114.9, 108.2, 58.4. **HRMS** (ESI) m/z: [M+Na] Calculated for: [$C_{14}H_{10}Br_2N_2ONa$] 402,9058; found 402,9055. **IR:** ν/cm^{-1} 3420, 3059, 2955, 2877, 1681, 1599, 1506, 1376, 1231, 1074, 1011.

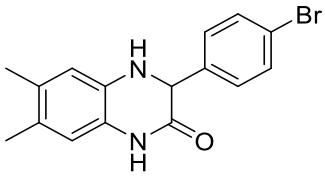
5.3.3 Compound 6c - 3-(4-bromophenyl)-6,7-dichloro-3,4-dihydroquinoxalin-2(1*H*)-one



The reaction was performed according to general procedure **A.** Following the microwave reaction, the crude was directly transferred to a Biotage 50 g SNAP precolumn. The product was isolated by automatic flash chromatography (0 % - 50 % ethyl acetate in heptane). Impure product fractions were collected and purified in a second column, to yield 69 % (259 mg) orange crystalline **6c** product.

TLC: 40 % EtOAc/heptane: $\boldsymbol{R_f}$ = 0,36. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 10.70 (s, 1H), 7.60 – 7.52 (m, 2H), 7.32 – 7.23 (m, 2H), 7.08 (d, *J* = 2.0 Hz, 1H), 6.93 (s, 1H), 6.88 (s, 1H), 5.06 (d, *J* = 1.8 Hz, 1H). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ 165.0, 139.0, 133.9, 131.4, 129.1, 125.5, 124.2, 121.1, 118.3, 115.6, 113.7, 58.1. **HRMS** (ESI) m/z: [M+Na] Calculated for: [$C_{14}H_9BrCl_2N_2ONa$] 392,9173; found 392,9168. **IR**: ν/cm^{-1} 3413, 3178, 3059, 2936, 1681, 1618, 1506, 1380, 1231, 1130, 1074, 1011.

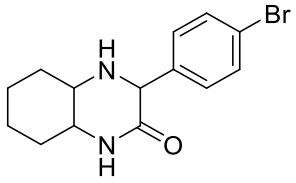
5.3.4 Compound 6d - 3-(4-bromophenyl)-6,7-dimethyl-3,4-dihydroquinoxalin-2(1*H*)-one



The reaction was performed according to general procedure **A.** Following the microwave reaction, yellow product precipitate was filtrated and washed with THF to isolate 171 mg (52 %) product. Product residue in the filtrate was purified by automatic flash column. The filtrate was concentrated and transferred to a Biotage 50 g SNAP precolumn, and purified by automatic flash chromatography (0 % - 100 % ethyl acetate in heptane) to isolate further 19 %. Impure product fractions were purified by an additional column running a slower solvent gradient to yield additional 7 % more product. The yellow crystalline product was collected in 78 % (257 mg) yield total.

TLC: 40 % EtOAc/heptane: $\boldsymbol{R_f}$ = 0,32. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 10.31 (s, 1H), 7.56 – 7.48 (m, 2H), 7.31 – 7.23 (m, 2H), 6.55 (s, 1H), 6.50 (s, 1H), 6.43 (d, *J* = 2.1 Hz, 1H), 4.85 (d, *J* = 1.9 Hz, 1H), 2.06 (s, 3H), 2.04 (s, 3H). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ 165.5, 139.7, 131.2, 131.2, 130.3, 129.1, 125.1, 123.1, 120.7, 116.0, 114.8, 58.9, 19.1, 18.6. **HRMS** (ESI) m/z: [M+Na] Calculated for [$C_{16}H_{15}BrN_2ONa$] 353,0265 found 353,0265. IR: ν/cm^{-1} 3305, 3182, 3063, 2966, 2940, 2918, 2862, 1663, 1596, 1518, 1488, 1415, 1402, 1275, 1071, 1011.

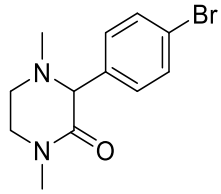
5.3.5 Compound 6e - 3-(4-bromophenyl) octahydroquinoxalin-2(1*H*)-one



The reaction was performed according to general procedure **A.** Precipitate from the reaction was filtrated and washed with toluene, to give 107 mg (27 %) product **6e** as a white solid.

TLC: EtOAc: R_f = 0,3. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 7.51 – 7.42 (m, 2H), 7.37 – 7.30 (m, 2H), 6.02 (s, 1H), 4.61 (s, 1H), 3.26 – 3.16 (m, 1H), 2.75 – 2.64 (m, 1H), 1.86 – 1.72 (m, 4H), 1.45 – 1.25 (m, 4H). **^{13}C-NMR** (101 MHz, Chloroform-*d*) δ 170.2, 138.7, 131.7, 130.5, 122.1, 64.7, 59.1, 58.4, 31.5, 30.7, 24.6, 23.9. **HRMS** (ESI) m/z: $[M+H]^+$ Calculated for $[C_{14}H_{18}BrN_2O]$ 309,0603; found 309,0597. **IR:** *v*/cm^{-1} 3283, 3208, 3082, 2933, 2854, 1659, 1592, 1488, 1402, 1354, 1316, 1246, 1074, 1015.

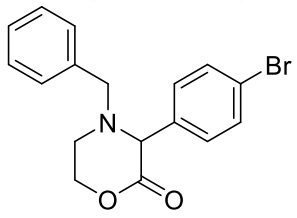
5.3.6 Compound 6f - 3-(4-bromophenyl)-1,4-dimethylpiperazin-2-one



The reaction was performed according to general procedure **A.** After the reaction, the solvent was evaporated, and the crude residue was transferred to a Biotage 10 g SNAP precolumn. The product was purified by the automatic flash chromatography (80 % - 100 % ethyl acetate in heptane). White solid product was isolated in 57 % (162 mg) yield.

TLC: EtOAc: R_f = 0,17. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 7.54 – 7.42 (m, 2H), 7.32 – 7.27 (m, 2H), 3.72 (td, *J* = 11.4, 4.3 Hz, 1H), 3.68 (s, 1H), 3.21 (ddd, *J* = 11.8, 3.8, 2.4 Hz, 1H), 3.02 (ddd, *J* = 11.9, 4.3, 2.3 Hz, 1H), 2.97 (s, 3H), 2.69 (td, *J* = 11.6, 3.8 Hz, 1H), 2.17 (s, 3H). **^{13}C-NMR** (101 MHz, Chloroform-*d*) δ 167.6, 138.3, 131.5, 130.8, 121.8, 72.6, 51.1, 48.4, 44.0, 34.8. **HRMS** (ESI) m/z [M+Na] calculated for $[C_{12}H_{15}BrN_2ONa]$ 305,0265; found 305,0265. **IR:** *v*/cm^{-1} 2951, 2847, 2873, 2799, 1640, 1596, 1491, 1458, 1406, 1346, 1257, 1238, 1156, 1071, 1011.

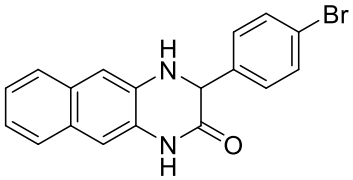
5.3.7 Compound 6h - 4-benzyl-3-(4-bromophenyl) morpholin-2-one



The reaction was performed according to general procedure **A.** NMR-yield was obtained after the reaction. NMR-solvent was removed, and the crude material was transferred to Biotage 10 g SNAP precolumn, and purified by automatic flash chromatography (3 % - 20 % ethyl acetate in heptane). Product was obtained as a clear oil in 35 % (122 mg) yield. NMR-yield: 37%

TLC: 40 % EtOAc/heptane: R_f = 0,5. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 7.56 – 7.52 (m, 2H), 7.50 – 7.45 (m, 2H), 7.35 – 7.27 (m, 3H), 7.25 – 7.19 (m, 2H), 4.55 (td, *J* = 11.1, 3.1 Hz, 1H), 4.37 (ddd, *J* = 10.9, 3.3, 2.1 Hz, 1H), 4.23 (s, 1H), 3.76 (d, *J* = 13.3 Hz, 1H), 3.19 (d, *J* = 13.3 Hz, 1H), 3.01 (ddd, *J* = 12.8, 3.1, 2.1 Hz, 1H), 2.66 (ddd, *J* = 12.9, 11.3, 3.3 Hz, 1H). **^{13}C-NMR** (101 MHz, Chloroform-*d*) δ 168.2, 136.5, 136.5, 132.0, 130.7, 129.0, 128.7, 127.9, 122.7, 69.9, 68.7, 59.0, 47.0. **HRMS** (ESI) m/z [M+Na] calculated for [$C_{17}H_{16}BrNO_2Na$] 368,0262; found 368,0263. **IR:** *v*/cm^{-1} 3029, 2959, 2813, 1741, 1491, 1458, 1410, 1302, 1205, 1063, 1015.

5.3.8 Compound 6i - 3-(4-bromophenyl)-3,4-dihydrobenzo[*g*]quinoxalin-2(1*H*)-one

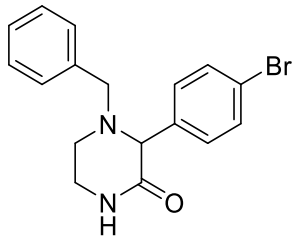


The reaction was performed according to general procedure **A.** NMR-yield was obtained after the reaction. The mixture was added ethyl acetate and washed with water, hydrochloric acid solution (pH 1-2) and brine. The organic layer was dried with Na_2SO_4, filtered and solvent was removed. The solid residue was transferred to a Biotage 50 g SNAP precolumn and purified by automatic flash chromatography (5 % - 30 % ethyl acetate in heptane), isolating 58 % product. The contents of the used column were flushed out with ethyl acetate, concentrated and purified by an additional manual flash chromatography on silica gel (5 % - 30 % ethyl acetate in

heptane), isolating additional 10 % product. Product **6i** was isolated in 67 % (239 mg) total. NMR-yield: 69 %.

TLC: 40 % EtOAc/heptane: $\boldsymbol{R_f}$ = 0,35. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 10.87 (s, 1H), 7.61 – 7.51 (m, 4H), 7.35 – 7.28 (m, 2H), 7.23 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.18 – 7.12 (m, 2H), 7.12 – 7.07 (m, 2H), 5.08 (d, *J* = 1.8 Hz, 1H). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ 166.3, 139.6, 134.0, 131.3, 130.9, 129.1, 127.4, 126.5, 125.3, 124.5, 122.5, 121.0, 110.6, 107.1, 58.6. **HRMS** (ESI) m/z [M+Na] calculated for [$C_{18}H_{13}BrN_2ONa$] 375,0109; found 375,0110. **IR:** ν/cm^{-1} 3298, 3175, 3052, 2959, 2791, 1670, 1644, 1592, 1536, 1488, 1398, 1335, 1272, 1190, 1074, 1015.

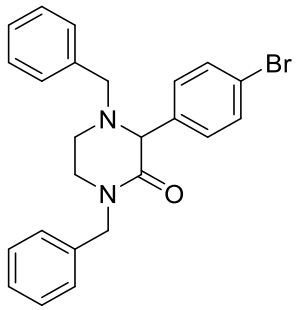
5.3.9 Compound 6j - 4-benzyl-3-(4-bromophenyl) piperazin-2-one



The reaction was performed according to general procedure **A.** Reaction solvent was evaporated, and the crude solid was transferred directly to a Biotage 50 g SNAP precolumn and purified by automatic flash chromatography (40 % - 80 % ethyl acetate in heptane). Fractions was collected as mixtures of product and diamine. Fractions containing product was recrystallized from ethyl acetate to yield 12 % (43 mg) product.

TLC: EtOAc: $\boldsymbol{R_f}$ = 0,22. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 7.98 (d, *J* = 4.1 Hz, 1H), 7.59 – 7.51 (m, 2H), 7.47 – 7.40 (m, 2H), 7.36 – 7.28 (m, 2H), 7.27 – 7.19 (m, 3H), 3.96 (s, 1H), 3.53 (d, *J* = 13.6 Hz, 1H), 3.29 (dd, *J* = 10.7, 3.9 Hz, 1H), 3.22 (d, *J* = 13.6 Hz, 1H), 3.14 (dq, *J* = 11.6, 3.6 Hz, 1H), 2.81 (dt, *J* = 12.0, 3.5 Hz, 1H), 2.42 (ddd, *J* = 11.9, 10.3, 3.6 Hz, 1H). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ 168.0, 139.3, 137.8, 131.2, 130.9, 128.4, 128.3, 127.1, 120.5, 69.3, 57.9, 46.1, 40.1. **HRMS** (ESI) m/z [M+H]$^+$ Calculated for [$C_{17}H_{18}BrN_2O$] 345,0597; found 345,0603. **IR:** ν/cm^{-1} 3178, 3029, 2951, 2895, 2825, 1678, 1596, 1491, 1421, 1350, 1328, 1071, 1019.

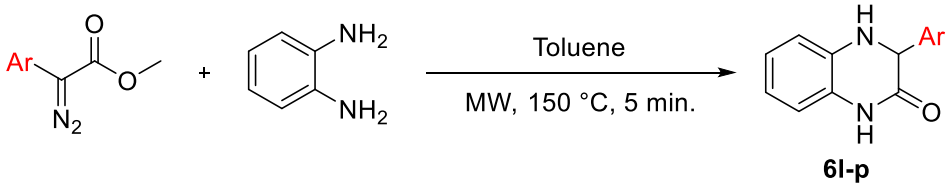
5.3.10 Compound 6k - 1,4-dibenzyl-3-(4-bromophenyl) piperazin-2-one



The reaction was performed according to general procedure **A.** Reaction solvent was evaporated, and the crude material was transferred directly to a Biotage 50 g SNAP precolumn and purified automatic flash chromatography (10 % - 30% ethyl acetate in heptane), to yield 45 % (198 mg) product.

TLC: 40 % EtOAc/heptane: R_f = 0,35. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 7.60 – 7.54 (m, 2H), 7.48 – 7.42 (m, 2H), 7.37 – 7.20 (m, 10H), 4.51 (s, 2H), 4.14 (s, 1H), 3.53 (d, *J* = 13.6 Hz, 1H), 3.40 (ddd, *J* = 11.8, 10.4, 4.0 Hz, 1H), 3.22 (d, *J* = 13.6 Hz, 1H), 3.17 (dt, *J* = 12.0, 3.4 Hz, 1H), 2.86 (dt, *J* = 12.0, 3.6 Hz, 1H), 2.54 – 2.43 (m, 1H). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ 166.8, 139.4, 137.5, 137.0, 131.1, 131.1, 128.6, 128.4, 128.3, 127.4, 127.2, 127.1, 120.6, 69.4, 57.8, 49.2, 46.1, 45.6. **HRMS** (ESI) m/z $[M+H]^+$ calculated for $[C_{24}H_{24}BrN_2O]$ 435,1067; found 435,1073. **IR**: *v*/cm^{-1} 3283, 3063, 3029, 2921, 2806, 2724, 1715, 1648, 1488, 1454, 1357, 1238, 1145, 1074, 1015.

5.4 Aryl derivatives



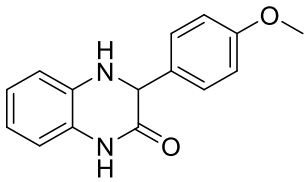
6l-p

General procedure B (microwave reaction 6l-p):

Aryl-diazoacetates (1 mmol), o-phenylenediamine (3 eq.), and toluene (2 ml), is mixed in a 10 ml microwave reactor. After addition the mixture is put in an ultrasonic bath for two minutes followed by degassing by bubbling with nitrogen gas. The microwave is set to heat as fast as possible to 150℃, hold for five minutes, and then cool to 55 ℃, with 900 rpm stirring rate.

General procedure C (Work-up of 6l-o): The reaction solvent was removed, and the crude material was dissolved in ethyl acetate and washed with water, hydrochloric acid solution (pH 1-2), and brine. The organic layer was dried with Na_2SO_4 and the solvent was removed. Products was purified by dry-loaded flash chromatography on silica gel using ethyl acetate in heptane mixtures.

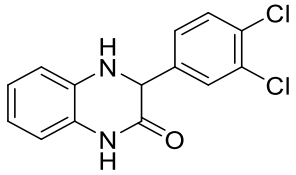
5.4.1 Compound 6l - 3-(4-methoxyphenyl)-3,4-dihydroquinoxalin-2(1*H*)-one



The reaction was performed according to general procedure **B**, and worked-up by general procedure **C**. Product was purified by flash chromatography on silica gel (10 % - 60 % ethyl acetate in heptane) to give 64 % (161 mg) product. TLC analysis was performed using 40 % ethyl acetate in heptane.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1H), 7.27 – 7.18 (m, 2H), 6.92 – 6.83 (m, 2H), 6.82 – 6.69 (m, 3H), 6.62 – 6.53 (m, 2H), 4.84 (d, J = 1.8 Hz, 1H), 3.71 (s, 3H). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ 166.1, 158.7, 133.8, 132.3, 128.0, 125.4, 122.9, 117.6 114.7, 113.7, 113.3, 58.7, 55.1. **HRMS** (ESI) m/z [M+Na] calculated for [$C_{15}H_{14}N_2O_2Na$] 277,0953; found 277,0948. **IR:** ν/cm^{-1} 3305, 3063, 3007, 2962, 2936, 2903, 2840, 1670, 1607, 1514, 1480, 1387, 1290, 1253, 1186, 1097, 1037.

5.4.2 Compound 6m - 3-(3,4-dichlorophenyl)-3,4-dihydroquinoxalin-2(1*H*)-one

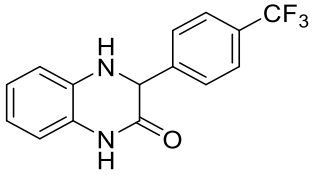


The reaction was performed according to general procedure **B**, and worked-up by general procedure **C**. Product was purified by flash chromatography on silica gel (20 % - 50 % ethyl

acetate in heptane) to yield 64 % (194 mg) of product. TLC analysis was performed using 40 % ethyl acetate in heptane.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.52 (s, 1H), 7.66 – 7.56 (m, 2H), 7.32 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.86 – 6.70 (m, 4H), 6.62 (ddd, *J* = 8.1, 6.6, 2.1 Hz, 1H), 5.01 (d, *J* = 1.9 Hz, 1H). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ 165.2, 141.0, 133.4, 130.9, 130.6, 130.3, 129.2, 127.4, 125.3, 123.2, 118.1, 115.0, 113.5, 58.2. **HRMS** (ESI) m/z [M-H]$^-$ Calculated for [$C_{14}H_9BCl_2N_2O$] 291,0097; found 291,0078. **IR**: *v*/cm^{-1} 3305, 3186, 3096, 3063, 2966, 2892, 2806, 1663, 1603, 1506, 1473, 1387, 1313, 1134, 1033.

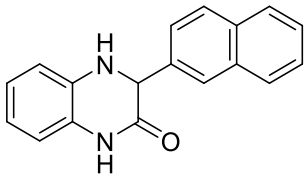
5.4.3 Compound 6n - 3-(4-(trifluoromethyl) phenyl)-3,4-dihydroquinoxalin-2(1*H*)-one



The reaction was performed according to general procedure **B**, and worked-up by general procedure **C**. Product was isolated and purified by flash chromatography on silica gel (20 % - 50 % ethyl acetate in heptane), to yield 55 % (161 mg) product. TLC analysis was performed using 40 % ethyl acetate in heptane.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 7.72 (d, *J* = 8.1 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 2H), 6.84 – 6.78 (m, 2H), 6.75 (dd, *J* = 5.8, 2.1 Hz, 2H), 6.62 (ddd, *J* = 8.2, 6.2, 2.5 Hz, 1H), 5.08 (d, *J* = 1.9 Hz, 1H). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ 165.3, 144.7, 133.6, 127.9, 125.3, 125.2, 123.1, 118.0, 114.9, 113.4, 59.0. (All carbon not shown, as CF_3 coupled carbon signals are too small to show up in the spectrum. See spectrum for oxidized product **7n** which show all carbons). **HRMS** (ESI) m/z [M+Na] Calculated for [$C_{15}H_{11}CF_3N_2ONa$] 315,0721; found 315,0714. **IR:** *v*/cm^{-1} 3309, 3201, 3064, 2962, 2925, 2787, 1670, 1607, 1506, 1380, 1324, 1175, 1130, 1071, 1022.

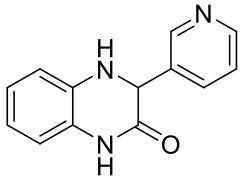
5.4.4 Compound 6o - 3-phenyl-3,4-dihydrobenzo[*g*]quinoxalin-2(1*H*)-one



The reaction was performed according to general procedure **B**, and worked-up by general procedure **C**. The reaction was performed according to general microwave procedure **B.** Product was isolated and purified by flash chromatography on silica gel (20 % - 100 % ethyl acetate in heptane) to give 55 % (186 mg) yield. TLC analysis was performed using 40 % ethyl acetate in heptane.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.47 (s, 1H), 7.91 – 7.81 (m, 4H), 7.54 – 7.46 (m, 3H), 6.83 – 6.73 (m, 4H), 6.61 (dq, *J* = 8.3, 4.1 Hz, 1H), 5.11 (d, *J* = 1.6 Hz, 1H). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ 165.9, 137.7, 133.9, 132.6, 132.5, 127.9, 127.8, 127.5, 126.3, 126.1, 125.7, 125.4, 125.3, 123.1, 117.7, 114.9, 113.4 59.5. **HRMS** (ESI) m/z $[M-H]^-$ calculated for $[C_{18}H_{13}N_2O]$ 273,1033; found 273,1033.

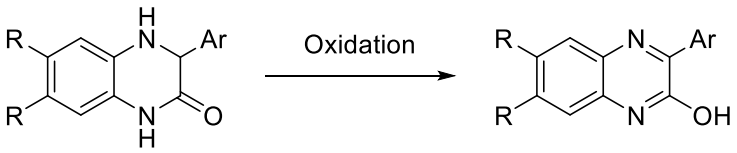
5.4.5 Compound 6p - 3-(pyridin-3-yl)-3,4-dihydroquinoxalin-2(1*H*)-one



The reaction was performed according to general microwave procedure **B**. Precipitated product was filtrated, and filtrate was concentrated by evaporation. Isolated product and filtrate were purified separately by flash chromatography on silica gel (50 % - 100 % ethyl acetate in heptane), to yield 66 % (149 mg) product. TLC analysis was performed using 70 % ethyl acetate in heptane.

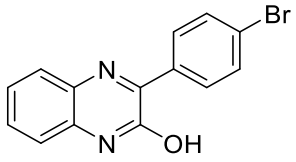
^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1H), 8.57 – 8.46 (m, 2H), 7.71 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.37 (dd, *J* = 7.9, 4.7 Hz, 1H), 6.85 – 6.74 (m, 3H), 6.64 (ddd, *J* = 14.7, 8.2, 1.9 Hz, 2H), 5.02 (d, *J* = 1.8 Hz, 1H). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ 165.6, 148.9, 148.6, 135.4, 134.8, 133.7, 125.5, 123.5, 123.1, 118.1, 115.0, 113.6, 57.4. **HRMS** (ESI) m/z $[M-H]^-$ calculated for $[C_{13}H_{10}ON_3]$ 224,0829; found 224,0821.

5.5 Oxidized products



6a, 6d, 6l-p **7a, 7d, 7l-p**

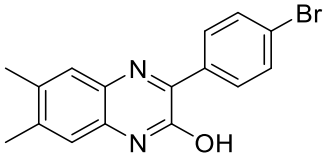
5.5.1 7a - 3-(4-bromophenyl)quinoxalin-2-ol



All glassware were oven dried prior to use, and the reaction was carried out under a drying tube ($CaCl_2$). **6a** (65,2 mg, 0,215 mmol) was added DDQ (54 mg, 0,237 mmol, 1,1 eq.), dissolved in dry THF (20 ml) and set to stir at room temperature for 1 hour. The reaction was followed by TLC. The crude reaction mixture was added water which led to product precipitation. Product was isolated by filtration, and washed with ethyl acetate to yield 85 % (55 mg) product.

TLC: 40 % EtOAc/heptane: $\boldsymbol{R_f}$ = 0,43. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.63 (s, 1H), 8.35 – 8.26 (m, 2H), 7.84 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.74 – 7.66 (m, 2H), 7.56 (td, *J* = 7.6, 1.4 Hz, 1H), 7.38 – 7.29 (m, 2H). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ 154.5, 152.8, 134.7, 132.1, 131.9, 131.2, 130.9, 130.6, 128.8, 124.0, 123.5, 115.2. **HRMS** (ESI) m/z [M+Na] Calculated for [$C_{14}H_9BrN_2ONa$] 322,9796; found 322,9798. **IR:** *v*/cm^{-1} 3301, 3096, 2944, 2880, 2828, 2732, 1655, 1588, 1536, 1477, 1436, 1398, 1283, 1182,1071, 1004.

5.5.2 Compound 7d - 3-(4-bromophenyl)-6,7-dimethylquinoxalin-2-ol



All glassware were oven dried prior to use, and the reaction was carried out under a drying tube ($CaCl_2$). **6d** (235 mg, 0,71 mmol) was added DDQ (161 mg, 0,71 mmol, 1 eq.), dissolved in dry THF (20 ml), and set to stir for 1 hour. The reaction was monitored by TLC. After the

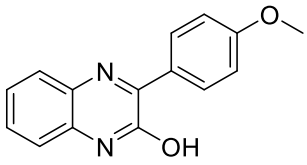
reaction had finished, the solvent was removed, and water was added. To the mixture was added ethyl acetate and transferred to the separation funnel. Product was observed in both phases. The water phase was extracted several times with ethyl acetate to get the product out. The organic phase was washed with brine, dried with Na_2SO_4, and the solvent was removed. The residue transferred to a Biotage 50 g SNAP precolumn, and purified by automatic flash chromatography (5% - 100% ethyl acetate in heptane). Pure product was obtained in 38 % yield from the column. Most solvent was removed from mixed fractions was added methanol to crystallize product. Precipitated product was filtered and washed with Methanol. In total 79% (185 mg) product was collected.

TLC: 40 % EtOAc/heptane: $\boldsymbol{R_f}$ = 0,42. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.50 (s, 1H), 8.31 – 8.25 (m, 2H), 7.72 – 7.63 (m, 2H), 7.59 (s, 1H), 7.07 (s, 1H), 2.31 (s, 3H), 2.29 (s, 3H). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ 154.6, 151.3, 140.4, 134.9, 132.2, 131.0, 130.9, 130.5, 130.2, 128.6, 123.7, 115.1, 19.9, 19.0. **HRMS** (ESI) m/z [M+Na] Calculated for [$C_{16}H_{13}BrN_2ONa$] 351,0109; found 351,0110. **IR:** ν/cm^{-1} 3301, 2914, 2854, 2828, 1655, 1585, 1529, 1491, 1402, 1261, 1074, 1011.

General procedure D (Chloranil oxidation procedure):

6l-p was added THF (20 ml), and Chloranil (1,1 eq.) and set to stir at room temperature. Reactions was followed by TLC. Following the reaction solvent was removed and the crude reside was purified by flash chromatography on silica gel using ethyl acetate in heptane mixtures to yield **7l-p** products.

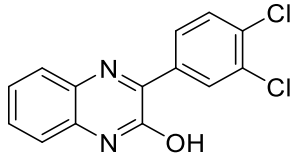
5.5.3 Compound 7l - 3-(4-methoxyphenyl)quinoxalin-2-ol



6l (135 mg, 0,53 mmol) was oxidized using general procedure **D**. The reaction was complete after 55 minutes. Flash chromatography on silica gel was performed (20 % - 40 % ethyl acetate in heptane) to yield 76 % (103 mg) product. TLC analysis was performed using 40 % ethyl acetate in heptane.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.50 (s, 1H), 8.44 – 8.35 (m, 2H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.51 (td, *J* = 7.7, 7.1, 1.4 Hz, 1H), 7.35 – 7.26 (m, 2H), 7.09 – 7.00 (m, 2H), 3.84 (s, 3H). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ 161.0, 154.7, 153.1, 132.1, 131.8, 131.0, 129.7, 128.5, 128.1, 123.3, 115.0, 113.3, 55.3. **HRMS** (ESI) m/z [M+Na] calculated for [$C_{15}H_{12}N_2O_2Na$] 275,0796; found 275,0791. **IR:** *v*/cm^{-1} 3316, 3093, 3007, 2940, 2888, 2840, 1663, 1599, 1510, 1469, 1436, 1290, 1257, 1175, 1030.

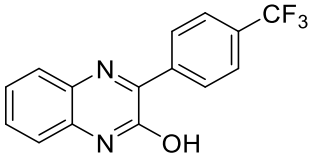
5.5.4 Compound 7m - 3-(3,4-dichlorophenyl)quinoxalin-2-ol



6m (175 mg, 0,62 mmol) was oxidized general procedure **D**. The reaction was complete after 3,5 hours. Product was isolated by flash chromatography on silica gel (10 % - 30 % ethyl acetate in heptane) to yield 67 % product. TLC analysis was performed using 40 % ethyl acetate in heptane.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.71 (s, 1H), 8.62 (d, *J* = 2.0 Hz, 1H), 8.35 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.87 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.58 (td, *J* = 7.6, 7.1, 1.4 Hz, 1H), 7.35 (ddd, *J* = 7.0, 3.7, 2.4 Hz, 2H). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ 154.5, 151.2, 136.0, 132.9, 132.3, 131.8, 131.0, 130.8, 130.7, 130.3, 129.2, 129.0, 123.6, 115.2. **HRMS** (ESI) m/z [M-H]$^-$ Calculated for [$C_{14}H_7Cl_2N_2O$] 288,9941; found 288,9936. **IR:** *v*/cm^{-1} 3111, 2933, 2880, 2847, 1666, 1614, 1529, 1469, 1436, 1383, 1033.

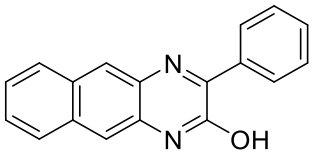
5.5.5 Compound 7n - 3-(4-(trifluoromethyl)phenyl)quinoxalin-2-ol



6n (152 mg, 0,52 mmol) was oxidized using general procedure **D**. The reaction was not complete after 6 hours and was left to stir over night. The product was isolated by flash chromatography on silica gel (10 % - 40 % ethyl acetate in heptane) to yield 94% (141 mg) product. TLC analysis was performed using 40 % ethyl acetate in heptane.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.70 (s, 1H), 8.51 (d, *J* = 8.2 Hz, 2H), 7.86 (dd, *J* = 8.5, 2.8 Hz, 3H), 7.58 (td, *J* = 7.6, 1.4 Hz, 1H), 7.35 (dd, *J* = 8.1, 6.7 Hz, 2H). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ 154.5, 152.8, 139.3, 132.3, 131.9, 131.0, 129.9 (q, *J* = 31.8 Hz), 129.9 (s, 2C), 129.0, 124.7 (q, *J* = 3.7 Hz, 2C), 124.2 (q, *J* = 272.3 Hz), 123.6, 115.2. **HRMS** (ESI) m/z $[M+H]^+$ Calculated for $[C_{15}H_{10}F_3N_2O]$ 291,0740; found 291,0755. **IR:** *v*/cm^{-1} 3316, 3104, 2951, 2888, 2836, 1663, 1611, 1536, 1413, 1331, 1156, 1112, 1074, 1007.

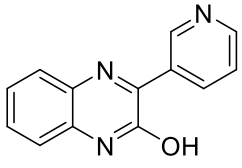
5.5.6 Compound 7o - 3-phenylbenzo[*g*]quinoxalin-2-ol



6o (153 mg, 0,56 mmol) was oxidized using general chloranil oxidation procedure. The reaction was complete after 4,5 hours. Product was purified by flash chromatography on silica gel (15 % - 100 % ethyl acetate in heptane) to yield 96 % (145 mg) product. TLC analysis was performed using 40 % ethyl acetate in heptane.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.65 (s, 1H), 9.11 (d, *J* = 1.6 Hz, 1H), 8.39 (dd, *J* = 8.7, 1.7 Hz, 1H), 8.10 – 7.92 (m, 3H), 7.89 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.65 – 7.51 (m, 3H), 7.41 – 7.29 (m, 2H). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ 154.8, 153.5, 133.6, 133.0, 132.3, 132.1, 132.0, 130.4, 129.8, 129.1, 128.8, 127.5, 127.4, 127.3, 126.5, 125.9, 123.5, 115.1. **HRMS** (ESI) m/z $[M+H]^-$ Calculated for $[C_{18}H_{11}N_2O]$ 271,0877 found; 271,0876. **IR:** *v*/cm^{-1} 3316, 3100, 3059, 2977, 2884, 2843, 2724, 1663, 1611, 1596, 1532, 1484, 1436, 1361, 1267, 1186, 1130.

5.5.7 Compound 7p - 3-(pyridin-3-yl)quinoxalin-2-ol



6p (142 mg, 0,63 mmol) was oxidized using general procedure **D**. The reaction was complete after 4 hours. The product was purified by flash chromatography on silica gel using (60% - 100% ethyl acetate in heptane), followed by 5 % methanol in ethyl acetate to yield 68% (95,8 mg) product. TLC analysis was performed using 70 % ethyl acetate in heptane.

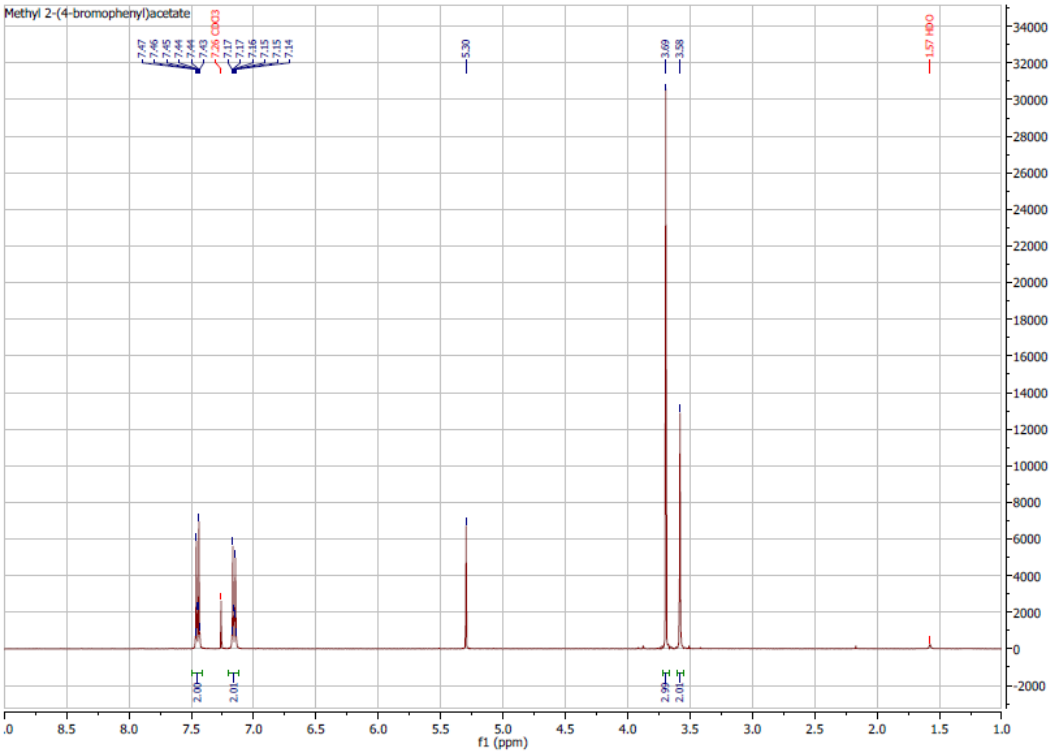
^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.67 (s, 1H), 9.41 (d, *J* = 2.1 Hz, 1H), 8.68 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.61 (dt, *J* = 8.1, 2.0 Hz, 1H), 7.86 (d, *J* = 7.9 Hz, 1H), 7.62 – 7.47 (m, 2H), 7.35 (t, *J* = 8.0 Hz, 2H). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ 154.5, 152.5, 150.5, 149.8, 136.5, 132.2, 132.0, 131.4, 130.8, 128.9, 123.6, 123.1, 115.3. **HRMS** (ESI) m/z $[M+H]^+$ calculated for $[C_{13}H_{10}N_3O]$ 224,0818; found 224,0823. **IR:** *v*/cm^{-1} 3320, 3100, 3003, 2951, 2888, 2840, 2735, 1666, 1614, 1596, 1395, 1305, 1194, 1011.

Appendices

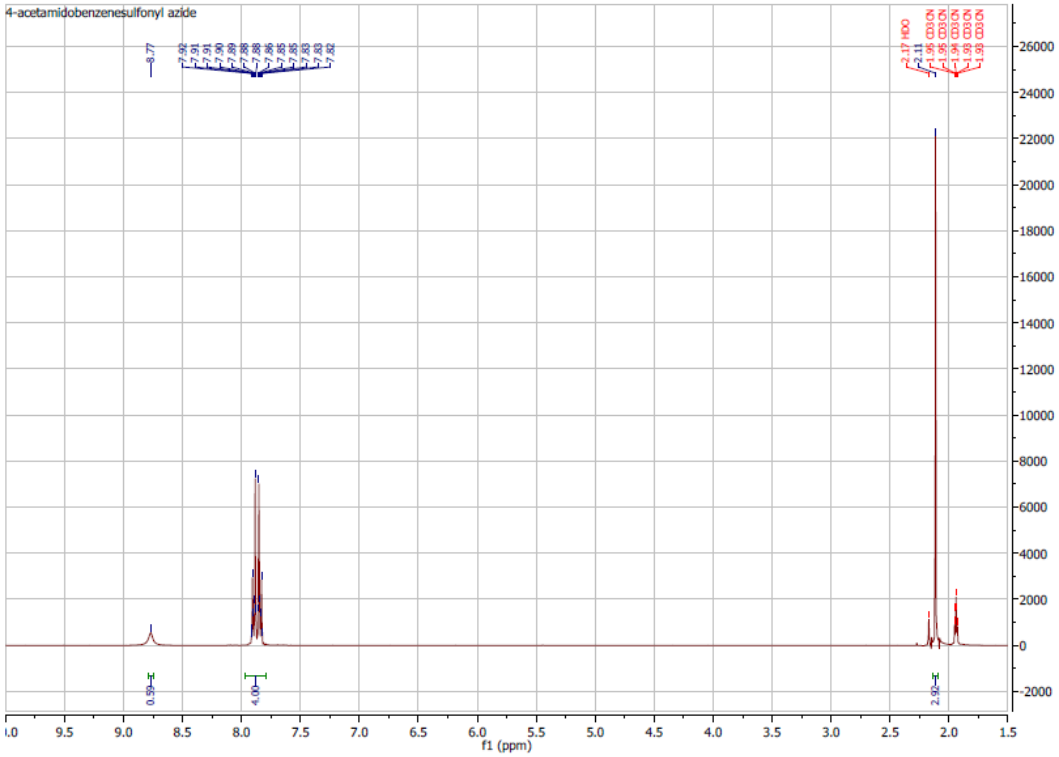
List of Appendices

Appendix 1: Spectra of molecules

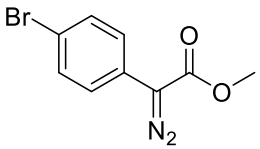
Compound **2** - Methyl 2(4-bromophenyl)acetate

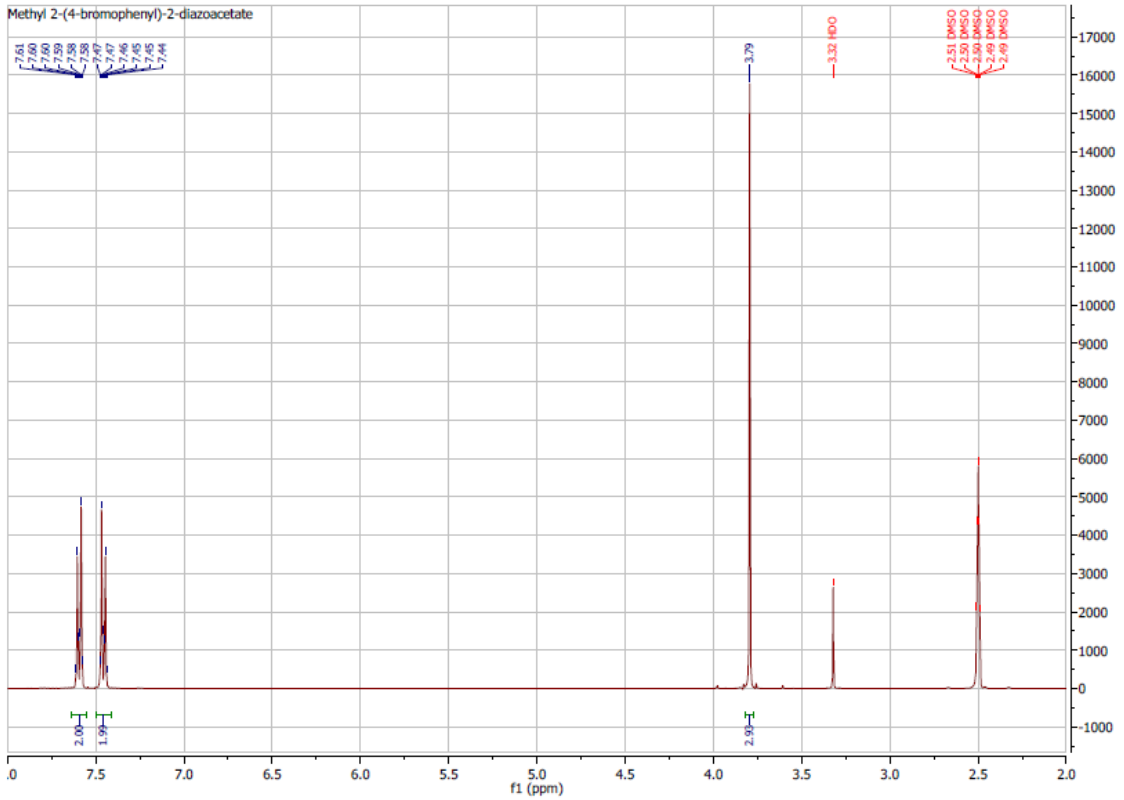


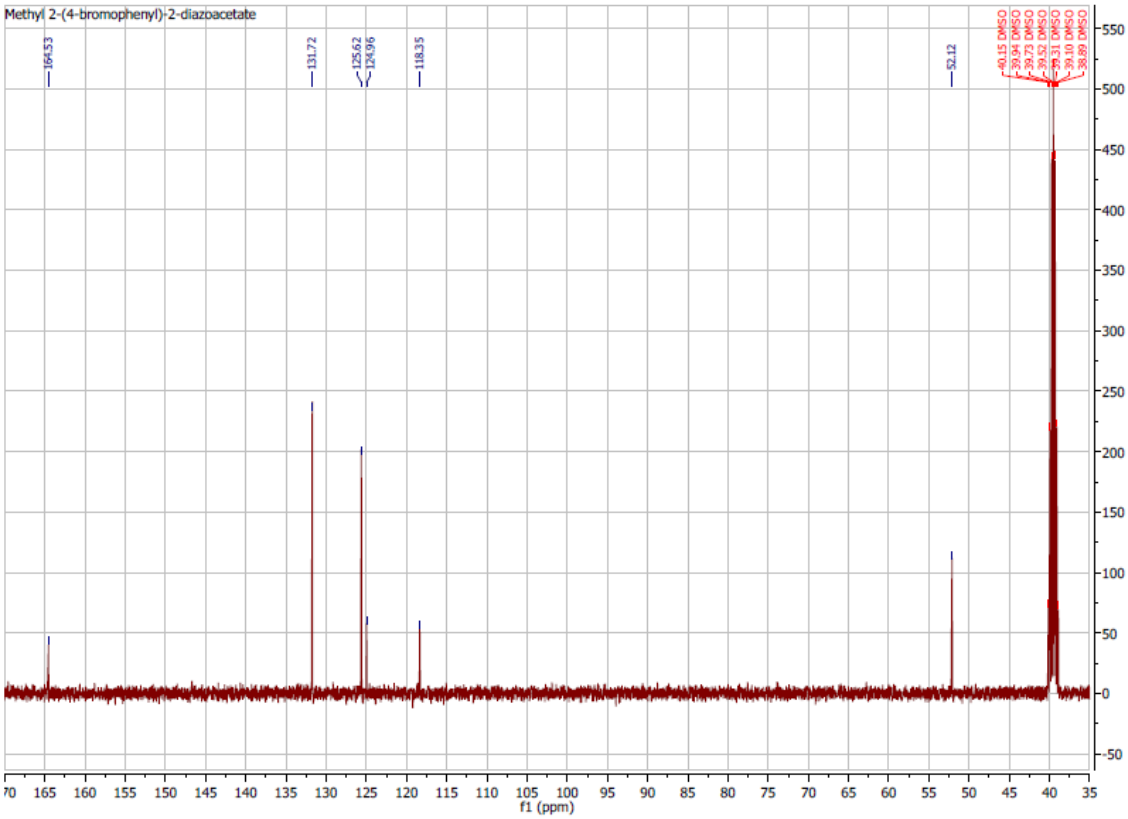
Compound **4** - p-ABSA

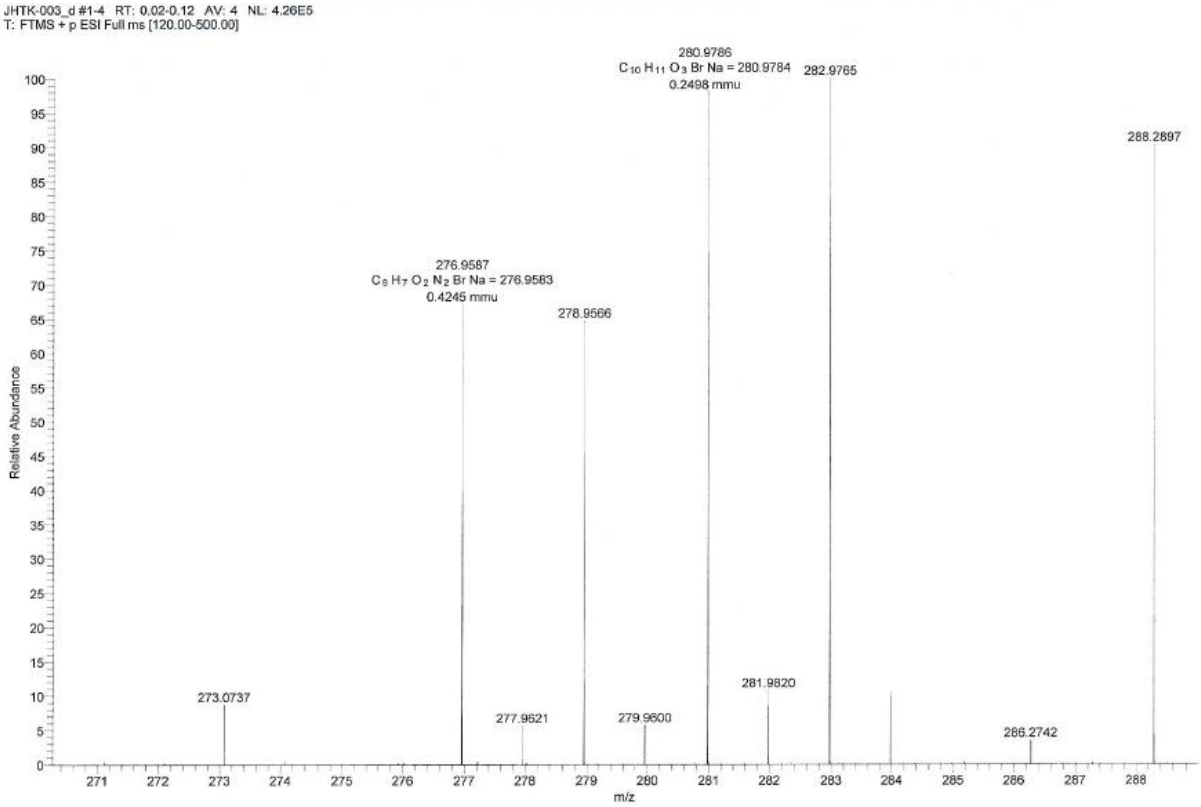


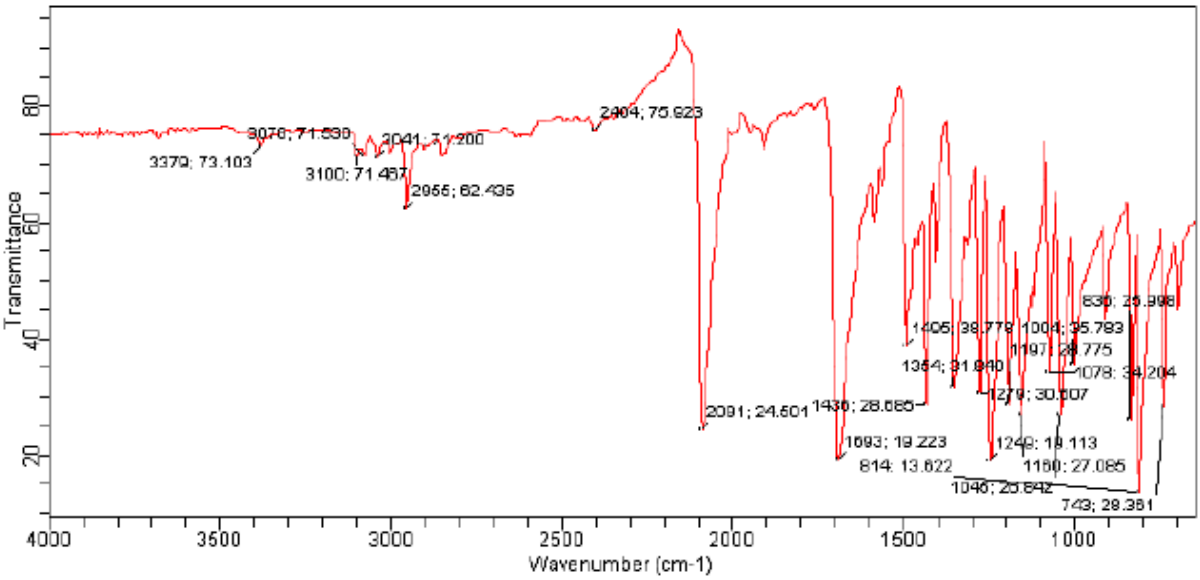
Compound **5a** - Methyl 2-(4-bromophenyl)-2-diazoacetate



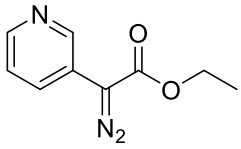


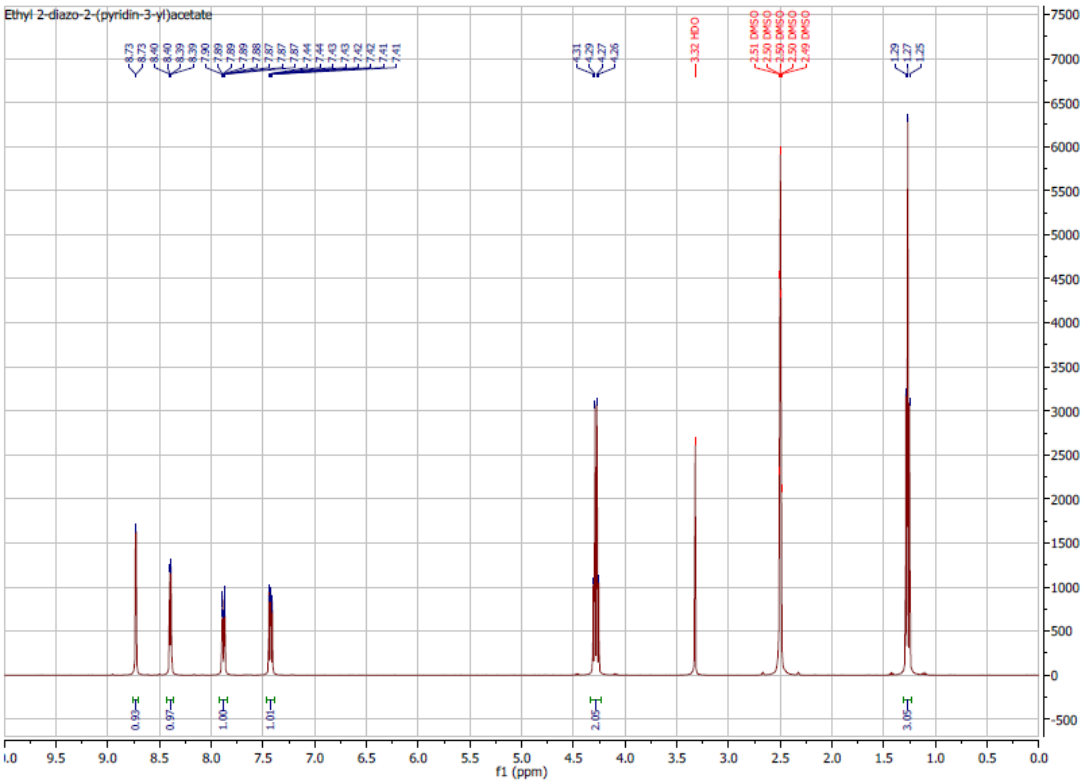


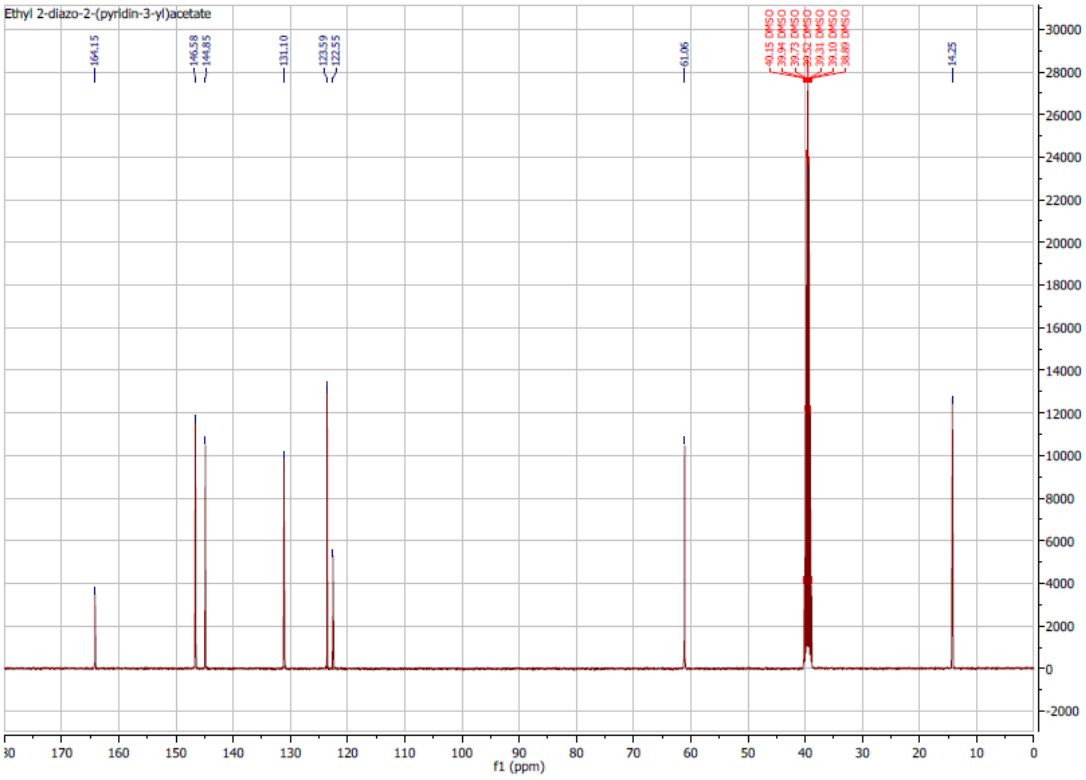

JHTK-003_d #1-4 RT: 0.02-0.12 AV: 4 NL: 4.26E5
T: FTMS + p ESI Full ms [120.00-500.00]
280.9786
C10 H11 O3 Br Na = 280.9784
0.2498 mmu
282.9765
288.2897
276.9587
C9 H7 O2 N2 Br Na = 276.9583
0.4245 mmu
278.9566
281.9820
273.0737
277.9621
279.9600
286.2742
Relative Abundance
m/z

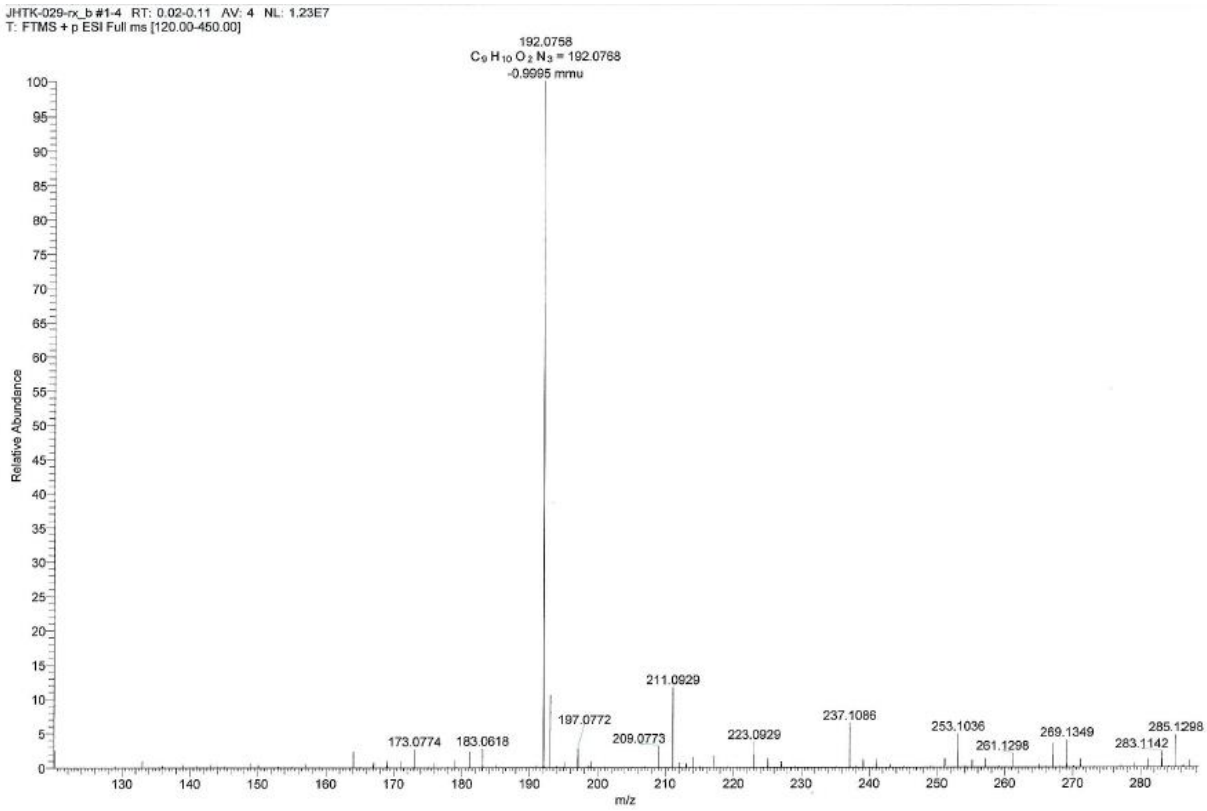

3379; 73.103
3076; 71.630
3041; 71.200
3100; 71.497
2955; 82.435
2404; 75.623
2091; 24.501
1430; 28.685
1693; 19.223
814; 13.622
1405; 38.778
1004; 35.783
1364; 31.940
1197; 28.775
1078; 34.204
1279; 30.507
1249; 19.113
1160; 27.085
1046; 25.642
743; 28.381
Transmittance
Wavenumber (cm-1)

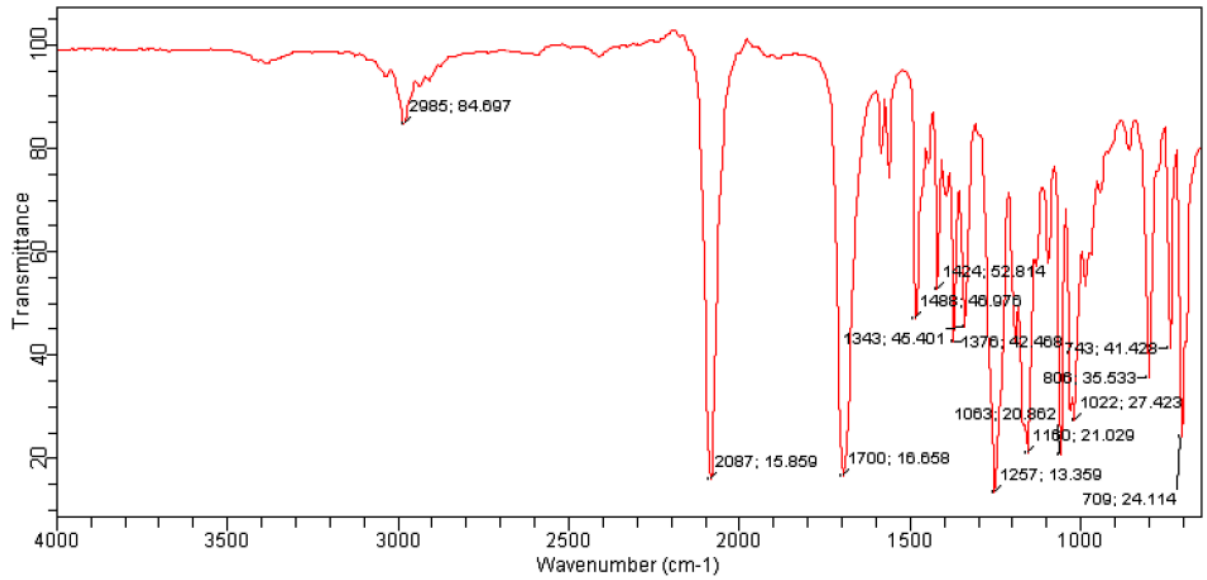
Compound **5b** - Ethyl 2-diazo-2-(pyridin-3-yl)acetate



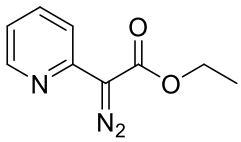


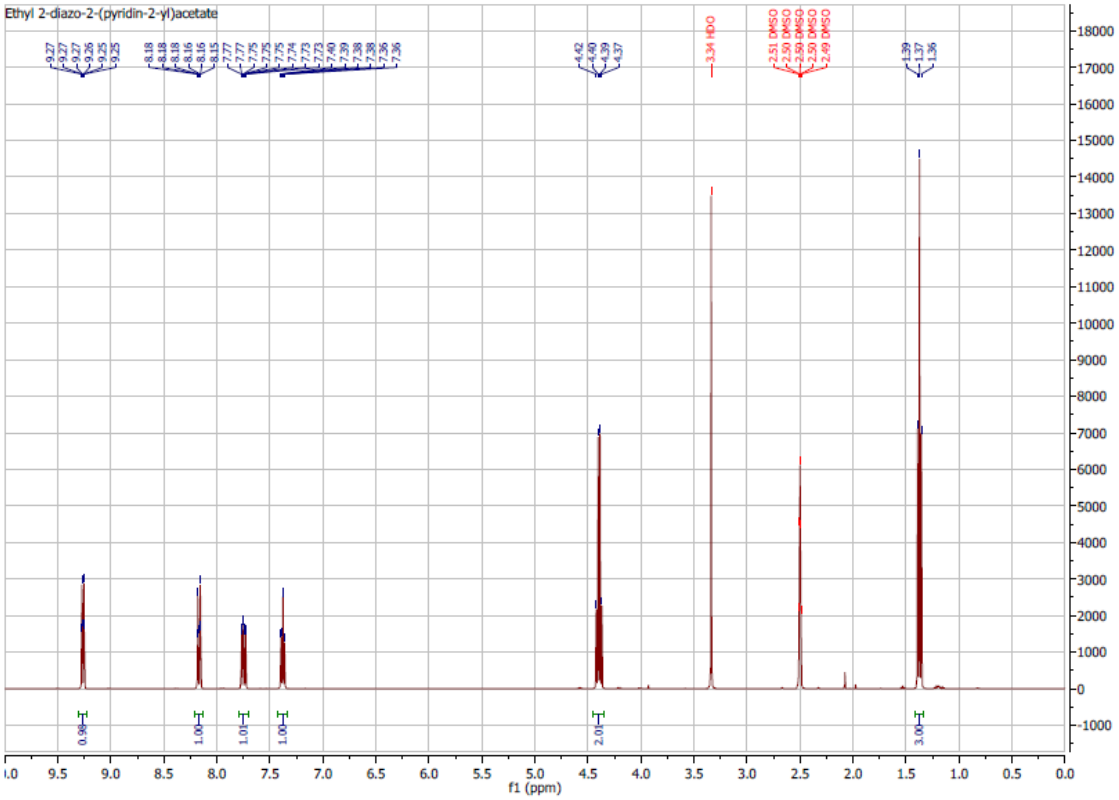


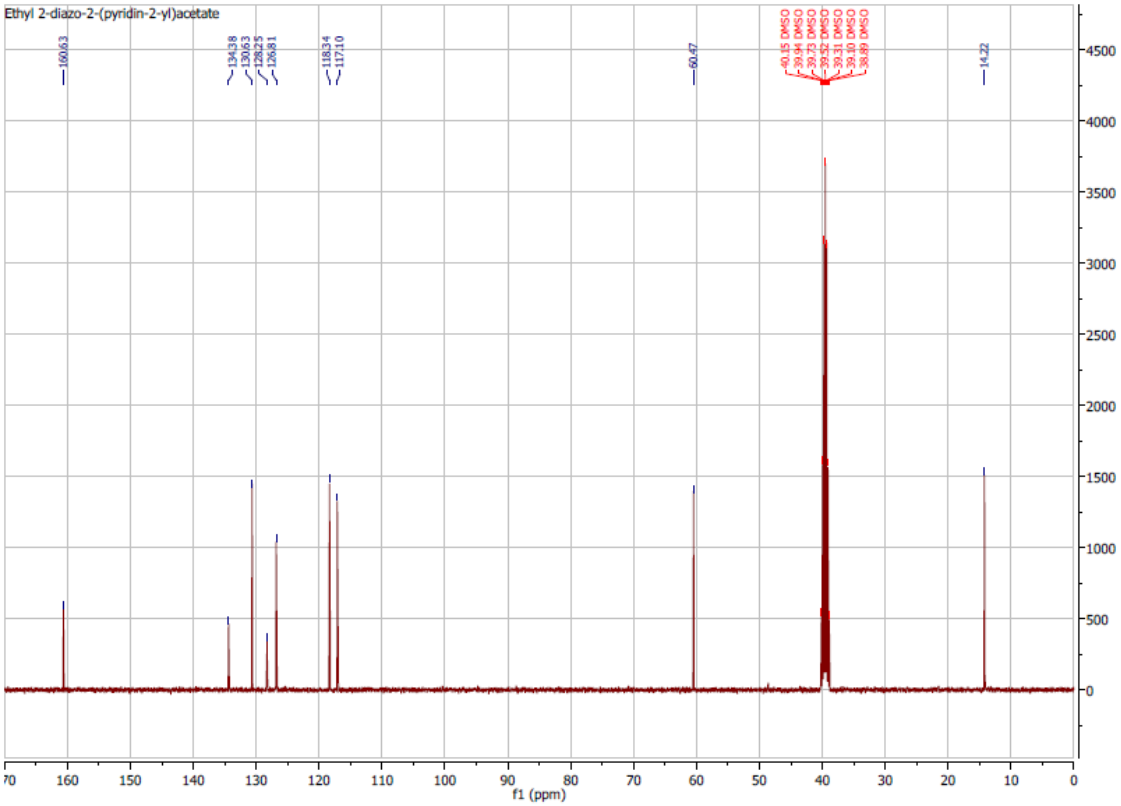

JHTK-029-rx_b #1-4 RT: 0.02-0.11 AV: 4 NL: 1.23E7
T: FTMS + p ESI Full ms [120.00-450.00]
192.0758
C9 H10 O2 N3 = 192.0768
-0.9995 mmu
Relative Abundance
m/z
211.0929
197.0772
237.1086
253.1036
269.1349
285.1298
173.0774
183.0618
209.0773
223.0929
261.1298
283.1142

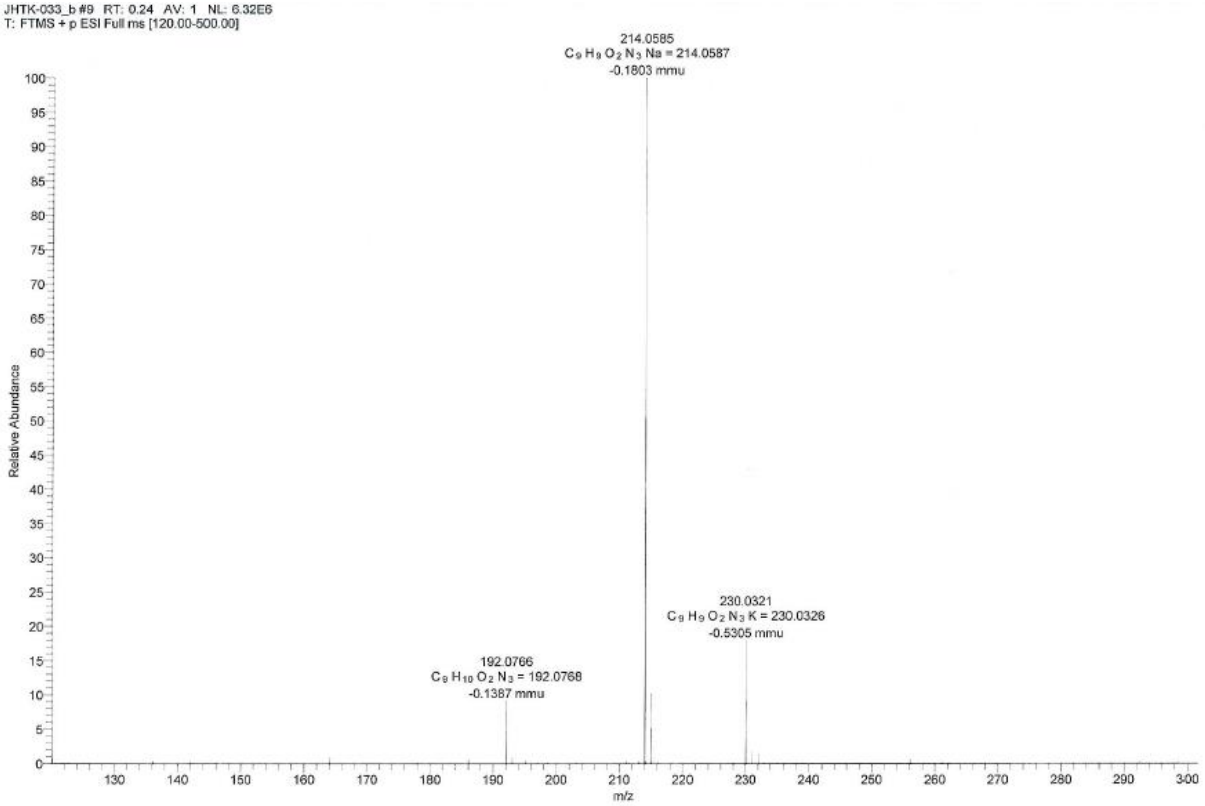

Transmittance
Wavenumber (cm-1)
2985; 84.697
2087; 15.859
1700; 16.658
1424; 52.814
1488; 46.975
1343; 45.401
1376; 42.468
743; 41.428
806; 35.533
1022; 27.423
1063; 20.862
1160; 21.029
1257; 13.359
709; 24.114

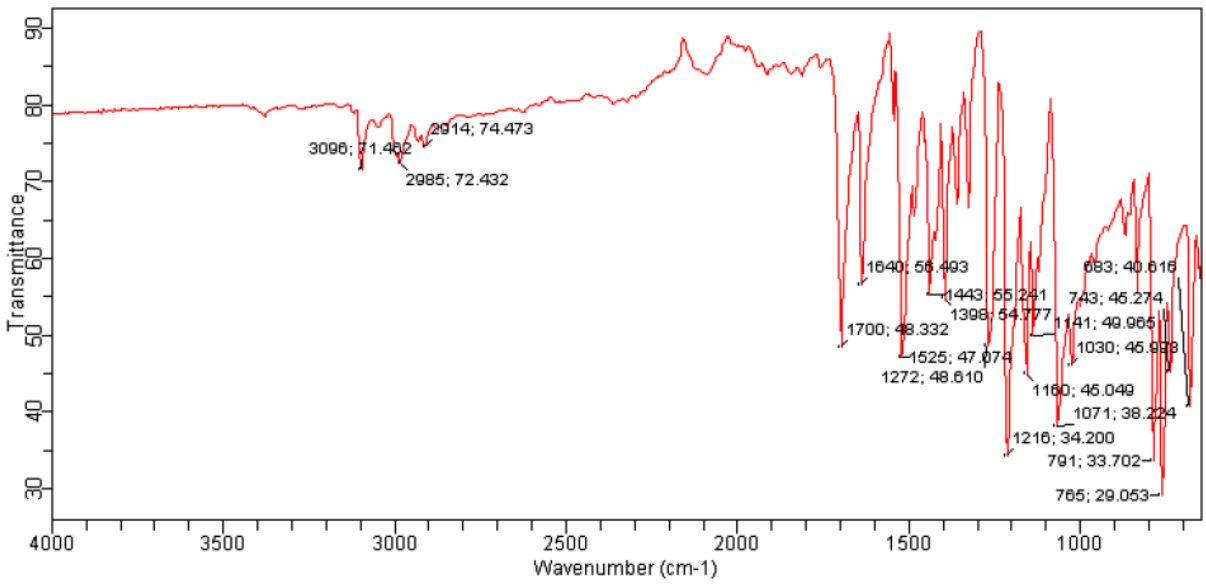
Compound **5c** - Ethyl 2-diazo-2-(pyridin-2-yl)acetate



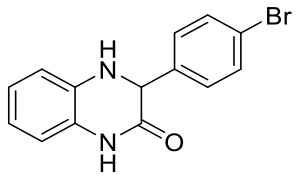


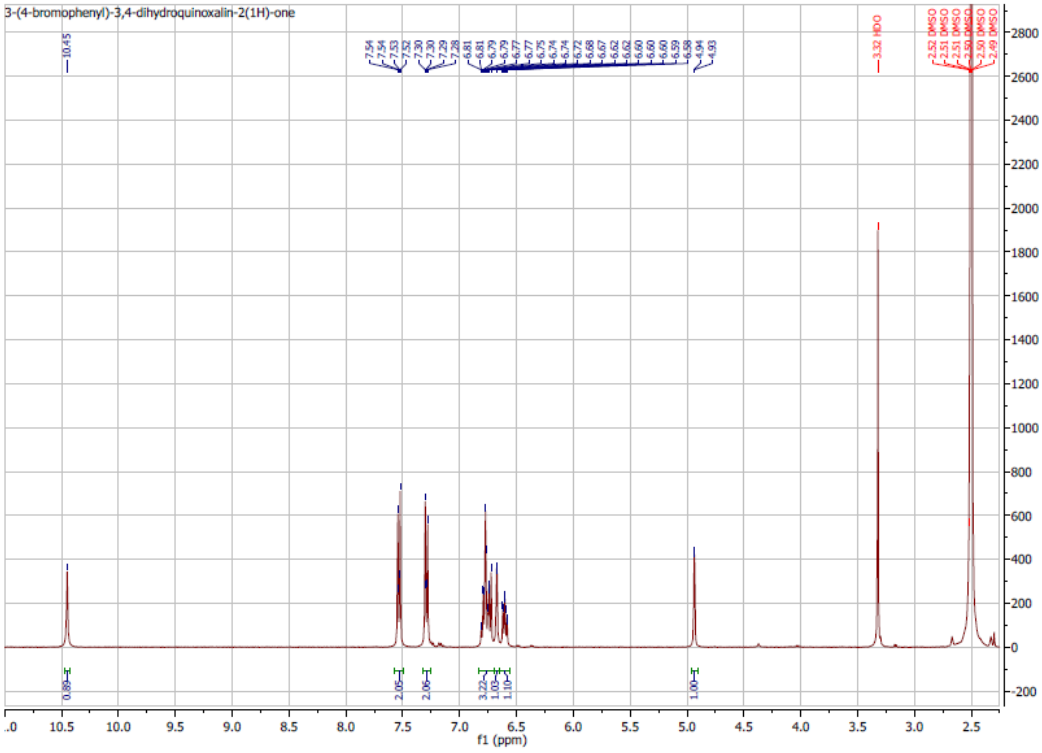


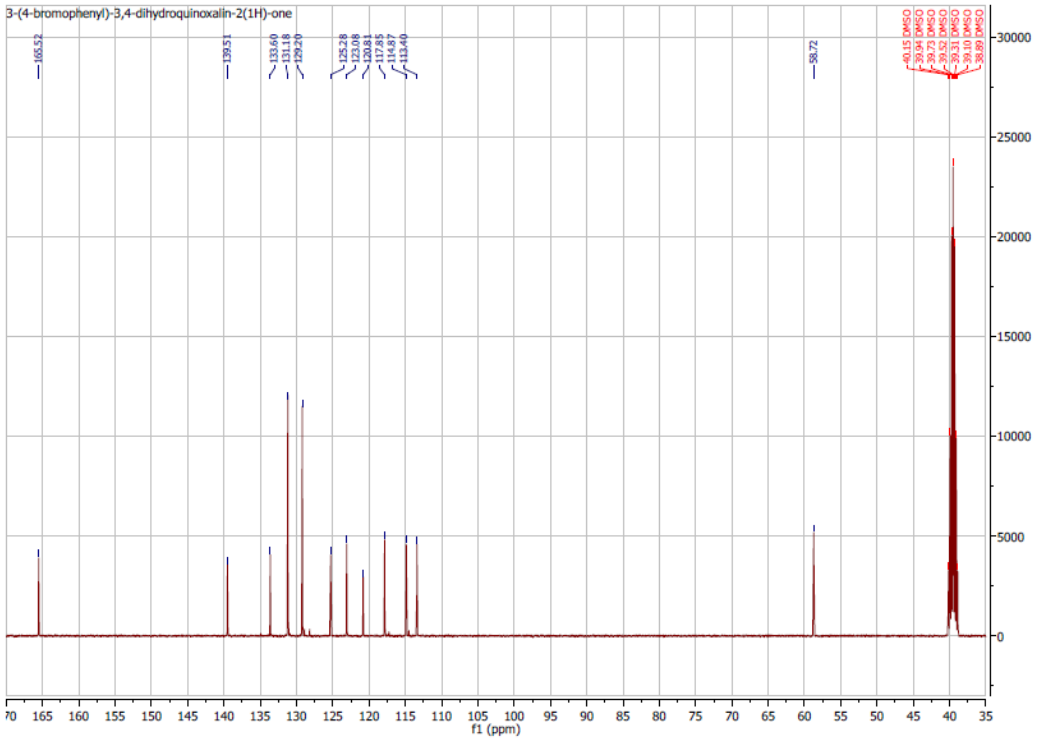

JHTK-033_b #9 RT: 0.24 AV: 1 NL: 6.32E6
T: FTMS + p ESI Full ms [120.00-500.00]
214.0585
C9 H9 O2 N3 Na = 214.0587
-0.1803 mmu
230.0321
C9 H9 O2 N3 K = 230.0326
-0.5305 mmu
192.0766
C9 H10 O2 N3 = 192.0768
-0.1387 mmu
Relative Abundance
m/z

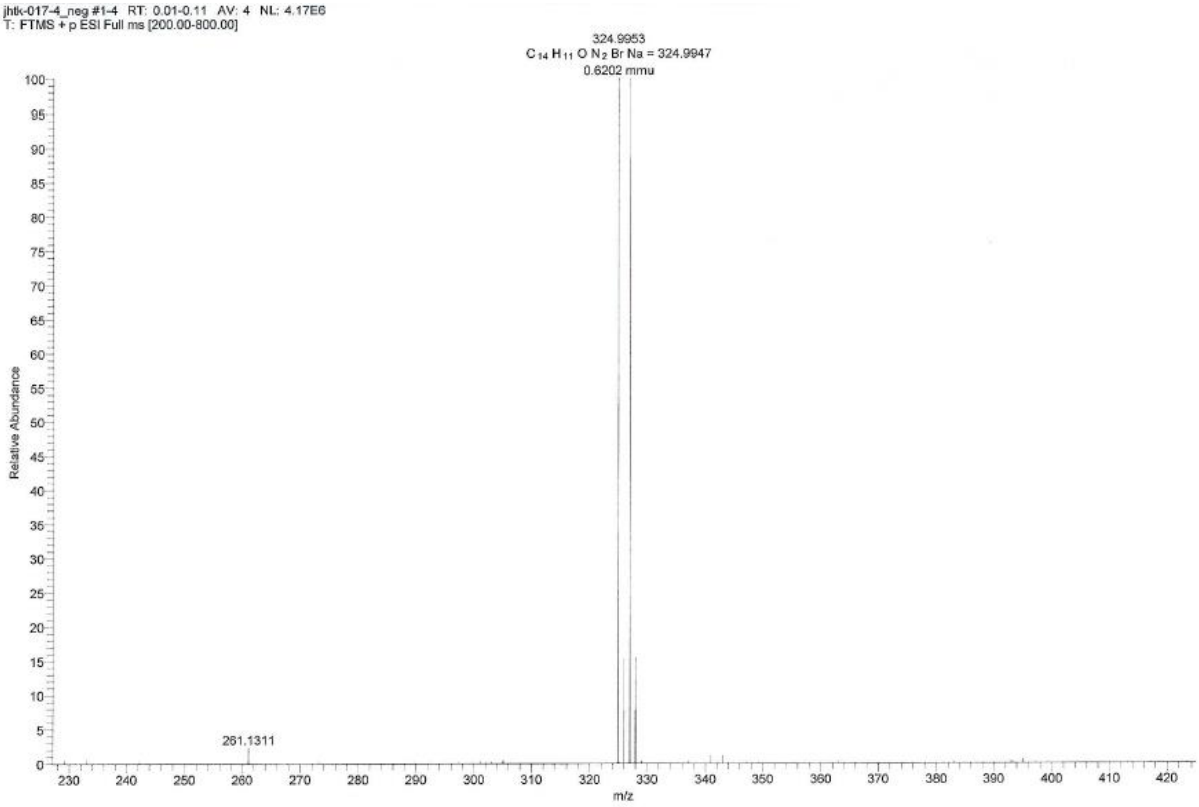

Transmittance
Wavenumber (cm-1)
3096; 71.462
2914; 74.473
2985; 72.432
1640; 56.493
1443; 55.241
1398; 54.777
1700; 48.332
1525; 47.074
1272; 48.610
1160; 45.049
1071; 38.224
1216; 34.200
791; 33.702
765; 29.053
683; 40.616
743; 45.274
1141; 49.965
1030; 45.993

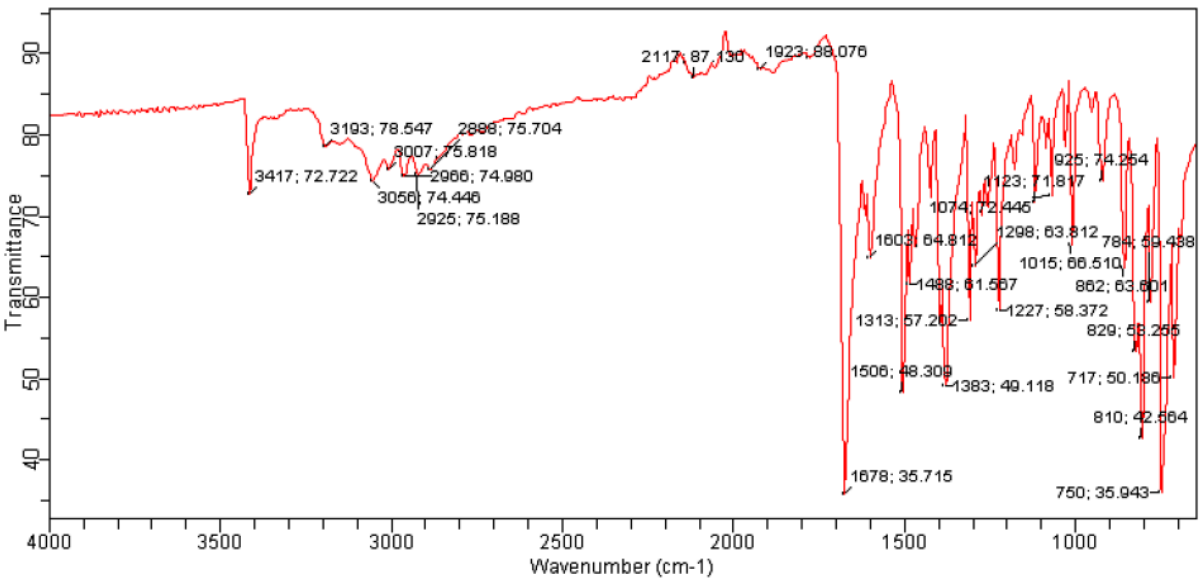
Compound **6a** –3(4-Bromophenyl)-3,4-dihydroquinoxalin-2(1*H*)-one



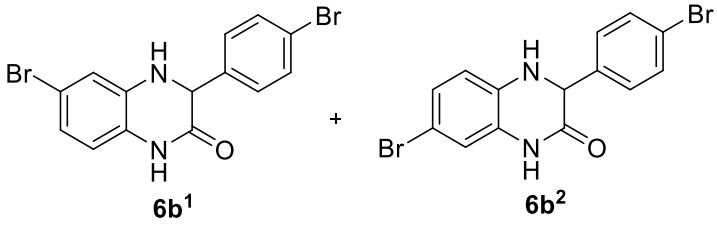




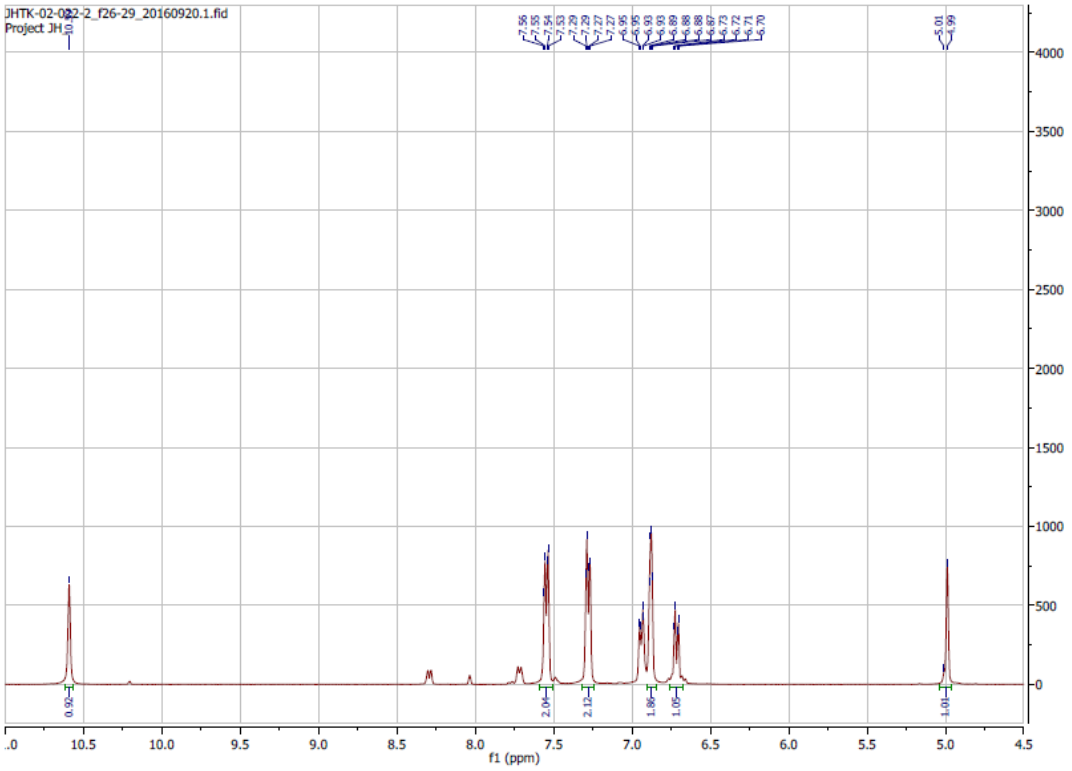

jhtk-017-4_neg #1-4 RT: 0.01-0.11 AV: 4 NL: 4.17E6
T: FTMS + p ESI Full ms [200.00-800.00]
324.9953
C14 H11 O N2 Br Na = 324.9947
0.6202 mmu
Relative Abundance
m/z
261.1311

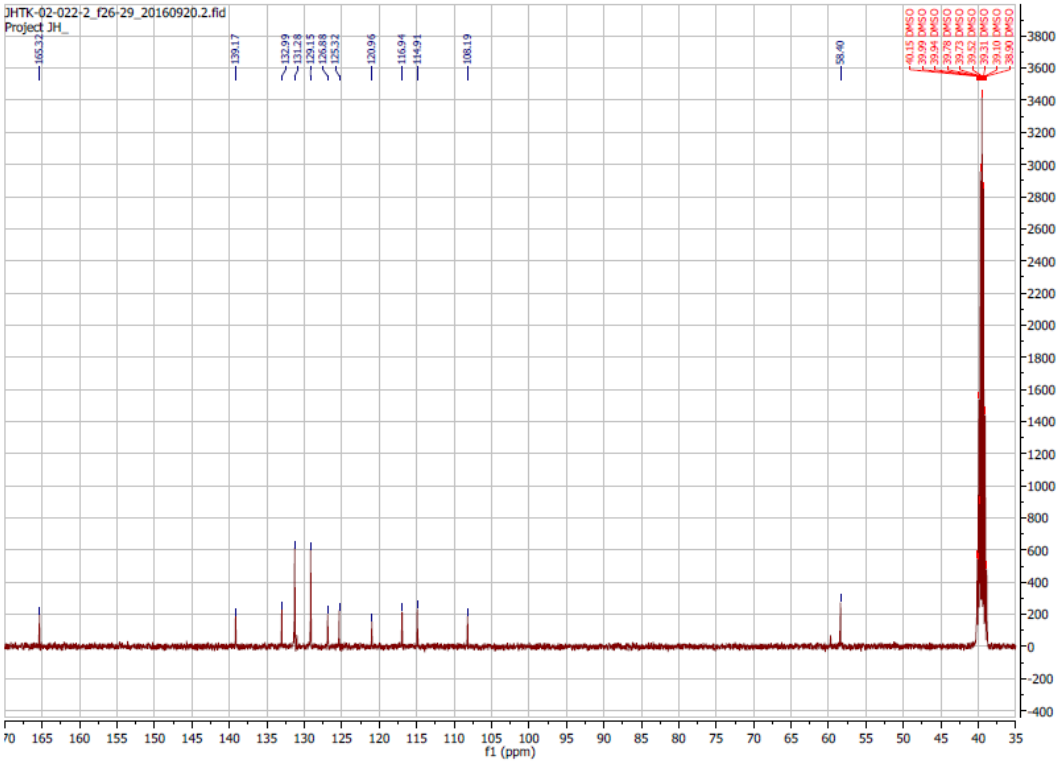

Transmittance
Wavenumber (cm-1)
3417; 72.722
3193; 78.547
3056; 74.446
3007; 75.818
2966; 74.980
2925; 75.188
2898; 75.704
2117; 87.130
1923; 88.076
1678; 35.715
1603; 64.812
1506; 48.309
1488; 61.567
1383; 49.118
1313; 57.202
1298; 63.812
1227; 58.372
1123; 71.817
1074; 72.446
1015; 66.510
925; 74.254
862; 63.601
829; 58.255
784; 59.438
717; 50.186
810; 42.564
750; 35.943

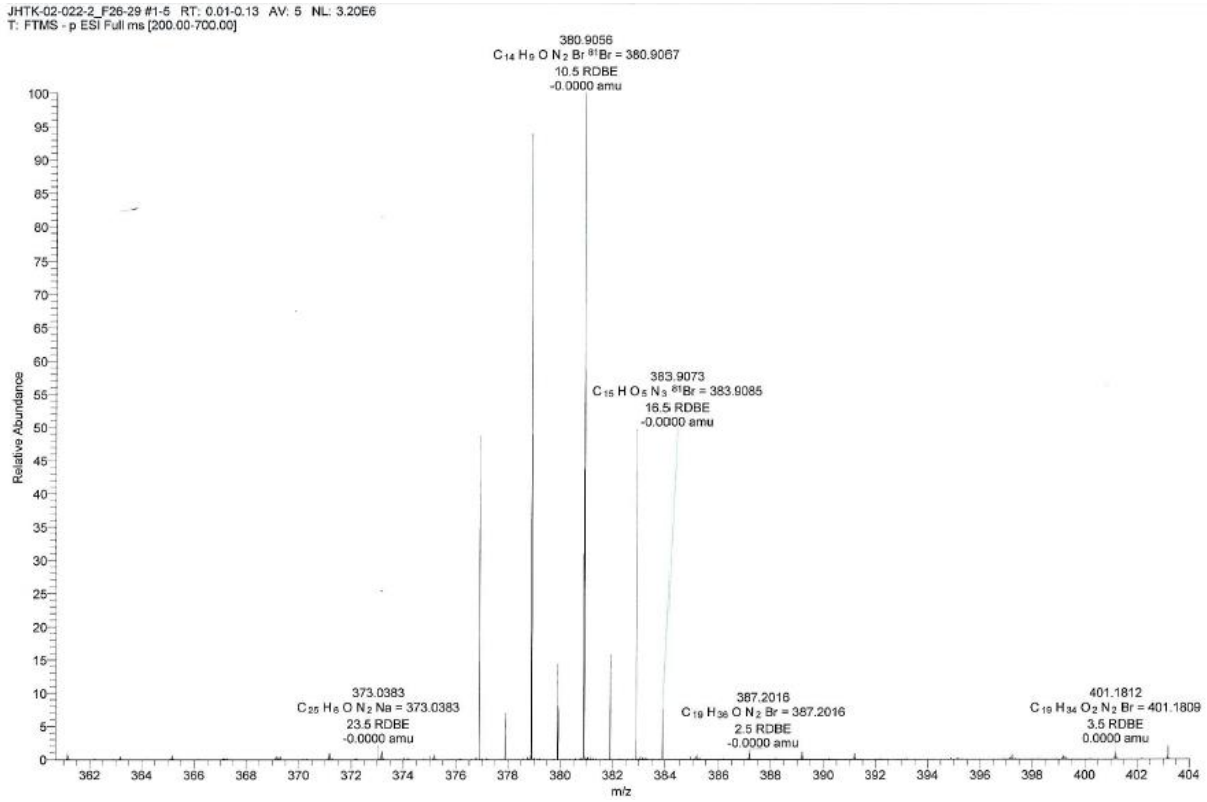
Compound **6b**

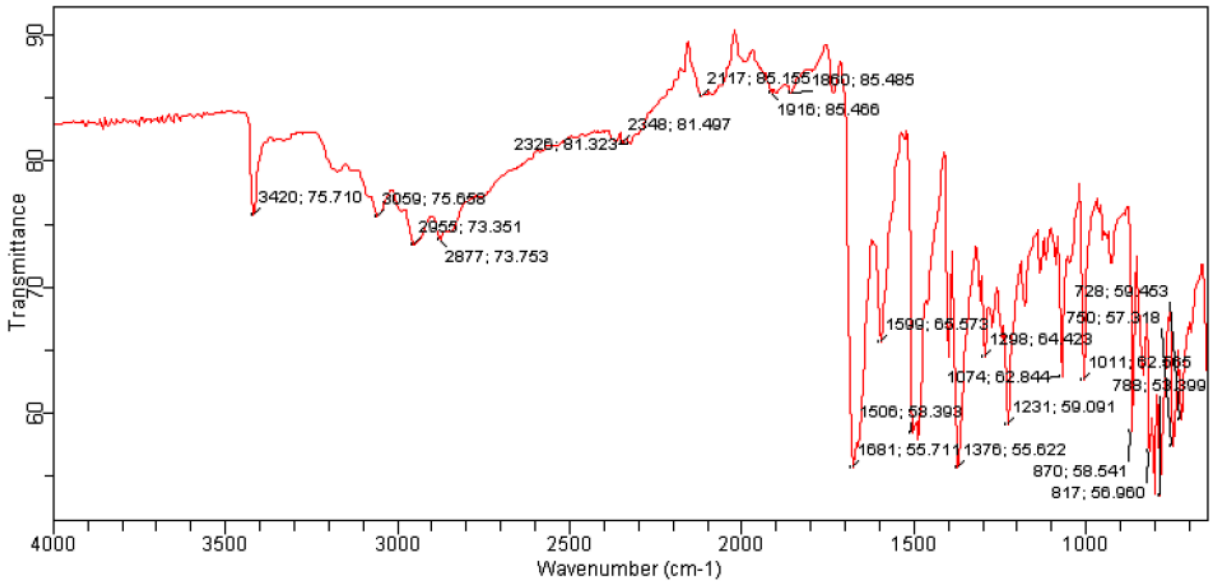


6b^1 **6b^2**

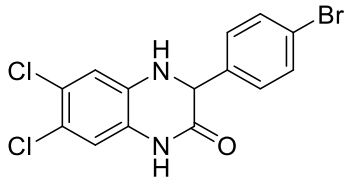


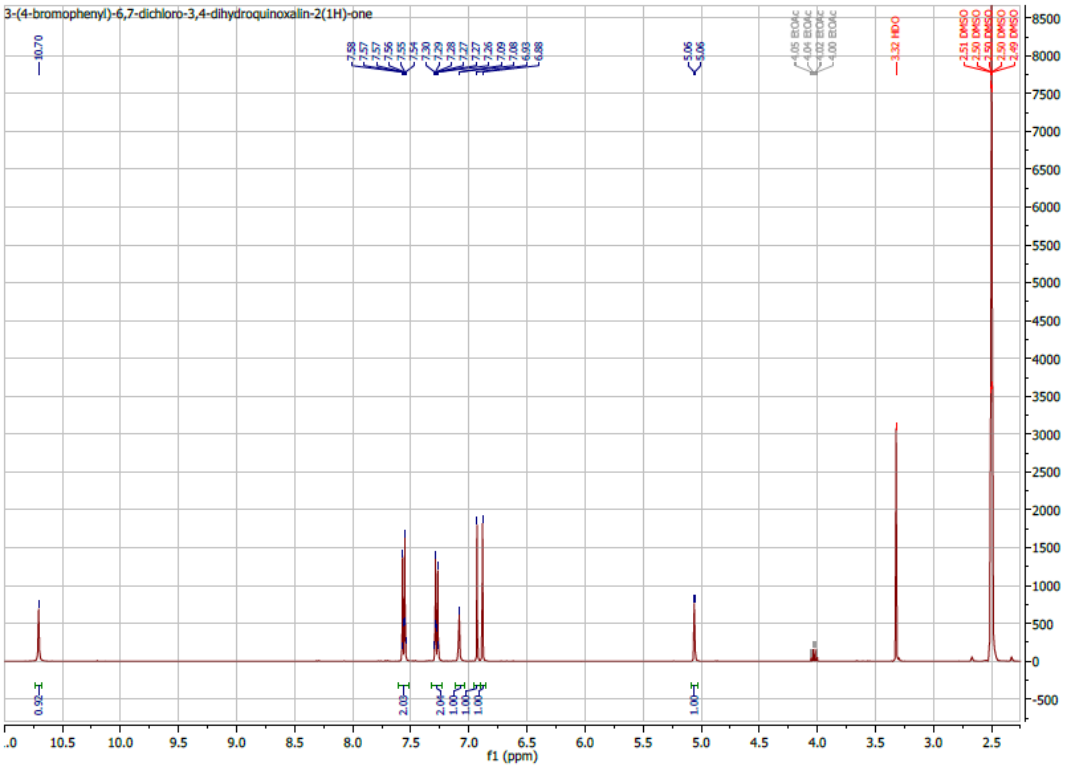


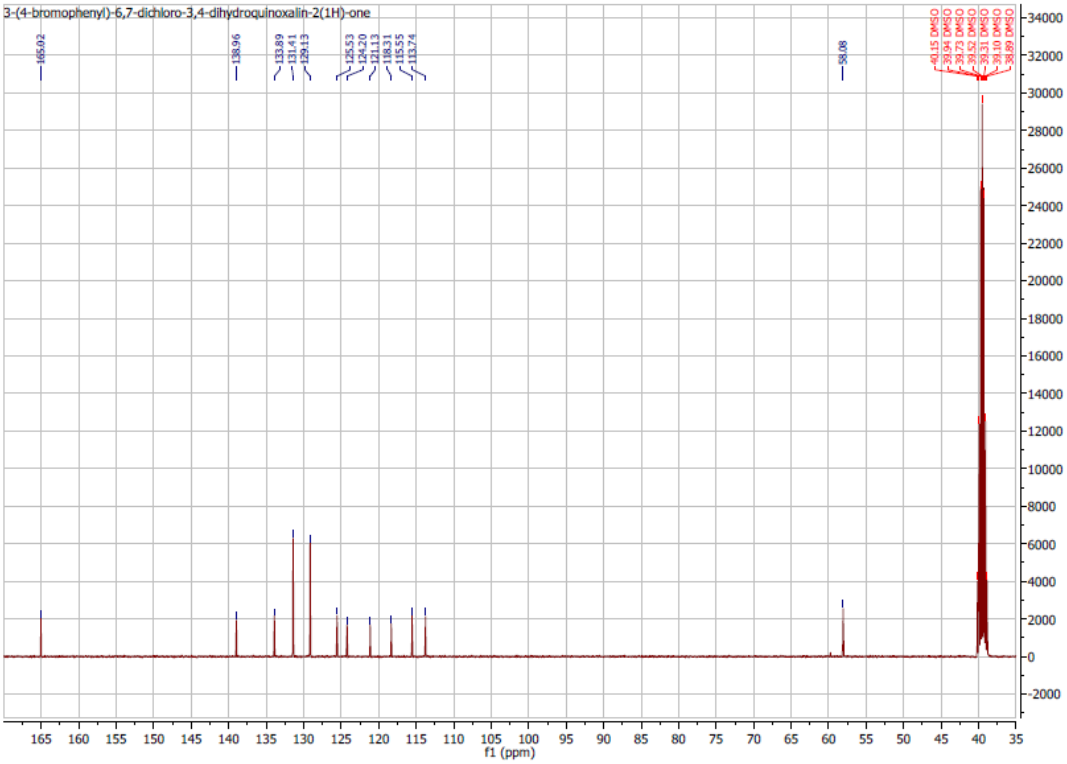

JHTK-02-022-2_F26-29 #1-5 RT: 0.01-0.13 AV: 5 NL: 3.20E6
T: FTMS - p ESI Full ms [200.00-700.00]
380.9056
C14 H9 O N2 Br 81Br = 380.9067
10.5 RDBE
-0.0000 amu
383.9073
C15 H O5 N3 81Br = 383.9085
16.5 RDBE
-0.0000 amu
373.0383
C25 H8 O N2 Na = 373.0383
23.5 RDBE
-0.0000 amu
387.2016
C19 H36 O N2 Br = 387.2016
2.5 RDBE
-0.0000 amu
401.1812
C19 H34 O2 N2 Br = 401.1809
3.5 RDBE
0.0000 amu
Relative Abundance
m/z

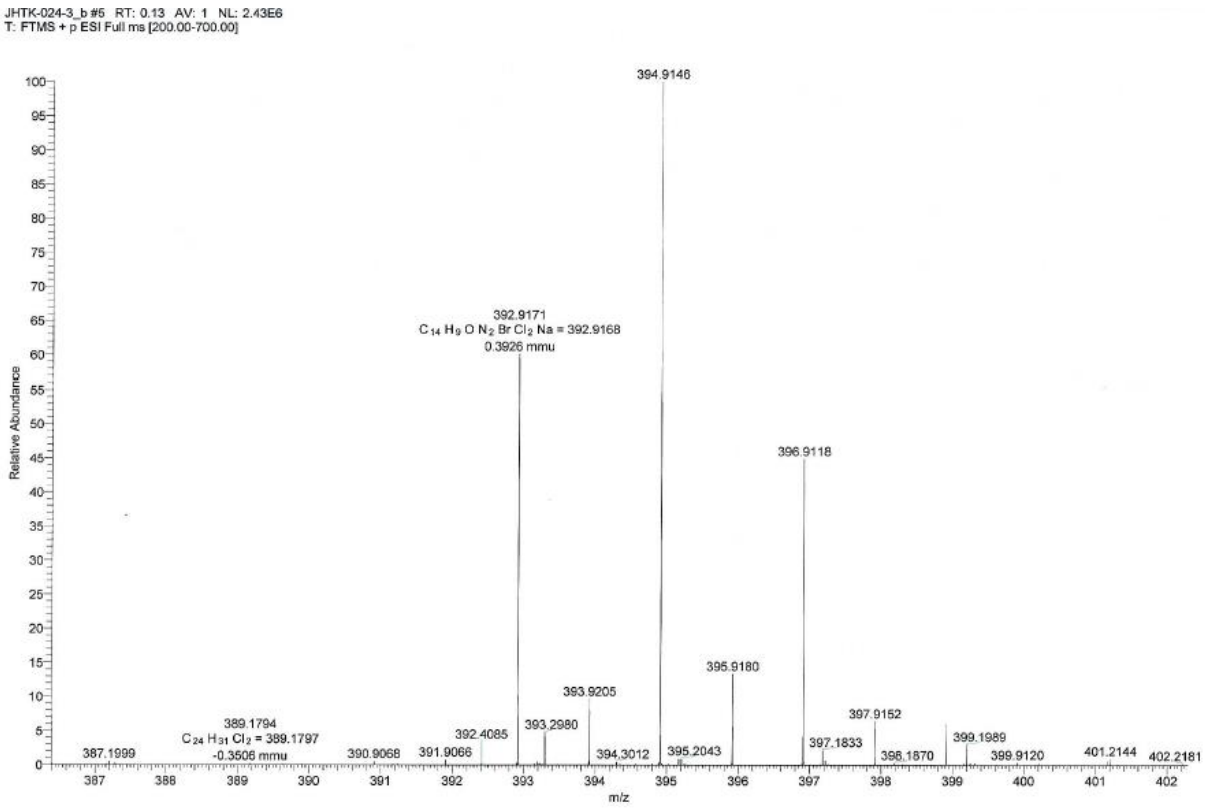

Transmittance
Wavenumber (cm-1)
3420; 75.710
3059; 75.658
2955; 73.351
2877; 73.753
2328; 81.323
2348; 81.497
2117; 85.155
1860; 85.485
1916; 85.466
1599; 65.573
1298; 64.423
1074; 62.844
1011; 62.565
1506; 58.393
1231; 59.091
1681; 55.711
1376; 55.622
870; 58.541
817; 56.960
728; 59.453
750; 57.318
788; 58.399

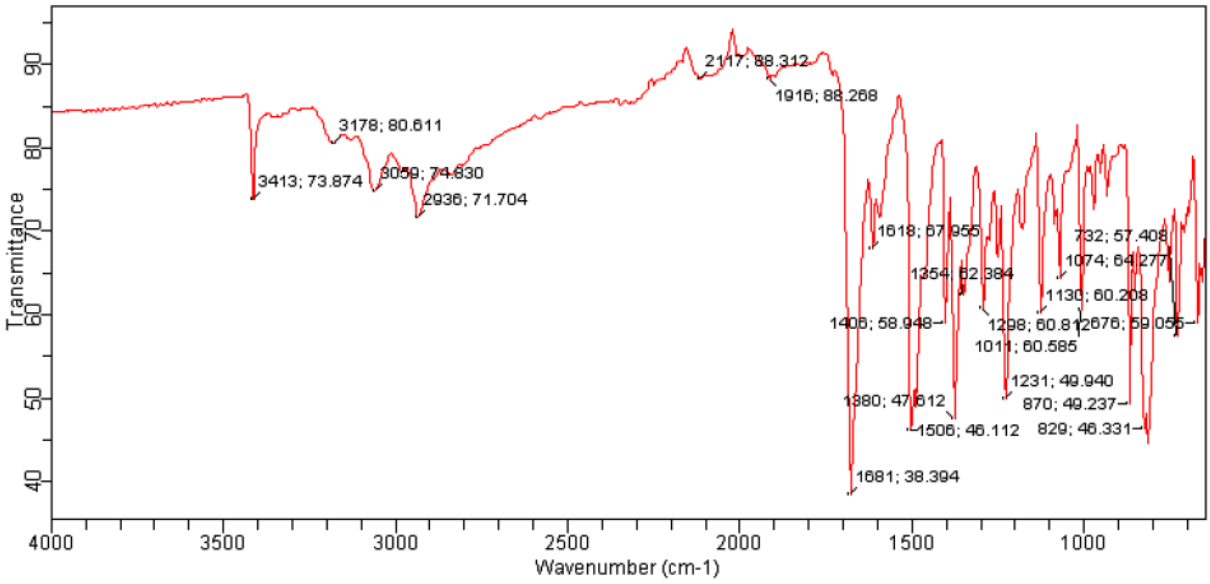
Compound **6c** - 3-(4-bromophenyl)-6,7-dichloro-3,4-dihydroquinoxalin-2(1*H*)-one



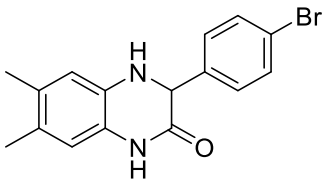


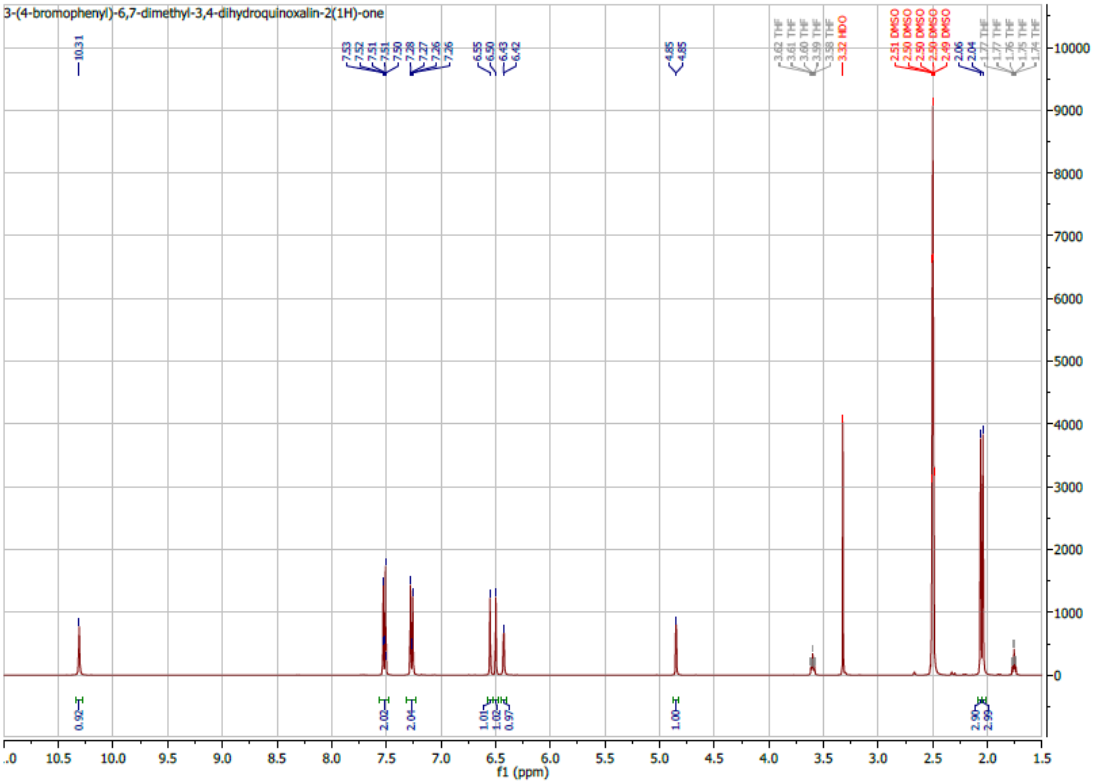


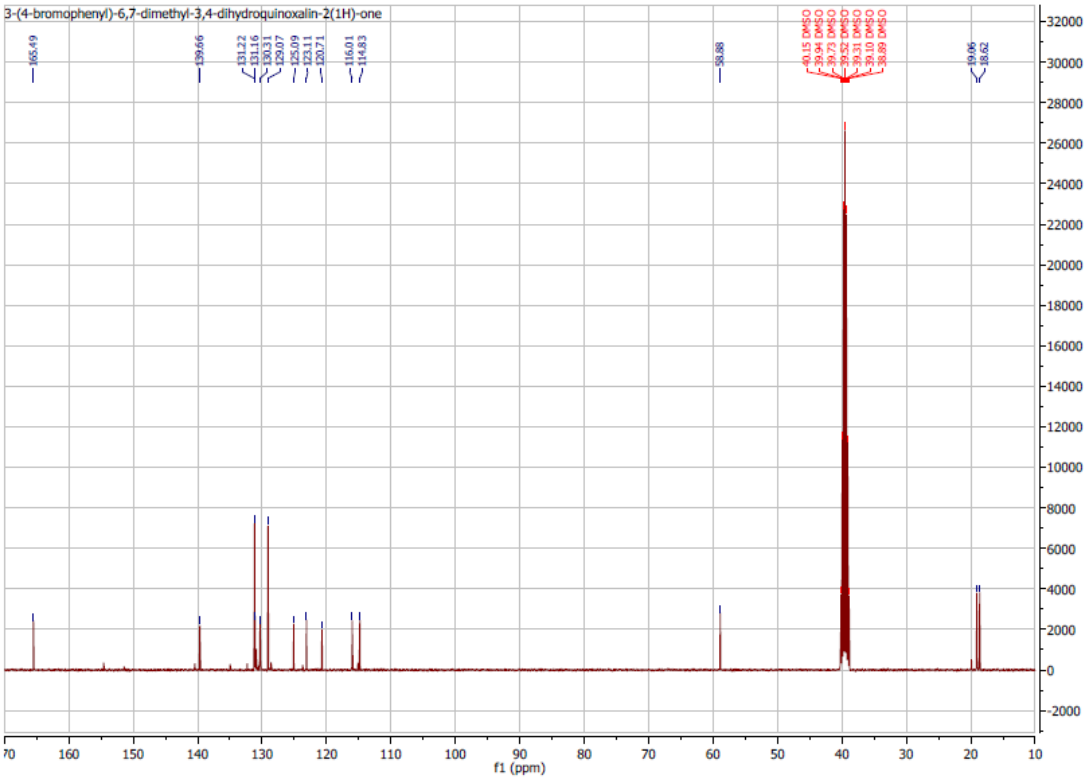

JHTK-024-3_b #5 RT: 0.13 AV: 1 NL: 2.43E6
T: FTMS + p ESI Full ms [200.00-700.00]
Relative Abundance
m/z
394.9146
392.9171
C14 H9 O N2 Br Cl2 Na = 392.9168
0.3926 mmu
396.9118
395.9180
393.9205
397.9152
389.1794
C24 H31 Cl2 = 389.1797
-0.3506 mmu
392.4085
393.2980
399.1989
387.1999
390.9068
391.9066
394.3012
395.2043
397.1833
398.1870
399.9120
401.2144
402.2181

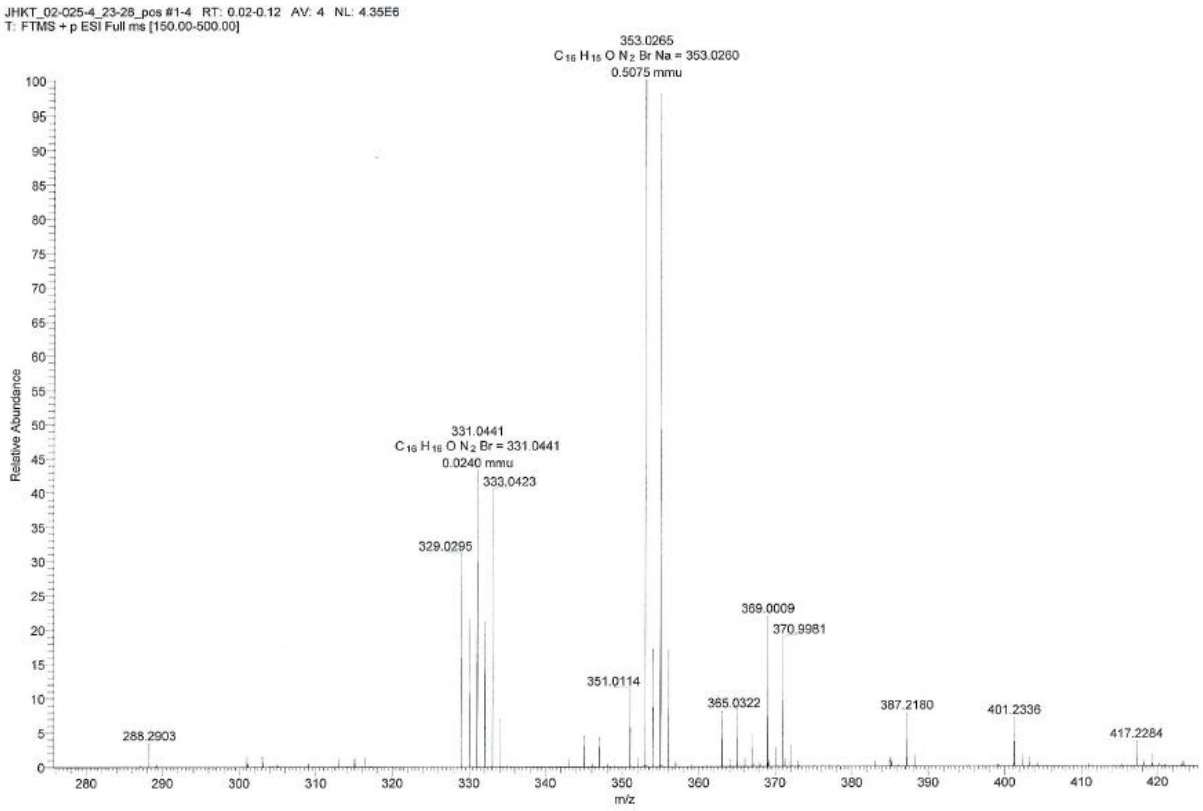

Transmittance
Wavenumber (cm-1)
2117; 88.312
1916; 88.268
3178; 80.611
3413; 73.874
3059; 74.830
2936; 71.704
1618; 67.955
732; 57.408
1074; 64.277
1354; 62.384
1130; 60.208
1406; 58.948
1298; 60.812
676; 59.055
1011; 60.585
1231; 49.940
1380; 47.612
870; 49.237
1506; 46.112
829; 46.331
1681; 38.394

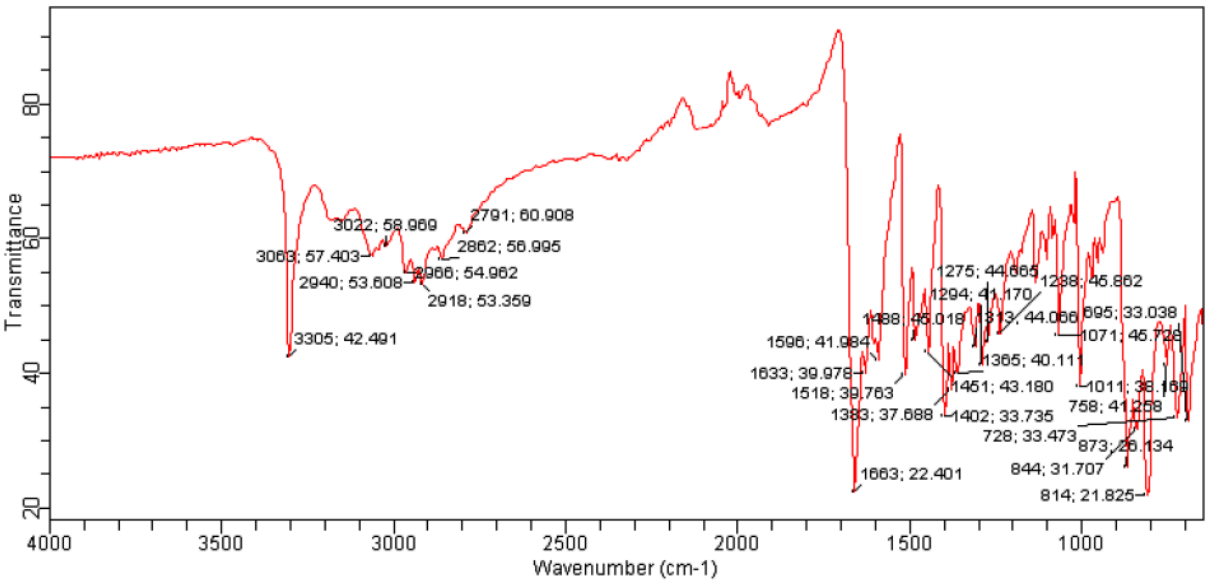
Compound **6d** - 3-(4-bromophenyl)-6,7-dimethyl-3,4-dihydroquinoxalin-2(1*H*)-one



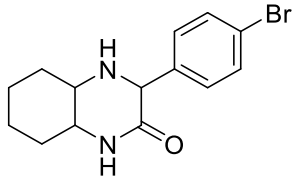


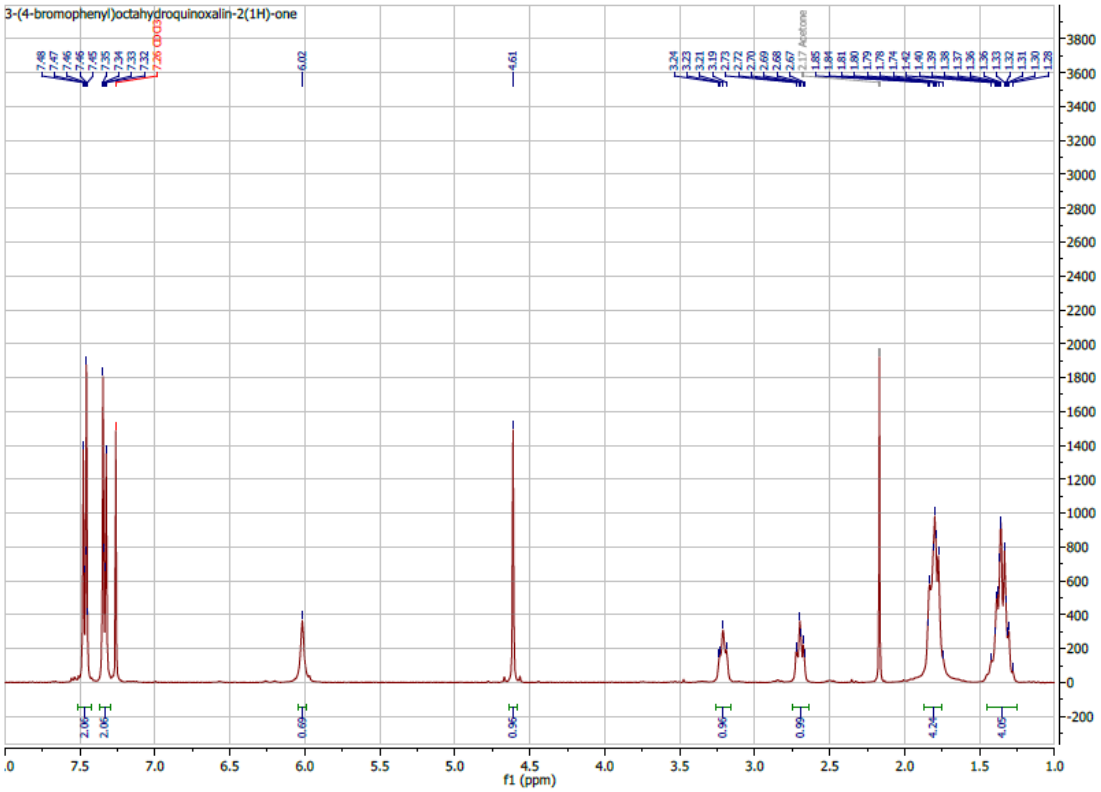


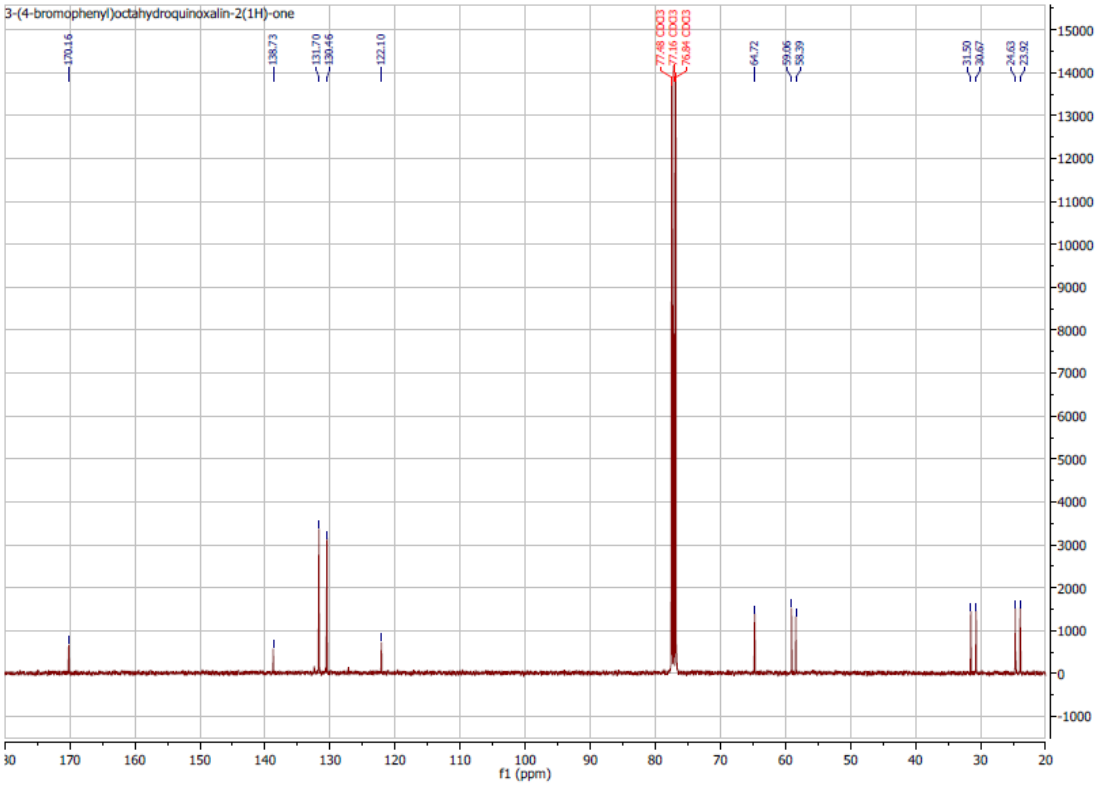

JHKT_02-025-4_23-28_pos #1-4 RT: 0.02-0.12 AV: 4 NL: 4.35E6
T: FTMS + p ESI Full ms [150.00-500.00]
353.0265
C16 H15 O N2 Br Na = 353.0260
0.5075 mmu
331.0441
C16 H16 O N2 Br = 331.0441
0.0240 mmu
333.0423
329.0295
369.0009
370.9981
351.0114
365.0322
387.2180
401.2336
417.2284
288.2903
Relative Abundance
m/z

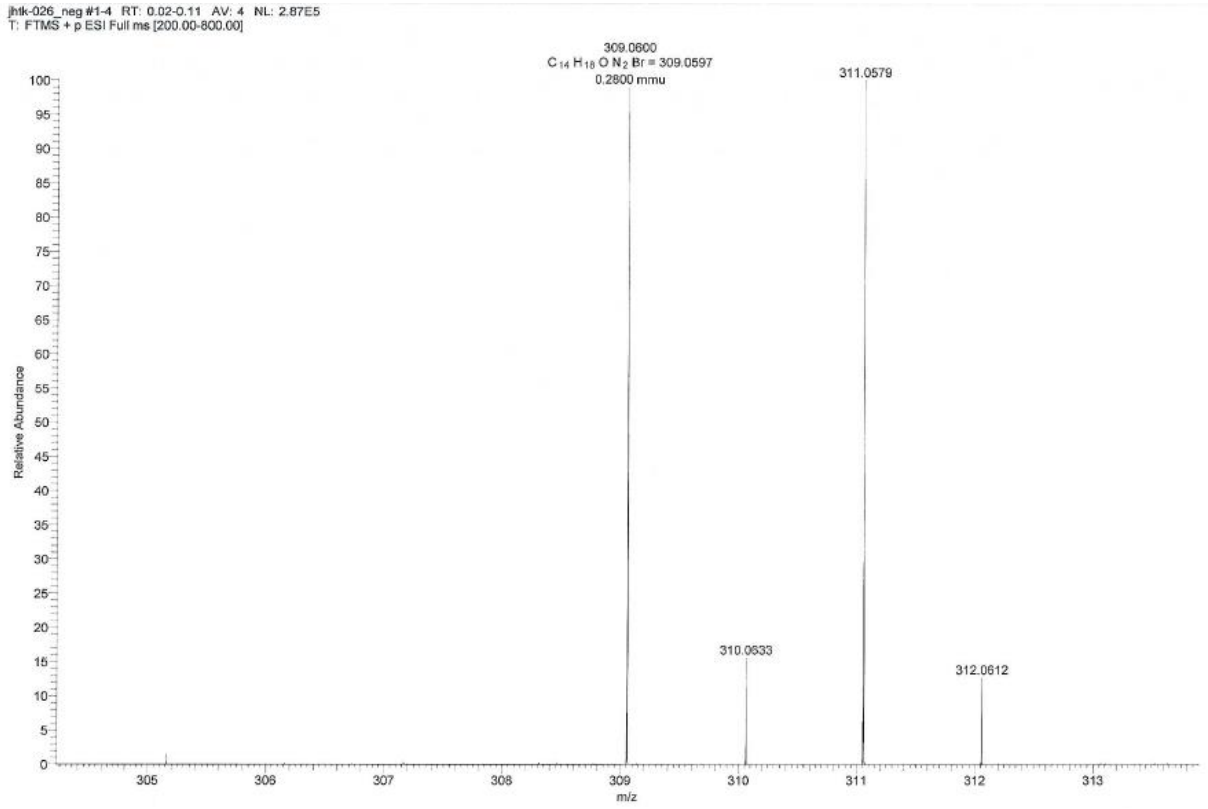

Transmittance
Wavenumber (cm-1)
3022; 58.969
2791; 60.908
3063; 57.403
2862; 56.995
2940; 53.608
2966; 54.962
2918; 53.359
3305; 42.491
1596; 41.984
1275; 44.665
1294; 41.170
1238; 45.862
1488; 45.018
1313; 44.066
695; 33.038
1071; 45.728
1633; 39.978
1365; 40.111
1518; 39.763
1451; 43.180
1011; 38.168
1383; 37.688
1402; 33.735
758; 41.258
728; 33.473
873; 26.134
844; 31.707
1663; 22.401
814; 21.825

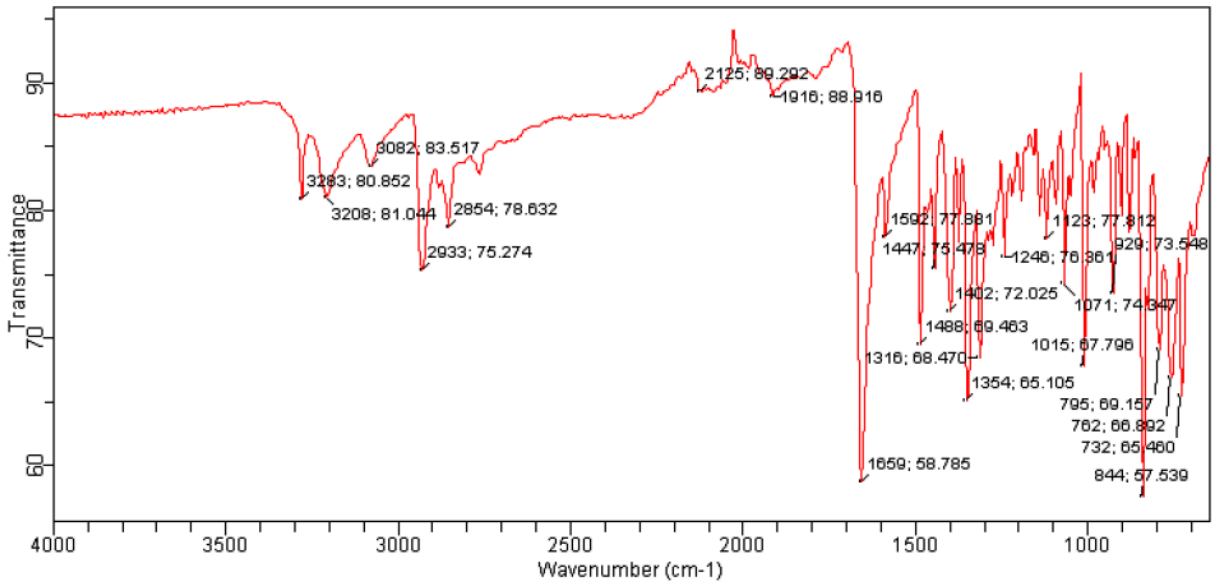
Compound **6e** - 3-(4-bromophenyl)octahydroquinoxalin-2(1*H*)-one



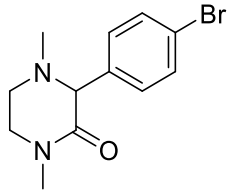


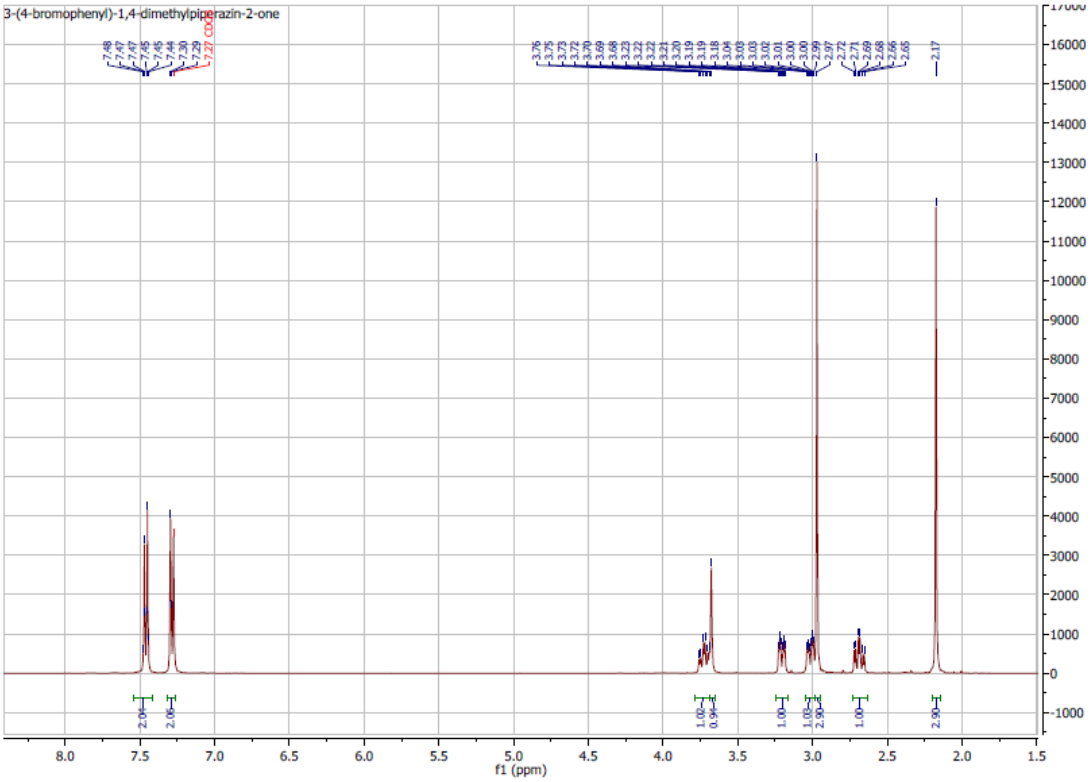


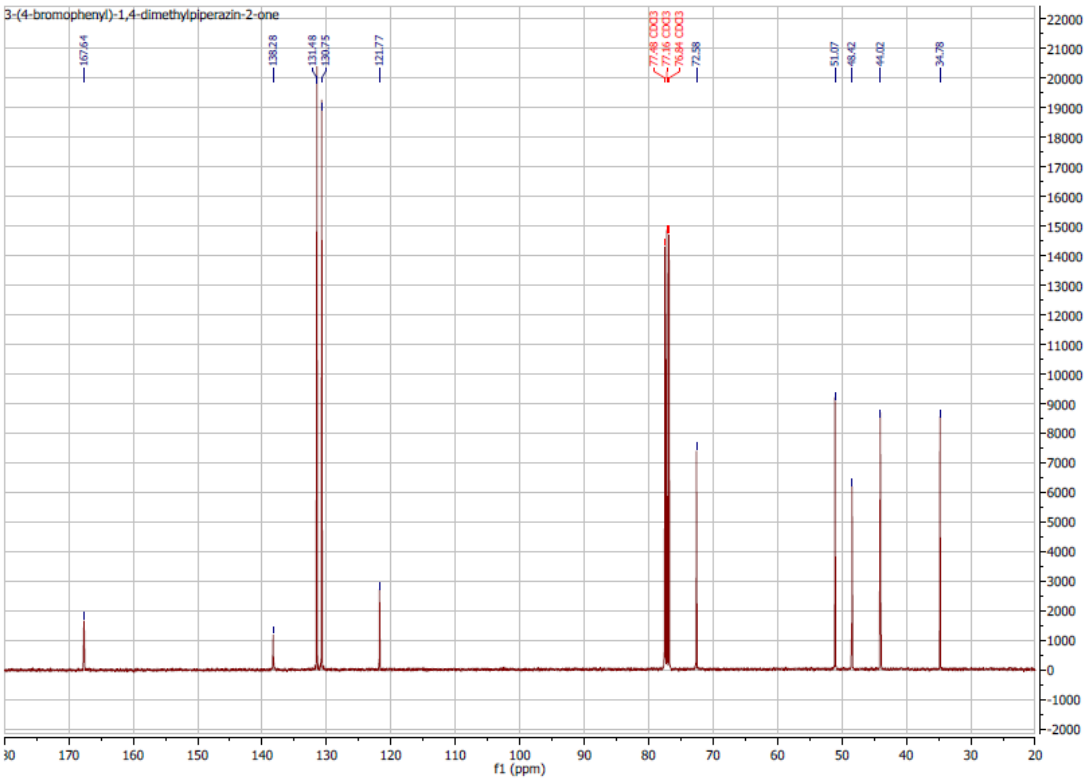

jhtk-026_neg #1-4 RT: 0.02-0.11 AV: 4 NL: 2.87E5
T: FTMS + p ESI Full ms [200.00-800.00]
309.0600
C14 H18 O N2 Br = 309.0597
0.2800 mmu
311.0579
310.0633
312.0612
Relative Abundance
m/z

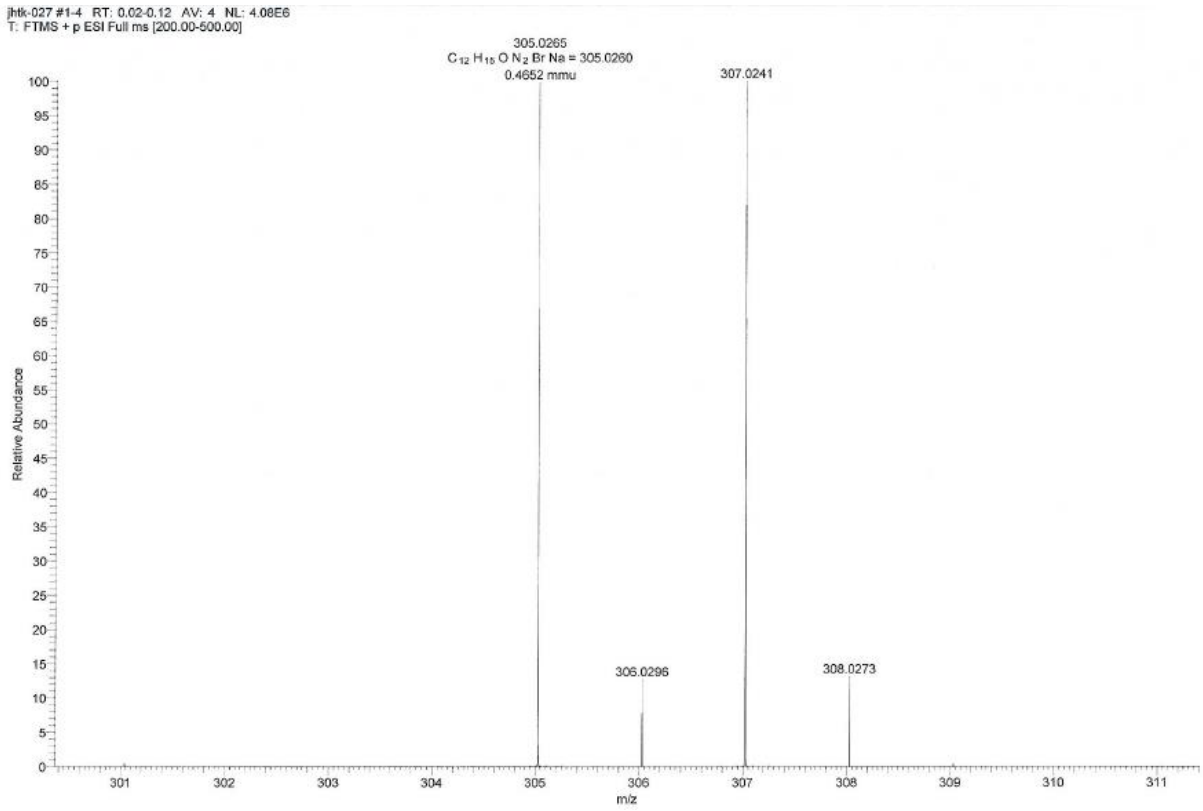

Transmittance
Wavenumber (cm-1)
3283; 80.852
3208; 81.044
3082; 83.517
2933; 75.274
2854; 78.632
2125; 89.292
1916; 88.916
1659; 58.785
1592; 77.881
1447; 75.478
1488; 69.463
1316; 68.470
1402; 72.025
1354; 65.105
1246; 76.361
1123; 77.812
1071; 74.347
1015; 67.796
929; 73.548
795; 69.157
762; 66.892
732; 65.460
844; 57.539

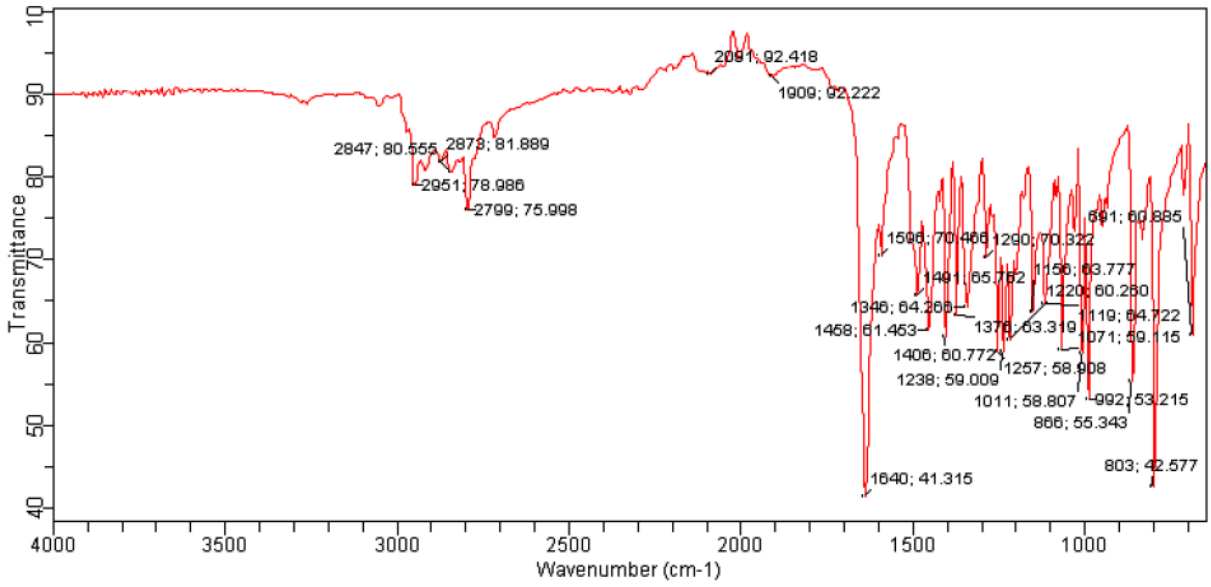
Compound **6f** - 3-(4-bromophenyl)-1,4-dimethylpiperazin-2-one



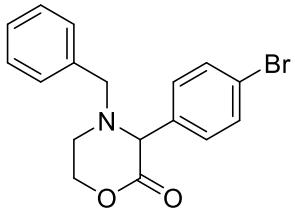


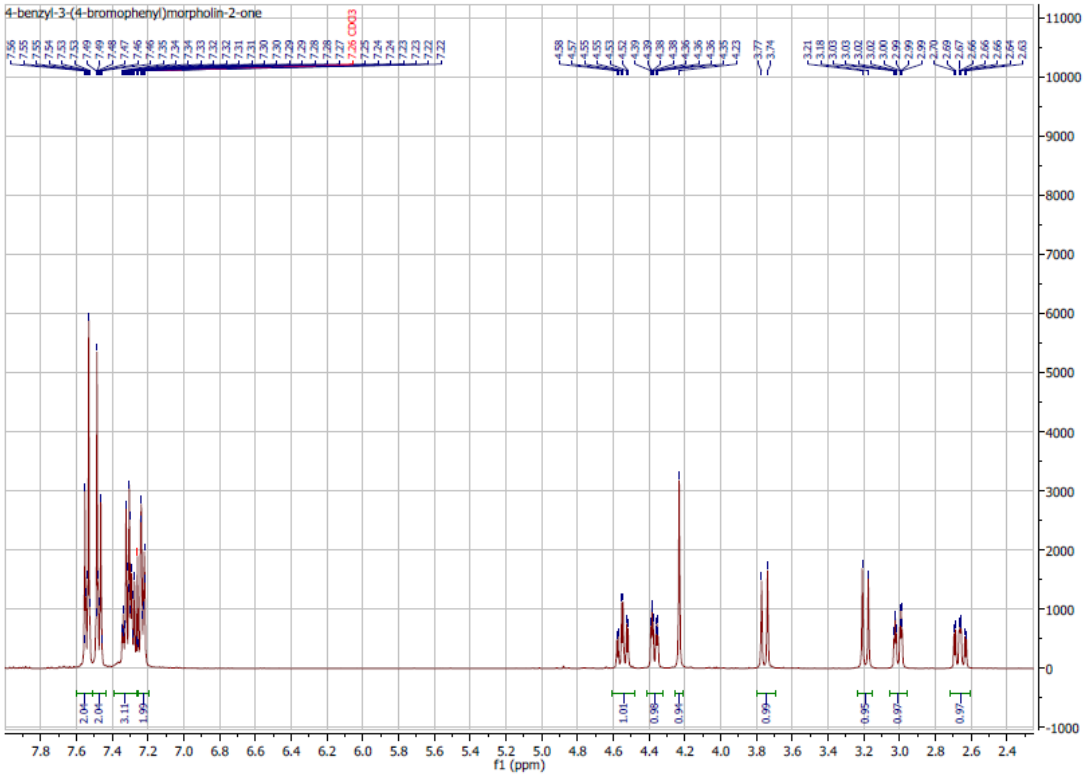


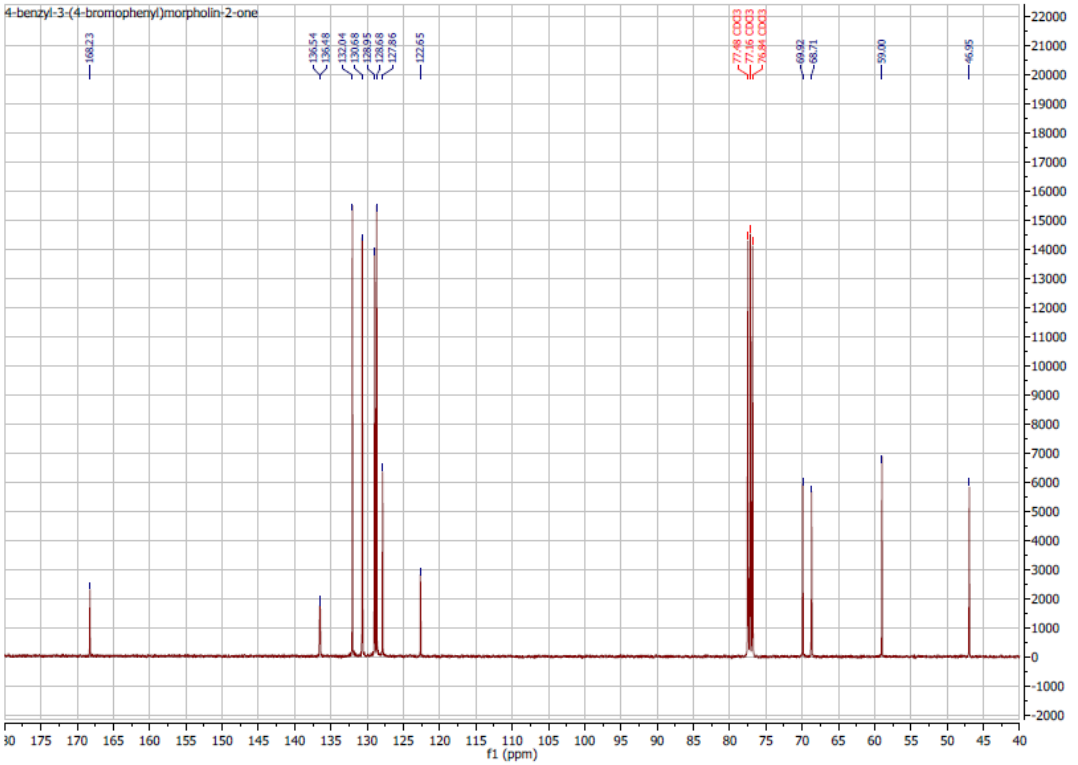

jhtk-027 #1-4 RT: 0.02-0.12 AV: 4 NL: 4.08E6
T: FTMS + p ESI Full ms [200.00-500.00]
305.0265
C12 H15 O N2 Br Na = 305.0260
0.4652 mmu
307.0241
306.0296
308.0273
Relative Abundance
m/z

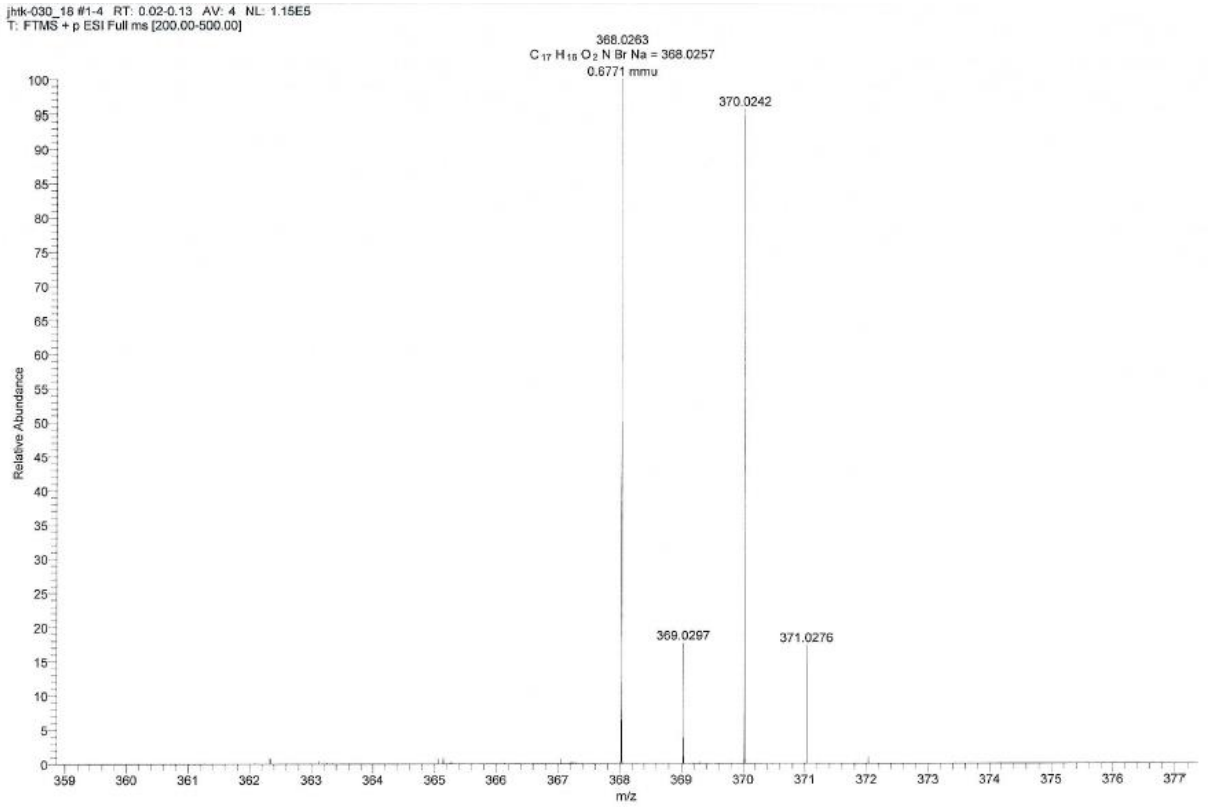

2091; 92.418
1909; 92.222
2847; 80.555
2873; 81.889
2951; 78.986
2799; 75.998
1596; 70.466
1290; 70.322
691; 60.885
1491; 65.752
1156; 63.777
1220; 60.250
1346; 64.266
1119; 64.722
1458; 61.453
1378; 63.319
1071; 59.115
1406; 60.772
1257; 58.908
1238; 59.009
1011; 58.807
992; 53.215
866; 55.343
803; 42.577
1640; 41.315
Transmittance
Wavenumber (cm-1)

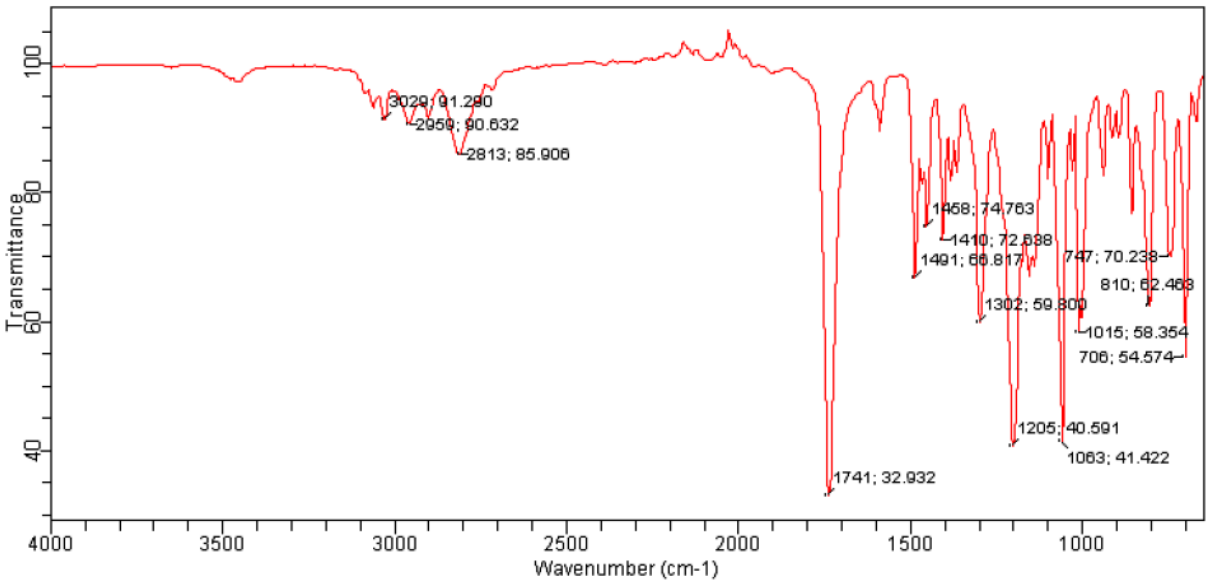
Compound **6h** - 4-benzyl-3-(4-bromophenyl)morpholin-2-one



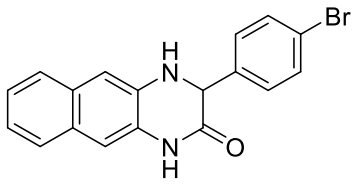


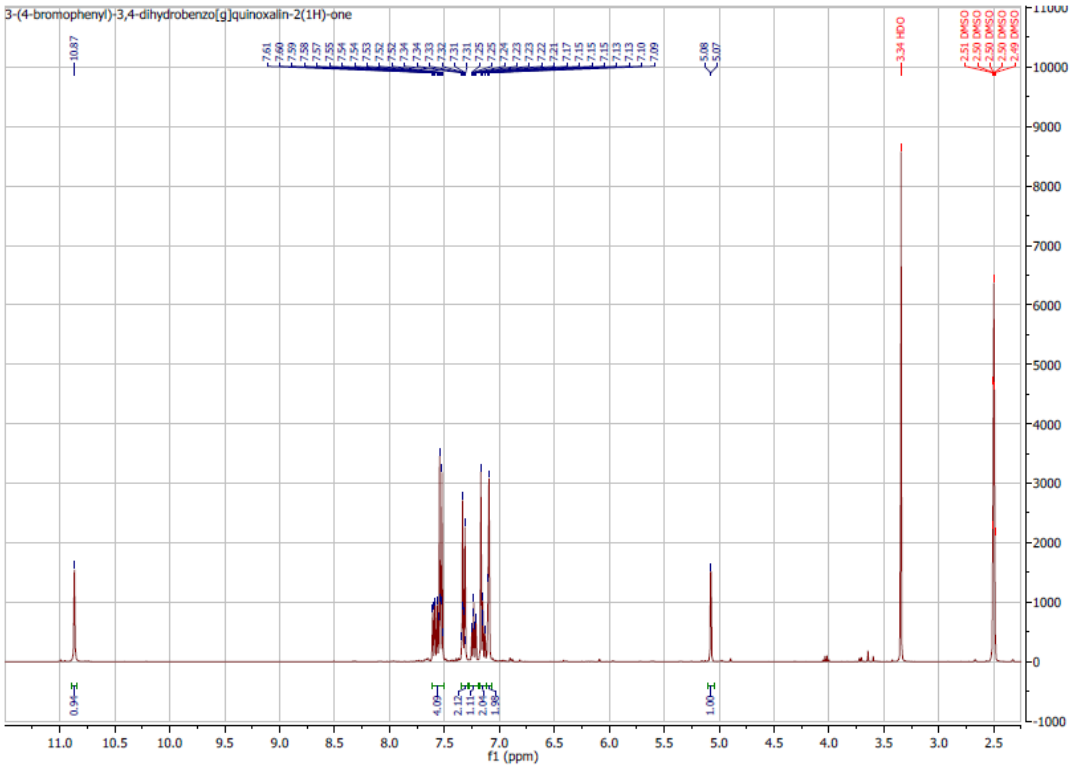


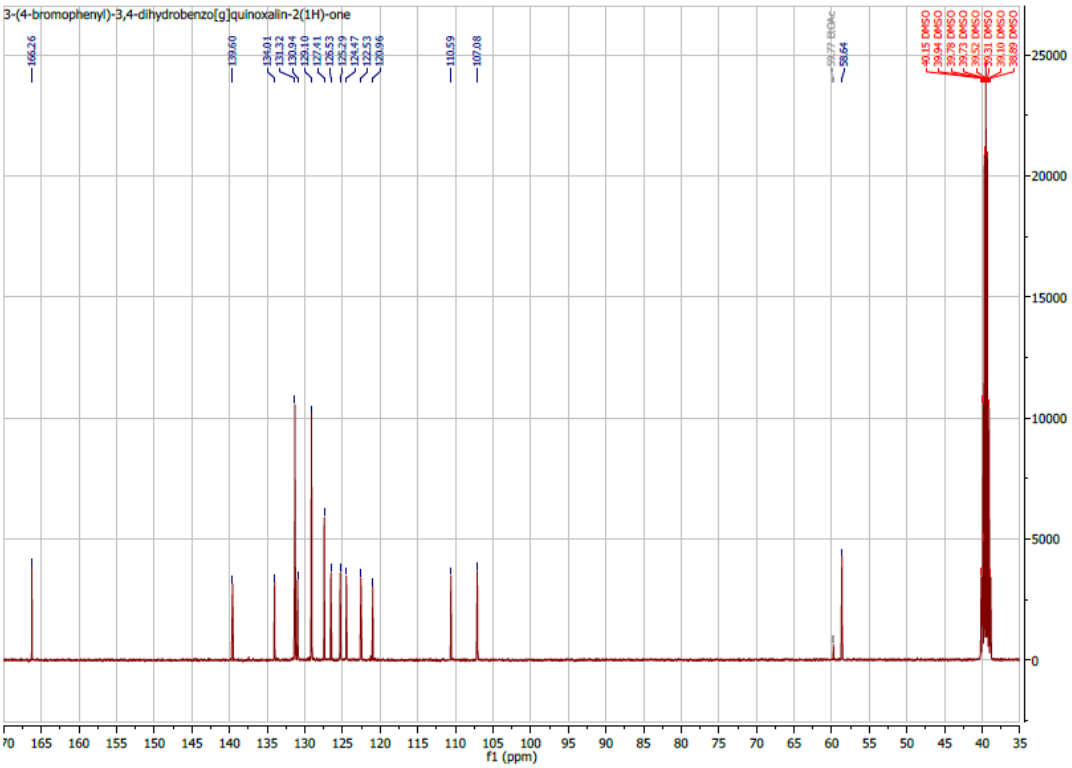

jhtk-030_18 #1-4 RT: 0.02-0.13 AV: 4 NL: 1.15E5
T: FTMS + p ESI Full ms [200.00-500.00]
368.0263
C17 H16 O2 N Br Na = 368.0257
0.6771 mmu
370.0242
369.0297
371.0276
Relative Abundance
m/z

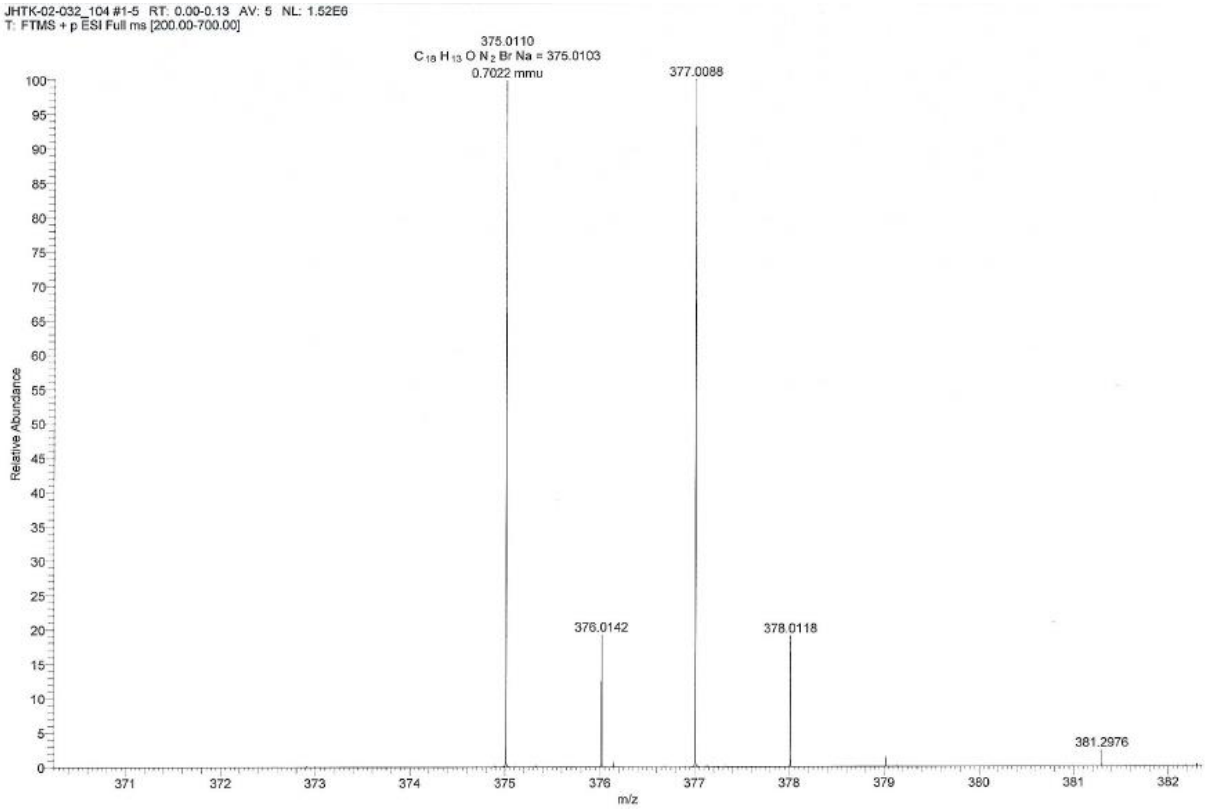

3029; 91.290
2959; 90.632
2813; 85.906
1468; 74.763
1410; 72.688
1491; 66.817
747; 70.238
810; 62.468
1302; 59.809
1015; 58.354
706; 54.574
1205; 40.591
1063; 41.422
1741; 32.932
Transmittance
Wavenumber (cm-1)

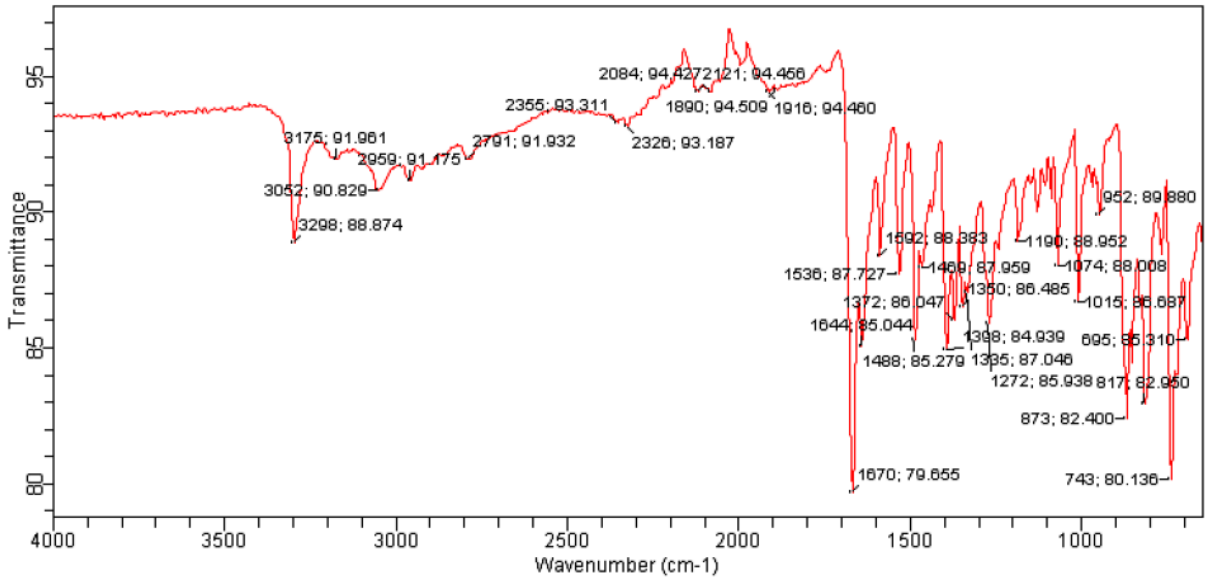
Compound **6i** - 3-(4-bromophenyl)-3,4-dihydrobenzo[*g*]quinoxalin-2(1*H*)-one



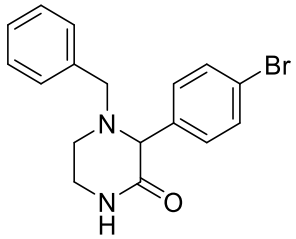


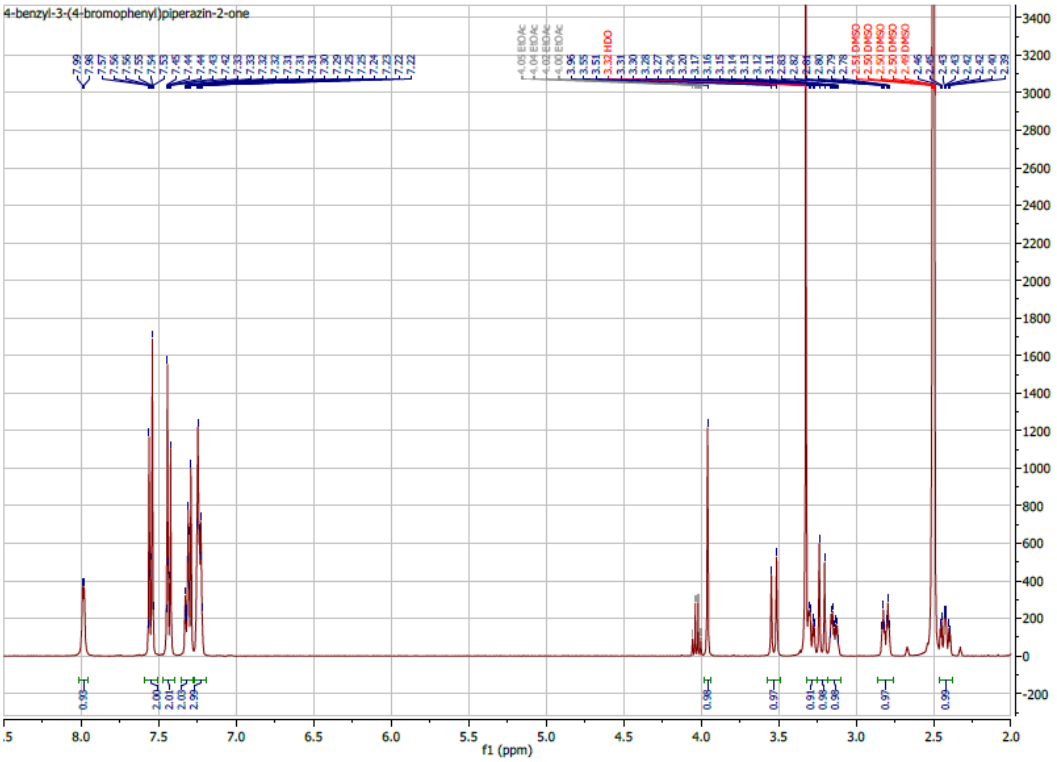


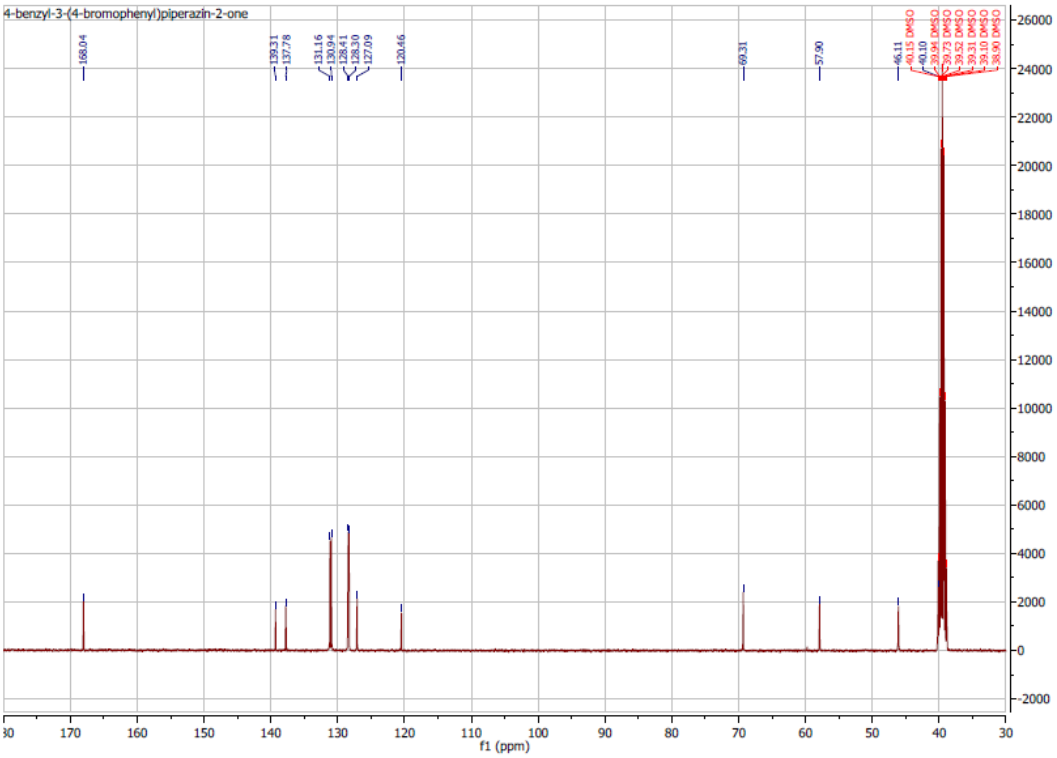

JHTK-02-032_104 #1-5 RT: 0.00-0.13 AV: 5 NL: 1.52E6
T: FTMS + p ESI Full ms [200.00-700.00]
375.0110
C18 H13 O N2 Br Na = 375.0103
0.7022 mmu
377.0088
376.0142
378.0118
381.2976
Relative Abundance
m/z


2084; 94.427
2121; 94.456
2355; 93.311
1890; 94.509
1916; 94.460
3175; 91.961
2791; 91.932
2326; 93.187
2959; 91.175
3052; 90.829
3298; 88.874
952; 89.880
1592; 88.383
1190; 88.952
1536; 87.727
1469; 87.959
1074; 88.008
1350; 86.485
1372; 86.047
1015; 86.687
1644; 85.044
1398; 84.939
695; 85.310
1488; 85.279
1335; 87.046
1272; 85.938
817; 82.950
873; 82.400
1670; 79.655
743; 80.136
Transmittance
Wavenumber (cm-1)

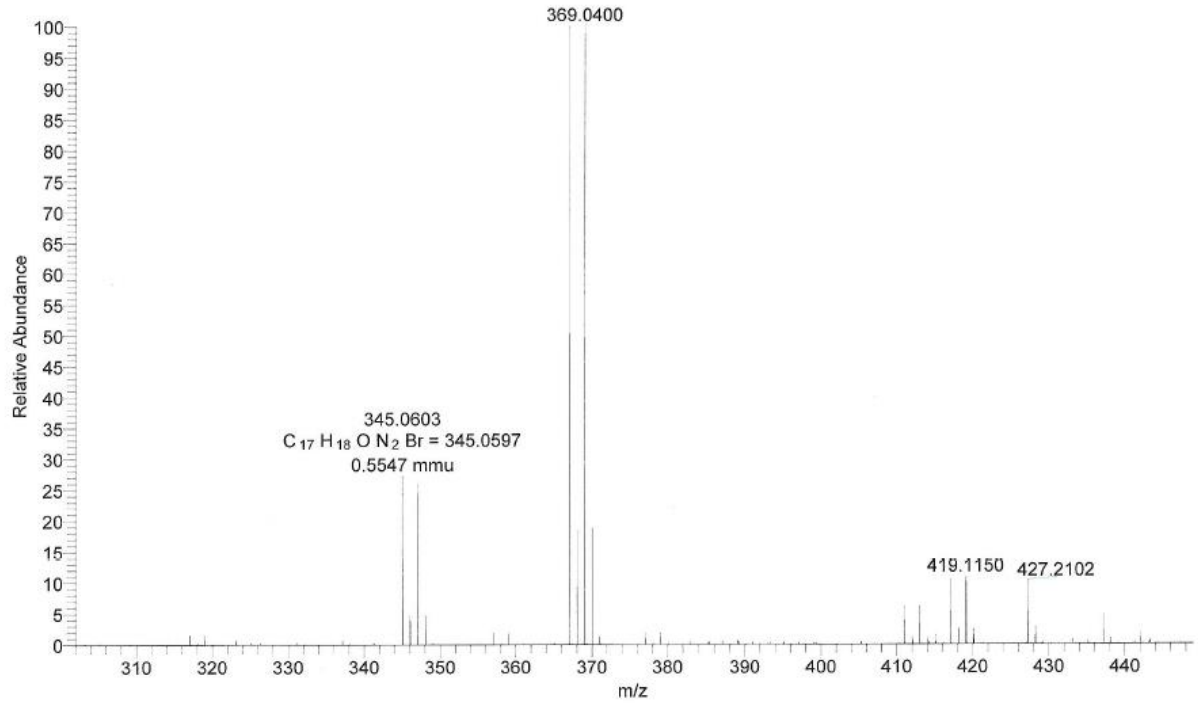
Compound **6j** - 4-benzyl-3-(4-bromophenyl)piperazin-2-one

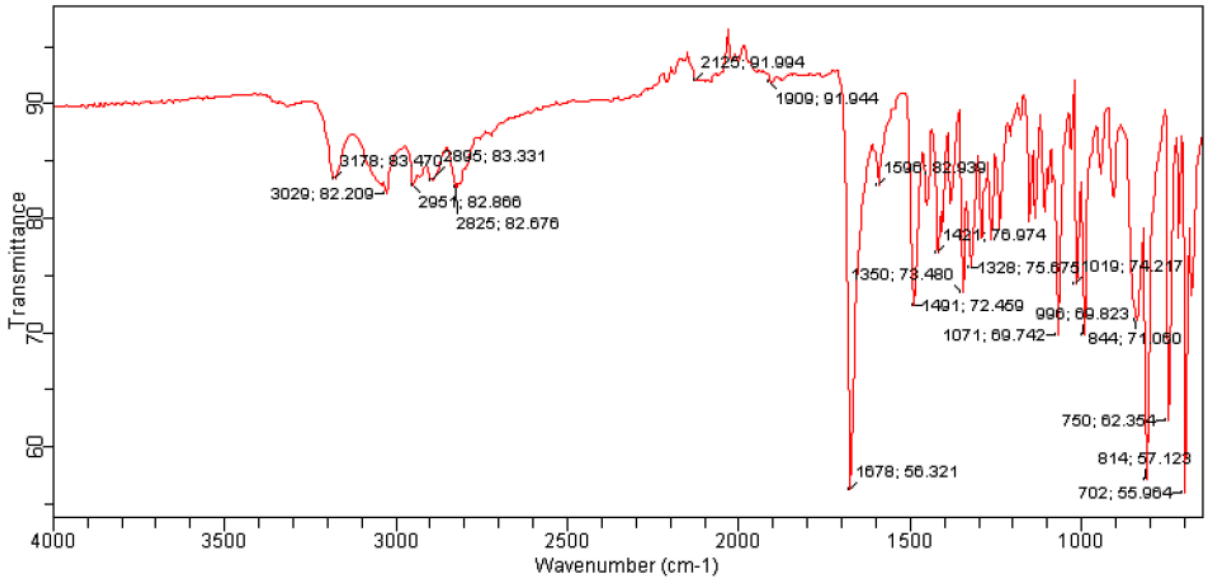




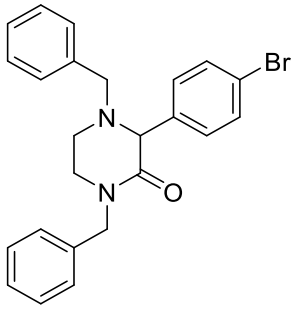


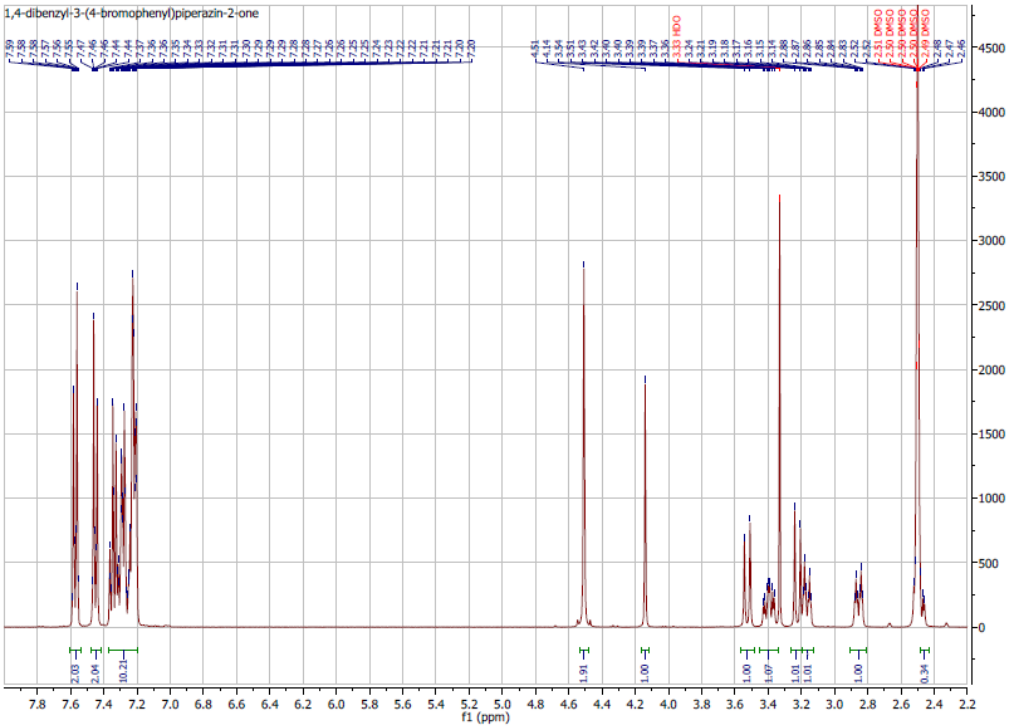
jhtk-034-rf22 #1-5 RT: 0.00-0.13 AV: 5 NL: 1.72E7
T: FTMS + p ESI Full ms [200.00-600.00]

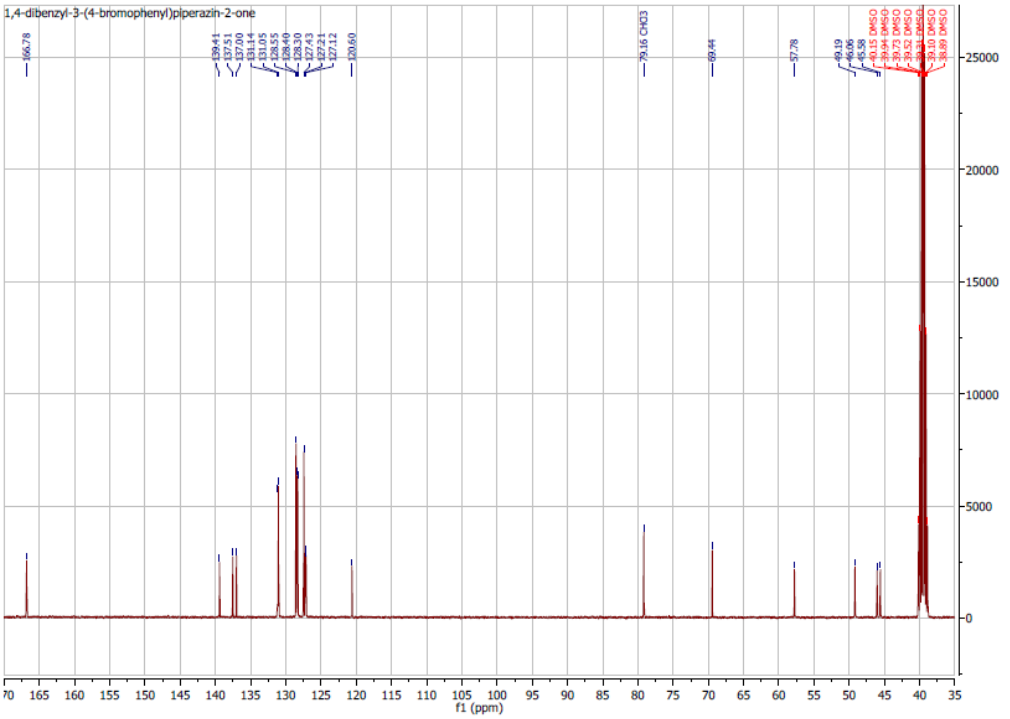


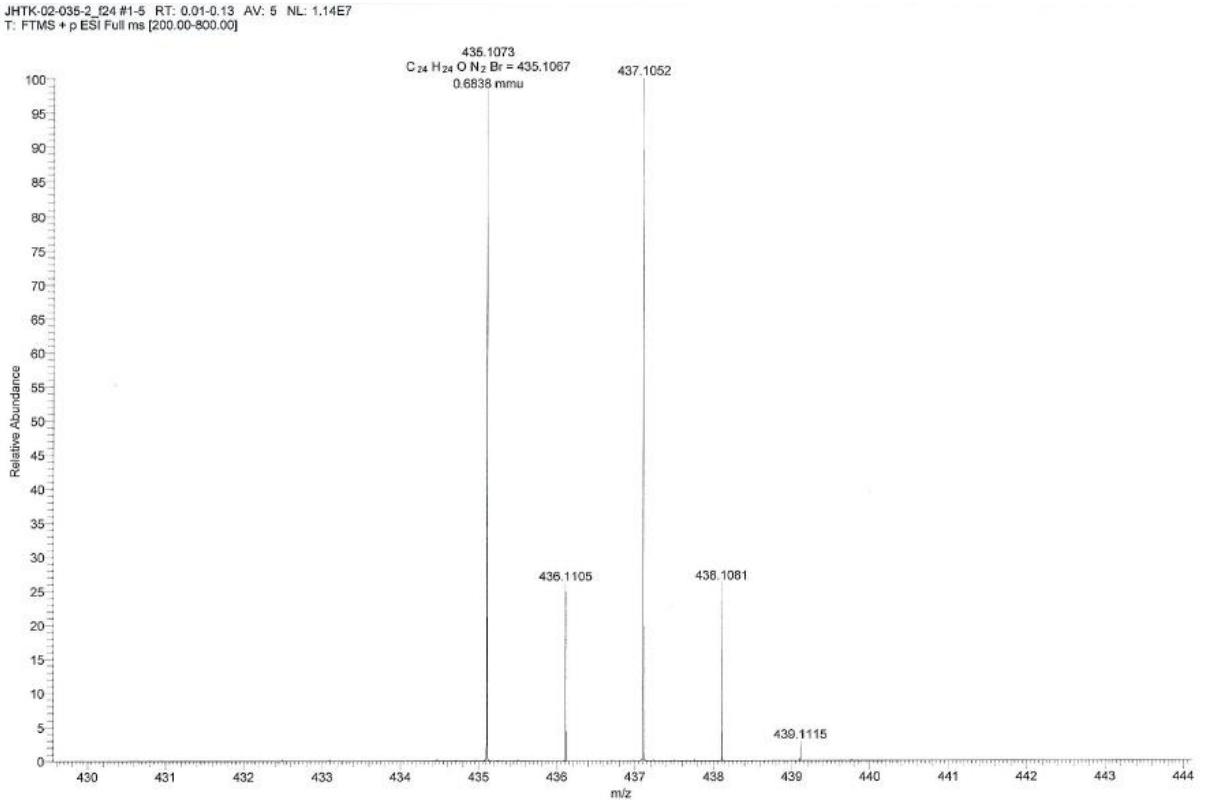


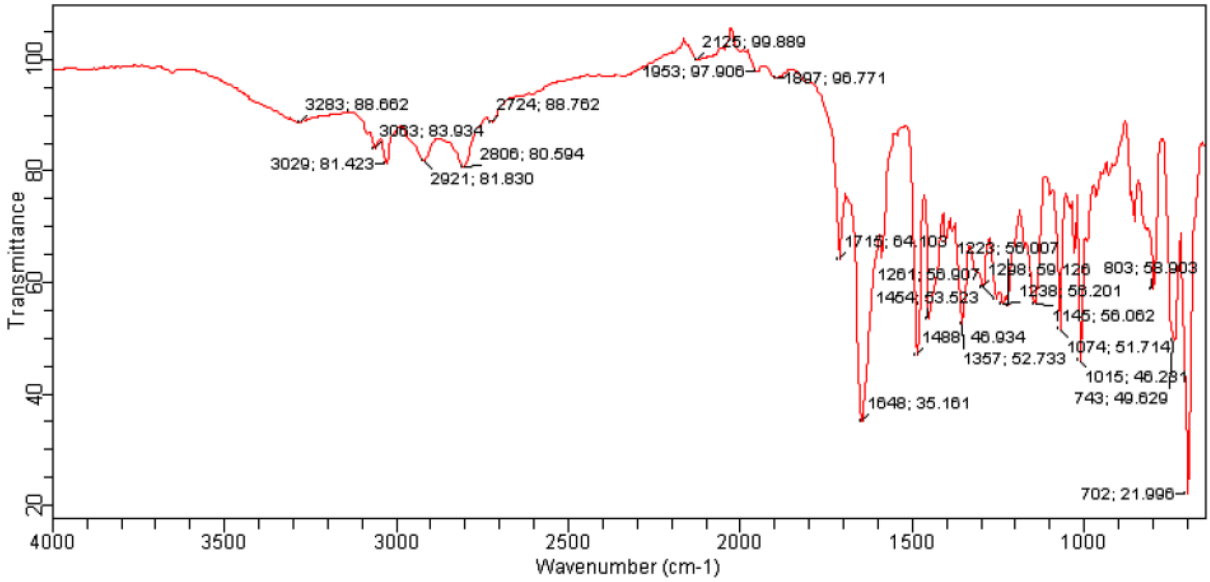
Compound **6k-** 1,4-dibenzyl-3-(4-bromophenyl)piperazin-2-one



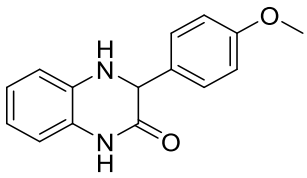


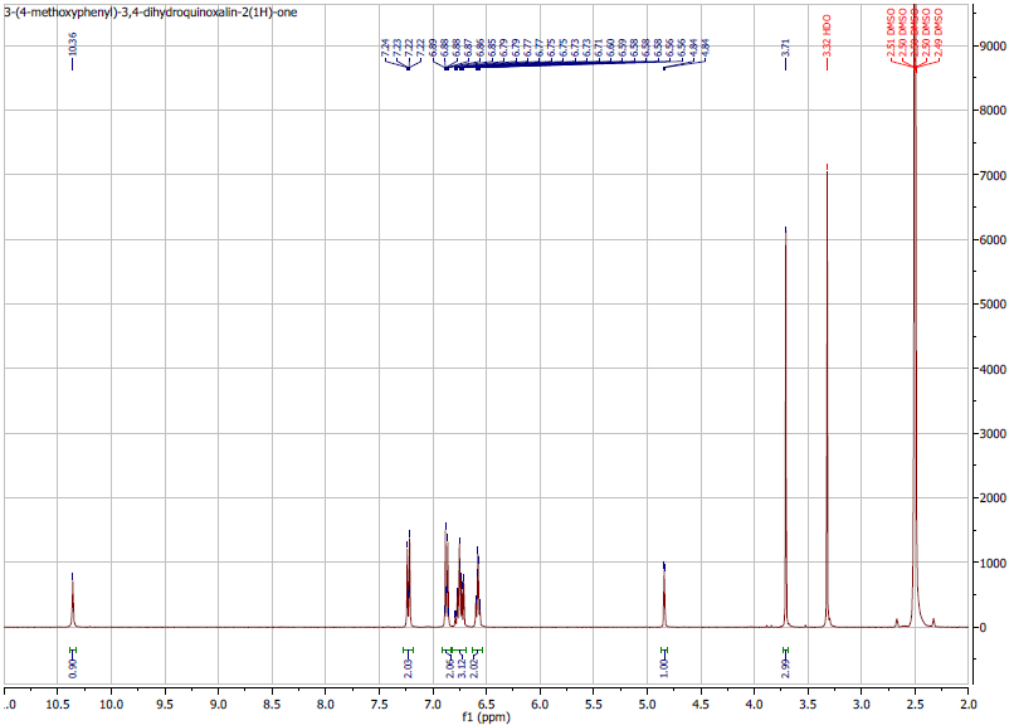


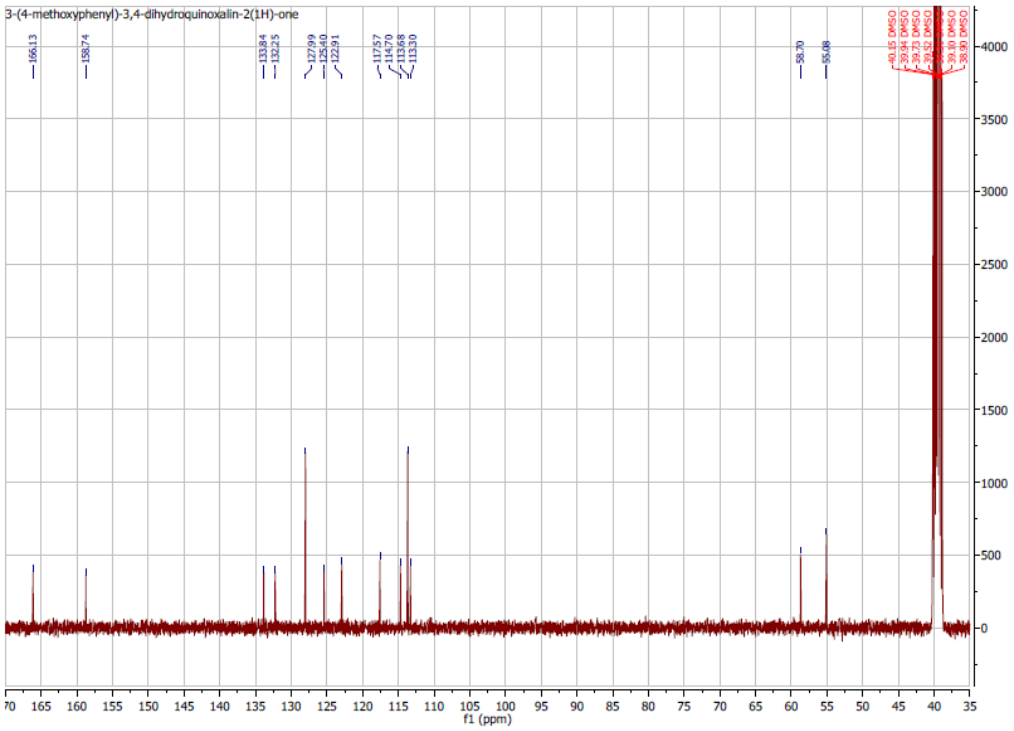

JHTK-02-035-2_f24 #1-5 RT: 0.01-0.13 AV: 5 NL: 1.14E7
T: FTMS + p ESI Full ms [200.00-800.00]
435.1073
C24 H24 O N2 Br = 435.1067
0.6838 mmu
437.1052
436.1105
438.1081
439.1115
Relative Abundance
m/z

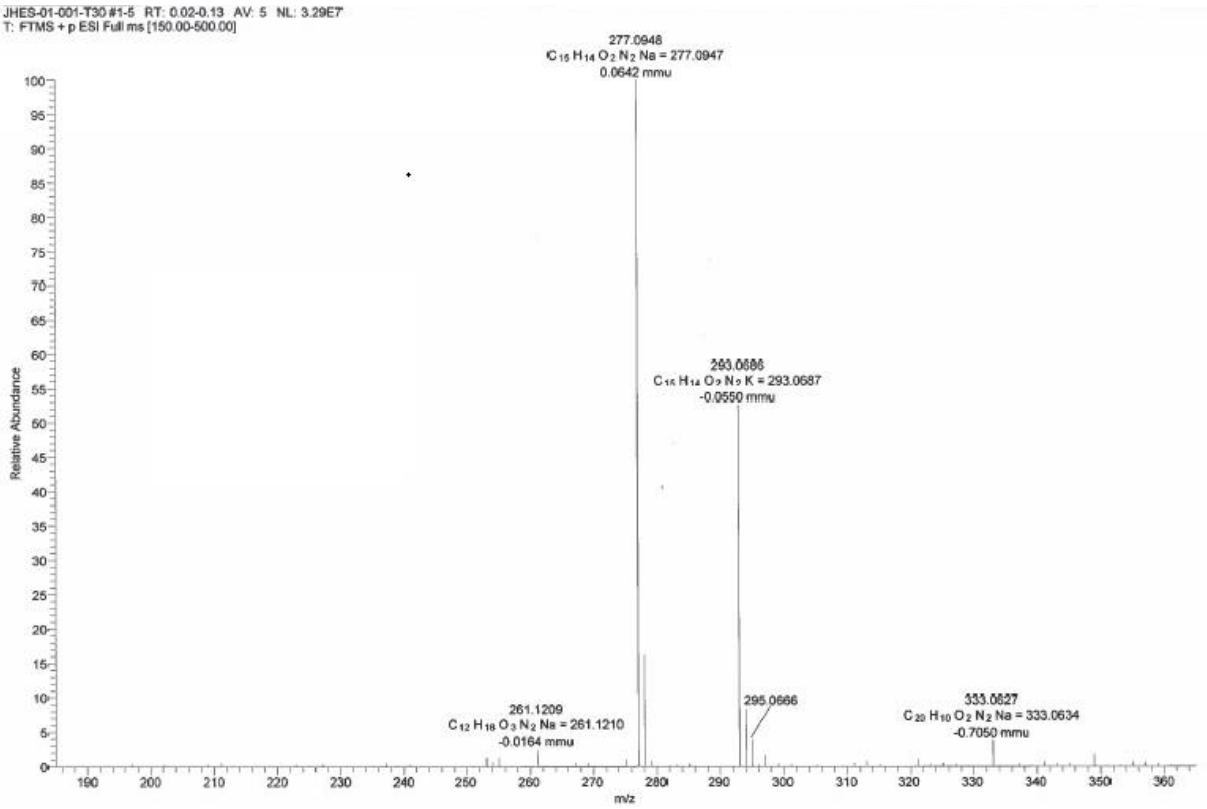

2125; 99.889
1953; 97.906
1897; 96.771
3283; 88.662
2724; 88.762
3063; 83.934
3029; 81.423
2806; 80.594
2921; 81.830
1715; 64.103
1223; 56.007
1261; 55.907
1298; 59.126
803; 58.903
1454; 53.523
1238; 55.201
1145; 56.062
1488; 46.934
1074; 51.714
1357; 52.733
1015; 46.231
743; 49.629
1648; 35.161
702; 21.996
Transmittance
Wavenumber (cm-1)

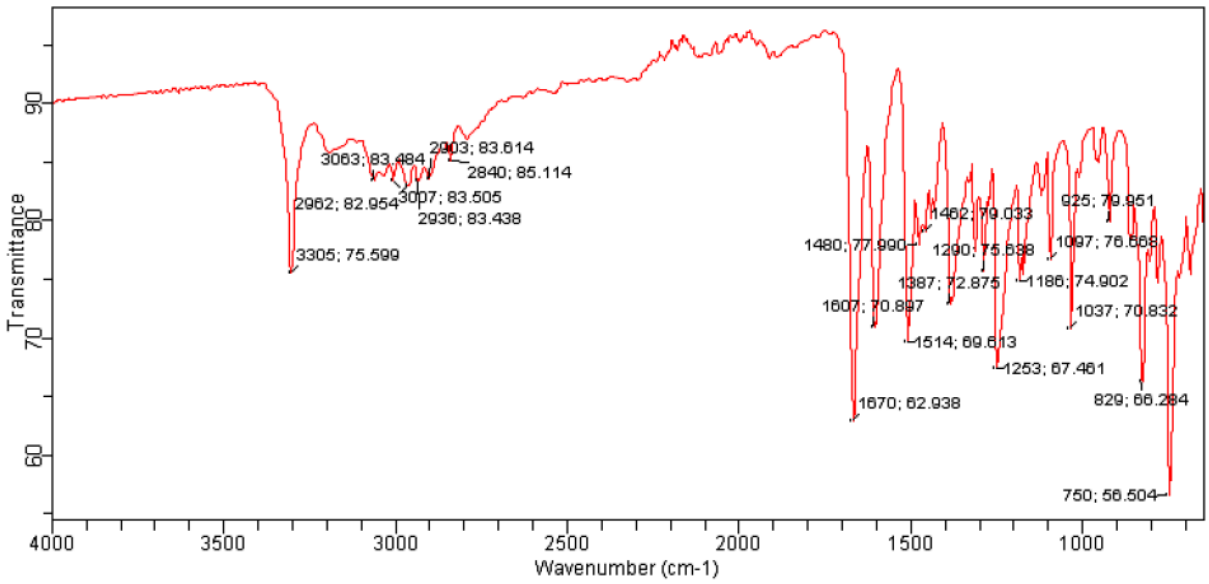
Compound **6l** - 3-(4-methoxyphenyl)-3,4-dihydroquinoxalin-2(1*H*)-one



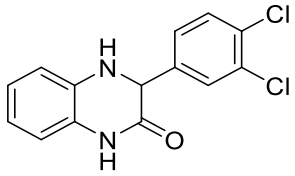


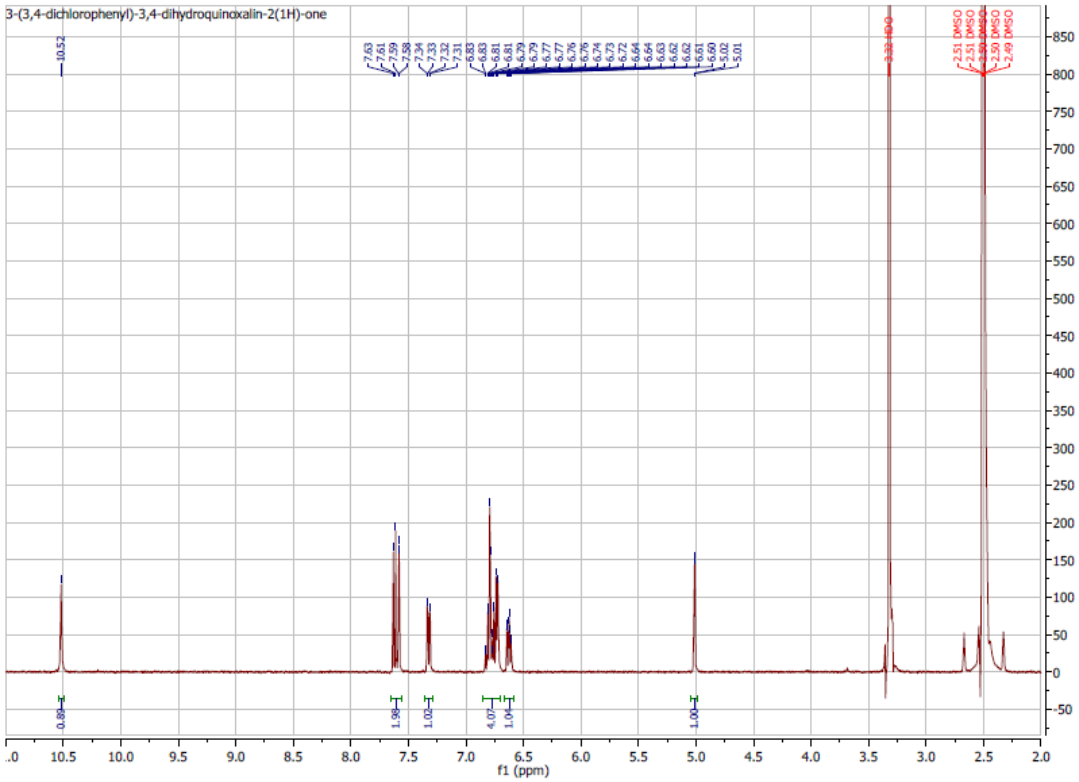


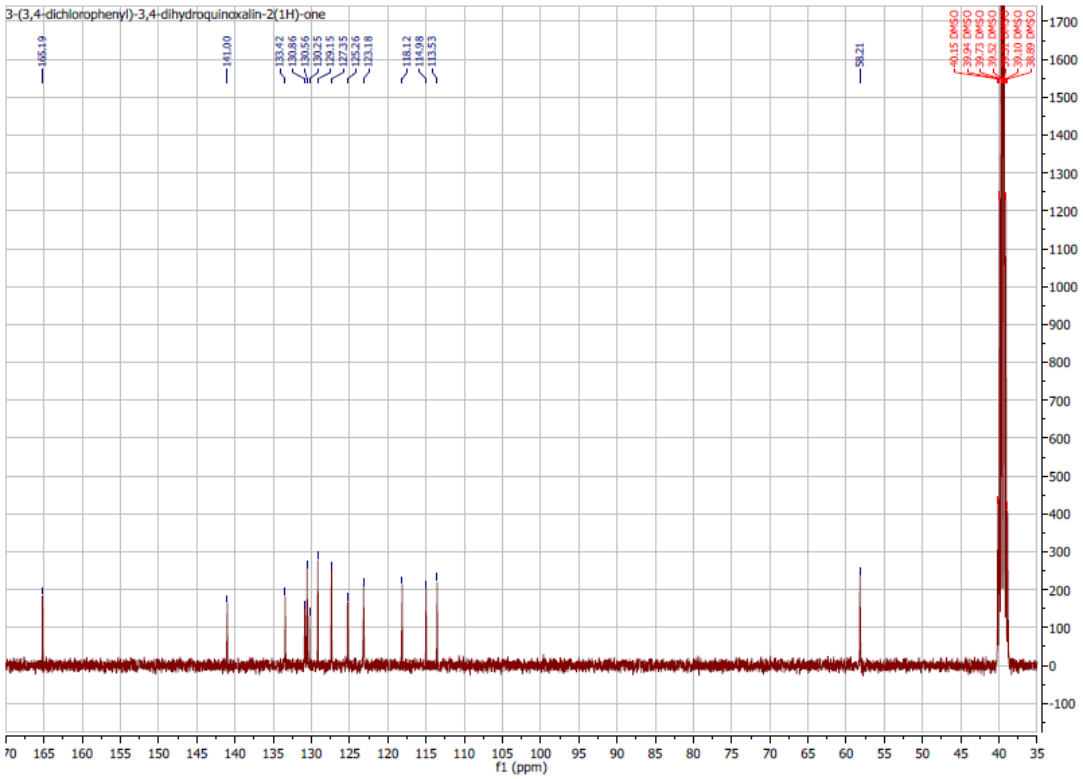

JHES-01-001-T30 #1-5 RT: 0.02-0.13 AV: 5 NL: 3.29E7
T: FTMS + p ESI Full ms [150.00-500.00]
277.0948
C15 H14 O2 N2 Na = 277.0947
0.0642 mmu
293.0686
C15 H14 O2 N2 K = 293.0687
-0.0550 mmu
261.1209
C12 H18 O3 N2 Na = 261.1210
-0.0164 mmu
295.0666
333.0627
C20 H10 O2 N2 Na = 333.0634
-0.7050 mmu
Relative Abundance
m/z

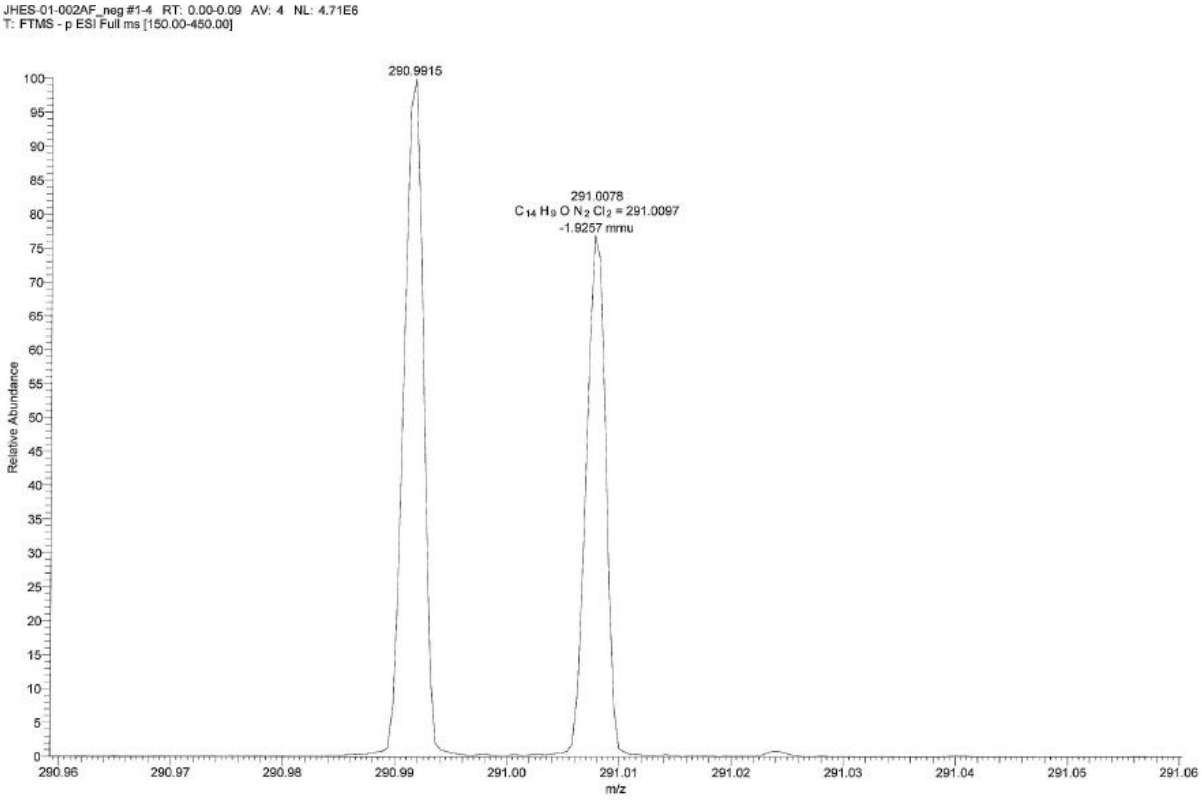

Transmittance
Wavenumber (cm-1)
3063; 83.484
2962; 82.954
3007; 83.505
2936; 83.438
2903; 83.614
2840; 85.114
3305; 75.599
1480; 77.990
1462; 79.033
1290; 75.638
1387; 72.875
1607; 70.897
1514; 69.613
1253; 67.461
1186; 74.902
1097; 76.668
925; 79.951
1037; 70.832
1670; 62.938
829; 66.284
750; 56.504

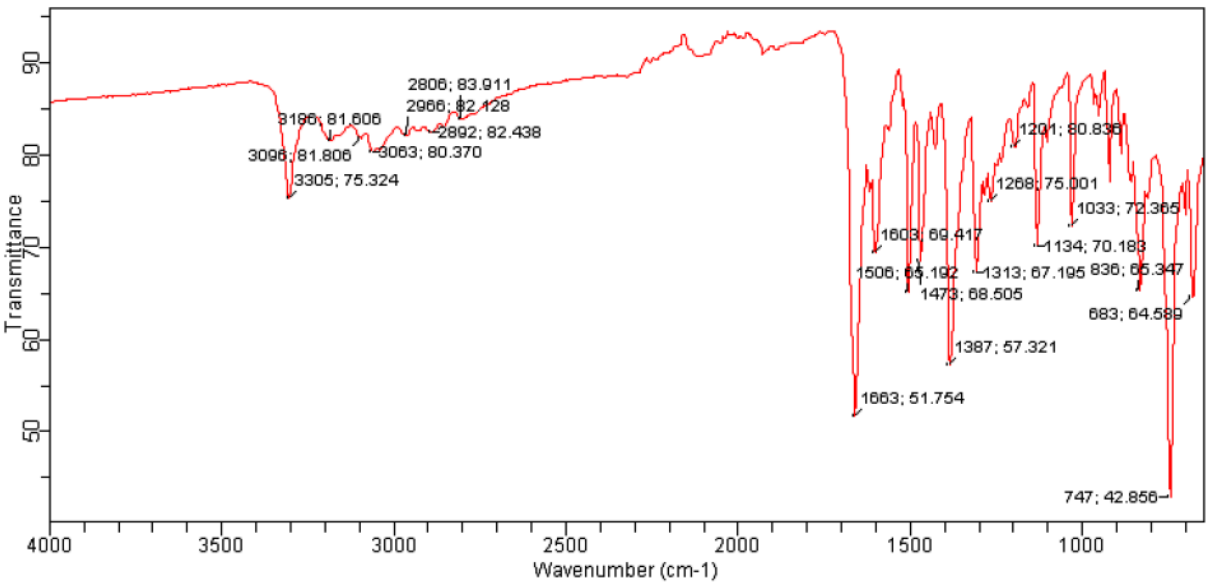
Compound **6m** - 3-(3,4-dichlorophenyl)-3,4-dihydroquinoxalin-2(1*H*)-one



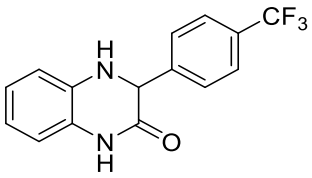


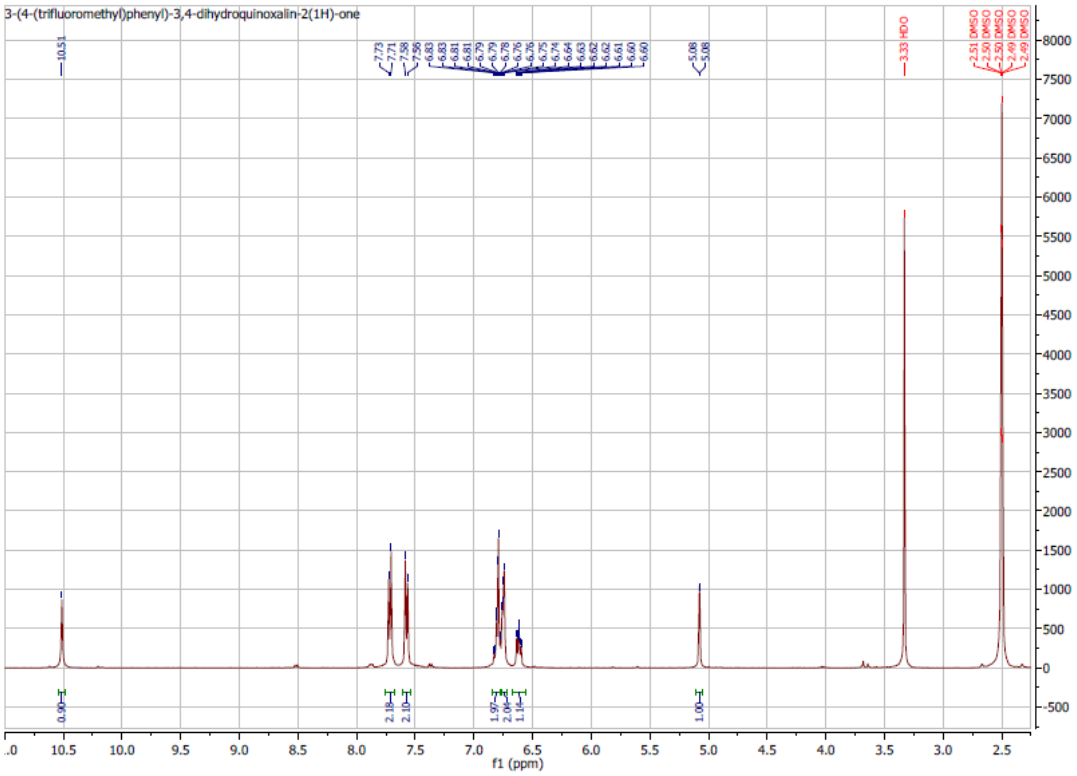


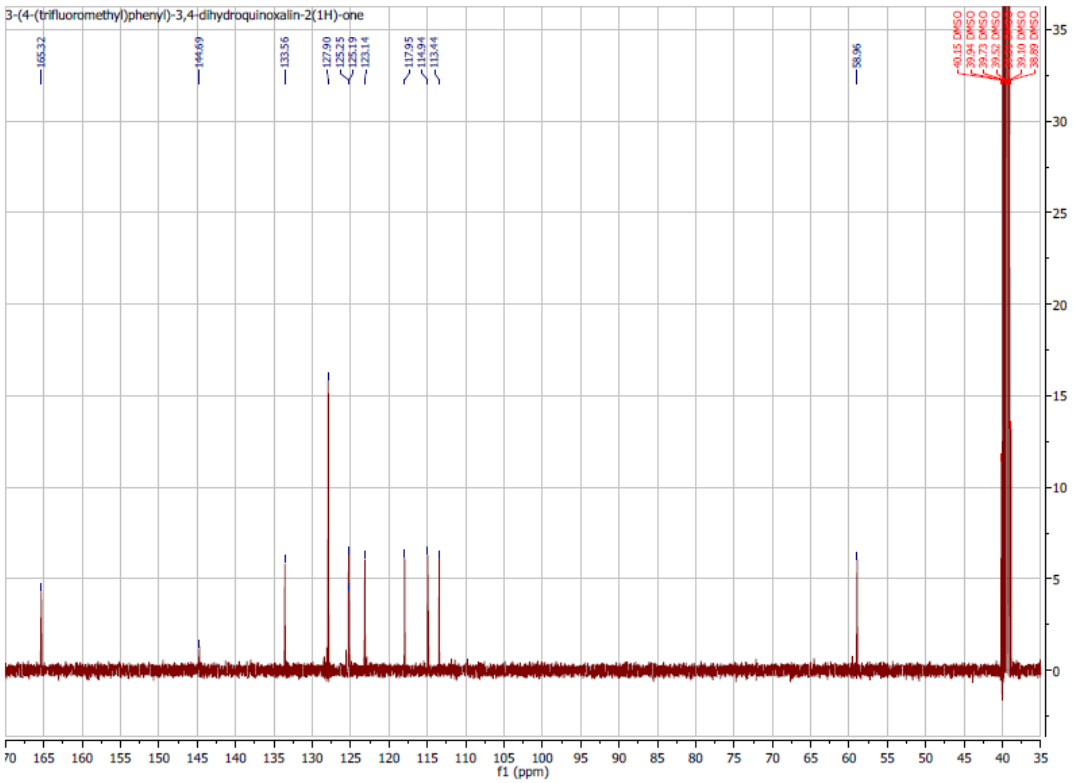

JHES-01-002AF_neg #1-4 RT: 0.00-0.09 AV: 4 NL: 4.71E6
T: FTMS - p ESI Full ms [150.00-450.00]
290.9915
291.0078
C14 H9 O N2 Cl2 = 291.0097
-1.9257 mmu
Relative Abundance
m/z

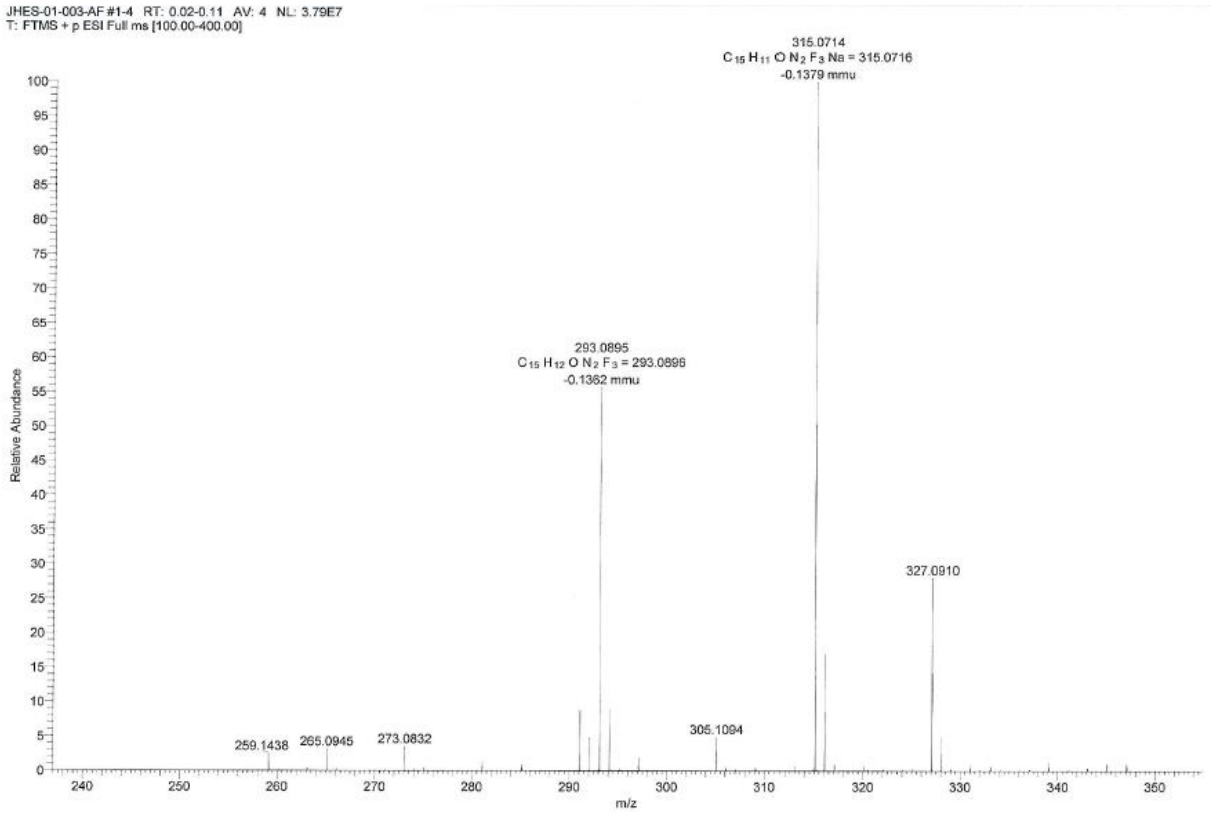

Transmittance
Wavenumber (cm-1)
2806; 83.911
2966; 82.128
3186; 81.606
2892; 82.438
3096; 81.806
3063; 80.370
3305; 75.324
1201; 80.836
1268; 75.001
1033; 72.365
1603; 69.417
1134; 70.183
1506; 65.192
1313; 67.195
836; 65.347
1473; 68.505
683; 64.589
1387; 57.321
1663; 51.754
747; 42.856

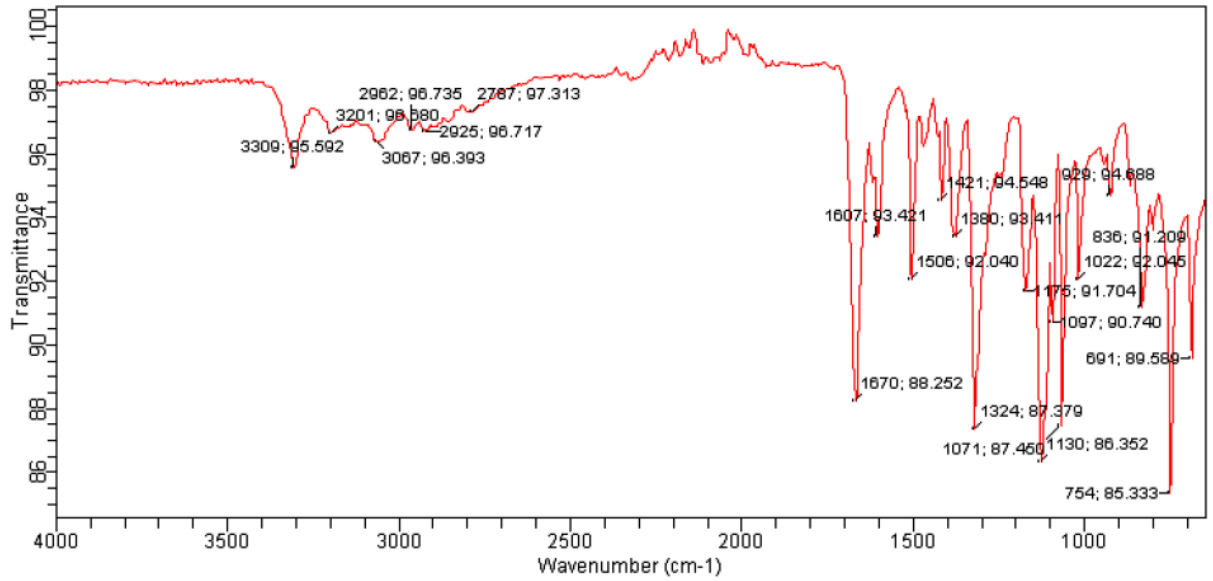
Compound **6n** - 3-(4-(trifluoromethyl)phenyl)-3,4-dihydroquinoxalin-2(1*H*)-one



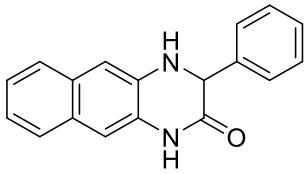


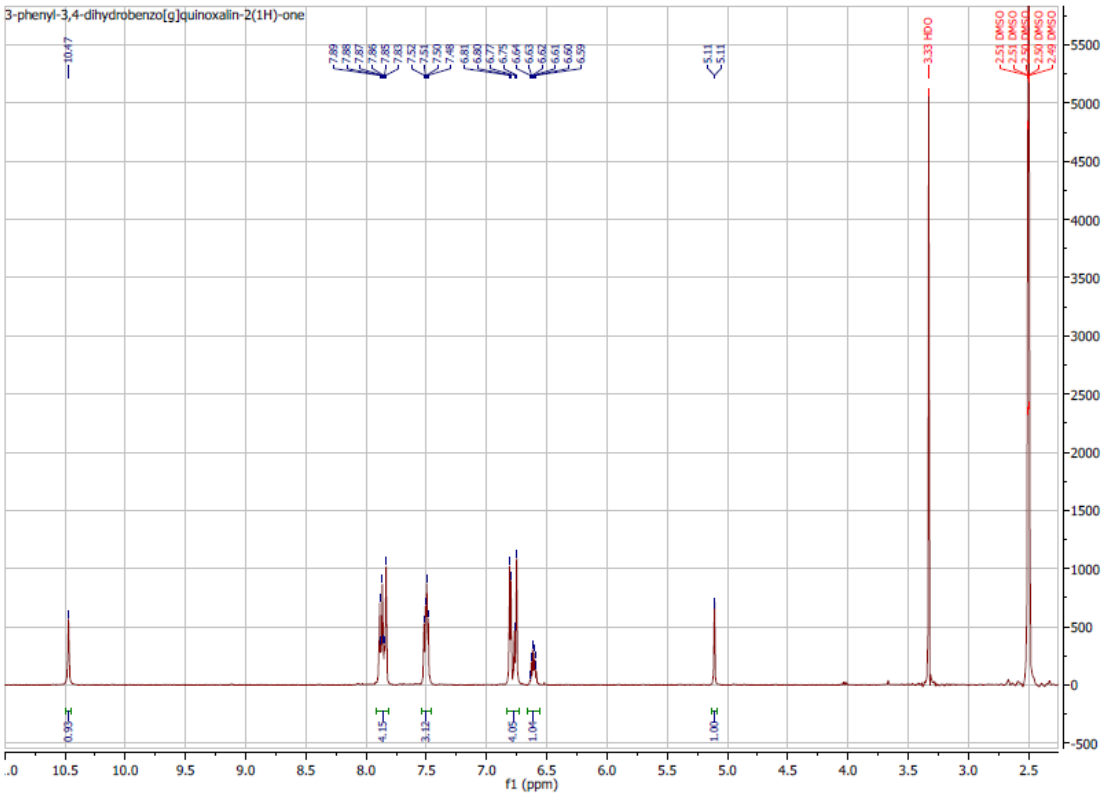


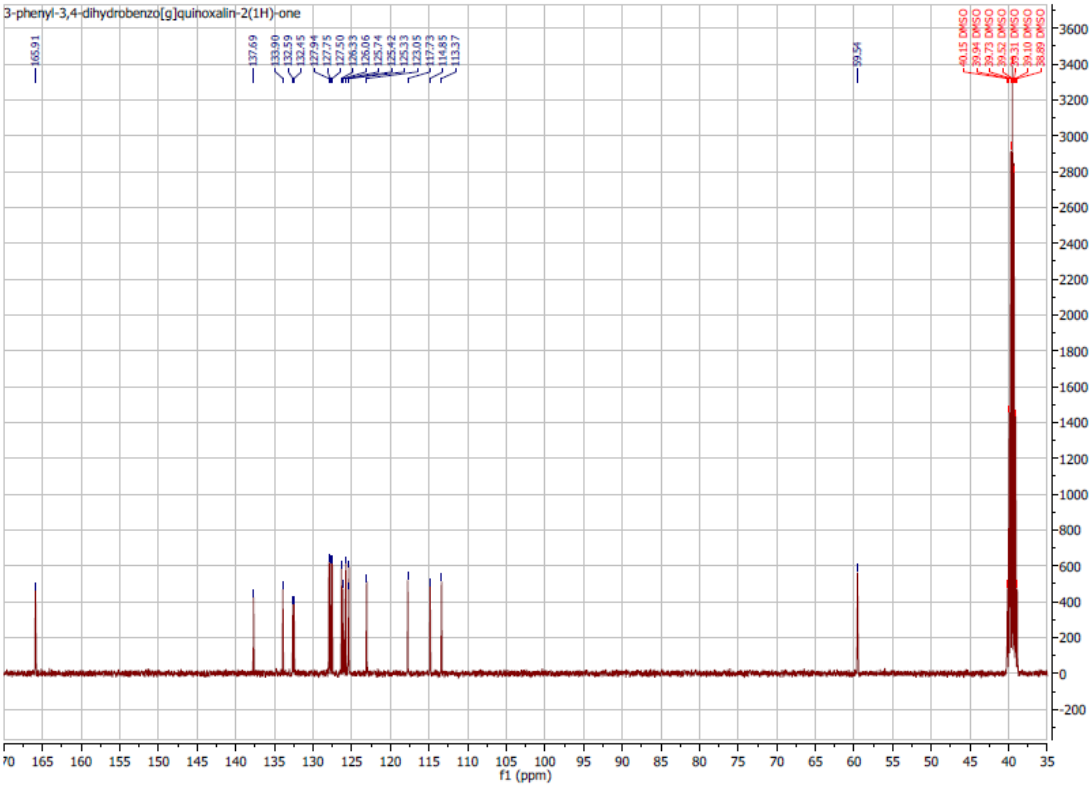

JHES-01-003-AF #1-4 RT: 0.02-0.11 AV: 4 NL: 3.79E7
T: FTMS + p ESI Full ms [100.00-400.00]
315.0714
C15 H11 O N2 F3 Na = 315.0716
-0.1379 mmu
293.0895
C15 H12 O N2 F3 = 293.0898
-0.1362 mmu
327.0910
305.1094
259.1438
265.0945
273.0832
Relative Abundance
m/z

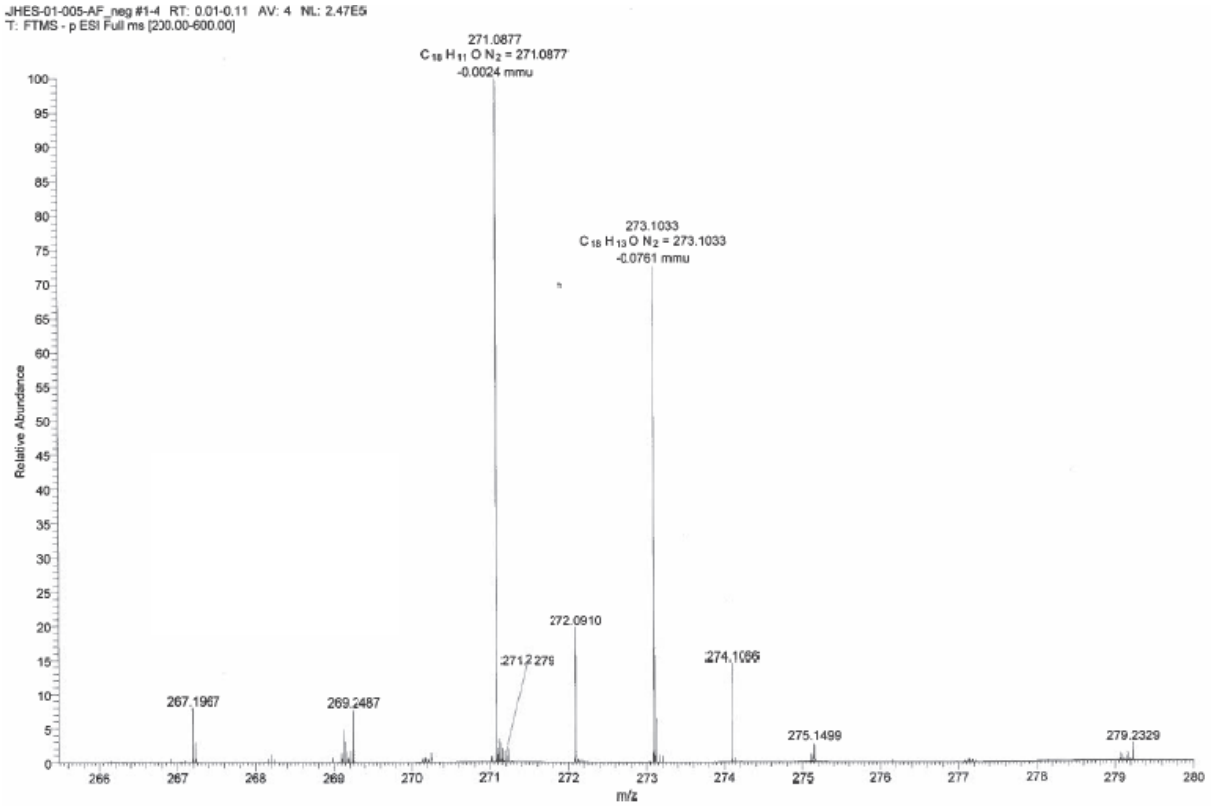

2962; 96.735
2787; 97.313
3201; 96.580
2925; 96.717
3309; 95.592
3067; 96.393
1421; 94.548
929; 94.688
1607; 93.421
1380; 93.411
836; 91.209
1506; 92.040
1022; 92.045
1175; 91.704
1097; 90.740
691; 89.589
1670; 88.252
1324; 87.379
1071; 87.450
1130; 86.352
754; 85.333
Transmittance
Wavenumber (cm-1)

Compound **6o** - 3-phenyl-3,4-dihydrobenzo[*g*]quinoxalin-2(1*H*)-one

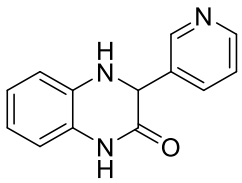


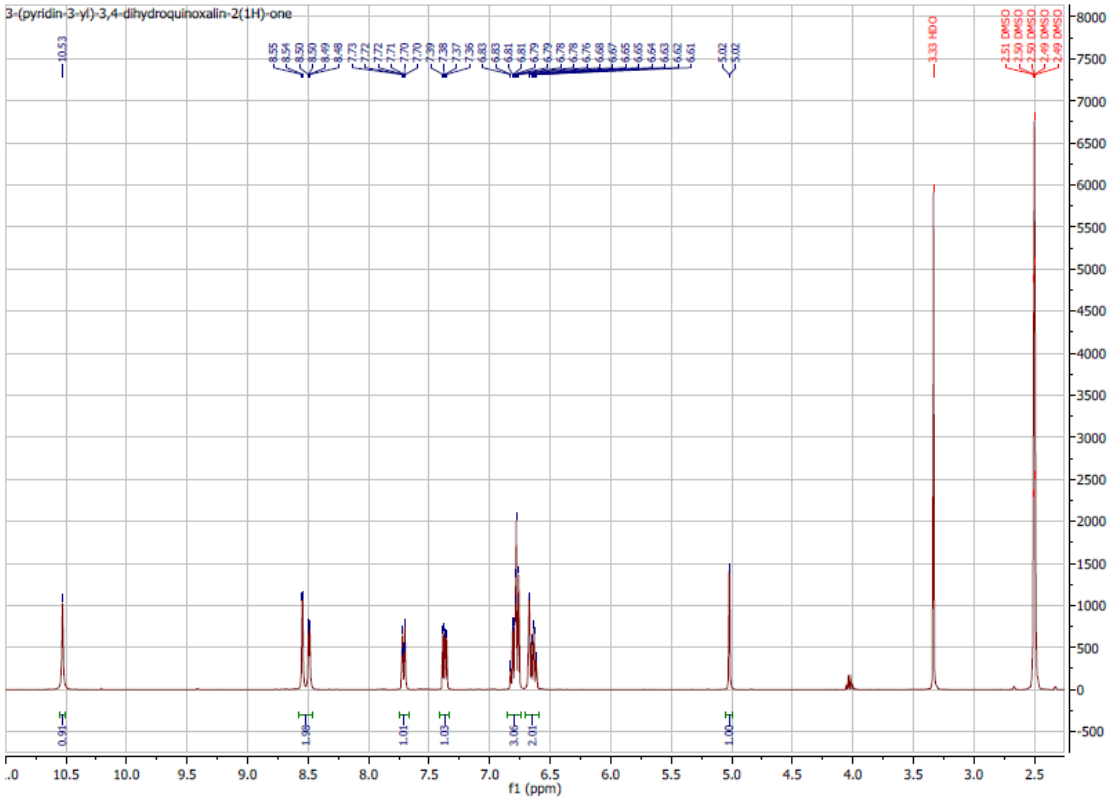


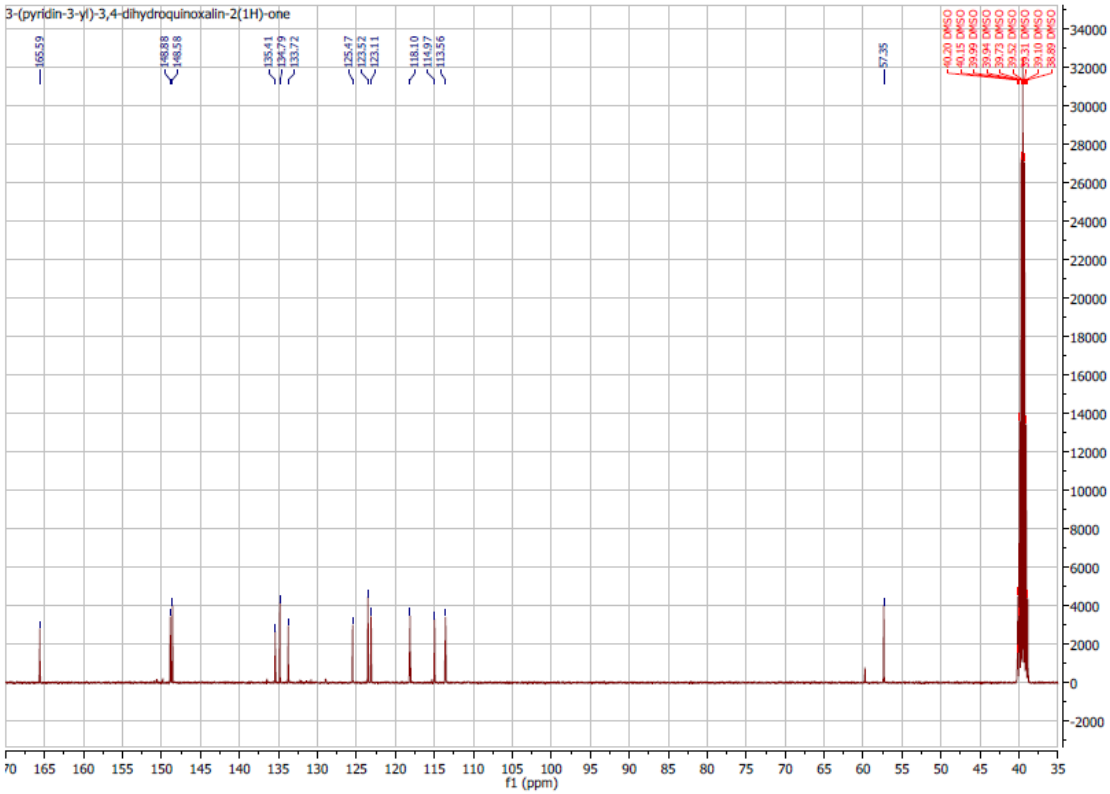


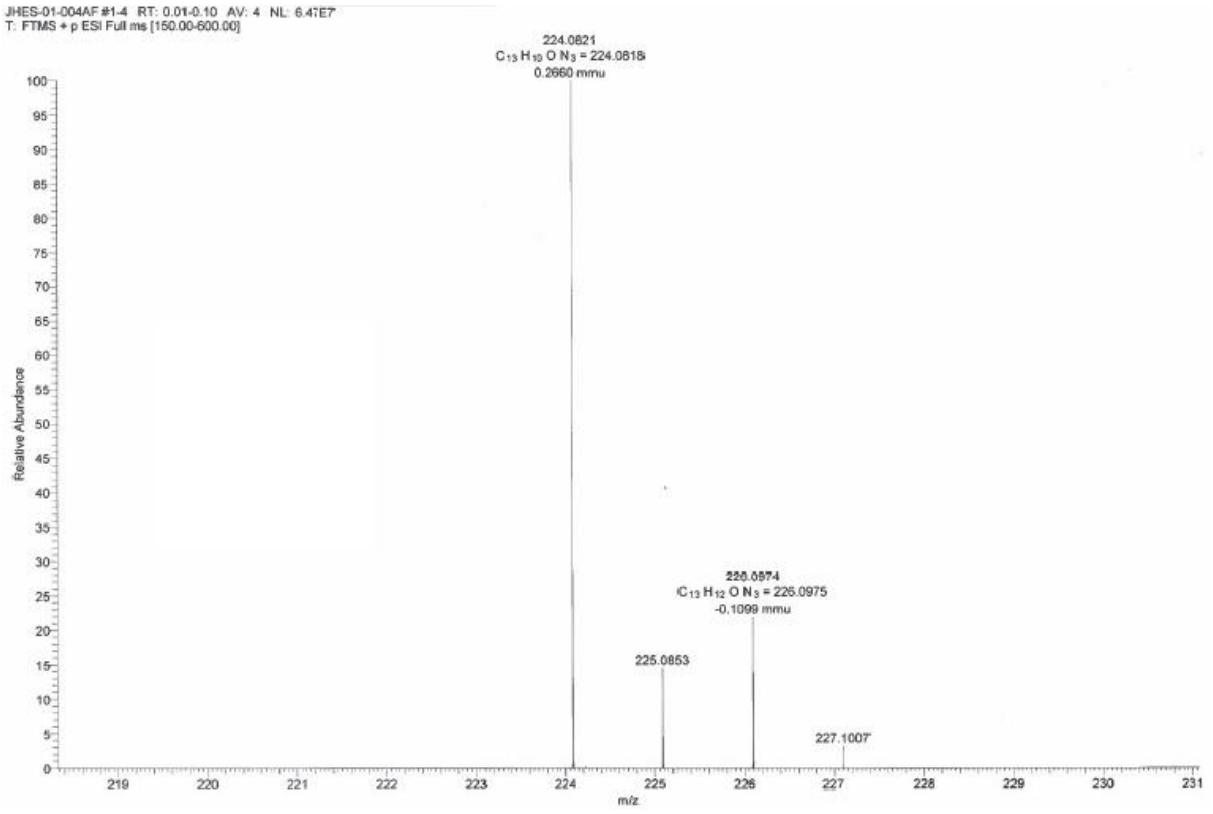

JHES-01-005-AF_neg #1-4 RT: 0.01-0.11 AV: 4 NL: 2.47E5
T: FTMS - p ESI Full ms [200.00-600.00]
271.0877
C18 H11 O N2 = 271.0877
-0.0024 mmu
273.1033
C18 H13 O N2 = 273.1033
-0.0761 mmu
272.0910
271.2279
274.1086
267.1967
269.2487
275.1499
279.2329
Relative Abundance
m/z

Compound **6p** - 3-(pyridin-3-yl)-3,4-dihydroquinoxalin-2(1*H*)-one

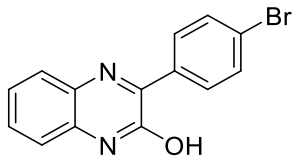


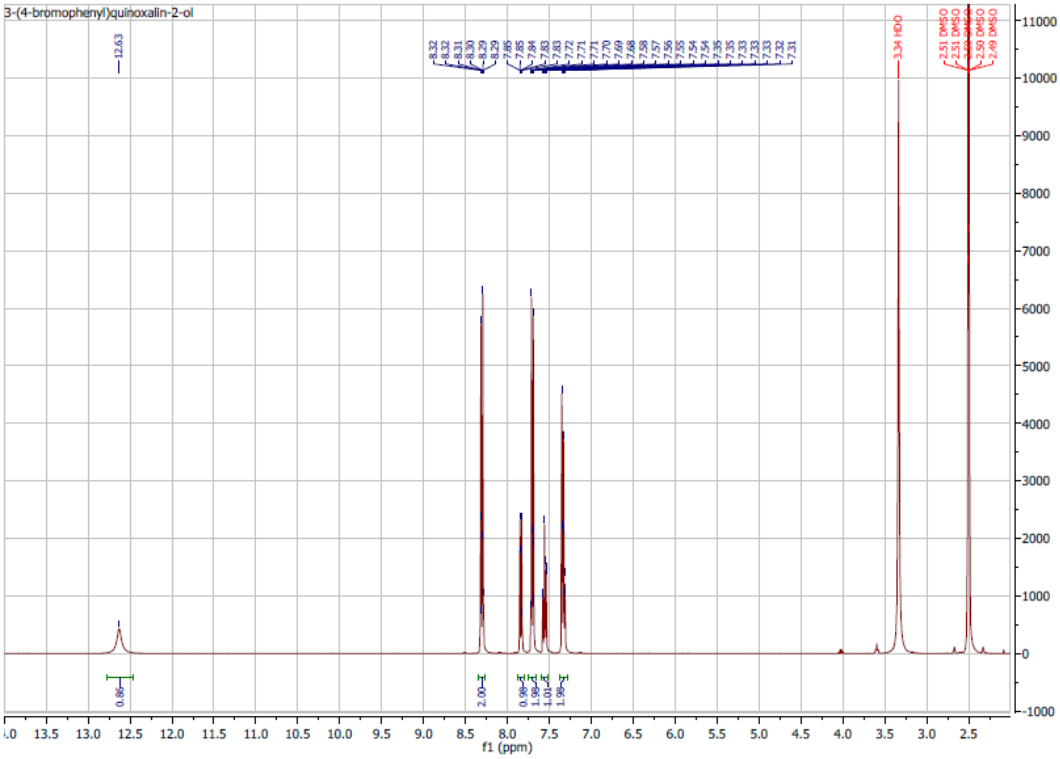


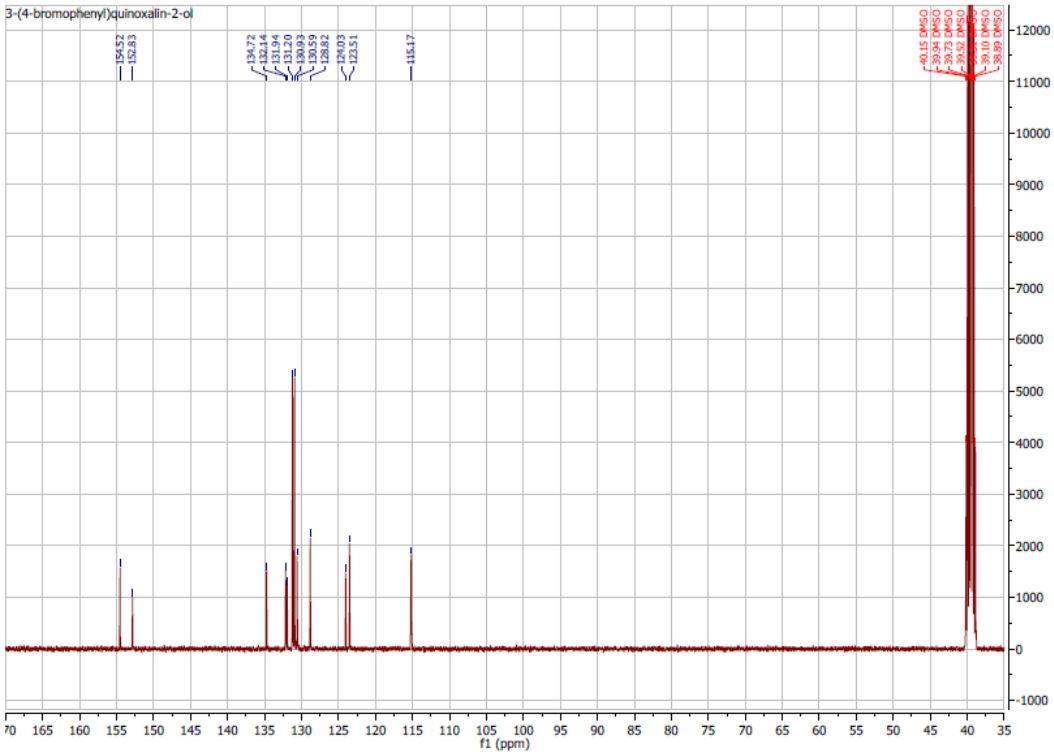


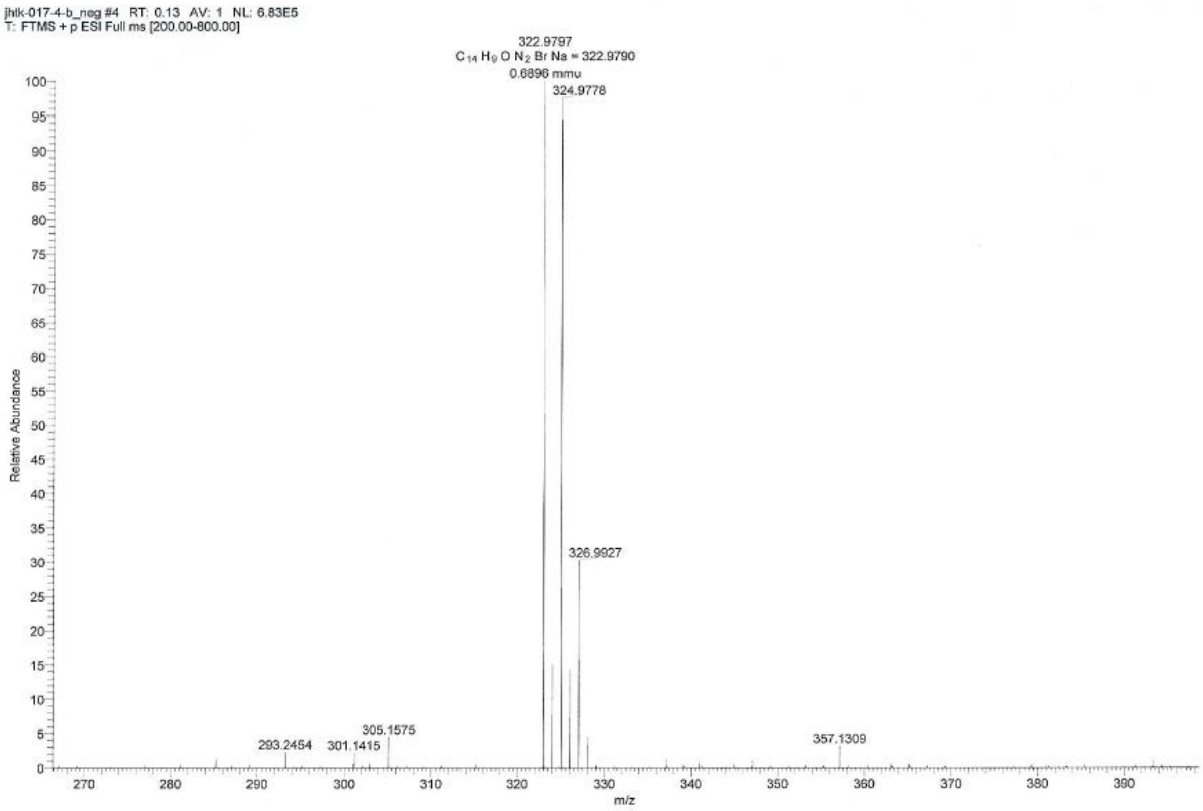

JHES-01-004AF #1-4 RT: 0.01-0.10 AV: 4 NL: 6.47E7
T: FTMS + p ESI Full ms [150.00-600.00]
224.0821
C13 H10 O N3 = 224.0818
0.2660 mmu
226.0974
C13 H12 O N3 = 226.0975
-0.1099 mmu
225.0853
227.1007
Relative Abundance
m/z

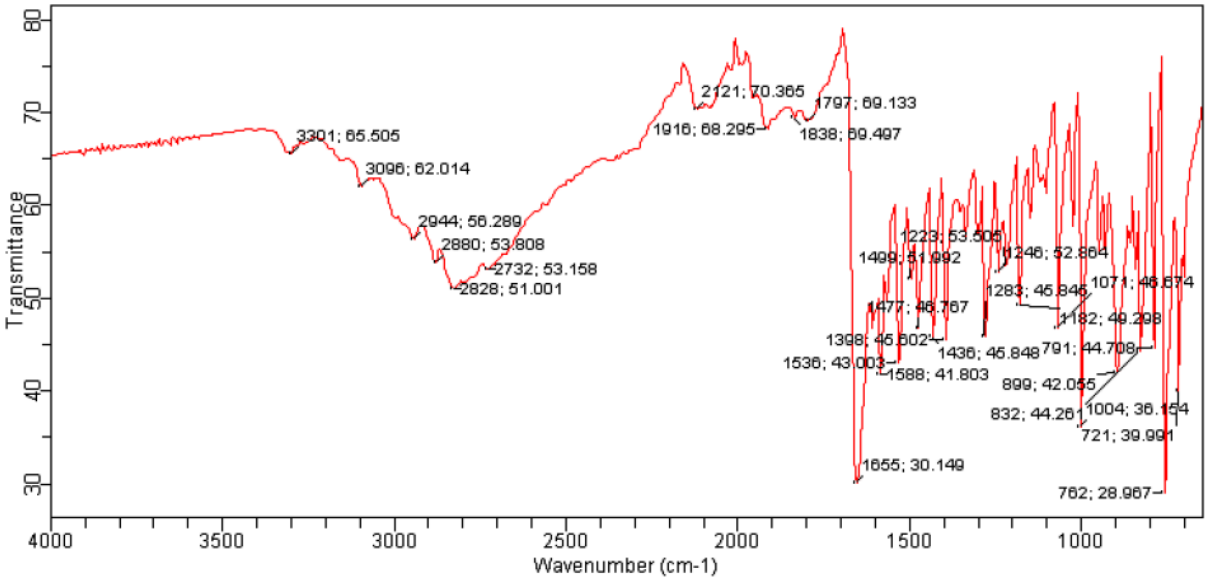
Compound **7a** - 3-(4-bromophenyl)quinoxalin-2-o



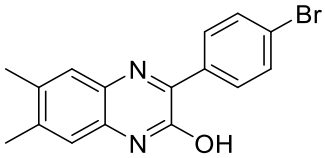


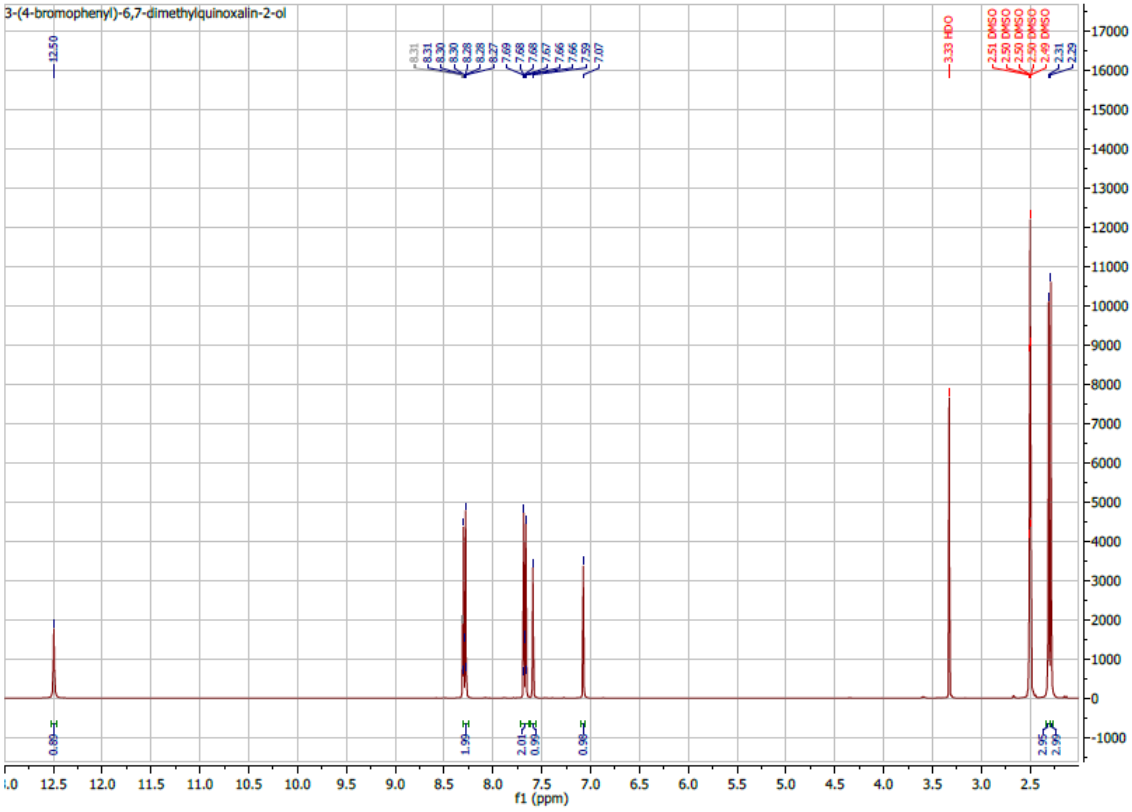


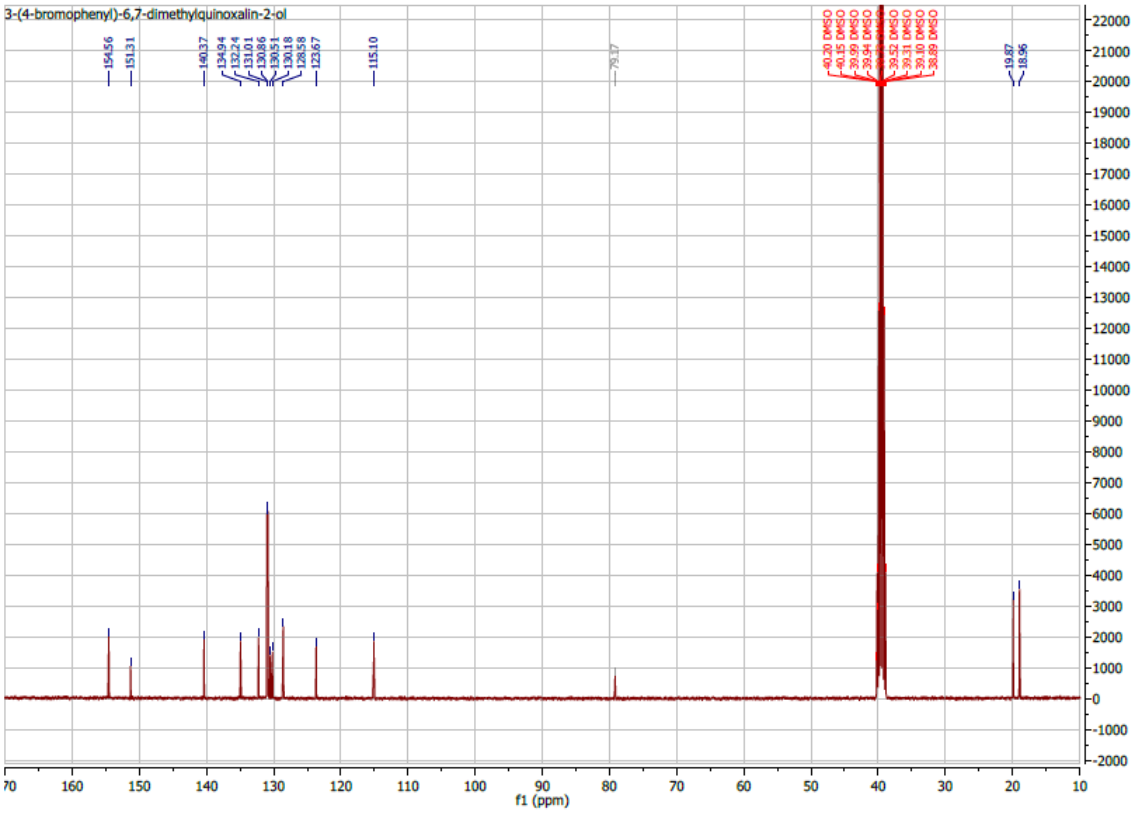

jhtk-017-4-b_neg #4 RT: 0.13 AV: 1 NL: 6.83E5
T: FTMS + p ESI Full ms [200.00-800.00]
322.9797
C14 H9 O N2 Br Na = 322.9790
0.6896 mmu
324.9778
326.9927
305.1575
293.2454
301.1415
357.1309
Relative Abundance
m/z

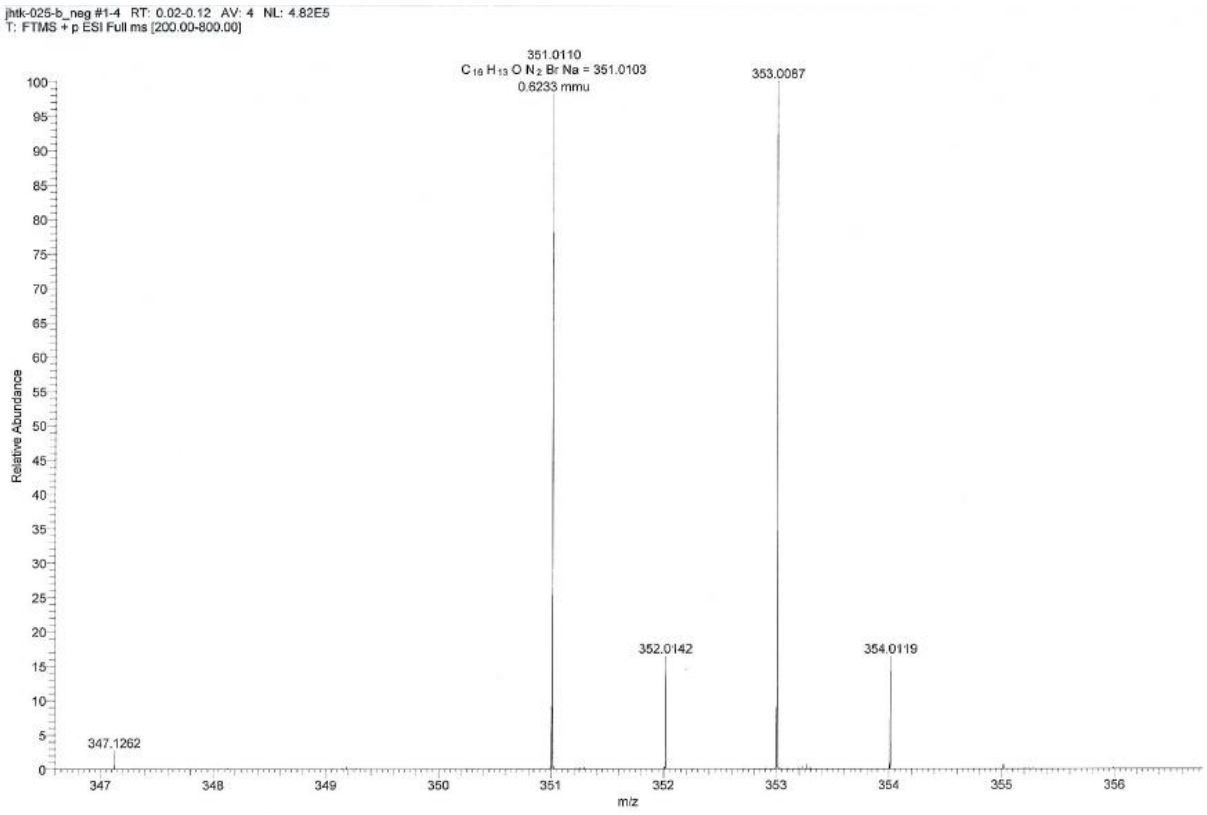

3301; 65.505
3096; 62.014
2944; 56.289
2880; 53.808
2732; 53.158
2828; 51.001
2121; 70.365
1916; 68.295
1797; 69.133
1838; 69.497
1655; 30.149
1588; 41.803
1536; 43.003
1436; 45.848
1398; 45.602
1477; 46.767
1499; 51.992
1223; 53.505
1246; 52.864
1283; 45.846
1071; 46.574
1182; 49.298
791; 44.708
899; 42.055
832; 44.261
1004; 36.154
721; 39.991
762; 28.967
Transmittance
Wavenumber (cm-1)

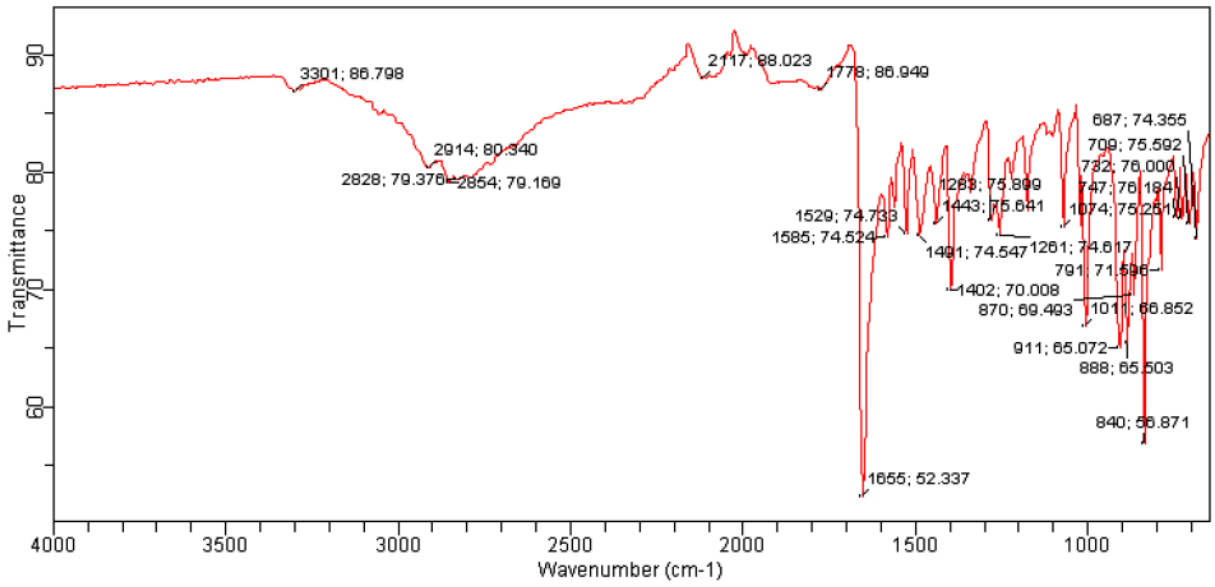
Compound **7d** - 3-(4-bromophenyl)-6,7-dimethylquinoxalin-2-ol



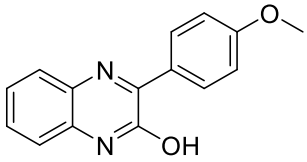


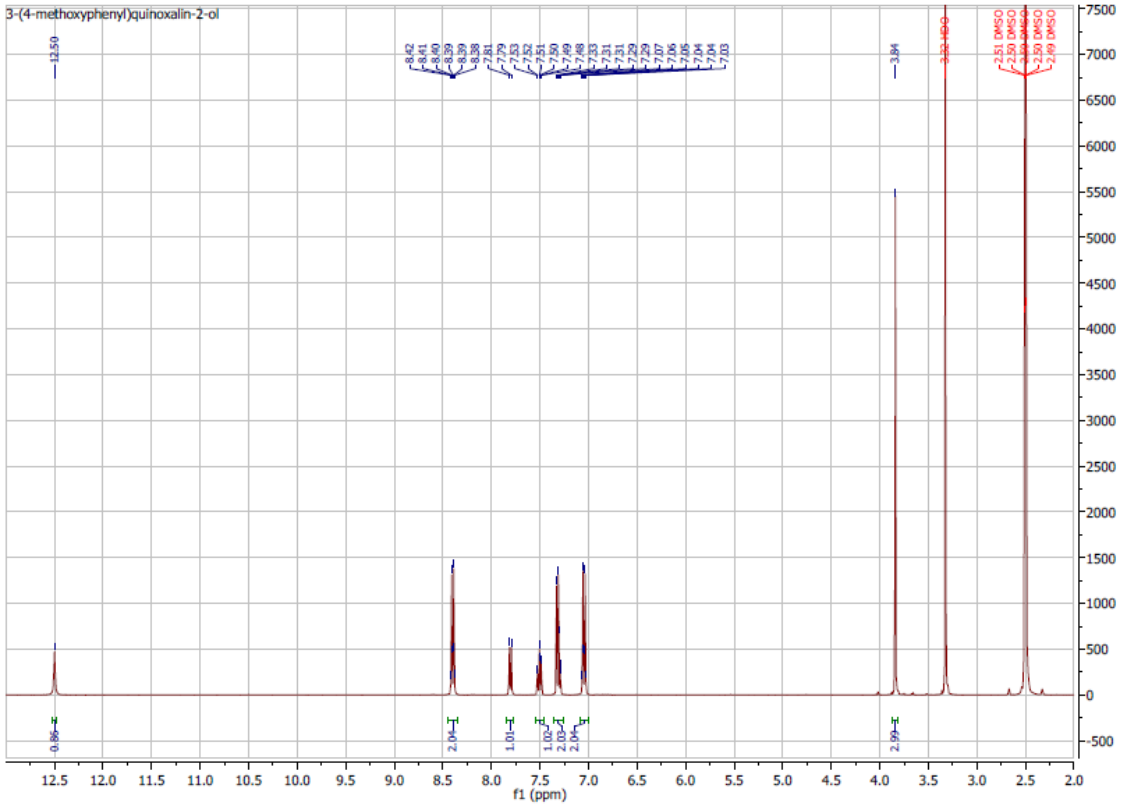


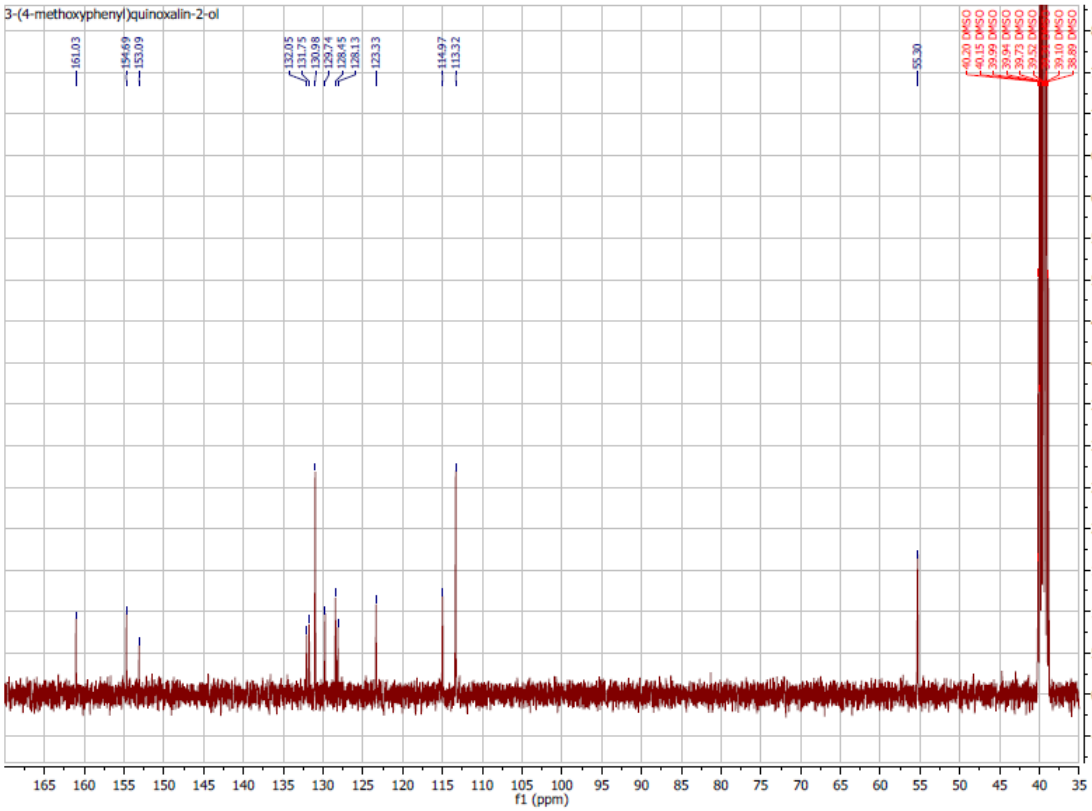

jhtk-025-b_neg #1-4 RT: 0.02-0.12 AV: 4 NL: 4.82E5
T: FTMS + p ESI Full ms [200.00-800.00]
351.0110
C16 H13 O N2 Br Na = 351.0103
0.6233 mmu
353.0087
352.0142
354.0119
347.1262
Relative Abundance
m/z

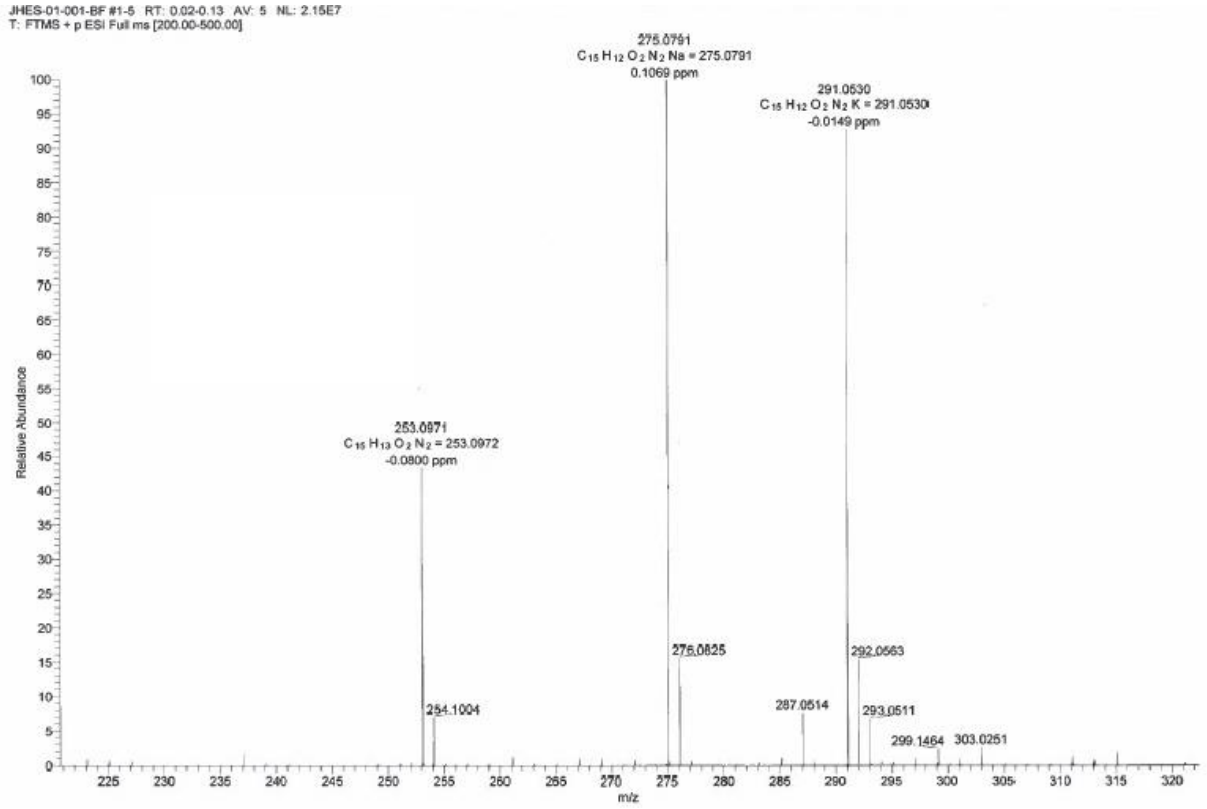

3301; 86.798
2914; 80.340
2828; 79.376
2854; 79.169
2117; 88.023
1778; 86.949
1529; 74.733
1585; 74.524
1491; 74.547
1283; 75.899
1443; 75.641
1261; 74.617
1402; 70.008
870; 69.493
911; 65.072
1655; 52.337
687; 74.355
709; 75.592
732; 76.000
747; 76.194
1074; 75.251
791; 71.596
1011; 66.852
888; 65.503
840; 66.871
Transmittance
Wavenumber (cm-1)

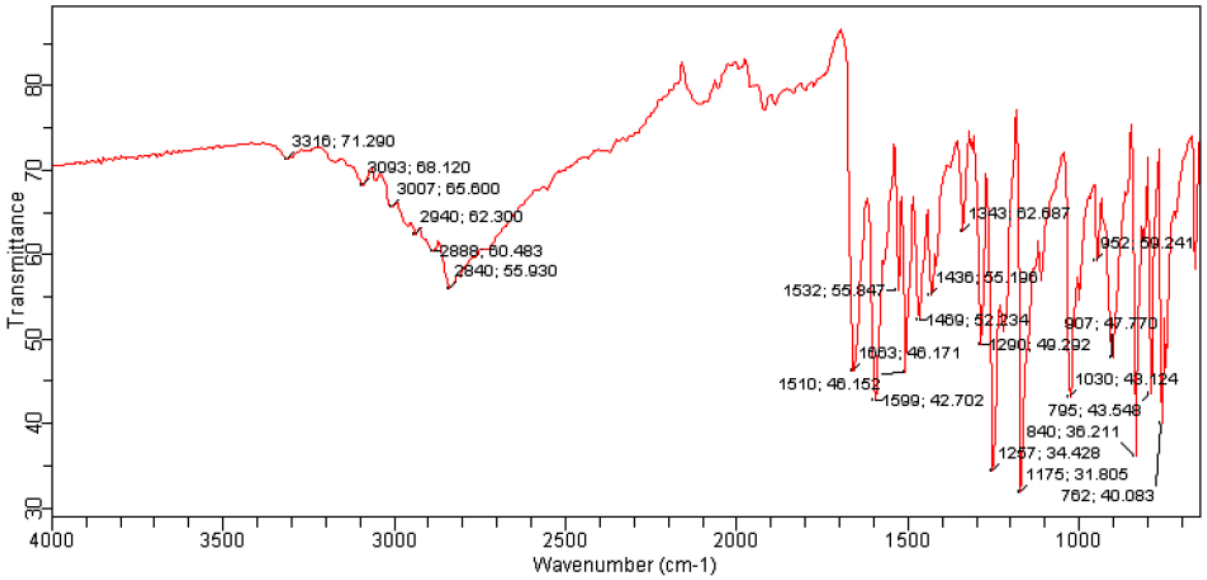
Compound **7l** - 3-(4-methoxyphenyl)quinoxalin-2-ol



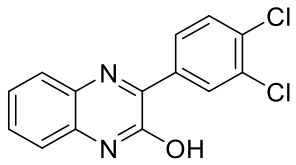


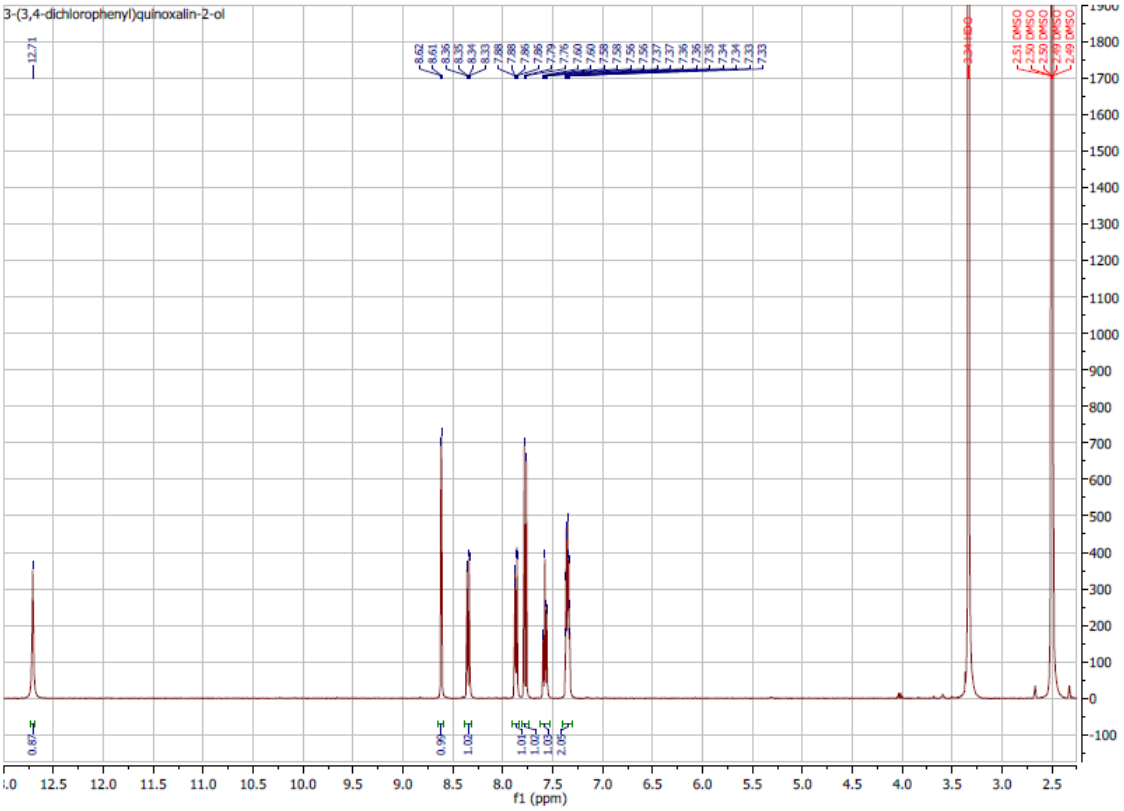


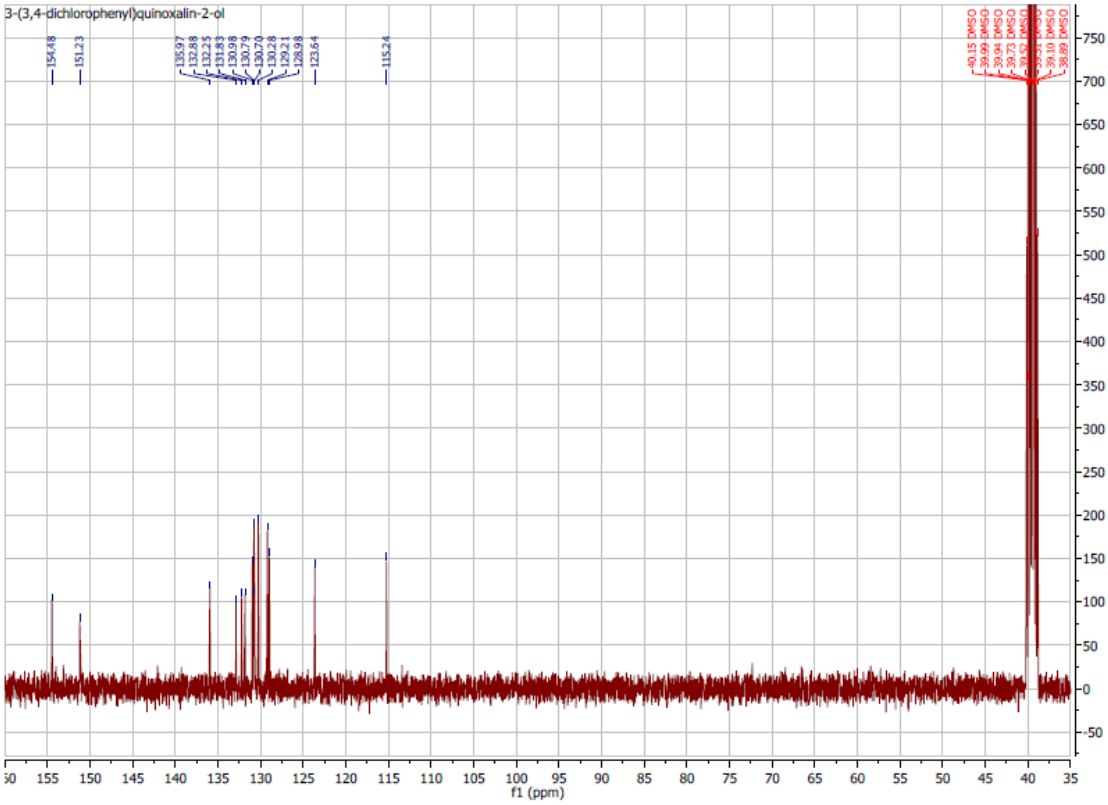

JHES-01-001-BF #1-5 RT: 0.02-0.13 AV: 5 NL: 2.15E7
T: FTMS + p ESI Full ms [200.00-500.00]
275.0791
C15 H12 O2 N2 Na = 275.0791
0.1069 ppm
291.0530
C15 H12 O2 N2 K = 291.0530
-0.0149 ppm
253.0871
C15 H13 O2 N2 = 253.0972
-0.0800 ppm
276.0825
292.0563
254.1004
287.0514
293.0511
299.1464
303.0251
Relative Abundance
m/z

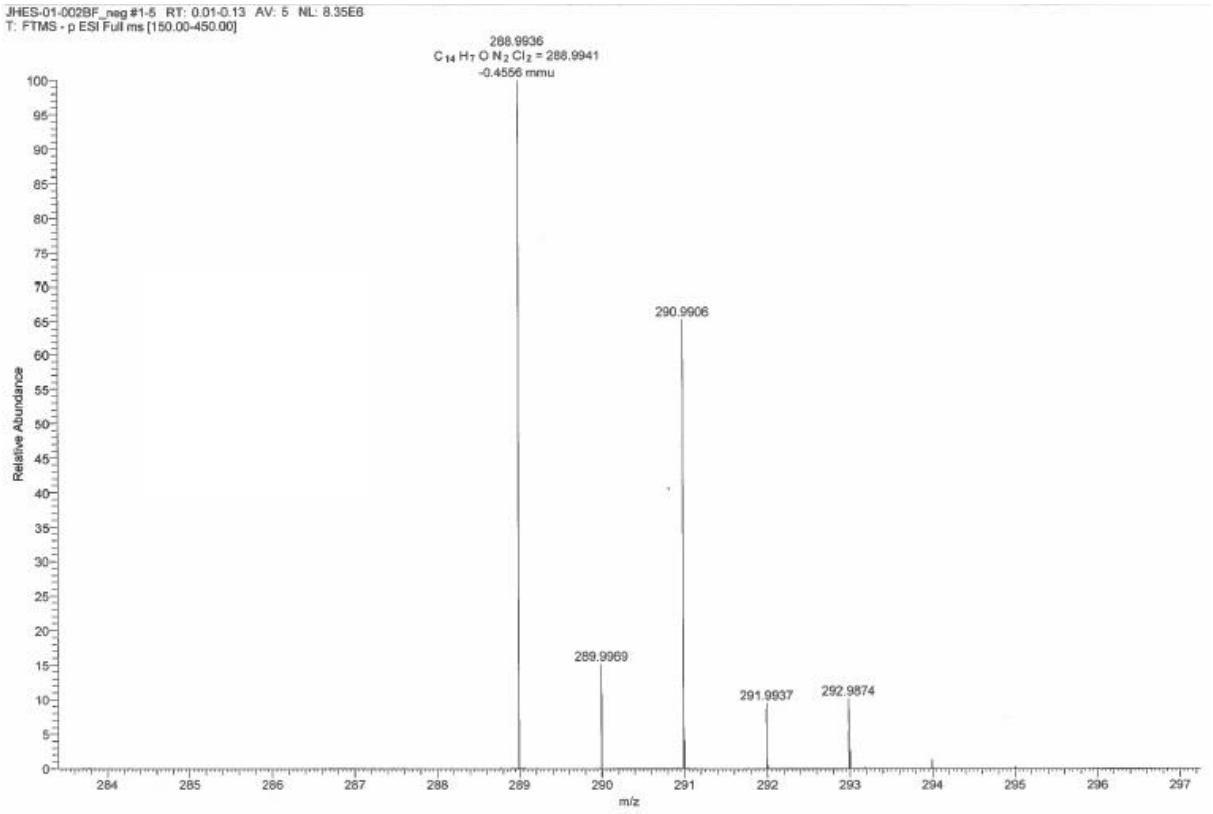

3316; 71.290
3093; 68.120
3007; 65.600
2940; 62.300
2888; 60.483
2840; 55.930
1532; 55.847
1436; 55.196
1343; 52.687
952; 50.241
1469; 52.234
907; 47.770
1290; 49.292
1663; 46.171
1510; 46.152
1599; 42.702
1030; 43.124
795; 43.548
840; 36.211
1257; 34.428
1175; 31.805
762; 40.083
Transmittance
Wavenumber (cm-1)

Compound **7m** - 3-(3,4-dichlorophenyl)quinoxalin-2-ol





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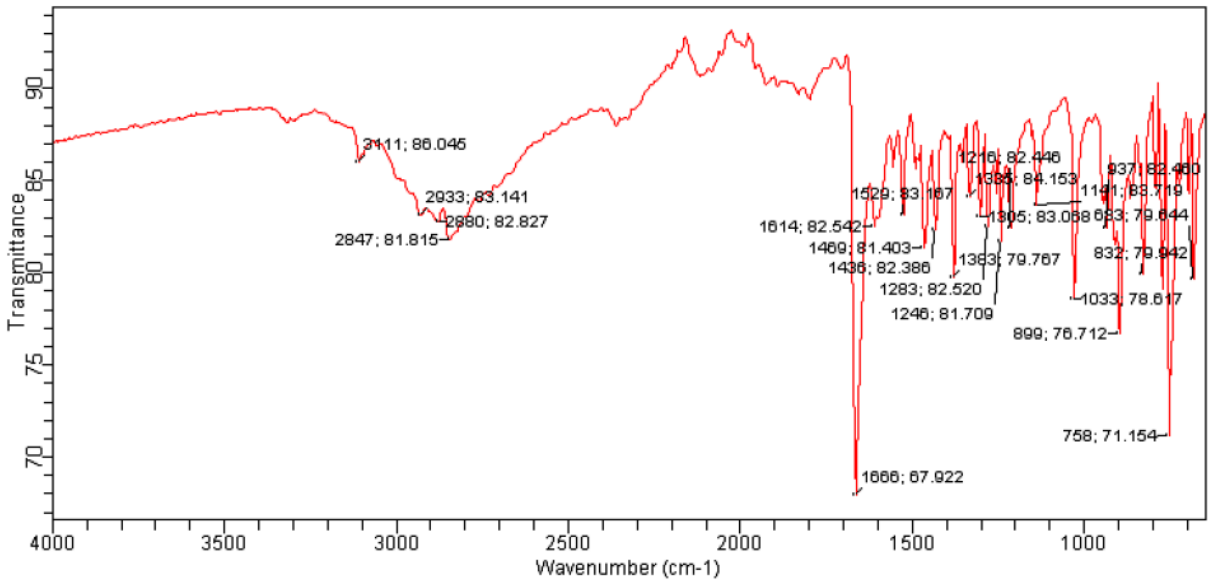
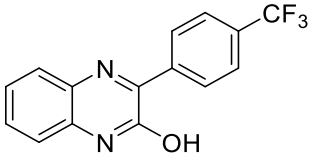
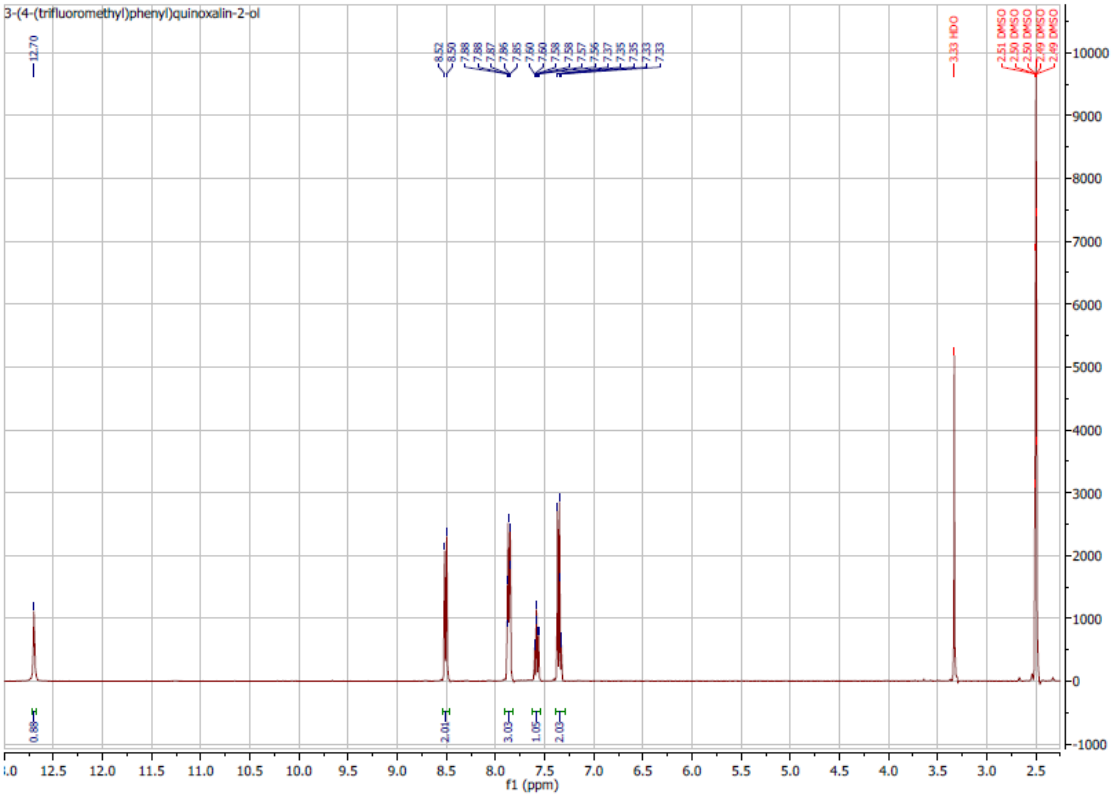
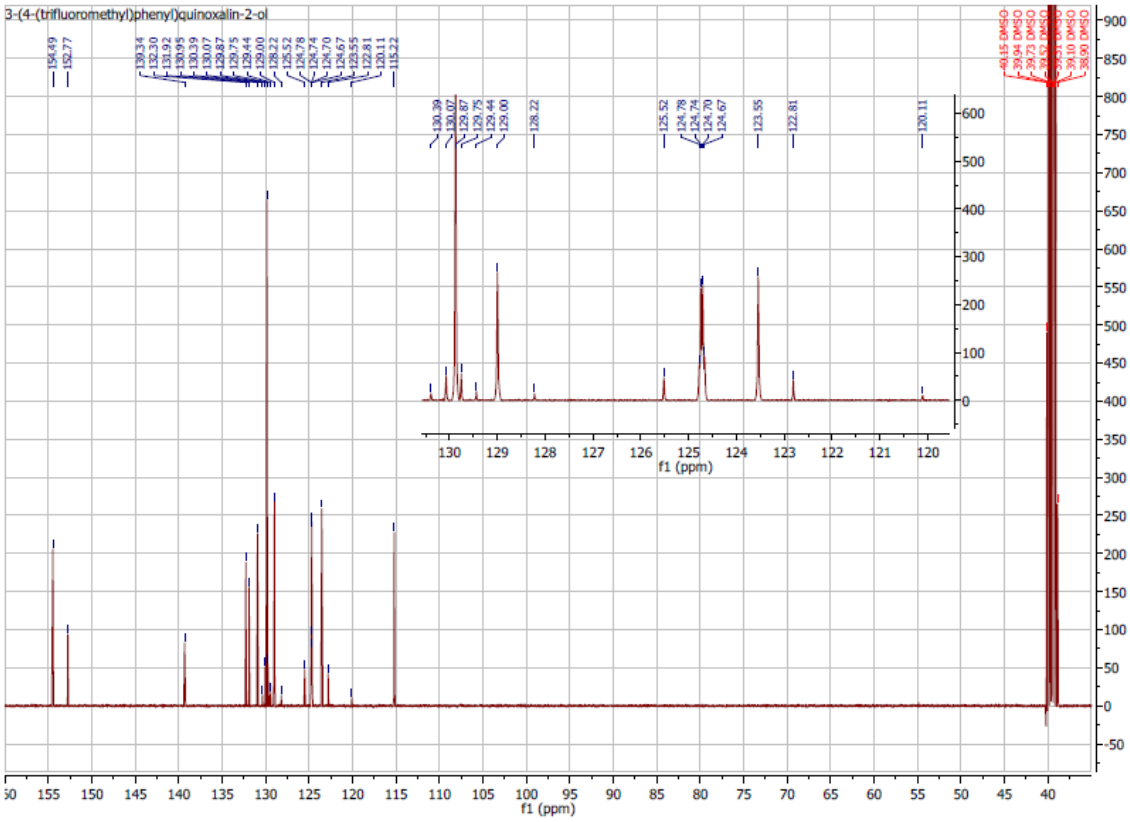
T: FTMS - p ESI Full ms [150.00-450.00]
288.9936
C14 H7 O N2 Cl2 = 288.9941
-0.4556 mmu
290.9906
289.9969
291.9937
292.9874
Relative Abundance
m/z

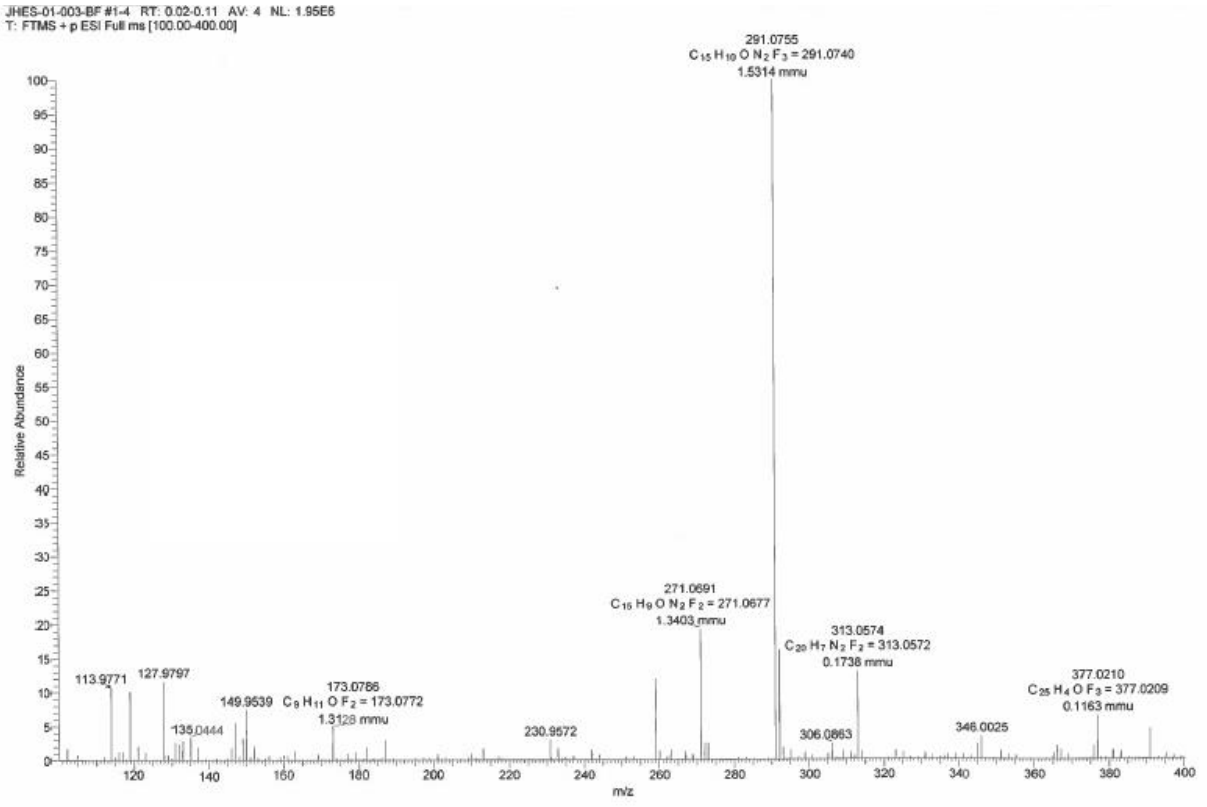

3111; 86.045
2933; 83.141
2880; 82.827
2847; 81.815
1614; 82.542
1529; 83.167
1469; 81.403
1436; 82.386
1383; 79.767
1305; 83.058
1283; 82.520
1246; 81.709
1216; 82.446
1185; 84.153
1141; 83.719
1083; 79.644
1033; 78.617
937; 82.460
899; 76.712
832; 79.942
758; 71.154
1666; 67.922
Transmittance
Wavenumber (cm-1)

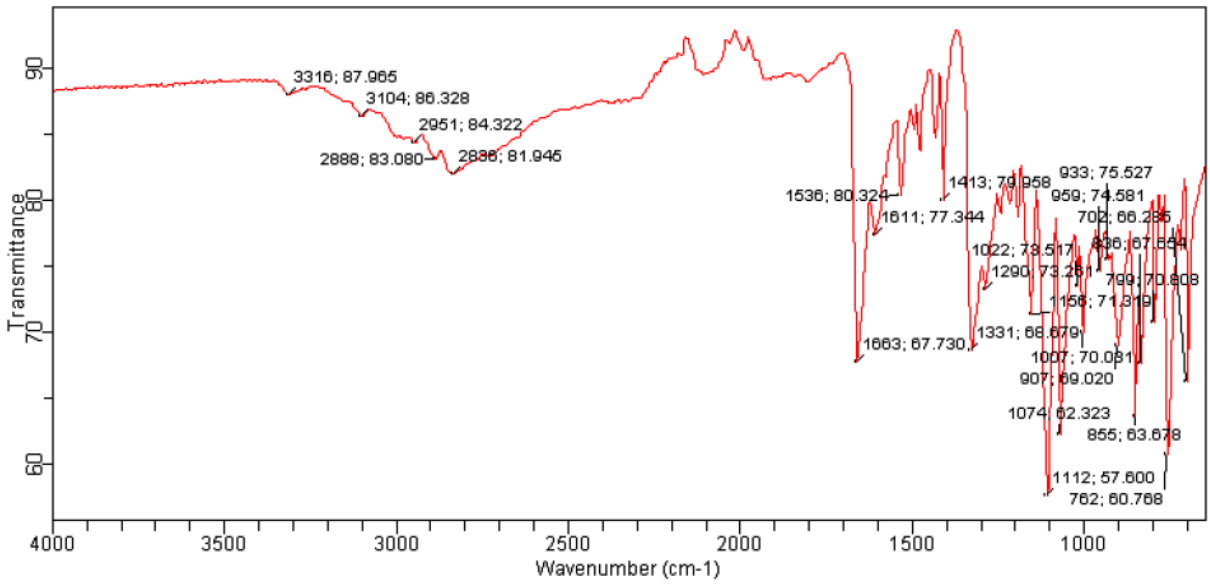
Compound **7n** - 3-(4-(trifluoromethyl)phenyl)quinoxalin-2-ol



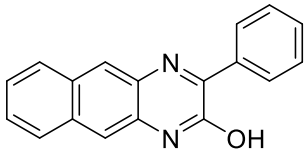


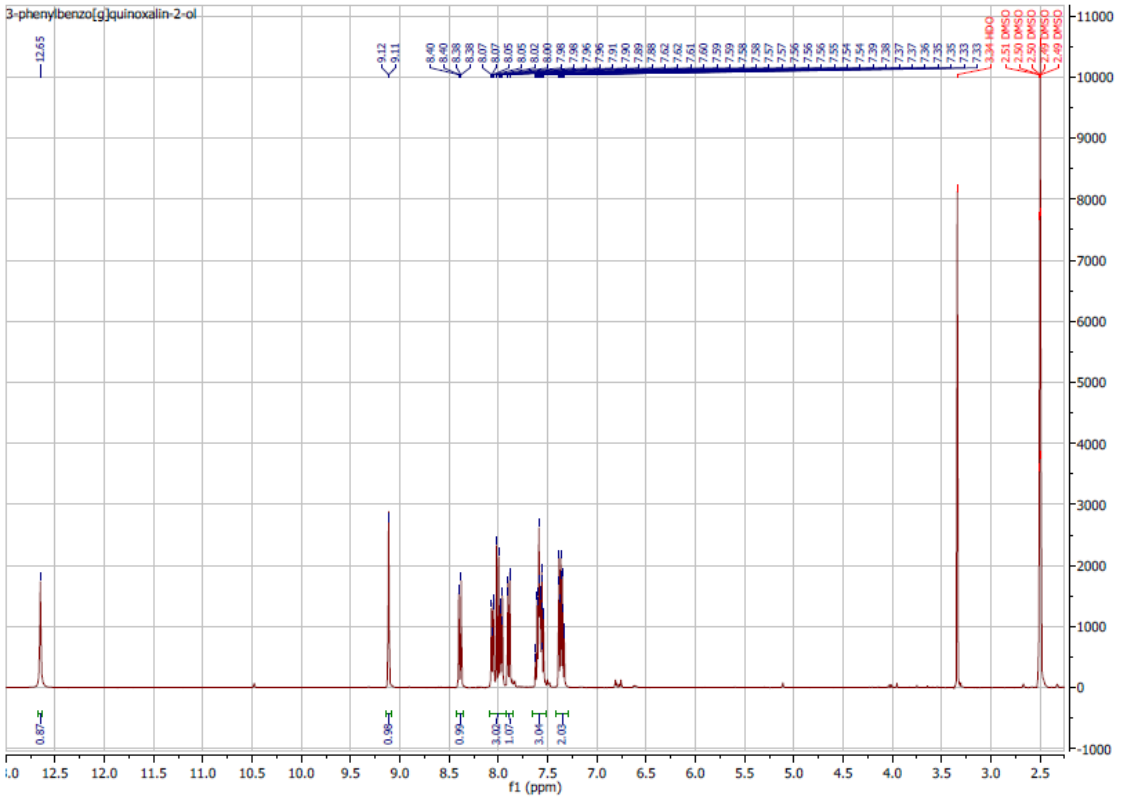


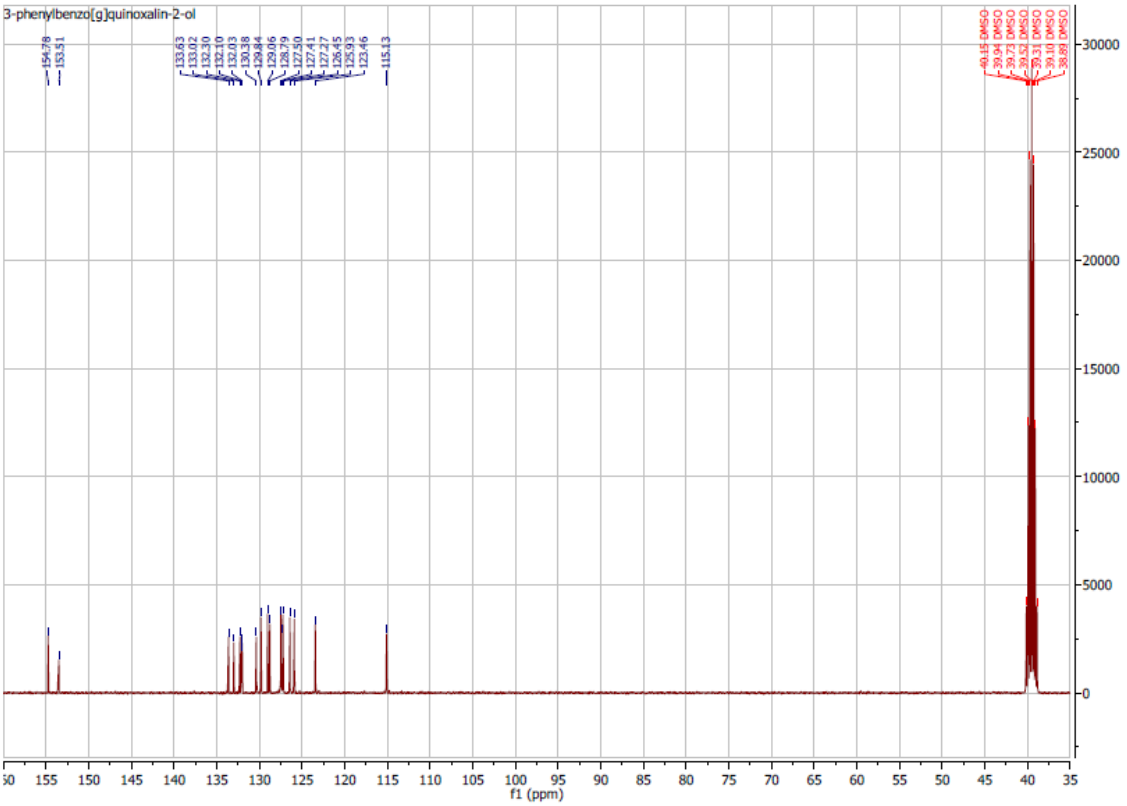

JHES-01-003-BF #1-4 RT: 0.02-0.11 AV: 4 NL: 1.95E6
T: FTMS + p ESI Full ms [100.00-400.00]
291.0755
C15 H10 O N2 F3 = 291.0740
1.5314 mmu
271.0691
C15 H9 O N2 F2 = 271.0677
1.3403 mmu
313.0574
C20 H7 N2 F2 = 313.0572
0.1738 mmu
377.0210
C25 H4 O F3 = 377.0209
0.1163 mmu
173.0786
C9 H11 O F2 = 173.0772
1.3128 mmu
113.9771
127.9797
149.9539
135.0444
230.9572
306.0863
346.0025
Relative Abundance
m/z

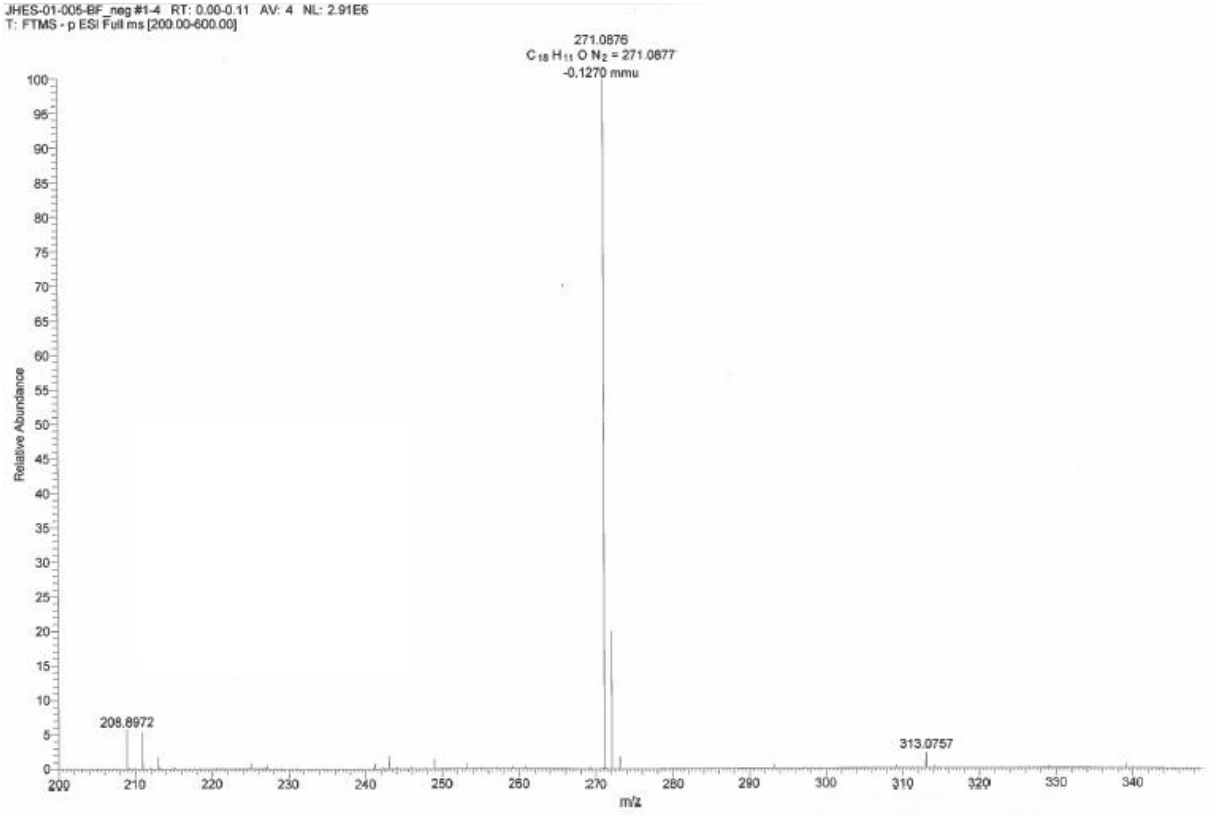

3316; 87.965
3104; 86.328
2951; 84.322
2888; 83.080
2836; 81.946
1536; 80.324
1611; 77.344
1413; 79.958
933; 75.527
959; 74.581
702; 66.286
836; 67.554
1022; 73.517
1290; 73.261
799; 70.608
1156; 71.319
1331; 68.679
1663; 67.730
1007; 70.081
907; 69.020
1074; 62.323
855; 63.678
1112; 57.600
762; 60.768
Transmittance
Wavenumber (cm-1)

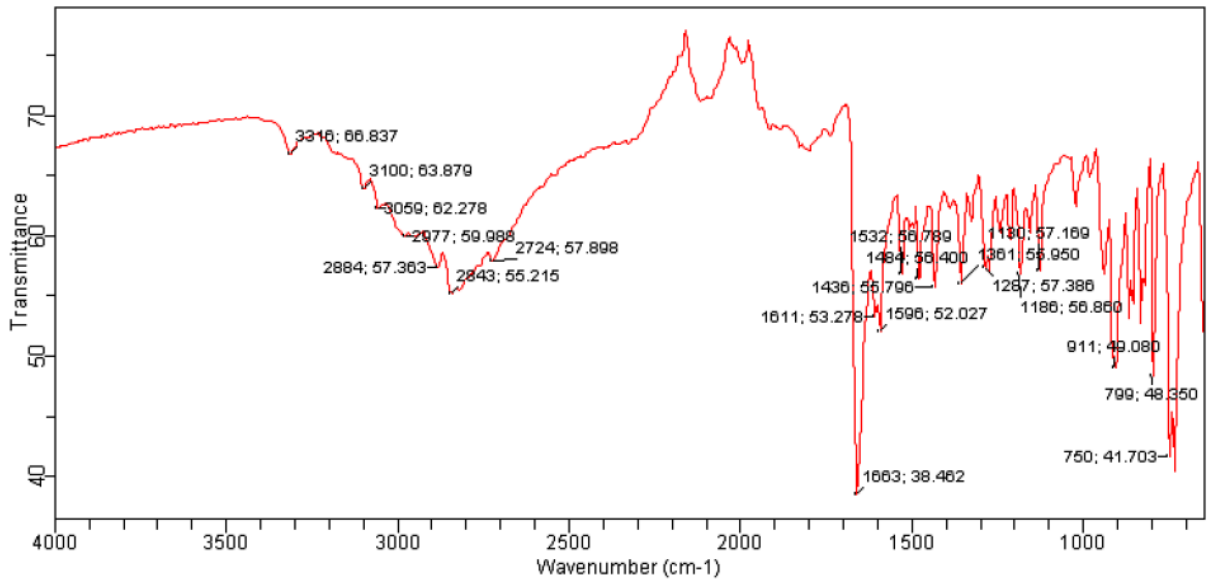
Compound **7o** - 3-phenylbenzo[g]quinoxalin-2-ol



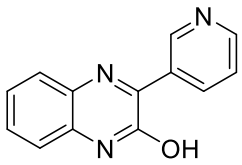


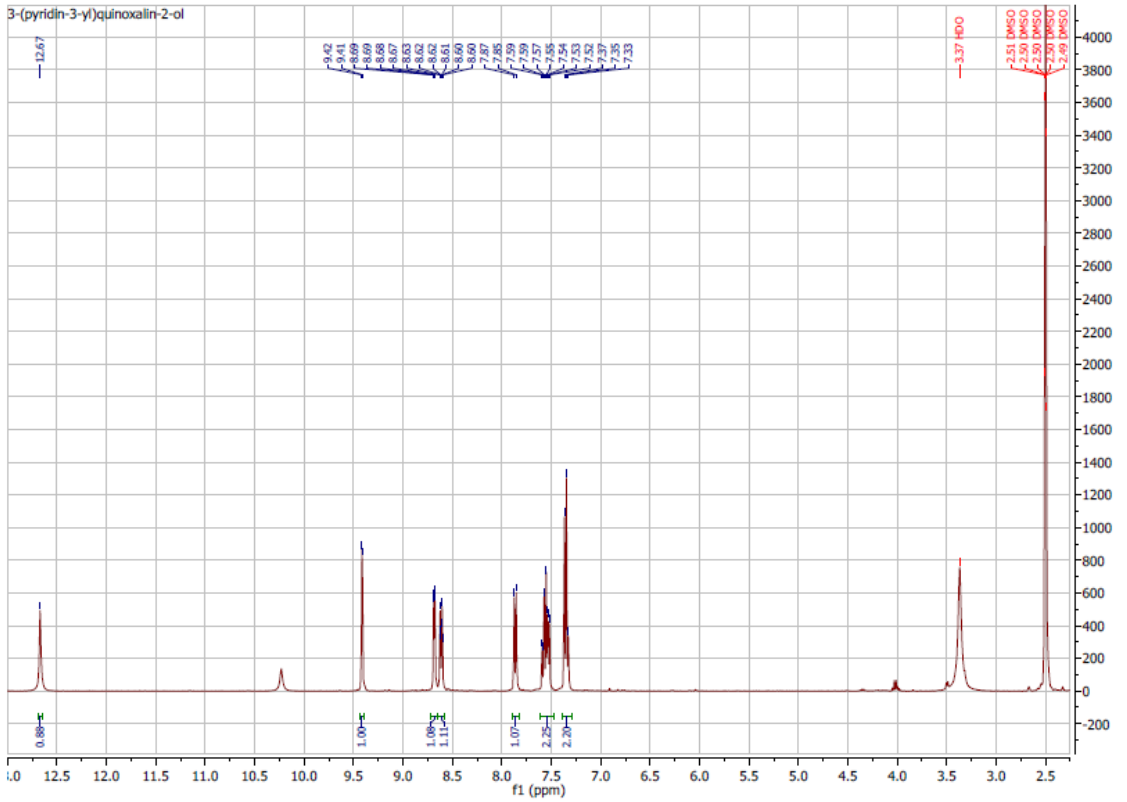


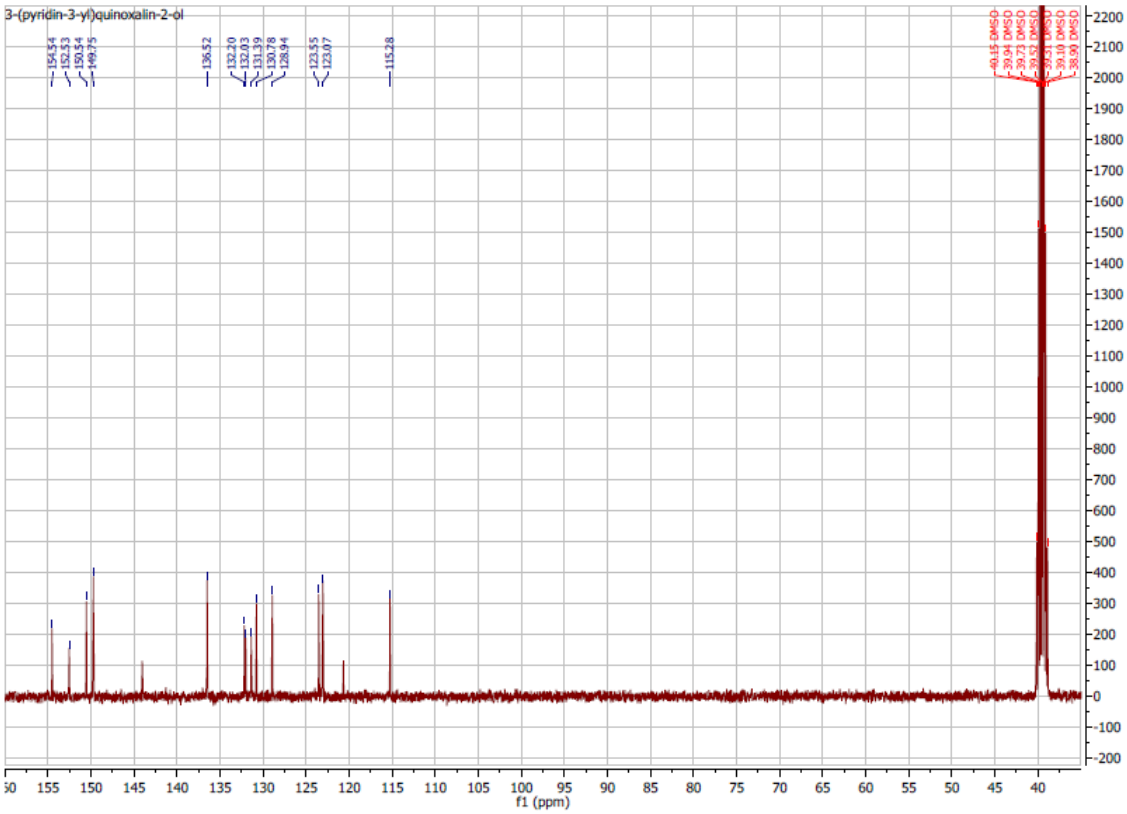

JHES-01-005-BF_neg #1-4 RT: 0.00-0.11 AV: 4 NL: 2.91E6
T: FTMS - p ESI Full ms [200.00-600.00]
271.0876
C18 H11 O N2 = 271.0877
-0.1270 mmu
Relative Abundance
m/z
208.8972
313.0757

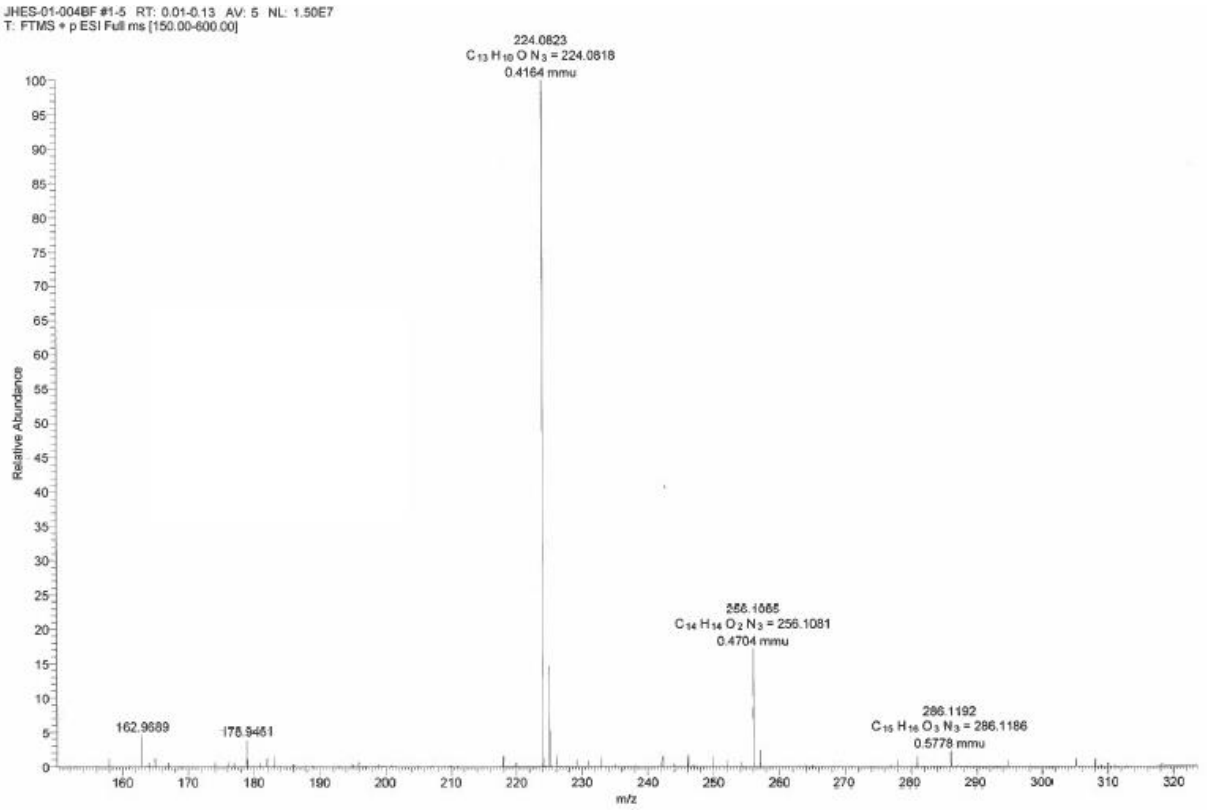

Transmittance
Wavenumber (cm-1)
3316; 66.837
3100; 63.879
3059; 62.278
2977; 59.988
2884; 57.363
2843; 55.215
2724; 57.898
1663; 38.462
1611; 53.278
1596; 52.027
1532; 56.789
1484; 56.400
1436; 55.796
1361; 55.950
1287; 57.386
1186; 56.860
1130; 57.169
911; 49.080
799; 48.350
750; 41.703

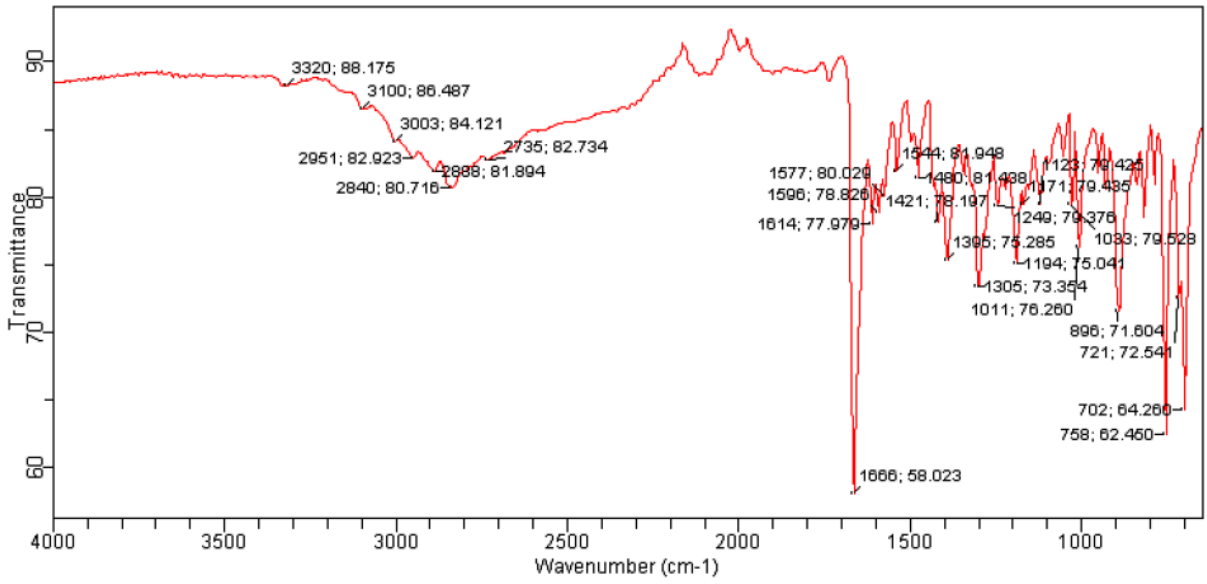
Compound **7p** - 3-(pyridin-3-yl)quinoxalin-2-ol








JHES-01-004BF #1-5 RT: 0.01-0.13 AV: 5 NL: 1.50E7
T: FTMS + p ESI Full ms [150.00-600.00]
224.0823
C13 H10 O N3 = 224.0818
0.4164 mmu
256.1085
C14 H14 O2 N3 = 256.1081
0.4704 mmu
286.1192
C15 H16 O3 N3 = 286.1186
0.5778 mmu
162.9689
178.9451
Relative Abundance
m/z


3320; 88.175
3100; 86.487
3003; 84.121
2951; 82.923
2735; 82.734
2888; 81.894
2840; 80.716
1577; 80.020
1596; 78.826
1614; 77.979
1544; 81.948
1480; 81.488
1421; 78.197
1171; 79.435
1249; 79.376
1123; 79.424
1033; 79.528
1395; 75.285
1194; 75.041
1305; 73.354
1011; 76.260
896; 71.604
721; 72.541
702; 64.266
758; 62.450
1666; 58.023
Transmittance
Wavenumber (cm-1)

Appendix 2: 3,4-Dihydroquinoxalin-2-ones: recent advances in synthesis and bioactivities (microreview)

DOI 10.1007/s10593-017-2052-6

Chemistry of Heterocyclic Compounds **2017**, *53*(3), 310–312

HETEROCYCLES IN FOCUS

3,4-Dihydroquinoxalin-2-ones: recent advances in synthesis and bioactivities (microreview)

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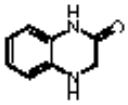
Accepted February 13, 2017



A summary of recent synthetic approaches to 3,4-dihydroquinoxalin-2-ones is discussed herein along with highlights of biological activity. The synthetic approaches include access to enantiopure 3,4-dihydroquinoxalin-2-ones from chiral pool amino acids *via* coupling/cyclization, Michael addition/cyclization cascades, 3,3-disubstituted systems from multicomponent couplings, Bargellini reaction, or photochemical reduction.

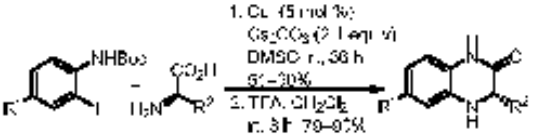
Introduction

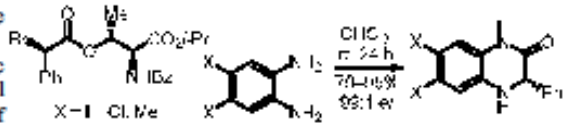
The dihydroquinoxalin-2-ones are bicyclic, benzene-fused ketopiperazines with the carbonyl group in position 2.[1,2] They are of broad interest due to their potential therapeutic properties, particularly antiviral and anti-inflammatory activities, as demonstrated in several studies.[3-5] Furthermore, this heterocyclic scaffold is particularly chemically versatile since multiple diversification strategies can be employed to produce a broad range of substitution patterns. In this microreview, we have surveyed the literature covering 2011–2016 emphasizing contemporary synthetic approaches to this valuable heterocycle, as well as highlights demonstrating some of its biological activities that have been reported since 2000.

Enantiopure dihydroquinoxalin-2-ones

De Brabander et al. have reported the synthesis of 3-substituted dihydroquinoxalin-2-ones *via* a mild Ullmann-type, ligand-free amination of enantiopure α-amino acids with *N*-Boc-2-iodoanilines followed by cyclization.[6] The coupling reaction worked well with moderate to good yields (51–90%) with the exception where the amino acid contains the strongly electron-withdrawing *p*-trifluoromethylphenyl group. Both methyl- and cyano-substituted iodoaniline, as well as unsubstituted iodoaniline were tolerated. Upon treatment with TFA, the coupling products were converted into substituted dihydroquinoxalin-2-ones in good yields (79–90%) for all substrates. Both the coupling reaction and the cyclization occurred without racemization, and the dihydroquinoxalin-2-ones were isolated in excellent enantiomeric excess (>98% *ee*).

Park and coworkers recently demonstrated an asymmetric formation of substituted quinoxalin-2-ones through a chiral auxiliary approach.[7,8] A stereoselective substitution of enantiopure α-bromophenylacetates with *o*-phenyldiamines was demonstrated, employing α-bromophenylacetates enantioenriched through crystallization-induced dynamic resolution. The reaction yielded quinoxalin-2-ones in good to excellent yields (79–95%) and in excellent enantiomeric excess (99:1 *er*).





Tone Kristoffersen was born in 1987 in Hammerfest, Norway. She is currently pursuing the Masters Degree in organic chemistry at UiT The Arctic University of Norway under the supervision of Assoc. Prof. Jørn H. Hansen. Her research interests include synthesis of heterocycles, applications of modern microwave methods in heterocyclic chemistry, and development of chemical libraries for medicinal research.

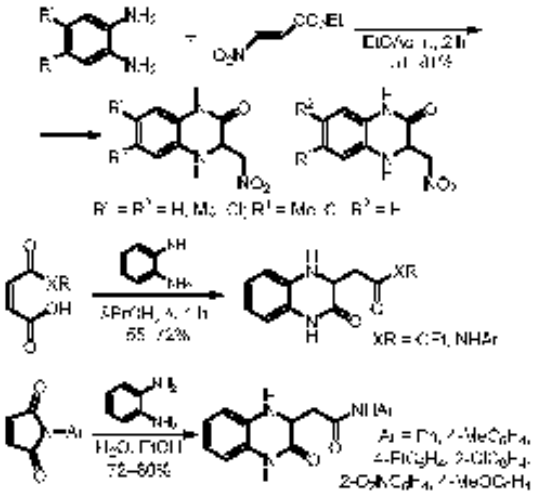
Jørn H. Hansen received his PhD in organic chemistry from Emory University, USA (Prof. H. Davies) in 2010, followed by postdoctoral research at Princeton University, USA (Prof. D. MacMillan), before joining UiT The Arctic University of Norway as an Associate Professor in 2012. His research interests – development and applications of novel late-stage functionalization methods, chemical library design with bioactive and functional heterocycles, computational mechanistic analysis, and chemical education.

0009-3122/17/53(03)-0310

Michael addition strategies

A simple method for the synthesis of 3-nitromethyl-substituted quinoxalin-2-ones was recently reported.[9] The reaction involves a Michael addition/cyclization cascade process in which both symmetrical and unsymmetrical *o*-phenylenediamines are used to obtain 3-nitromethyl-substituted quinoxalin-2-ones in moderate to good yields (51–81%). Reactions with unsymmetrical *o*-phenylene-diamines afforded regioisomeric mixtures without notable selectivity. Upon refluxing in aqueous solution, the nitromethyl group eliminates, yielding the corresponding quinoxalin-2(1*H*)-ones.

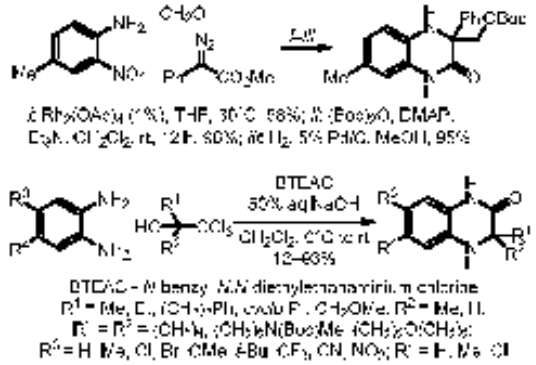
Rozhkov and coworkers demonstrated a different Michael addition approach, in which the reaction of *o*-phenylene-diamine with maleic acid derivatives afforded 3-substituted 3,4-dihydroquinoxalin-2-ones in moderate to good yields (55–72%).[10] The reaction also works with diethyl maleate and cyclic anhydrides. By employing the Michael addition strategy starting with pyrrole-2,5-diones, they were able to achieve generally higher yields (72–80%) of the desired heterocycle.



3,3-Disubstituted quinoxalin-2-ones

Hu and coworkers presented an effective Rh(II)-catalyzed three-component coupling method for producing α-arylserine derivatives by trapping carbene-derived ammonium ylides with formaldehyde.[11] Further it was demonstrated that the α-serine product upon Boc-protection and subsequent Pd-catalyzed hydrogenolysis gives 3,3-disubstituted quinoxalin-2-one in overall 54% yield for the sequences. Although only one example was presented, the method is of potential interest for the synthesis of 3,3-disubstituted systems.

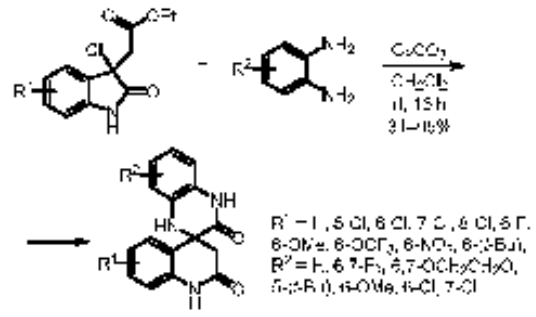
Recently Stokes and coworkers demonstrated the formation of 3,3-disubstituted dihydroquinoxalin-2-ones using the Bargellini reaction of *o*-phenylenediamines and substituted trichloromethylcarbinol electrophiles under phase-transfer conditions.[12] The reaction works with differently substituted trichloromethylcarbinols resulting in racemic products and can be extended to heteroatom-containing substrates as well as spirocyclic systems. The best yields were observed with trichloromethylcarbinol bearing methyl groups. A variety of electronically diverse phenylenediamines could be employed in moderate to excellent yields (33–93%). For unsymmetrical diamines, the regioselectivity was generally low, but up to 4.7 : 1 ratio could be achieved with electron-withdrawing substituents. Notably, the regioselectivity switched when going from electron-donating to electron-withdrawing substituents.



Spirocyclic quinoxalin-2-ones

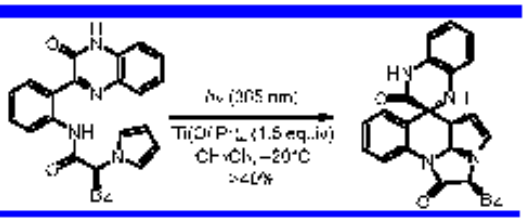
Zou and coworkers reported a clever approach for the synthesis of spirocyclic 3,4-dihydroquinoxalin-2-ones in moderate to excellent yields (31–95%) under mild conditions through a condensation of α-chlorooxoindoles with *o*-phenylene-diamines.[13] The reaction proceeds by initial ring opening of the oxoindole by the diamine, followed by double cyclization to generate the spirocyclic system. A variety of substitution patterns were tolerated both on the oxoindole and the phenylenediamine substrates.

Kutateladze and coworkers reported an exotic photoassisted intramolecular cycloaddition offering an alternative route to access spirocyclic quinoxalin-2-one scaffold incorporated into molecules with highly complex ring systems.[14]



Spirocyclic quinoxalin-2-ones (continued)

Utilizing the photoactive core of quinoxalonone and a pyrrole-containing unsaturated pendant based on L-phenylalanine, they demonstrated a stereoselective (4+2) cycloaddition resulting in enantiopure product (>40% yield). This represents an innovative synthetic approach to substituted enantiopure 3,4-dihydroquinoxalin-2-one systems starting directly from the fully oxidized quinoxalin-2(1*H*)-one system.



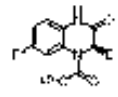
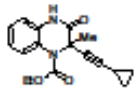
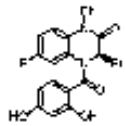
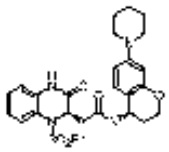
Highlights of biological activity

Several studies have established biological activities for 3,4-dihydroquinoxalin-2-ones.[3–5,15,16] 3,4-Dihydroquinoxalin-2-one GW420867X (entry 1) has undergone clinical trials started in 2001. It was administered to HIV-1 infected patients, both alone and in combination with already approved antiHIV-1 drugs. The compound was well tolerated and displayed potent antiviral activity in this study.[17]

Patel and coworkers combined features from two potent antiHIV drug candidates to study the SAR of hybrid structures such as 3-cyclopropylethynyl-4-ethoxycarbonyl-3-methyl-3,4-dihydroquinoxalin-2-one (entry 2). The hybrids included structural elements inspired by the drug efavirenz, as well as the quinoxalin-2-one core of GW420867X. Although the compound displayed potency as a non-nucleoside reverse transcriptase inhibitor (NNRTI), it was not further developed due to poor bioavailability in rhesus monkeys.[18]

Mahaney and coworkers studied several compounds containing the 3,4-dihydroquinoxalin-2-one core as estrogen receptor ligands. The two main types studied had N-4 arylsulfonyl and benzoyl substituents. Several of the derivatives tested displayed ligand potency, but compounds such as represented in entry 3 yielded the best results.[19]

Chen et al. studied dihydroquinoxalin-2-one acetamides containing bicyclic amines as bradykinin B1 receptor antagonists. Previous studies have shown that 3-chloro-4-methyl substitution on the *N*-phenylsulfonamide was preferred. In this study, they mainly investigated different substituents at the piperidine ring and showed that a switch to more lipophilic groups (e.g., piperidine), instead of more simple amines, caused increased potency, while maintaining a simpler, unsubstituted phenylsulfonamide group (entry 4).[20]

Entry	Compound	Mechanism of action	Target	Biological activity	Ref.
1	 GW420867X	NNRTI	HIV-1	IC_{50} 179 μM IC_{90} 11 μM	17,18,21
2		NNRTI	HIV-1	IC_{50} 118 μM IC_{90} 9 μM	18
3		Estrogen receptor E2-$NF_κB$ antagonist	Inflammation	IC_{50} 118 nM E2-$NF_κB$ 92% EC_{50} 9 nM E2-CK 44%	19
4		Bradykinin B1 receptor antagonist	Inflammation	K_i ± SEM 0.19 ± 0.05 nM IC_{50} ± SEM 0.12 ± 0.1 nM	20

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