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Synthesis of *N*,*N*'-substituted imidazole-2-thiones from *N*-substituted imidazoles

Master's thesis
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Abstract

The literature review of this thesis was done by reviewing articles considering synthesis of *N*,*N*'-substituted imidazole-2-thiones and theory regarding them. *N*,*N*'-Substituted imidazole-2-thiones can be synthesized with many different starting materials and catalysts, resulting in various different sized molecules. As all azoles, these imidazole derivates are bioactive. This is the reason why many of the practical applications of imidazole-2-thiones are in the fields of bio-, agricultural- and pharmaceutical chemistry, although there are some other applications in coordination chemistry as well.

The experimental section of this thesis is about synthesizing *N*,*N*'-substituted imidazole-2-thiones from different bromomethylbenzenes and imidazole derivatives. Many imidazole derivatives are known, and they can be used as reagent in this synthesis. All the experiments made worked out to some degree, giving raw product in good yields. Products were dirty or mixtures and needed purification. Purification made yields drop and some products could not be purified or were lost during purification. Standard ^{1}H-, ^{13}C-, ^{1}H, ^{13}C HMBC- and ^{1}H, ^{15}N correlation NMR and ESI-MS spectra were measured from every purified sample and some of the raw products. Also melting points of the pure products were measured. Ten crystal structures from the synthetic products and four of their complexes with halogen bonding donors were determined with single crystal X-ray diffraction method.

Tiivistelmä

Työn kirjallisuuskatsauksessa tutkittiin N,N’-substituoitujen imidatsoli-2-tionien synteesiä ja niihin liittyvää teoriaa. N,N’-Substituoituja imidatsoli-2-tioneita voidaan syntetisoida käyttämällä monia eri lähtöaineita ja katalyyttejä. Lopputuloksena on iso skaala tuotteita. Nämä imidatsolijohdannaiset ovat bioaktiivisia, aivan kuten muutkin atsolit. Tästä syystä imidatsoli-2-tionien käytännön sovellutukset ovat bio-, maanviljely- ja lääkekemian parissa. Myös koordinaatiokemiasta löytyy sovellutuksia imidatsoli-2-tioneille.

Käytännön osuudessa syntetisoitiin N,N’-substituoituja imidatsoli-2-tioneita erilaisista bromimetyylibentseeneistä ja imidatsolijohdannaisista. Kyseisessä reaktiossa hyödynnettäviä imidatsolijohdannaisia tunnetaan paljon. Kaikki tehdyt reaktiot tuottivat raakatuotetta hyvällä saannolla, mutta monet tuotteista olivat puhdistusta kaipaavia seoksia. Osa tuotteista ei puhdistunut yrityksistä huolimatta tai ne menetettiin puhdistusprosessissa. Tuotteista mitattiin 1H-, 13C-, 1H, 13C HMBC- ja 1H, 15N korrelaatio NMR ja ESI-MS spektrit. Myös sulamispiste mitattiin puhtaista tuotteista. Kymmenen kiderakennetta saatiin määritettyä syntetisoiduista tuotteista ja neljä niiden komplekseista halogeenisidosdonorien kanssa yksikideröntgendiffraktiomenetelmällä.

Preface

This thesis was written for the Department of Chemistry at the University of Jyväskylä in 2022-2023. Practical work was done in the laboratory spaces of department of organic chemistry, using the equipment available there. Subject of the thesis was chosen due it fits already ongoing interesting organic synthesis chemistry research. Literature was found on the internet by using multiple search engines and multiple publishers' articles. As imidazoles are very common, there was lot of material to go through, and not everything could be included in this thesis, as it would have taken unreasonable amount of time and space to process. Supervisor of this thesis was academy researcher Arto Valkonen, and I would like to thank him very much for being patient and kind supervisor as well as for funding my thesis project. I would also like to thank Elina Sievänen for being the second reviewer of my thesis.

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Used abbreviations:

Ac	Acetone
ACN	Acetonitrile
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCM	Dichloromethane
DMF	Dimethylformamide
ESI-MS	Electrospray Ionisation Mass Spectrometry
EtOAc	Ethyl acetate
EtOH	Ethanol
Hex	Hexane
Me	Methyl
MeOH	Methanol
NAF	Sodium fluoride
NMR	Nuclear magnetic resonance
PetEt	Petrol ether
Ph	Phenyl
r.t.	room temperature
TFDA	Trimethylsilyl 2,2-difluoro-2-(fluorosulfonyl)acetate
THF	Tetrahydrofuran
US	Ultra sound

1. Introduction

This Master's thesis discusses about different synthesis routes of *N*-substituted imidazoles into *N,N'*-substituted imidazole-2-thiones and their applications. Imidazole is type of azole. Azoles have high reactivity due their aromatic structure. They are very important in biomolecules and without them life as we know it would be impossible. Many azoles have applications in bio- and pharmaceutical chemistry and industry as is demonstrated in literature review. Azoles usually appear as derivatives and there is a wide range of possible substituents, as well as many places for the joining groups to bond. General structure of imidazole is presented in Figure 1. In non-substituted imidazole R = H.

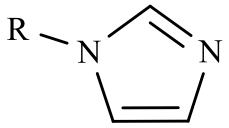


Figure 1. General structure of imidazole, where R = H or substituent.

Literature review includes background of azoles, *N*-substitution, sulphur addition, applications of *N,N'*-substituted imidazole-2-thiones and related reactions found from the literature. They can be easily substituted to make *N*-substituted variants, which gives them high versatility. *N,N'*-Substituted imidazole-2-thiones have two *N*-substituents and a sulphur atom in position 2 of the imidazole ring. Sulphur can work as an electron donor, which enables it to bond with, for example iodine. General structure of imidazole-2-thione is presented in Figure 2.

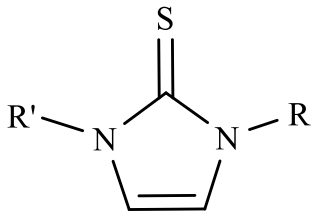


Figure 2. General structure of imidazole-2-thione.

In experimental section *N,N*'-substituted imidazole-2-thiones were synthesized from different *N*-substituted imidazoles and mono-, bis- or tris-bromomethylbenzenes. Eight different *N*-substituted imidazoles, which include methyl-, ethyl-, benzyl, *tert*-butyl-, phenyl and trityl-imidazoles as well as *N*-methyl benzimidazole and caffeine, were used with five different bromomethylbenzene cores. The used cores were 1,3,5-tri(bromomethyl)-2,4,6-triethylbenzene, 1,3,5-tri(bromomethyl)-2,4,6-trimethylbenzene, 1,4-bis(bromomethyl)benzene, 1,4-bis(bromomethyl)-2,3,5,6-tetramethylbenzene and benzyl bromide. The utilized reaction included two steps. In the first step imidazole substituted bromine in bromomethylbenzene while a new C-N bond was generated, and organic bromide salt was formed. This was achieved by 3h or 24h reflux in THF. Sulphur and potassium carbonate base were added to the intermediate product and the resulting mixture was refluxed in MeOH for 24h. The biggest problem in the synthesis was purification. Most of the raw products were impure. Many of the products were purified by recrystallization and some by column chromatography, although most of the product was lost in the column. Some of the products could not be purified at all.

2. Azoles, imidazole-2-thiones and their applications

Imidazole-2-thiones are aromatic azole derivates. Aromaticity greatly affects the properties of the molecule, which makes it react the way it does. Bonding between sulphur and imidazole ring is to be defined to understand forming and properties imidazole-2-thiones. Formed molecules have many applications and functions in different fields of science and nature. Imidazole-2-thiones can form supramolecular compounds as well, having applications in supramolecular chemistry too.

2.1. Azoles and imidazoles

Azoles are aromatic compounds that usually consist of carbon, nitrogen and hydrogen atoms, but often they incorporate oxygen and sulphur. Azole ring is formed from five non-hydrogen atoms, of which at least one is nitrogen and the other one is non-carbon atom and the unit contains two double bonds. Azoles can have substituents as well. Many azoles have high biological activity and

are important in biological applications and pharmacy. Supramolecular chemistry and agriculture are the fields of applications for azoles too. Aromaticity is very important phenomenon for understanding the high reactivity of azoles. Imidazole is only one azole, but it is the focus in this thesis, as it is one of the most common azoles. Other azoles have similar properties to imidazole and imidazole can be transformed into other azoles in right conditions and vice versa.

2.1.1. Concept of aromaticity and its effects

Understanding aromaticity is important when trying to understand reactions and reactivity of aromatic molecules like azoles. There is much research about aromaticity from a long period of time due its importance in chemical reactions. Benzene is the most well-known aromatic compound as it was the first aromatic compound identified. Same concepts apply for all aromatic compounds. [1]

Aromaticity is much more than what is usually taught in lectures. Being aromatic means that cyclic, usually but not always, planar and conjugated molecule has resonance structure where π-electrons delocalize, increasing the stability of the compound and giving it magnetic properties. Commonly known Hückel's rule is an easy way to determine aromaticity, but it does not work for every aromatic molecule as some of them can be aromatic without obeying the rule.[1]

Term "aromaticity" has rich history, and it has changed many times, becoming more accurate and forming to be, little by little, the modern-day definition of aromaticity as we know it. Benzene compounds have distinctive aroma unlike pure hydrocarbons. Therefore, before 1825 this class of molecules got the name "aromatic". Michael Faraday isolated benzene in 1825 from compressed oil gas and called it "bi-carburet of hydrogen". This means he assumed 2:1 carbon-hydrogen ratio, which translated into molecular formula of C_6H_3. This is of course wrong according to present knowledge, but this gave the base for structural information that was formed considering the molecule later.[2] The conclusion made was that aromatic compounds have high, 1:1 carbon-hydrogen ratio and that they are undersaturated but stable. Faraday determined density, melting

and boiling points of benzene as well as made some derivatives, which could not be characterized at the time.[3] In 1865 structure of benzene was formulated by Kekulé and year after that in 1866 Erlenmeyer found out that substitution is more favourable than addition in reactions with benzene and possibly with other aromatic compounds. Next big milestone in aromaticity was not until the next century, in 1910, when Pascal found out that aromatic compounds have exalted diamagnetic susceptibilities. In 1925 Armit-Robinson made a theory of electron sextet and heteroaromaticity, after which Hückel formed the famous Hückel's rule for cyclic (4n+2) π-systems. It is used as one of the modern-day definitions for aromaticity, although it is deficient and there are aromatic molecules that do not follow this rule.[3] Pauling made ring current theory in 1936, which assumes that the electrons in benzene ring are delocalized and therefore have free circulation in the benzene ring. Year after this, in 1937, it was realized that the π-electron current contributes to magnetic susceptibility. Theory was called London diamagnetism.[4] Concept of nuclear magnetic resonance (NMR) was found in 1938 by Isidor Rabi, and it was followed by first NMR instrument in 1952.[5,6] This led to investigation of aromatic compounds with this new technology in new perspective. So, in 1956 Pople noticed that ring current effect affects the chemical shifts on NMR. Dauben released modern study of diamagnetic susceptibility exaltation in 1969. Flygare released his article about anisotropy of magnetic susceptibility one year later, in 1970.[7] Kutzelnigg released study about quantum chemical calculation of magnetic properties: chemical shifts, magnetic susceptibilities and anisotropy of magnetic susceptibility in 1980, combining many of the previous concepts form previous studies.[3,8] After this, new classes of aromatic compounds including fullerenes, nanotubes and trannulenes as well as a concept of d-orbital aromaticity have been discovered.[9]

After all the research and theories made about aromaticity, a certain list of properties has formed to be the criteria of aromaticity: chemical behavior, as well as structural, energetic and magnetic properties. First, aromatic compounds are electrophilic and therefore are susceptible for aromatic substitution. Secondly, the bond lengths of an aromatic compound are equal due to cyclic delocalization. Third criterion is considering the energy of the molecule. Aromatic molecules have enhanced stability which corresponds with large resonance energy. Fourthly, aromatic compounds have magnetic properties due to ring current effects. These cause anomalous chemical shifts, large magnetic anisotropies, and diamagnetic susceptibility exaltation. [3,8]

Being aromatic means that imidazole is planar like other azoles, has two double bonds, has reduced analog and six π-electrons, which means Hückel's aromaticity rule (4n+2) gets fulfilled. When investigating the drawn structure of imidazole, there are two possible ways to draw it where there are no charges involved. In practice electrons are delocalized and neither option is right. Resonance structures of imidazole are shown in Figure 3.

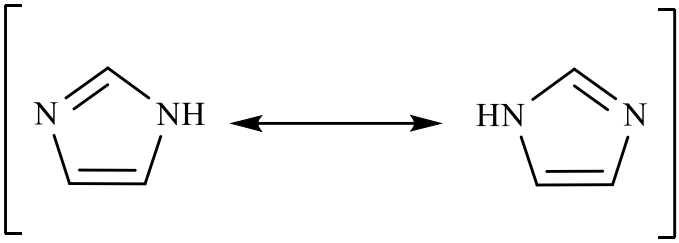


Figure 3. Resonance structures of imidazole.

Studies have shown that both σ and π orbitals participate on delocalization. Bond length of aromatic compound is something between single bond double bond. This proves that the bonds are neither single nor double, but they are delocalized. Therefore, a hybrid structure best describes the real situation.[10] The hybrid structure shows the electrons delocalized across the whole structure, which is demonstrated in Figure 4.

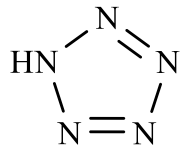
Figure 4. Structure of delocalized imidazole.

Aromaticity is observed in analysis of molecules that contain aromatic parts. As the magnetic anisotropy deshields the protons, the chemical shifts move towards downfield compared to non-aromatic compounds. Due to their different magnetic properties, the chemical shifts of hydrogen

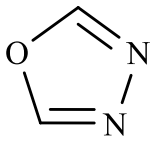
and carbon atoms in aromatic molecules vary from the spectrum to the other, but they are most often seen at 7 − 9 ppm in ^{1}H and at 100 − 150 ppm in ^{13}C NMR spectra.[11,12]

2.1.2. Base compounds

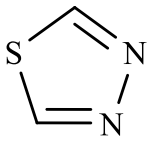
Azoles are five-membered heterocyclic compounds. Being heterocyclic means that the ring structure has at least two different elements, such as nitrogen (at least one in azole), oxygen or sulphur in different positions in the cycle in addition to carbon atoms. The structures and names of different azoles are presented in Figure 5. Imidazole is the focus on this thesis, therefore other azoles received less attention. Numbering of atoms start form the non-double-bonded heteroatom, heteroatom being atom other than carbon. Azoles, especially the ones with two nitrogen atoms (such as imidazole), are common in nature and important in biomolecules, which can be found inside many living organisms. Importance to biochemistry is based on high reactivity caused by aromaticity and electronegative nitrogen and oxygen atoms.



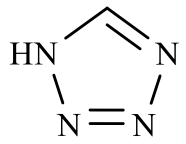
1*H*-pentazole



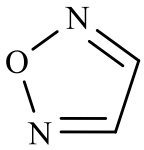
1,3,4-oxadiazole



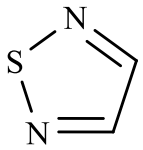
1,3,4-thiadiazole



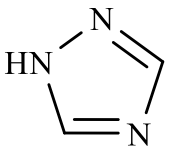
1*H*-tetrazole



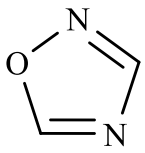
1,2,5-oxadiazole



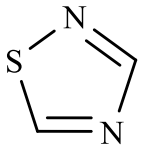
1,2,5-thiadiazole



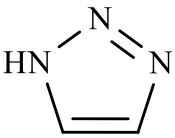
1*H*-1,2,4-triazole



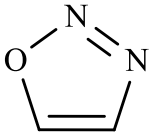
1,2,4-oxadiazole



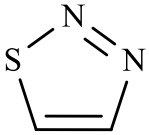
1,2,4-thiadiazole



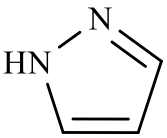
1*H*-1,2,3-triazole



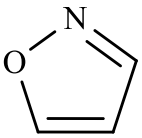
1,2,3-oxadiazole



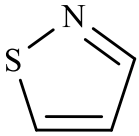
1,2,3-thiadiazole



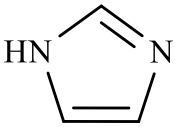
1*H*-pyrazole



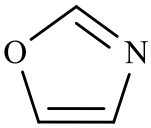
isoxazole



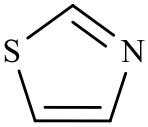
isothiazole



1*H*-imidazole



oxazole



thiazole

Figure 5. Structures of azoles.

Imidazole is aromatic, has two double bonds and two nitrogen atoms, which are in 1- and 3-positions. For convenience, the double bonds are usually shown in same two places — between two carbon atoms and between carbon and nitrogen atoms. Imidazole works as a moderately strong base with pK_b=7.0 value. [13]

The first time that imidazole was reported was in 1858 by Heinrich Debus.[14] Debus created synthetic route for imidazole with ammonia and glyoxal. He named the compound as glyoxalin. The name imidazole came later, in 1887, by Hantzsch. Debus-Radziszewski reaction uses the same principle as Debus's reaction. Imidazole and many imidazole derivatives can be synthesized using this reaction. Combining 1,2-dicarbonyl, aldehyde, amine and ammonia and heating the mixture in appropriate solvent, like water or water-alcohol, results in pure product (>99%) after distillation with a decent yield of 60-85% for simple imidazoles. Simpler molecules tend to have better yields. Debus-Radziszewski reaction can be used to produce imidazolium-containing polymers as well. Debus-Radziszewski reaction is presented in Figure 6.[13–16]

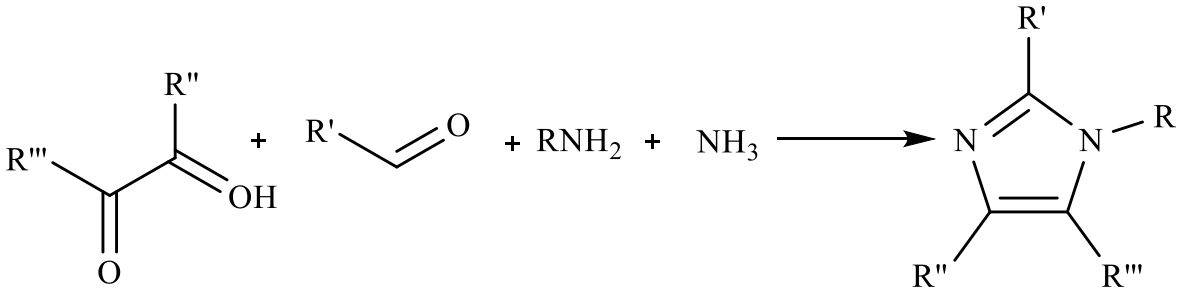


Figure 6. Debus-Radziszewski reaction.

Simple imidazole can be modified into more complex imidazoles. Different imidazoles can be also prepared by dehydrogenation of imidazolines. There are many other routes for the synthesis as well, but Debus-Radziszewski reaction is the most important industrial reaction in production of simple imidazoles that can be then modified if needed.[13,14]

Pure imidazole has only little applications itself. The imidazole moiety is usually a part of larger compound or derivatised for other uses. Imidazole is common part of alkaloids. Alkaloids are a group of natural, basic, compounds that contain at least one nitrogen atom. They are mainly produced by many living things, like bacteria, plants and animals, but some can be synthesized. They are essential to life, as we know it, and have many essential pharmaceutical applications because of their high bioactivity.[17]

2.1.3. Imidazole derivatives

Imidazole derivatives are more important in many senses, as pure imidazole itself has very few applications in industry, as well as in biochemistry. Derivatization of imidazole is easy, as it can be easily produced in different forms, reduced and it can be substituted from any atom. Imidazole has many different viable substituents, for example methyl, ethyl or benzyl attached to nitrogen atom. The generic numbering of atoms in imidazole(s) is shown in Figure 7. In one of the most common case the substituent is attached to position 1 and replaces the hydrogen atom.

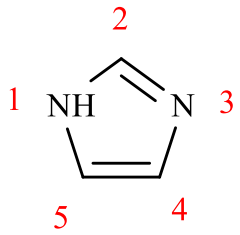


Figure 7. Imidazole atom positions labelled.

A ring conjugation in positions 4 and 5 is very common in imidazole derivatives. This forms a heterocyclic double ring structure. Purines and benzimidazole derivatives are good examples of such compounds. Single groups can also join into positions 4 and 5. Position 2 is also often occupied by substituent(s). Some examples of different imidazole derivatives are given in Figure 8.

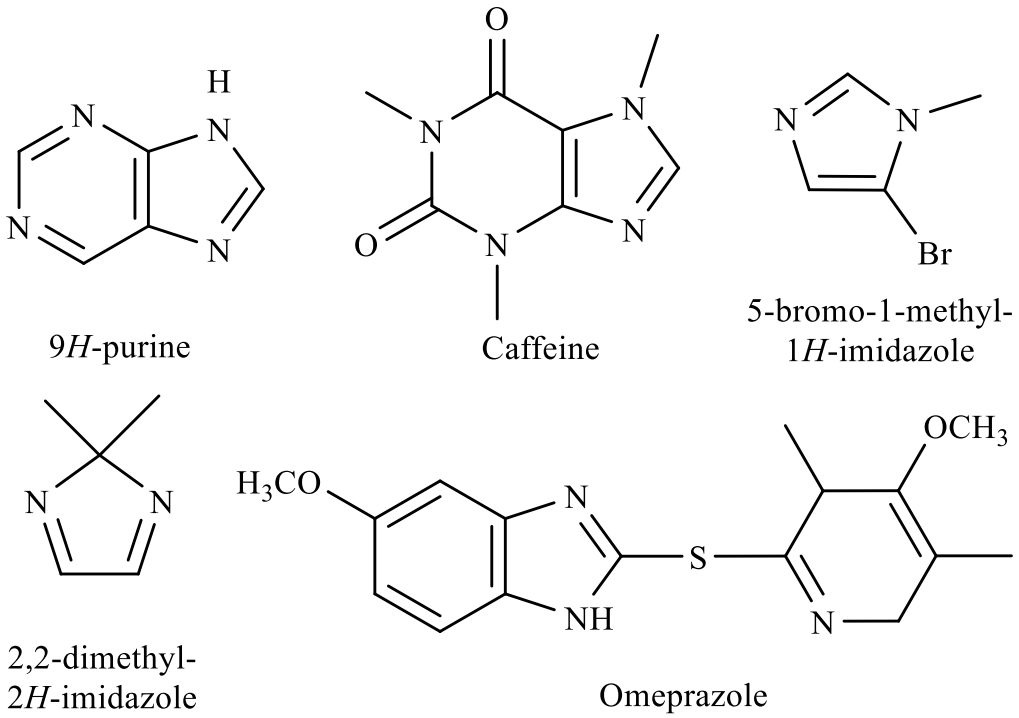


Figure 8. Differently substituted imidazole derivatives.

Imidazole has reduced derivatives with one or zero double bonds. Imidazolines are imidazole derivatives that have only one double bond as a result of a reduction reaction. The derivative with both double bonds reduced is called imidazolidine. Adding hydrogen cation to imidazole will result in imidazolium cation with delocalized electrons pair. All mentioned derivatives are shown in Figure 9.[18]

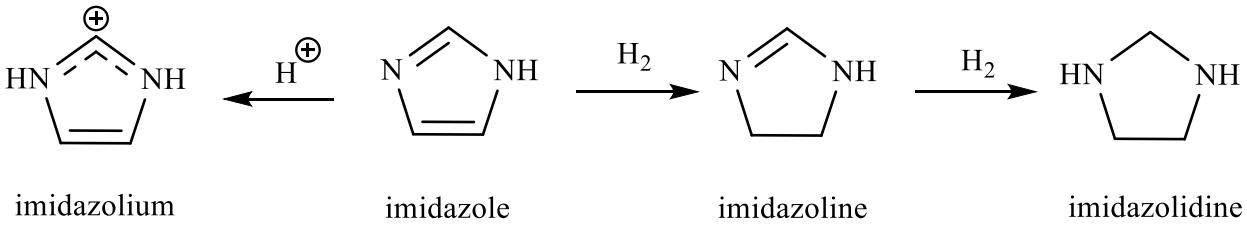


Figure 9. Structures of reduced imidazole derivatives and imidazolium cation.

Imidazolium is an important derivative for forming 2-substituted imidazole compounds without *N*-substituents. Imidazoline is highly reactive and therefore useful derivative as well. Imidazoline has three isomers, which enable it to form highly diverse molecules. Isomers of imidazoline are shown in Figure 10. Especially, 2-imidazoline has high biological activity and, therefore, it is a common part of many drugs.[18]

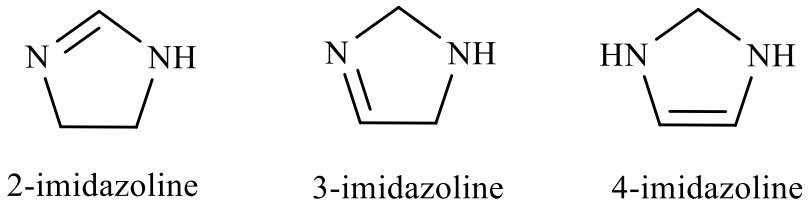


Figure 10. Isomer structures of imidazoline.

Imidazole derivatives, like purine, histamine, histidine and different nucleic acids are important part of pharmaceutical production. They are bioactive, and structurally very close or same, as the compounds encountered in nature. Nitroimidazoles are chemotherapeutic agents.[13]

2.2. Substitution

Substitution means replacing one functional group, most commonly hydrogen, with another group. Substitution reactions are very important and are basically the base of organic chemistry. Reactants in substitution reaction can be divided in electrophilic or nucleophilic atoms and groups. Electrophiles want electrons. Nucleophiles, like halogens, want to donate electrons. Mechanism of the reaction depends on reagents and the chemical environment.[19,20]

Imidazole can be substituted on every atom, but especially the nitrogen atoms are usually the most reactive due to the nature of nitrogen. Nitrogen is more electronegative than carbon and, therefore, having more electron density. Nitrogen atoms in imidazole have theoretical free electron pairs, although they are delocalized in aromatic structure. Existing substituents guide joining

substituents. This effect can be seen best in substituted benzenes, in which it affects the most. This effect is slighter in imidazole and many other factors, like chemical and physical conditions, play a role as well.[21]

Many different substituents are known to work with imidazole, as imidazole can have substituents in carbons as well as in nitrogen. One of most common substitutions of imidazole is *N*-substitution. *N*-substitution means that the substitution happens on the nitrogen atom. *N*-substitution in case of imidazole usually happens with nucleophilic aromatic substitution reaction mechanism because imidazole is aromatic. Some simple *N*-substituted imidazoles are shown in Figure 11.[21]

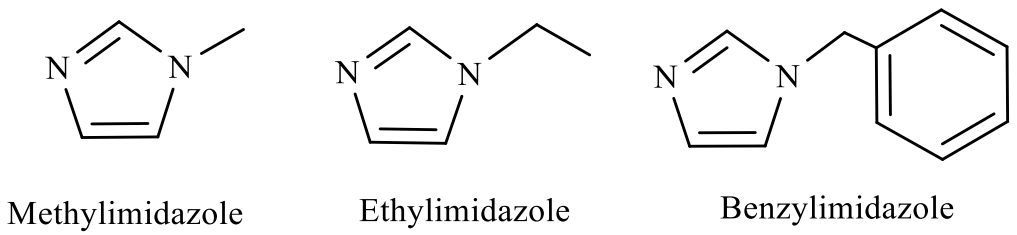


Figure 11. Example structures of *N*-substituted imidazole.

Imidazole ring contains two nitrogen atoms and most derivatives have already one *N*-substituent in position 1. Further substituents can be added to the other nitrogen in position 3. One reaction mechanism breaks the π-bond of the C=N double bond and forms a new σ-bond between nitrogen and substituent, forming *N,N'*-substituted imidazoline ion. This is demonstrated in Figure 12.[21]

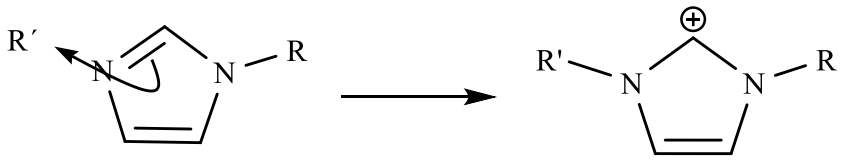


Figure 12. Reaction mechanism of *N*-substituted imidazole reacting into *N,N'*-substituted imidazoline ion.

Substitution can also form *N,N'*-substituted imidazolium salt, which can further react with different nucleophiles, like oxygen, sulphur or tellurium. The carbon in position 2 is already electron deprived as it sits between two nitrogen atoms, being the most liable atom to get attacked by these nucleophiles. Reaction mechanism of *N,N'*-substituted imidazolium ion reacting with nucleophile into position 2 substituted *N,N'*-substituted imidazole is drawn in Figure 13.[21,22]

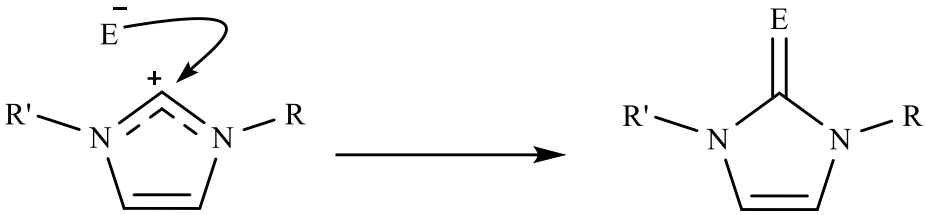


Figure 13. Reaction mechanism for position 2 substituted *N,N'*-substituted imidazole from imidazoline ion. E = nucleophile, such as oxygen, sulphur or tellurium.

N,N'-substituted imidazole can also form larger compounds. With 1,3,5-tris(bromomethyl)-2,4,6-timethylbenzene imidazole can form bridged, sandwich-like compound, having three imidazoles and two 1,3,5-tris(bromomethyl)-2,4,6-timethylbenzene in one molecule. This shows the flexibility of imidazole with its substituents. This leads to some supramolecular applications of imidazole and its derivates. Sandwich-like compound formed by imidazole and trismethylbenzene presented in Figure 14.[23]

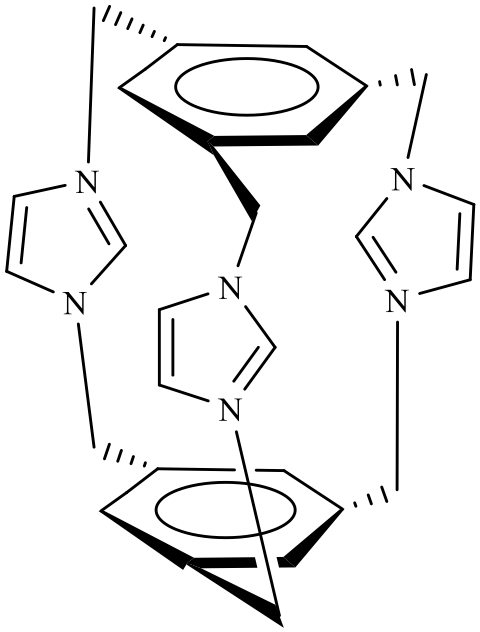


Figure 14. Imidazole sandwich-like compound.

2.3. Imidazole-2-thione

N,N'-substituted imidazole can be also 2-substituted with electronegative atom, like oxygen, sulphur or tellurium. When substituent is sulphur, the compound is called as thione. Imidazolium salt has positive charge, caused by lack of electrons. Nucleophile attacks the electropositive part in imidazole salt, joining in position 2. Structure of 2-substituted *N,N'*-substituted imidazole is presented in Figure 15.

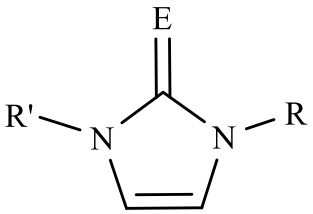


Figure 15. Structure of *N,N'*-substituted E-2-imidazoline, where R and R' are substituents like H, Me, Et and E= O, S or Se.

Angles and bond lengths indicate the type of bonding and orbitals used in bonding as well as properties of the bonded atoms. Angles and bond lengths determined from crystallographic data in *N*,*N*'-substituted imidazole-2-thione are shown in Figure 16. From the figure we can see effect of different derivatives on the bonds and bonding. More electronegative *N*-substituents have shorter bond between the substituent and the nitrogen atom due stronger interaction between the atoms. Bond angles between carbon and nitrogen atoms on the imidazole ring are affected by different substituents and bond angels on the ring show more constant values with less electronegative *N*-substituents. All these properties affect the behaviour of the molecule to some degree.[24]

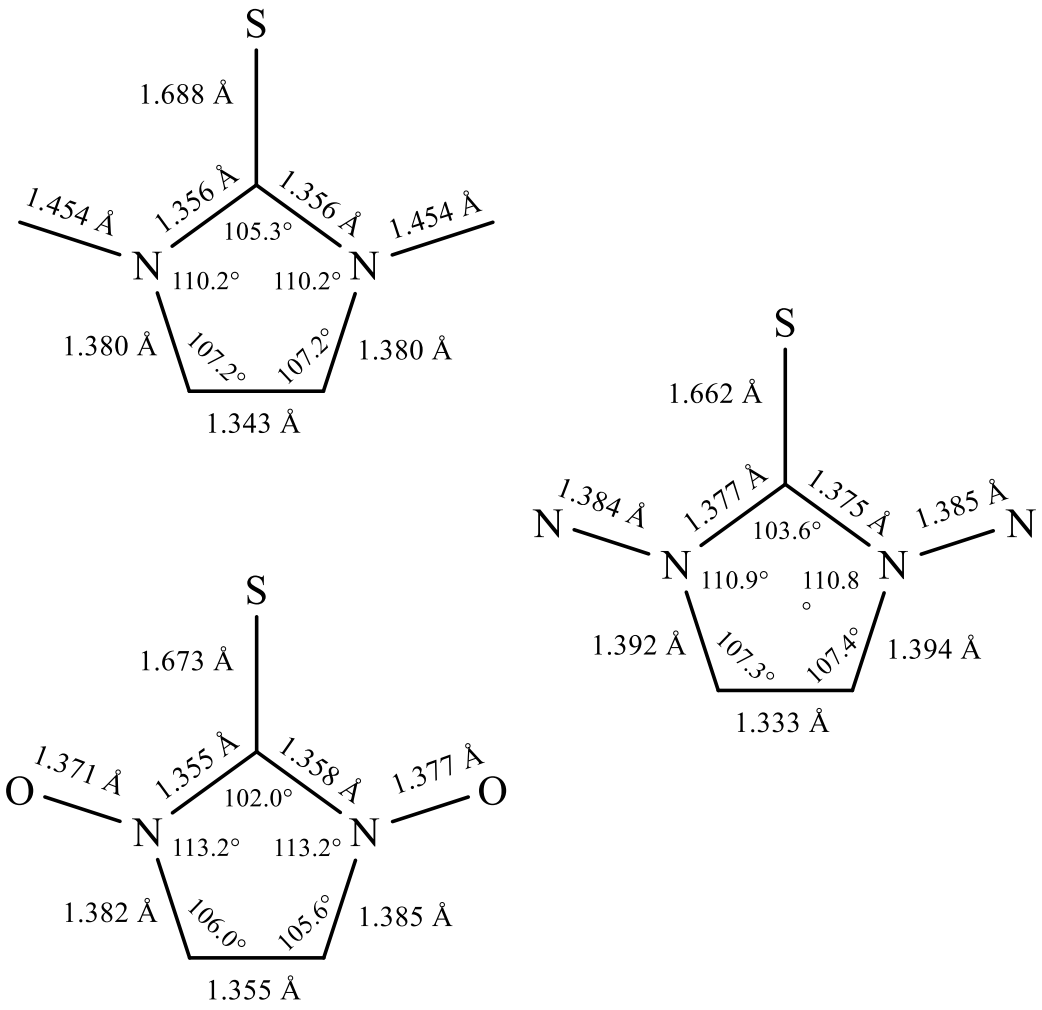


Figure 16. Bond lengths and angles in imidazoline-2-thiones.[24]

2.4. Applications of *N,N*'-substituted imidazole-2-thiones

N-substituted imidazole can be added to alkyl halides from the nitrogen, forming larger compounds. Halogen will form salt with the formed imidazoline cation. After this sulphur can be added to the imidazole position 2. Bromine is the most common halogen in this type of reaction but other halogens, like chlorine or iodine work too although there are much less studies using them.[25]

Although applications for *N,N*'-substituted imidazole-2-thiones are not as widely known as for imidazoles themselves, there are many existing uses for them. Imidazole-2-thiones work as sulphur bond donors, meaning they can coordinate with acceptors. Sulphur gives the molecule two acceptor sites. Imidazole-2-thiones can bond with halogens, like iodine, enabling the formation of bigger molecules and giving imidazole-2-thiones more possibilities to be used further. Sulphur also gives molecules with two imidazole-2-thione units a possibility for the molecule to work as a bidentate ligand. All of these properties give many imidazole-2-thiones high versatility and bioactivity.[26]

Many studies mention the importance of imidazole-2-thiones to pharmaceutical industry. Some imidazole-based drugs are already on the market, and some are being researched as possible drug candidates. Methimazole, 6-propyl-2-thiouracil and carbimazole are *N,N'*-substituted imidazole-2-thione drugs given as treatment for hyperthyroidism. Hyperthyroidism is caused by over activity of thyroid gland when it produces thyroxine. The drugs work by blocking the biosynthesis of thyroxine. [27,28]

1,3-Diethylimidazole-2-thione can form a polymorphous compound, like many crystalline materials can, with $ZnCl_2$. These crystals transform from shape preserving single crystals into amorphous intermediates. Research found new information about mechanism of the transformation. This is an important result as it challenges the popular views of polymorphic phase transition mechanisms.[29]

As mentioned earlier, some imidazole-2-thione molecules with two imidazole-2-thione units can work as bidentate ligand in coordination chemistry. This enables the two sulphurs in imidazole-2-thiones to bond with a central atom, forming bigger molecules. Imidazole-2-thione working as bidentate ligand is demonstrated in Figure 17.[26] Some molecules with three imidazole-2-thione units can work as soft scorpionate ligands as well. Imidazole-2-thione containing scorpionate ligand can bond with three sulphurs instead of two, otherwise working similarly to bidentate ligands.[30]

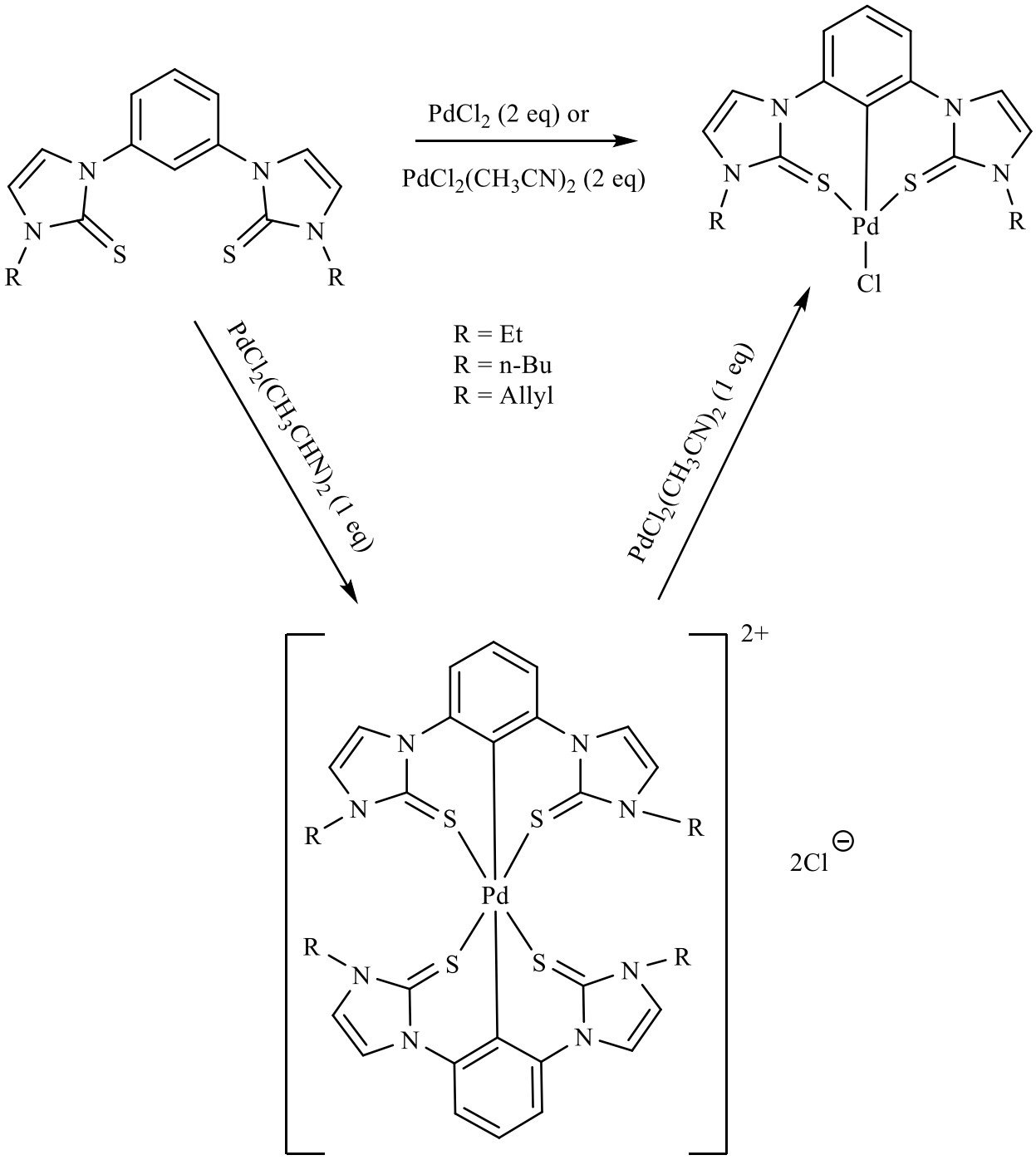


Figure 17. Reaction scheme of imidazole-2-thione working as bidentate ligand.[26]

Another reported application of imidazole-2-thiones in supramolecular chemistry is binding of smaller entities together to form larger supramolecular assemblies. Like shown in Figure 18, imidazole-2-thiones can provide structural integrity to a complex, potentially providing even more applications for supramolecular chemistry.[31]

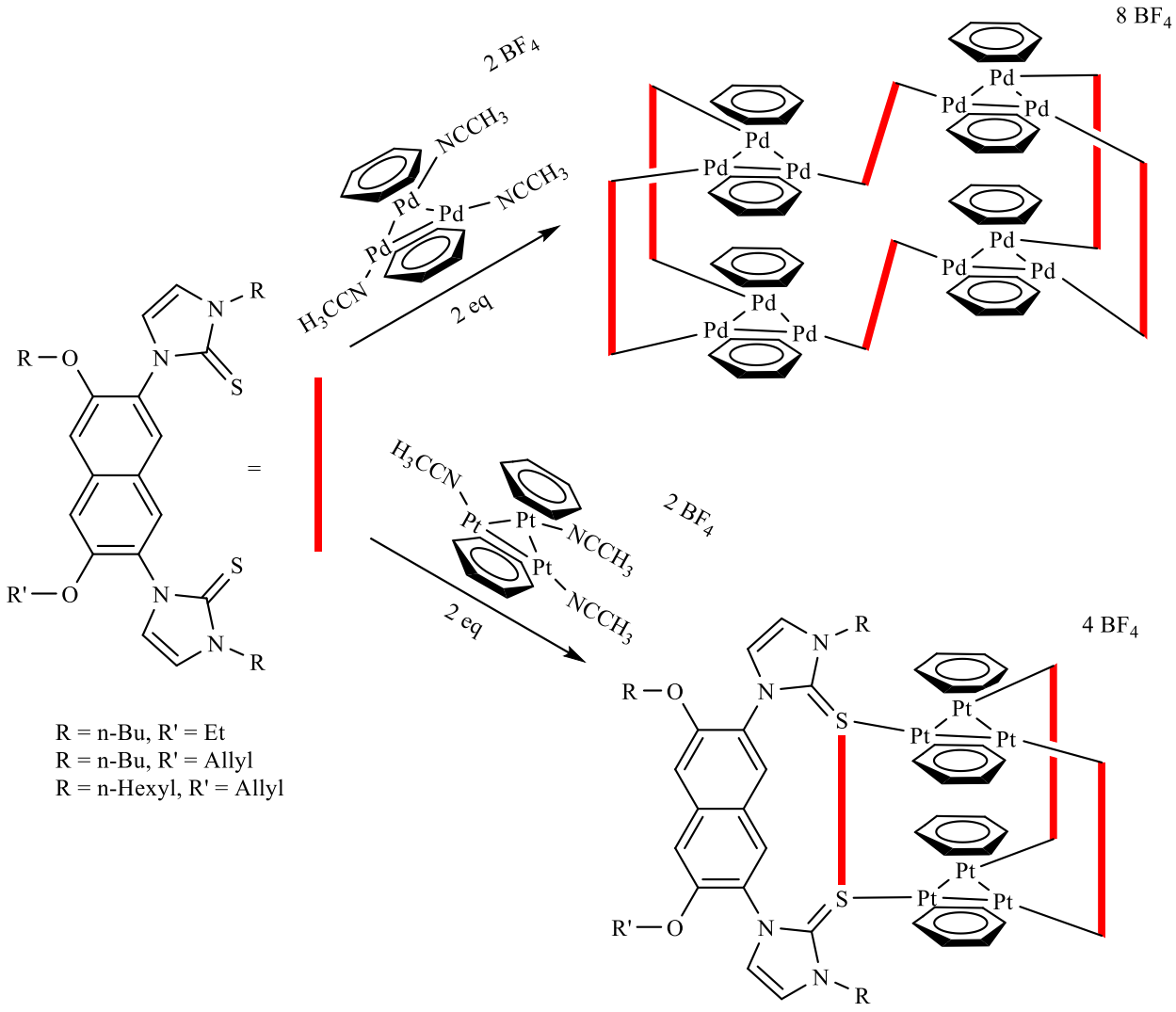


Figure 18. Supramolecular complex with imidazole-2-thione.

3. Synthesis for *N,N'*-substituted imidazole

The literature contains numerous reports about reactions of *N*-substituted imidazoles. Many published articles report reactions starting from *N*-substituted imidazole or *N*-substituted benzimidazole and ending up to imidazole-2-thiones and benzimidazole-2-thiones as products. This thesis focuses on imidazole-2-thiones, as number of applicable molecules would be very high without narrowing the scope. Generic starting materials and products are shown in Figure 19. Many reports about the same reactions done with selenium instead of sulphur are found as well. It is also possible to start with *N,N'*-substituted imidazole-2-thione and get rid of the substituent, but it is not very relevant to this thesis, and it will not be discussed any further. In this thesis focus is on *N,N'*-substituted imidazole-2-thione products. [24]

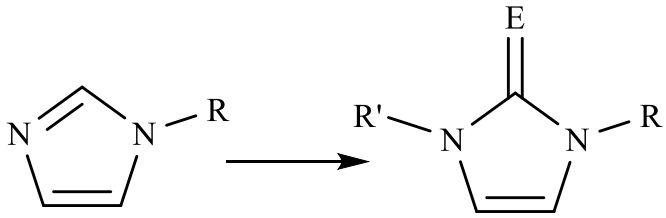


Figure 19. Structures of generic starting materials and products of many reactions reviewed where E = S or E = Se.

3.1. Preparation of *N*-substituted imidazole-2-thione

N-substituted imidazoles are commercially well available. They can also be easily produced with previously mentioned Debus-Radziszewski reaction (see 2.1). *N*-substituted imidazole-2-thione can be produced easily with two-step reaction as well. 1-Substituted imidazole-2-thione can be made from isothiocyanide and amino acetal with Marcwald's method and theoretically another *N*-substituent could be added later, although this could be hard and unconventional. One-pot reaction for this method was reported to be successful with varying R-groups in isothiocyanide. Toluene was required as a solvent, while the reaction in EtOH did not yield any product. Reaction formula is in Figure 20.[32]

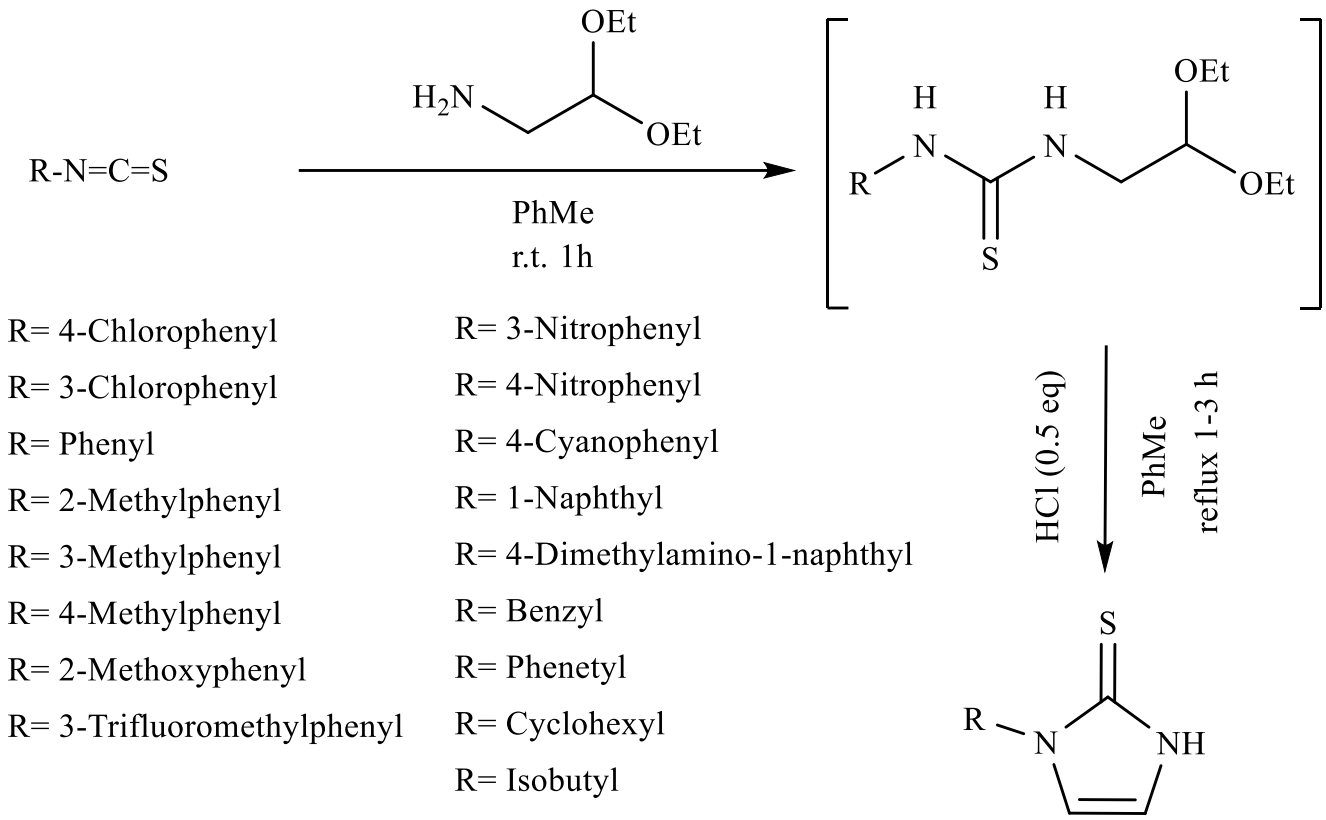


Figure 20. Preparation of *N*-substituted imidazole-2-thione.

3.2. Synthesis of imidazole-2-thiones

Many different reaction paths, conditions and catalysts are known and used in synthesis of various *N,N'*-imidazole-2-thiones. Most reactions start with *N*-substituted imidazole and the range of substituents is varying widely. Yields vary from trace amounts to over 90% depending on the reaction used but focus on this thesis is on reactions that have at least somewhat decent yields.

Most common way to synthesize *N,N*'-substituted imidazole-2-thione is the preparation of intermediate salt in the first step and addition of sulphur to this *N,N'*-substituted imidazole salt in refluxing methanol in the second step, while potassium carbonate acts as a base. Intermediate salt forms when *N*-substituted imidazole forms a bond with the free nitrogen atom, leaving a positive charge on carbon at position 2. This carbon is now electrophilic and substances like sulphur and

selenium will react with it, forming a new double bond while dislodging the hydrogen. This synthesis route is very versatile and known to work with many different *N*-substituted imidazoles combined with different alkyl halides. These types of reactions are demonstrated in Figure 21. Same kind of reactions have also been made with DBU in a mixture of pyridine and methanol. New methods of using triethylamine and dichloromethane as well as potassium *tert*-butoxide and THF have been made and reported in some studies.[24,25]

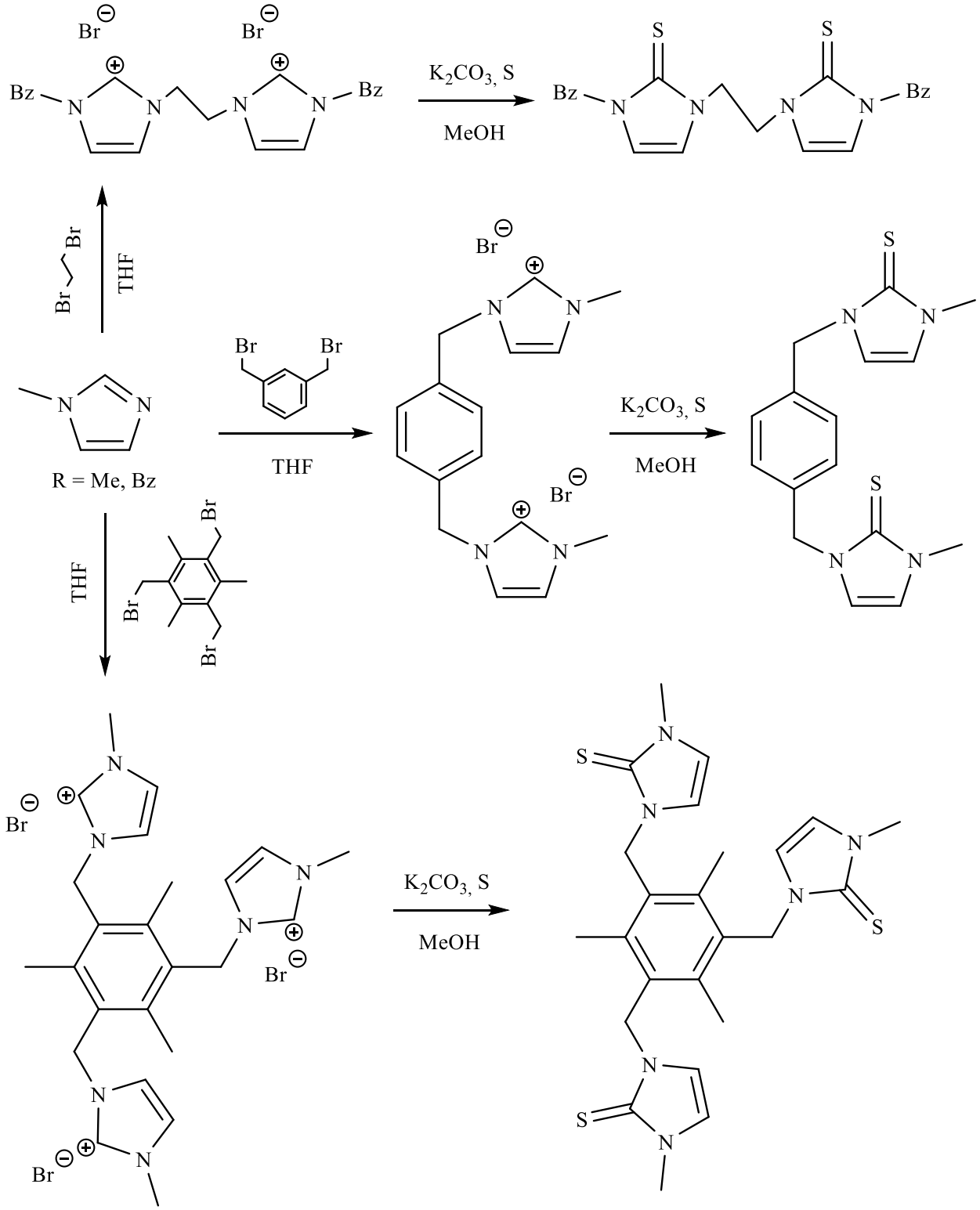


Figure 21. Synthesis of imidazole-2-thiones with potassium carbonate.

Different sulphites can act as a catalyst in reactions of *N*-substituted imidazole with sulphur and ethyl bromofluoroacetate. Sulphites increase the yield noticeably. Many sulphites were tried in the study, but sodium dithionite can be used in some reactions to achieve as high as (92%) yields and it was found to be one of the most efficient catalysts for the purpose of the study. Reactions made in the study are presented in Figure 22.[33,34]

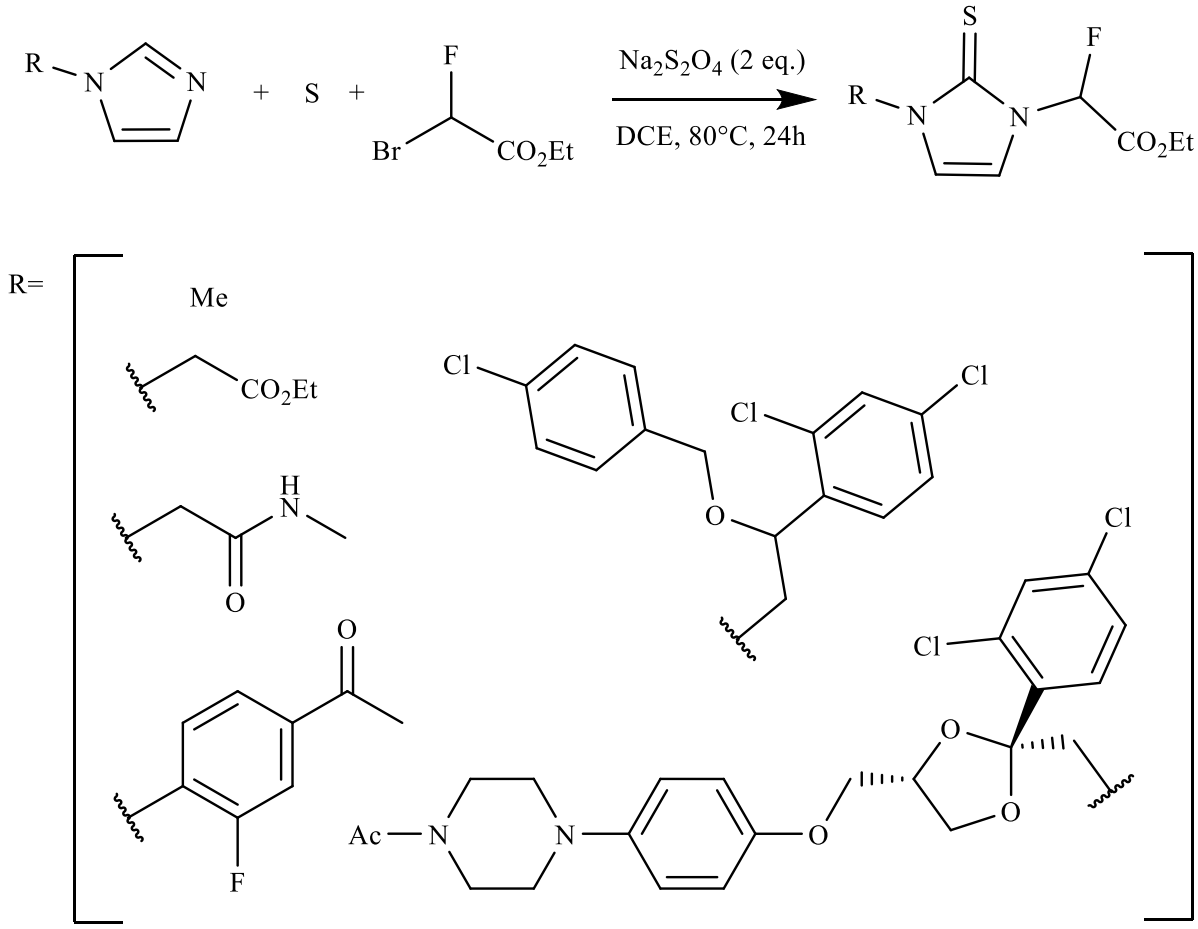


Figure 22. Products with *N*-substituted imidazole.

Reactions with other catalysts are investigated too. A way to synthesize *N,N'*-substituted imidazoles with difluoromethyl substituent was found by using sodium fluoride (NAF) as a catalyst in a reaction with *N*-benzylimidazole and trimethylsilyl 2,2-difluoro-2-

(fluorosulfonyl)acetate (TFDA). Reaction reached yields around 50-65%. These reactions are depicted in Figure 23.[35]

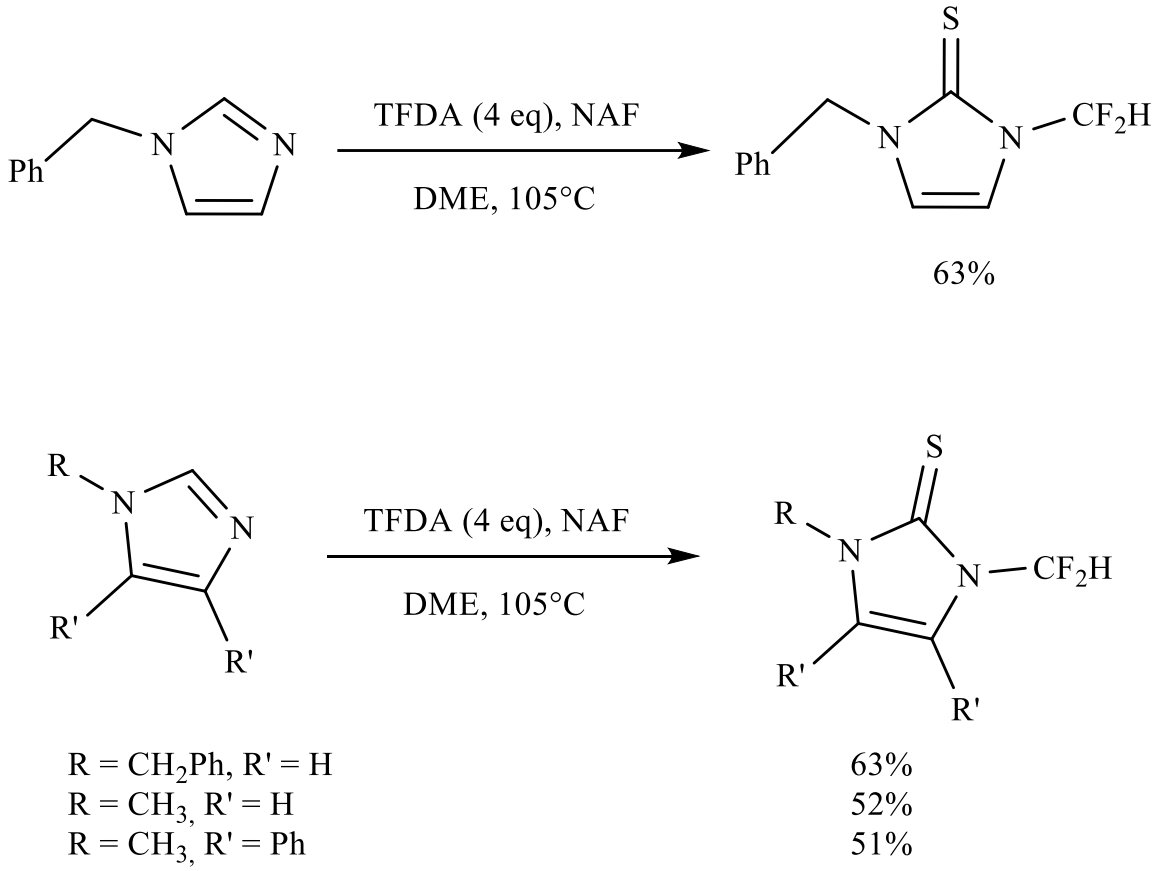
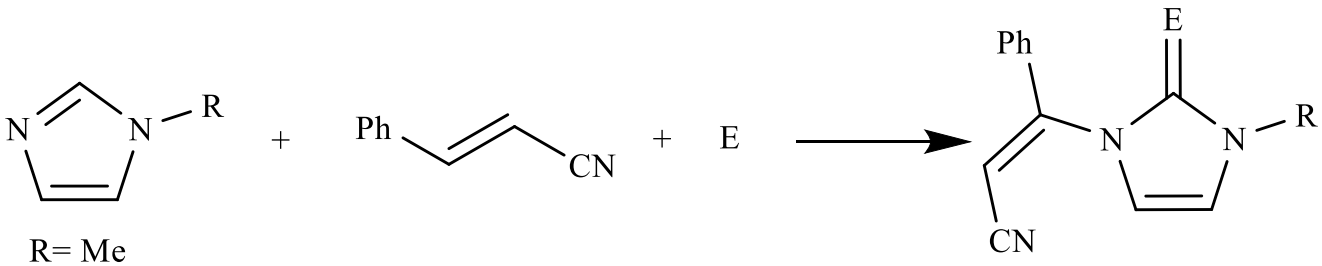


Figure 23. Reaction of *N*-substituted imidazole and TFDA under catalysis of NAF.

Various *N*-substituted imidazoles were shown to be successfully combined with cinnamonitrile and sulphur or selenium. These form *N,N'*-substituted imidazoles, which have a free cyanide group in the end of alkyl chain. Cyanide is used in many reactions, so these imidazole derivatives might have many applications. Reactions performed with simple *N*-substituted imidazoles show good yields, which enables them to be used in industrial scale synthesis if any application is found. The scheme of this reaction is presented in Figure 24.[36]



R= Me

R= *n*Bu

R= *i*Bu

R= $(CH_2)_2SBu$-*n*

R= Bn

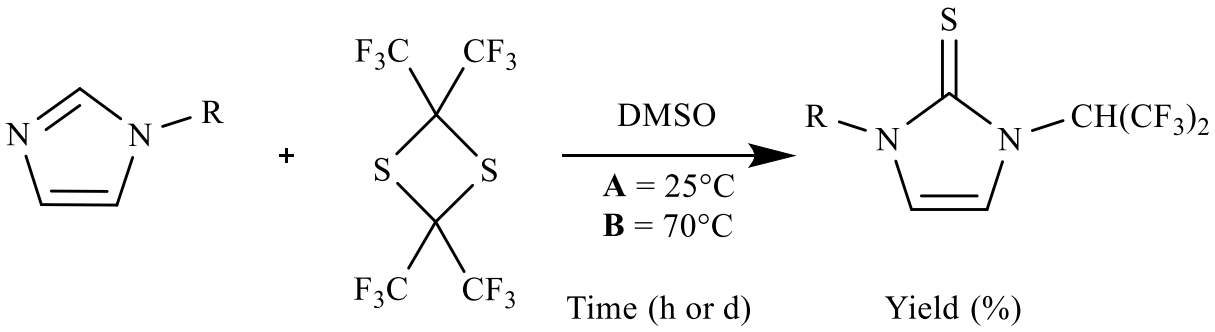
R= Allyl

E= S (r.t, 24h)

E= Se (MeCN, 82°C, 5-15 h)

Figure 24. Preparation of *N,N'*-substituted imidazole-2-thione with cyanide group.

One study showed that using 1,1,3,3-tetrakis-(trifluoromethyl)-1,3-dithietane as a combined source of sulphur and second *N*-alkyl substituent is successful way to synthesize *N,N'*-substituted imidazole-2-thiones. Several reactions were tried, and yields were mostly good. Reactions with aryl substituents were studied as well. They required increased temperature of 70°C due to the electron withdrawing nature of aryl substituents. The synthetic scheme for these reactions with reaction times and yields are presented in Figure 25.[37]



	Time (h or d)	Yield (%)
A:		
R=CH_3	16	85
R=C_2H_5	30	85
R=n-C_3H_7	16	88
R=i-C_3H_7	16	85
R=n-C_4H_9	4d	73
R=$C_6H_5CH_2$	16	71
R=CH_2=$CHCH_2$	16	69
B:		
R= C_6H_5-	28	72
R= p-$CH_3OC_6H_4$-	16	67
R= p-$CH_3C(O)C_6H_4$-	16	48
R= p-$HC(O)C_6H_4$-	16	57
R=CH=CH_2	3d	76
R=$CH(CF_3)_2$	10d	11

Figure 25. Synthesis of fluoride substituent containing imidazole-2-thione.

Sodium salt of imidazole anion (sodium schematically as *N*-substituent) can also be used as starting material and it enables the use of different reaction conditions than *N*-alkyl imidazoles. In the reaction of this study sodium forms a salt with bromide, which is liberated from the second starting material, enabling the imidazole to react with nucleophilic substitution. As the reaction was one pot reaction, intermediate product was not isolated. The yield of reaction was pretty low

but could possibly be improved with different conditions. The schematic presentation of this two-step reaction is shown in Figure 26. [37]

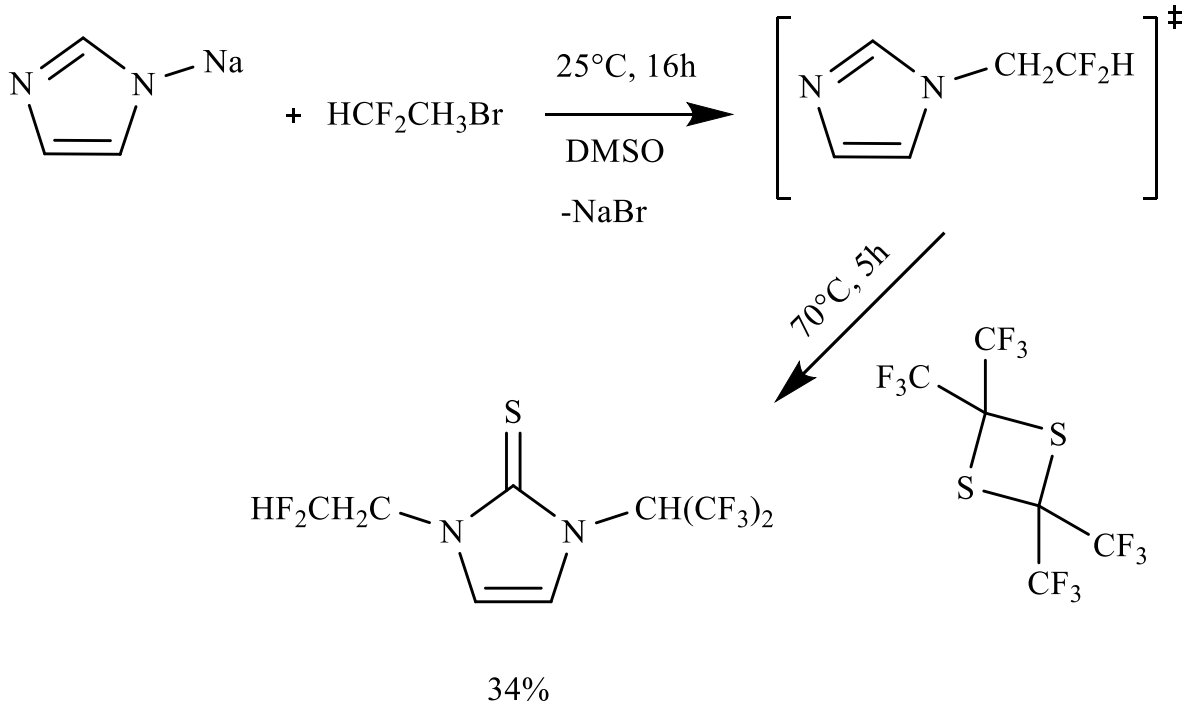


Figure 26. Preparation of *N,N'*-substituted imidazole-2-thione from sodium salt of imidazole.

N-Methylimidazole with bromo-substituent in position 5 was also reacted with 1,1,3,3-tetrakis-(trifluoromethyl)-1,3-dithietane to yield *N,N'*-substituted imidazole-2-thione as shown in Figure 27. The bromo-substituent in position 5 could open up some new synthetic opportunities for further derivatives, as bromine atom can be easily replaced. [37]

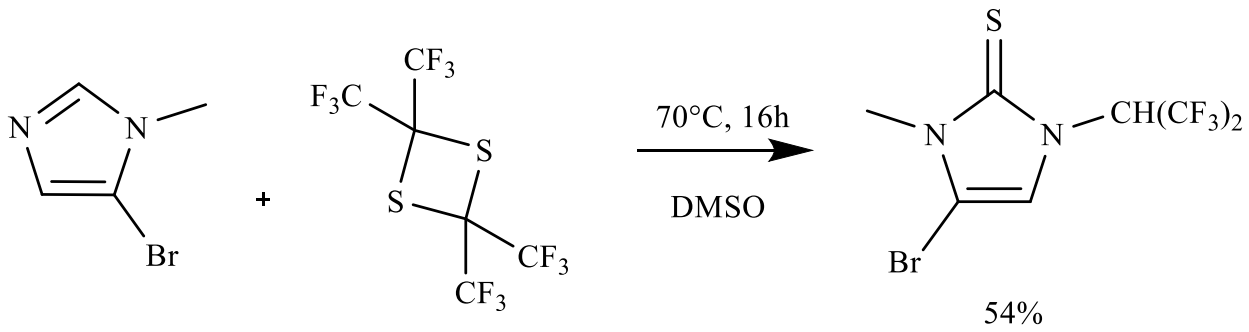


Figure 27. Imidazole-2-thione with bromo-substituent in position 5.

Imidazoles have pharmaceutical applications, as already discussed. One common drug used to treat hyperthyroidism is 6-n-propyl-2-thiouracil. Sulphurless analog of this molecule, 1-methylimidazole, is the starting material of this study. Derivates of the drug molecule with second *N*-substituent were formed. Synthesis of pharmaceutical molecules and their derivatives have been performed with *n*-BuLi as shown in Figure 28. In the first part *n*-BuLi forms organolithium intermediate, from which the lithium is replaced with sulphur or selenium. Reaction is exothermic so cooling is required in the first part. In the second part electrophile is added to reaction and lithium chloride is formed as side product. Formed intermediates undergo a facile migration of the methoxycarbonyl group and form the desired product. [27]

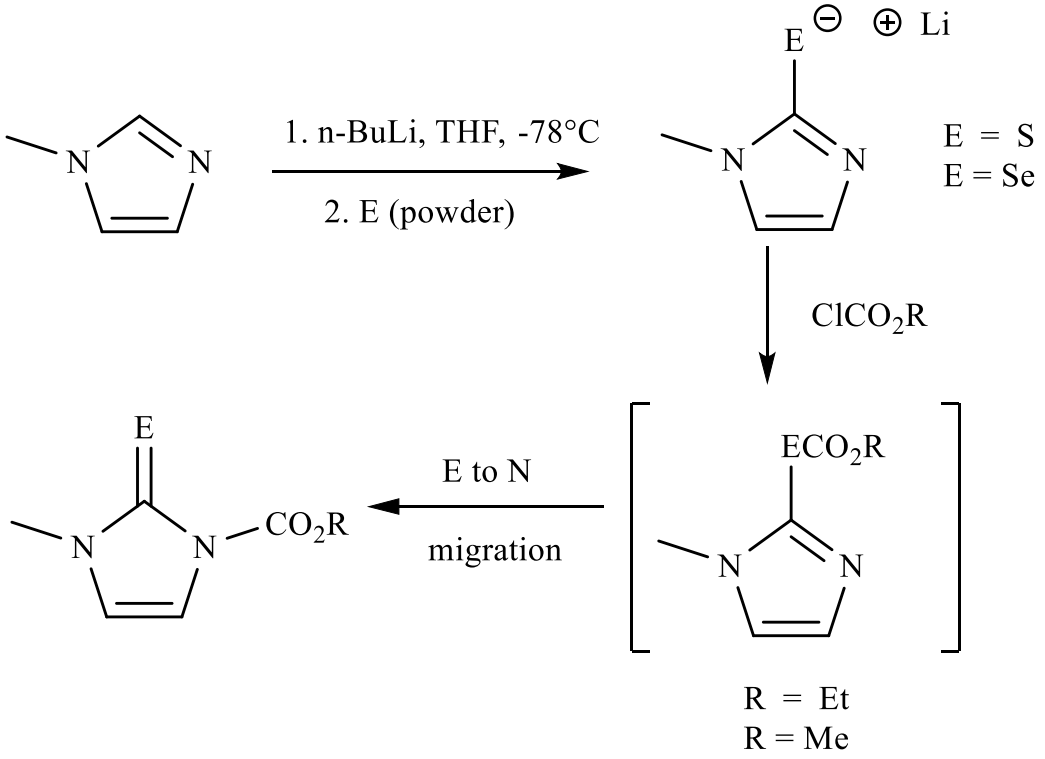


Figure 28. Synthesis of pharmaceutical imidazole derivates.

The same product can be achieved by using different method and materials, as can be seen from Figure 29. The intermediate salt here is different than in the previous example due to different order of substituent addition. In the first reaction intermediate is 1,2-dsubstituted imidazole salt, whereas in the second reaction the intermediate is *N*,*N'*-substituted imidazolinium salt. Having alternative options for synthesis is important, as some side products can be hard to get rid of and they can be toxic, which is a bad drawback, especially for pharmaceutical products. [25]

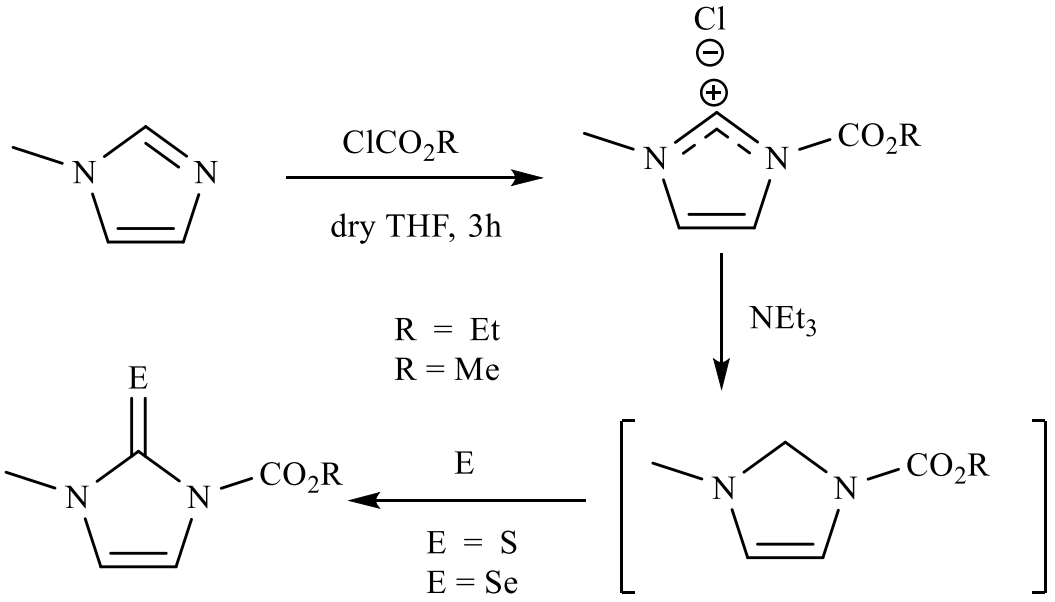


Figure 29. Synthesis of pharmaceutical imidazole derivates with different reaction mechanism.

It was also observed that different reagents can yield the same product, but same starting materials can also lead to dissimilar product in different conditions. As shown in Figure 30, the same intermediate, which is already *N,N'*-substituted imidazole-2-thione, causes two completely different products depending on the conditions of the second reaction part. Intermediate product can be produced in two different ways, which does not affect the next part. When heated, reaction produces different imidazole-2-thione, whereas spontaneous elimination of the carbon dioxide in room temperature without heating causes migration reaction, resulting in *N*-substituted imidazole compound which is considered side product in this thesis. Same reactions can be done with selenium instead of the sulphur as well. Previous observations of heat-induced rearrangement reactions with similar compounds were mentioned as well and these results were in agreement with previous experiments.[27]

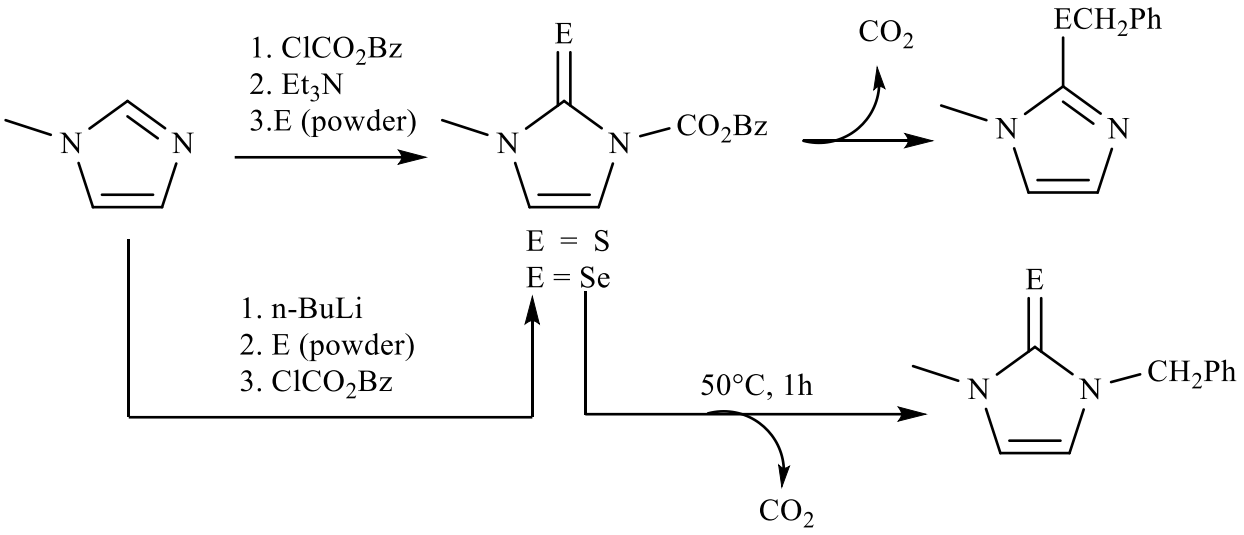
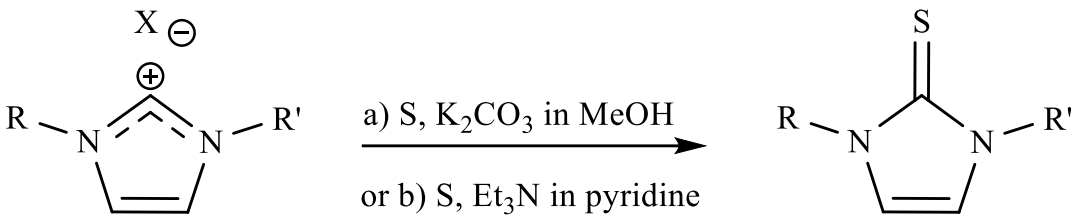


Figure 30. Synthesis of 2-substituted *N*-methyl imidazole as a side product and *N,N'*-substituted imidazole-2-thione from the same intermediate product.

Common way to synthesize *N,N'*-substituted imidazole-2-thiones is by first producing imidazole salt. Then the isolated intermediate is reacted with sulphur in the presence of potassium carbonate in refluxing methanol for extended period of time. Alternative way is to add sulphur and triethylamine to the salt, using pyridine as a solvent. Newer techniques exist, but these well-established synthetic routes are still popular. If addition of sulphur in imidazole-2-thione is done through the salt intermediate, the counter ion affects reactivity of the imidazoline ion. Different *N*-substituents affect reactivity as well. Exemplary reactions are presented in Figure 31. [24]



R= Me, R'= Me, X= CH_3OSO_3

R= OCH_2Ph, R'= Me, X= PF_6

R= OCH_3, R'= Me, X= I

R= OCH_3, R'= OCH_3, X= PF_6

R= NH_2, R'= CH_2Ph, X= Cl

R= N=CHPh, R'= Me, X=BF_4

R= NH_2, R'= Me, X= Cl

R= N=CHPh, R'= N=CHPh, X= Cl

R= NH_2, R'= OCH_3, X= Cl

Figure 31. Preparation of imidazole-2-thione from imidazole salt. Different combinations of *N*-substitutes and counter ions for the salt affect the reaction.[24]

N-substituted imidazole-2-thione can be combined with sodium borohydride to form *N,N'*-substituted imidazole-2-thione soft scorpionate ligands. Scorpionate ligands can bind on the sites, in this case from the sulphurs of the imidazole-2-thione. Reaction was done in solvent-free melt reaction (at melting point) and then Soxhlet extracted with hexane followed by chloroform, which was utilized to remove the excess starting materials. Synthesis of imidazole-2-thione soft scorpionate ligand is shown in Figure 32.[30]

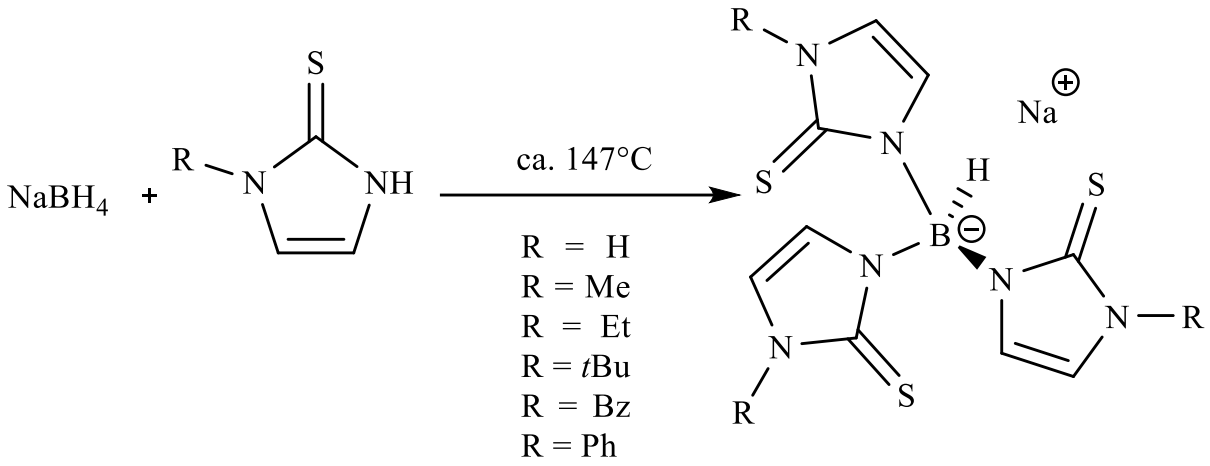
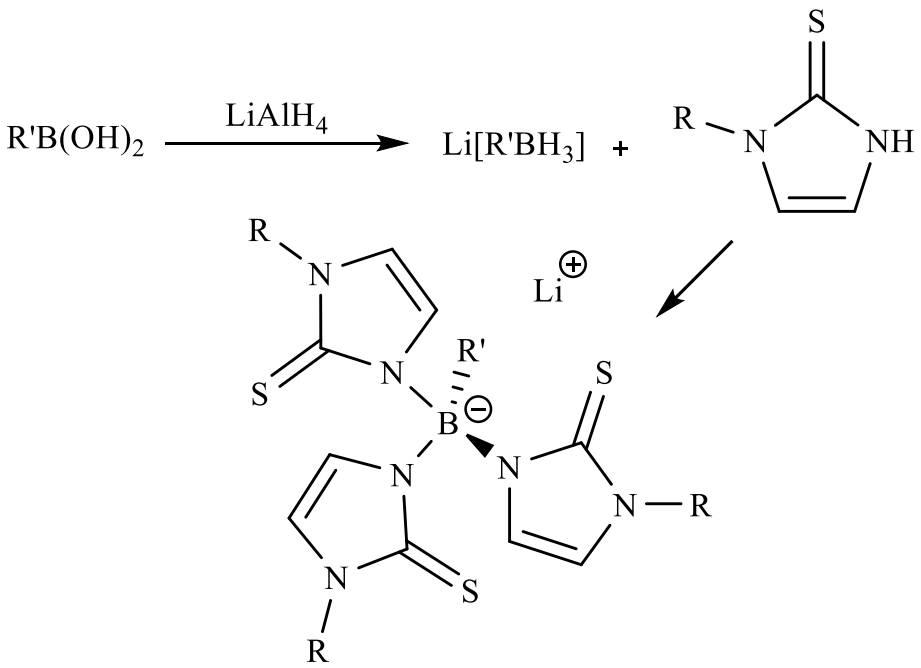


Figure 32. Preparation of imidazole-2-thione based soft scorpionate ligands.

Hydrogen attached to boron can be replaced with other groups as well as the counter ion by the choice of starting materials. Reaction can be done with lithium and potassium borohydrides as a starting materials, resulting in different counter ion. Different *N*-substituted imidazoles were tried as well. Synthesis with different substituents and with lithium as counter ion is shown in Figure 33. When *N*-substituent of imidazole is methyl, boron can be bonded to methyl, *t*-butyl or phenyl. When hydrogen is bonded with boron, there is a large variety of *N*-substituents that imidazole can have.



R = H, R' = H
R = Me, R' = H or R' = Me or R' = Ph
R = Et, R' = H
R = *t*Bu, R' = H
R = Bz, R' = H
R = Ph, R' = H

Figure 33. Preparation of the soft scorpionate ligand with lithium counter ion and generic substitute.

Imidazole-2-thiones can also be synthesized by the use of ultrasound and electrochemical synthesis from ionic 1,3-dialkylimidazolium liquids. Reaction does not use strong bases or produce side products and yields are very high. Different *N*-substituted imidazoles were tried with varying conditions. Different anions, various amounts of sulphur, heat and ultrasound with varying irradiation times were tried. Ten minutes of ultrasound was concluded to be the optimal with 2 mol of sulphur powder while tetrafluoroborate was the anion. In these conditions 99% yield were achieved with *n*-butyl, ethyl, *n*-hexyl, *n*-octyl and *n*-decyl imidazoles. Ultrasound and electrochemical synthesis of imidazole-2-thiones are shown in Figure 34.[38]

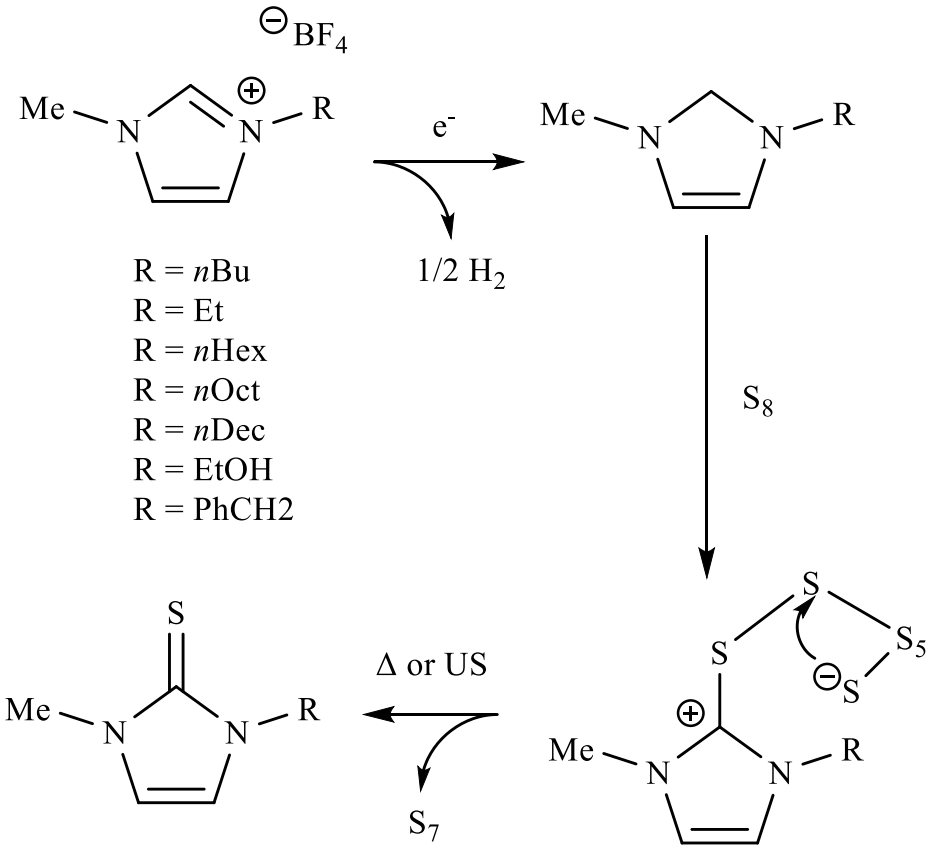


Figure 34. Electrochemical and ultrasound synthesis of imidazole-2-thione.

The literature contains several methods to synthetize *N,N'*-substituted imidazoles and there are many reported studies that were not covered in this review, as it would take unreasonable amount of time to cover all of them. Line of study is very popular as it has many applications in different fields. New methods are constantly developed, as imidazole synthesis has numerous applications in pharmaceutical and supramolecular chemistry. In industrial chemistry the faster and cheaper production with better yields is very important and that is why the same product might have many different industrial scale synthetic routes with different catalysts and conditions as well as with various starting materials.

3.3. Purification and analysis

Purification of products is essential for removing the side products and, therefore, for the realistic yield. Starting materials as well as different isomers are commonly found in raw products and getting rid of the unwanted substances is crucial to determine yield and for further use of the product. Finding the right purification method can be hard. Purification methods working for similar substances might not work at all for other substance. One of the most popular purification methods is flash column chromatography for its speed, easiness, and cost effectiveness. Recrystallization is another easy way to purify product, although it does not apply to all products. Problem with both methods is finding the right solvents. There are other ways to purify chemicals, but they are not the focus on this thesis as these two are used in most of the studies made, as well as in the experimental section of this thesis.

Flash column chromatography seemed to be the most common way to purify products in the reviewed studies. Flash column chromatography is an easy and cheap way to purify products and if done well, results in pure product. This is the reason for the popularity of the method. Flash column chromatography is done by filtering raw product trough stationary phase, usually silica or alumina, with appropriate solvent combo (e.g., EtOAc/Hex or PetEt/EtOAc), which is called mobile phase or eluent. Molecules in raw product, infused in the mobile phase, interact with the stationary phase differently and therefore they move at different speeds and take different time to go through the column. This causes different compounds to separate from each other. Small fractions are taken from the liquid coming through the column to get specific compounds in each test tube. Pure product can be obtained from one or many of the fractions, depending how well eluent was chosen for the purpose as well as amount of the product. This procedure can be done by hand in column, taking different fractions in test tubes and checking the change in substance by TLC or by using specific automated instruments for flash chromatography.

Few of the studies reviewed used recrystallization as a purification method or as a method to form crystals. Recrystallization is not as popular as flash column chromatography, as finding the right solvents can be challenging and even then, getting just the pure product to crystallize might be

impossible, as many impurities might crystallize too. Recrystallization happens by dissolving the raw product usually in minimal amount of hot solvent. When solution cools down, product crystallizes. Impurities in the best case remain dissolved in the solvent. Sometimes another solvent is needed to solidify the product from the other solvent. Solid material is filtered, and it should be mostly pure product, if solvents were appropriate.

Analysis of the products is important for finding out the purity of the product. Usually, best certainty is achieved by using multiple methods. NMR is the fastest and therefore most popular analysis method in many organic reactions to see if the reaction has happened correctly. MS is fairly fast and accurate method as well. Single crystal X-ray is by far the most accurate method in determining the structure of the molecule, but it takes time and only works for crystalline products.

In organic synthesis, purities of starting materials and products are usually analysed with NMR and MS. Also, single crystal X-ray data can be collected from well crystallized products, which gives the best information about the molecular structure of the compound and its interaction sphere in the solid-state. In almost all literature studies reviewed in this thesis the authors had analysed their products with NMR, most of them with X-ray, some with MS as well.

EXPERIMENTAL SECTION

4. Aims and goals

As stated before in the literature review, one of the most common ways to produce *N,N'*-substituted imidazole 2-thiones is two-step reaction, in which an intermediate salt is formed in the first part and sulphur is added to that salt in the second part. In this experimental work the synthesis of *N,N'*-substituted imidazole-2-thiones were aimed to be done with the most common method of the two-step reaction, by the use of potassium carbonate and sulphur powder in methanol in the second part. Series of eight different *N*-substituted imidazoles would first to be added to five different mono-, bis- and tris- bromomethylbenzenes.

Goal for a series of experiments conducted as a part of preceding project was to produce *N,N'*-substituted imidazole-2-thiones from different alkyl bromides and thiocarbonyls. However, reaction resulted in a bond between carbon and sulphur, which was not the wanted result. Therefore, new two-step reaction method to prepare *N,N'*-substituted imidazole 2-thiones starting from alkyl bromides and *N*-substituted imidazoles was found from literature. The found method turned out to be functional and trifurcated products E1 and E2 (see below) were obtained. Synthesized molecules were found to be good acceptors for hydrogen and halogen bonds and therefore they can form interesting supramolecular structures. This gave the spark to try other substituents and cores as well. This resulted to the application of that reaction in this thesis. General scheme of utilized reaction of alkyl bromide and *N*-substituted imidazole is presented in Figure 35.

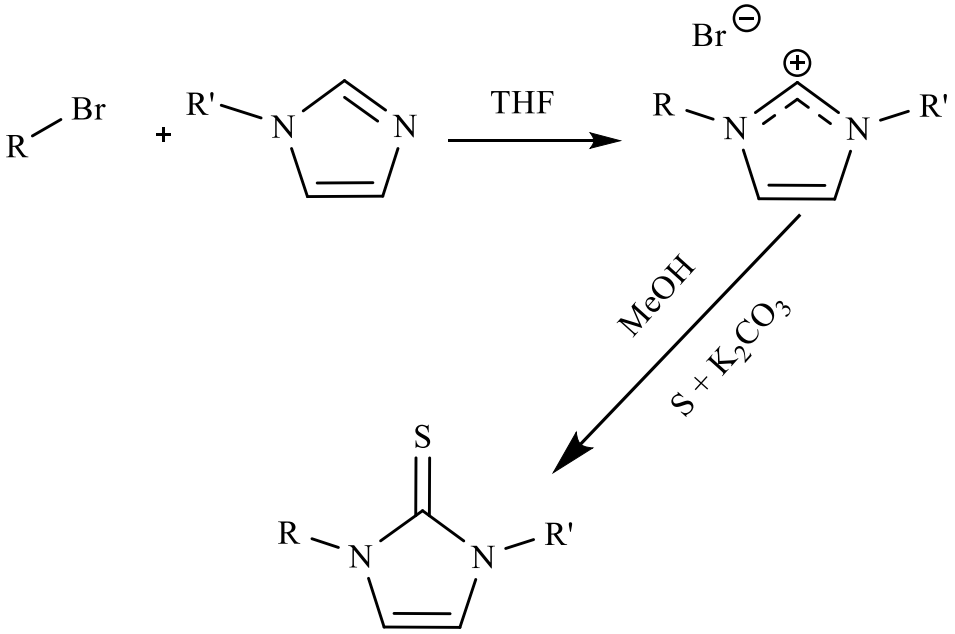


Figure 35. General scheme of two-step reaction between alkyl bromide and *N*-substituted imidazole with addition of sulphur.

Most of the performed reactions worked, at least to some degree. Caffeine (**13**) was only ligand that did not react with **1** or **5** at all (Figure 36). The product after the reaction was almost pure **13** and no signs of desired reaction were observed. For successful products crystallization experiments were made with 1,2-diiodotetrafluorobenzene, 1,4-diiodotetrafluorobenzene and iodine to obtain halogen-bonded complexes. The used ratios were 2:3 (product/donor) and 1:1 for trifurcated products and 1:1 for other products. These crystallizations were made in chloroform, dichloromethane and acetonitrile. Crystallization experiments were made in pure solvents as well. All used starting materials in this experimental work are listed in Figure 36.

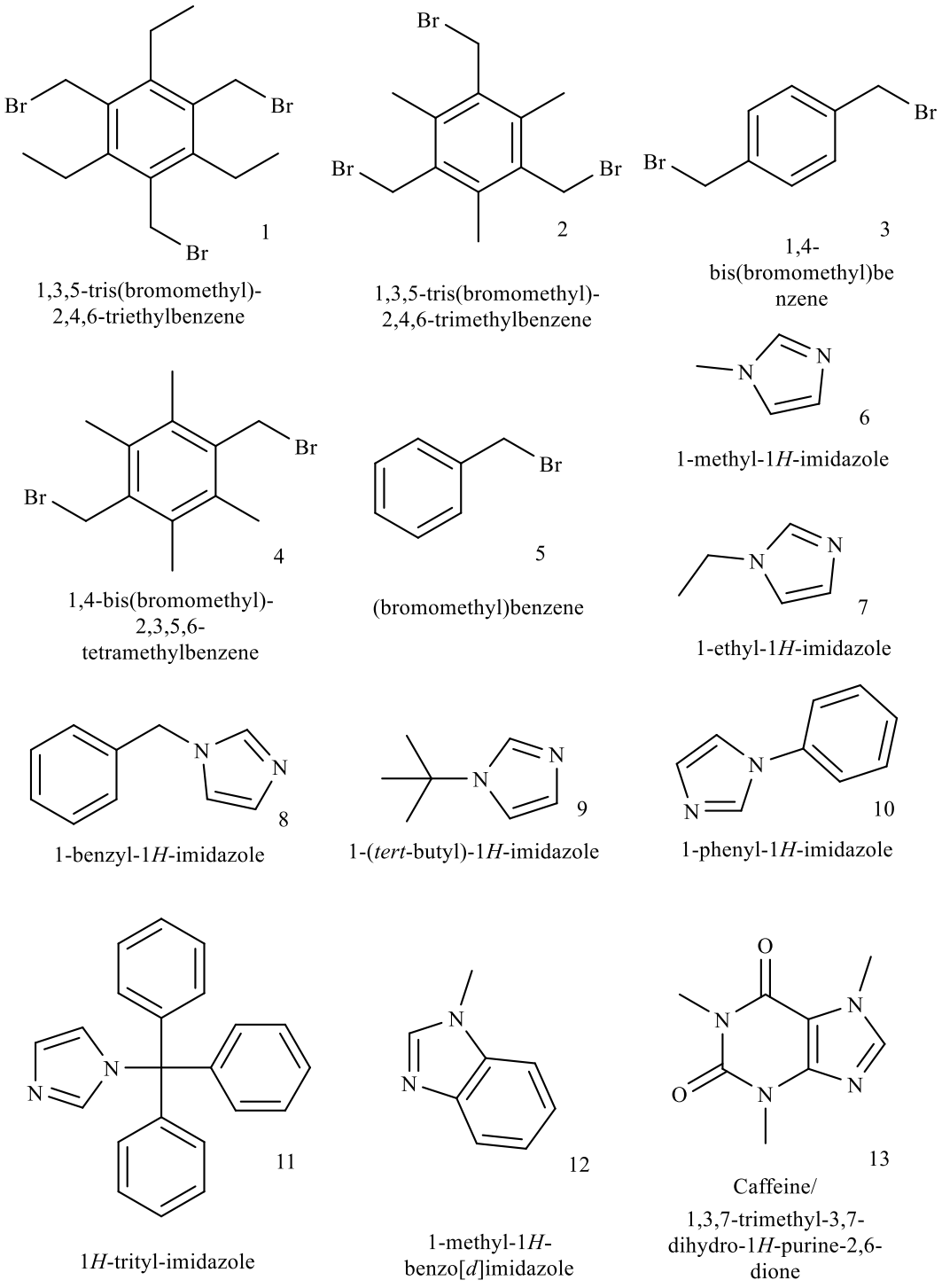


Figure 36. Starting materials of the experiments.

5. Experimental reactions and results

5.1. General synthesis plan

Original synthesis plan for *N*,*N*'-substituted imidazole-2-thiones was modified from the literature and it was applied in every reaction.[25] Compounds **E1** – **E21** were synthetized with two-step reaction from five different benzylic bromides **1** – **5** and eight differently substituted imidazoles **6** – **13** (Figure 36). Three different methods related to number of bromomethyl groups in starting material (see Chapter 7) were utilized in the study. Molar amounts were kept constant, although they vary a little bit due human inaccuracy in measurements. Reflux time is also different in step 1 due to slower reactions of some starting materials. Reflux times and the exact reagent amounts used in step 1 of three separate preparation methods are listed in Table 1.

When the starting materials were refluxed in THF (tetrahydrofuran) for 3 – 28 h they formed an intermediate salt. Reaction was monitored with TLC, eluents being 1:1 Hex/EtOAc, 2:1 Hex/EtOAc or 1:1 PetEt/EtOAc, depending on the compound. The product was filtered and washed with ether and dried overnight in fume hood or 2h in vacuum. Then the intermediate salt was refluxed in methanol with sulphur powder and potassium carbonate for 24h and final product with sulphur attached to the imidazoles was supposed to form. TLC was not measured at this point as the starting material of the reaction, the intermediate salt, did not move on the plate. Residue was dissolved into chloroform and filtered through Celite (Hyflo Super-Cel). To check the purity of obtained crude product ^{1}H NMR spectrum was acquired. Purification was done by flash column chromatography or recrystallization, if needed. ^{1}H-, ^{13}C-, ^{1}H,^{13}C HMBC- and ^{1}H,^{15}N HMBC NMR- and ESI-MS spectra were measured from every product and the spectra of successful products are found as Appendices of this thesis. Crystallization experiments for successful compounds were also performed (see below).

Table 1. Exact amounts of used reagents and reflux time on step 1.

Core: tris- **bis-** **mono-**	**m(Core)** **1.0 mmol** **1.0 mmol** **1.0 mmol**	**m(Imidazole)** **3.0 mmol** **2.0 mmol** **1.0 mmol**	**m(S) (mg)** **3.0 mmol** **2.0 mmol** **1.0 mmol**	**m(K_2CO_3) (mg)** **3.7 mmol** **2.5 mmol** **1.4 mmol**	**Reflux time in step 1 (h)**
E1	444 mg (**1**)	241 µl (**6**)	105	552	3.5
E2	406 mg (**2**)	242 µl (**6**)	102	540	3
E3	448 mg (**1**)	289 µl (**7**)	96	515	3.5
E4	400 mg (**2**)	289 µl (**7**)	95	513	3
E5	440 mg (**1**)	474 mg (**8**)	101	515	24
E6	390 mg (**2**)	477 mg (**8**)	105	520	3.5
E7	441 mg (**1**)	343 µl (**9**)	90	478	3
E8	400 mg (**2**)	404 µl (**9**)	100	505	3
E9	440 mg (**1**)	381 µl (**10**)	96	509	24.5
E10	404 mg (**2**)	381 µl (**10**)	95	508	27.5
E11	440 mg (**1**)	929 mg (**11**)	112	518	3
E12	399 mg (**2**)	930 mg (**11**)	111	513	5
E13	270 mg (**3**)	159 ml (**6**)	65	349	4
E14	320 mg (**4**)	160 µl (**6**)	66	346	3
E15	319 mg (**4**)	193 µl (**7**)	68	351	4
E16	317 mg (**4**)	319 mg (**8**)	66	346	3
E17	319 mg (**4**)	270 µl (**9**)	66	344	3
E18	119 µl (**5**)	311 mg (**11**)	36	176	24
E19	119 µl (**5**)	135 mg (**12**)	33	170	24
E20	398 mg (**2**)	396 mg (**12**)	105	518	3.5
E21	119 µl (**5**)	127 µl (**10**)	34	173	24

5.2. Synthetic results

Almost all reactions produced at least some desired product but most of the products were impure mixtures and needed purifying, which was problematic in some cases. Some compounds could not be purified at all because no suitable method was found in the limited time. The purification was performed by flash column chromatography or recrystallization, depending on the properties of the product. Products **E9** and **E10** were not able to be purified at all, by either of the methods. Products **E7**, **E8** and **E20** almost completely disappeared in purification by flash column chromatography, although the trace amounts that came trough were pure. This is why chromatographic attempts were abandoned for **E11-E15** that were clearly mixtures and they could not be recrystallized. Products **E1-E6** were managed to purify by recrystallization and **E16-E19** and **E21** were pure enough in crude form without extra purification.

As we can see from the MS spectra, for most of the tris-imidazole-2-thione products $[M-S+H]^+$ adduct ions were observed. This is likely due to either the second step of reactions were not happening completely even with slight excess amounts of sulphur or sulphur were unexpectedly cleaved from the compound in the ionization process (ESI). However, NMR spectra do not show clear evidence of deficient reactions. Longer mixing time and usage of catalyst could fix this, although finding suitable catalyst could be hard. Strong $[M+K]^+$ adducts were found in MS spectra due to the use of potassium carbonate in the second part of synthesis and the removal of potassium salt traces (KBr) were not complete. In second patch of MS measurements done in 03.06.2022 there seems to be systematic error, probably problem in calibration. Results seem to be systematically at least m/z 0.05 units under the theoretical value.

5.3. Crystal structures

Single crystal X-ray diffraction analyses were done for those synthetic products, which gave suitable crystals after (re)crystallizations. Crystals were grown in variety of common organic solvents (Table 2) or their mixtures and the best ones, if obtained, were selected for the analysis. Ten crystal structures of products, which were **E1**, **E3**, **E5**, **E7**, **E15** – **E17** and **E19** – **E21**, were

obtained. Most of them crystallized as such, but for **E1** a dihydrate (**E1**·2H_2O) and for **E5** and **E20** solvate (2**E5**·3MeOH and **E20**·2$CHCl_3$) structures were found. The obtained crystal structures are shown in Figure 37. The other products did not produce analysable single crystals.

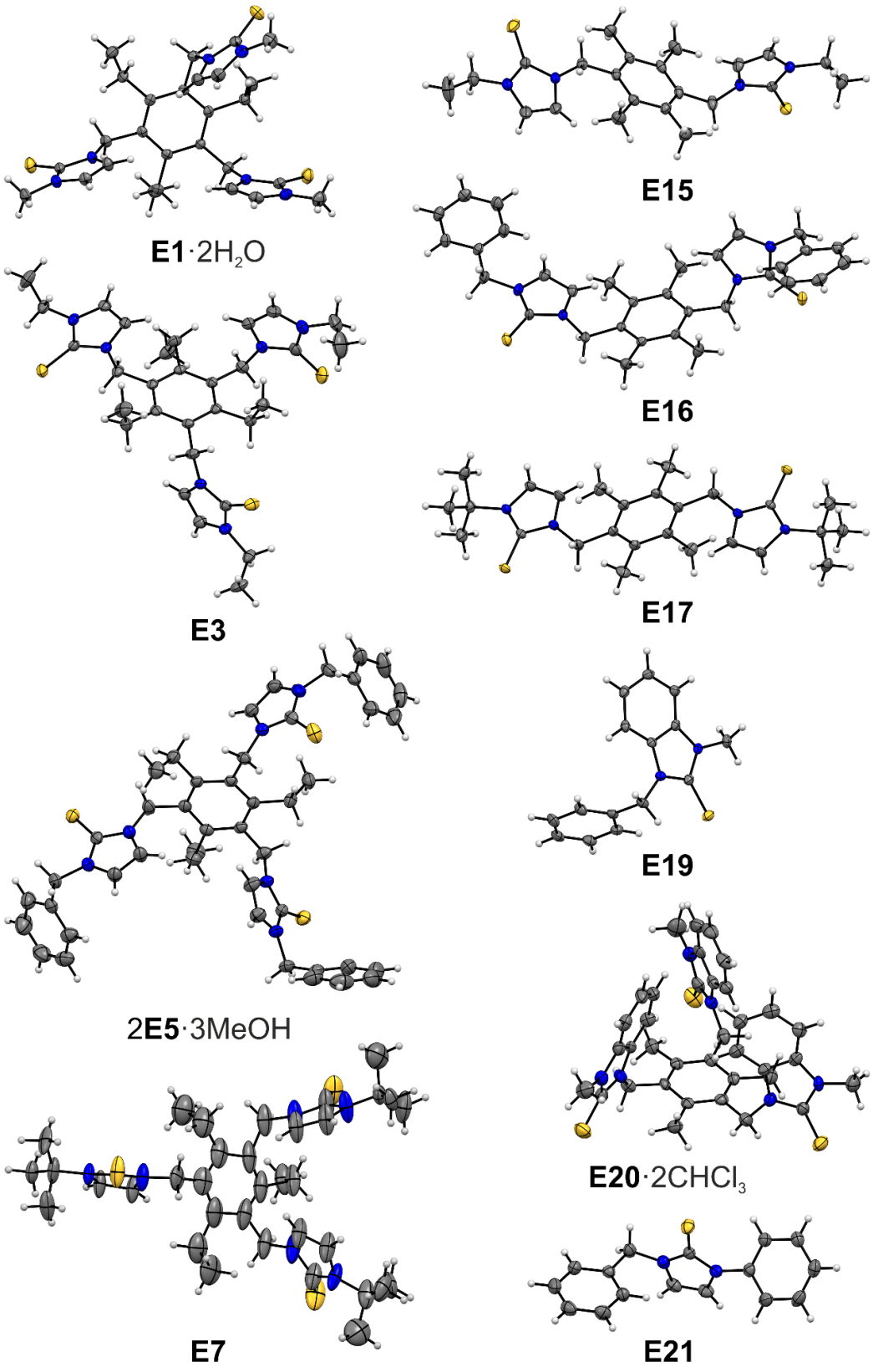


Figure 37. Crystal structures of synthetic products. Solvent molecules removed for clarity.

The crystallizations with iodine the products **E2**, **E13** and **E16** provided structures of halogen-bonded complexes from DCM solutions. The complexes with **E2** and **E16** crystallized as DCM solvates (**E2**·3I_2·DCM and **E16**·2I_2·2DCM) and all sulphur atoms in both structures accept halogen bonds from I_2 molecule. Product **E13** provided a polymeric structure with $[S–I–S]^+$ halogen-bonded units and I_3^- counterions ($[\mathbf{E13}\cdot I]^+I_3^-$), which is the first polymeric $[S–I–S]^+$ system ever observed. Product **E14** crystallized with 1,2-diiodotetrafluorobenzene (1,2-DITFB) from ACN solution to give halogen-bonded complex **E14**·2(1,2-DITFB)·2ACN. The obtained crystal structures of halogen-bonded complexes are shown in Figure 38. The other crystallization attempts to obtain structures of did not give analysable during in the course of this thesis.

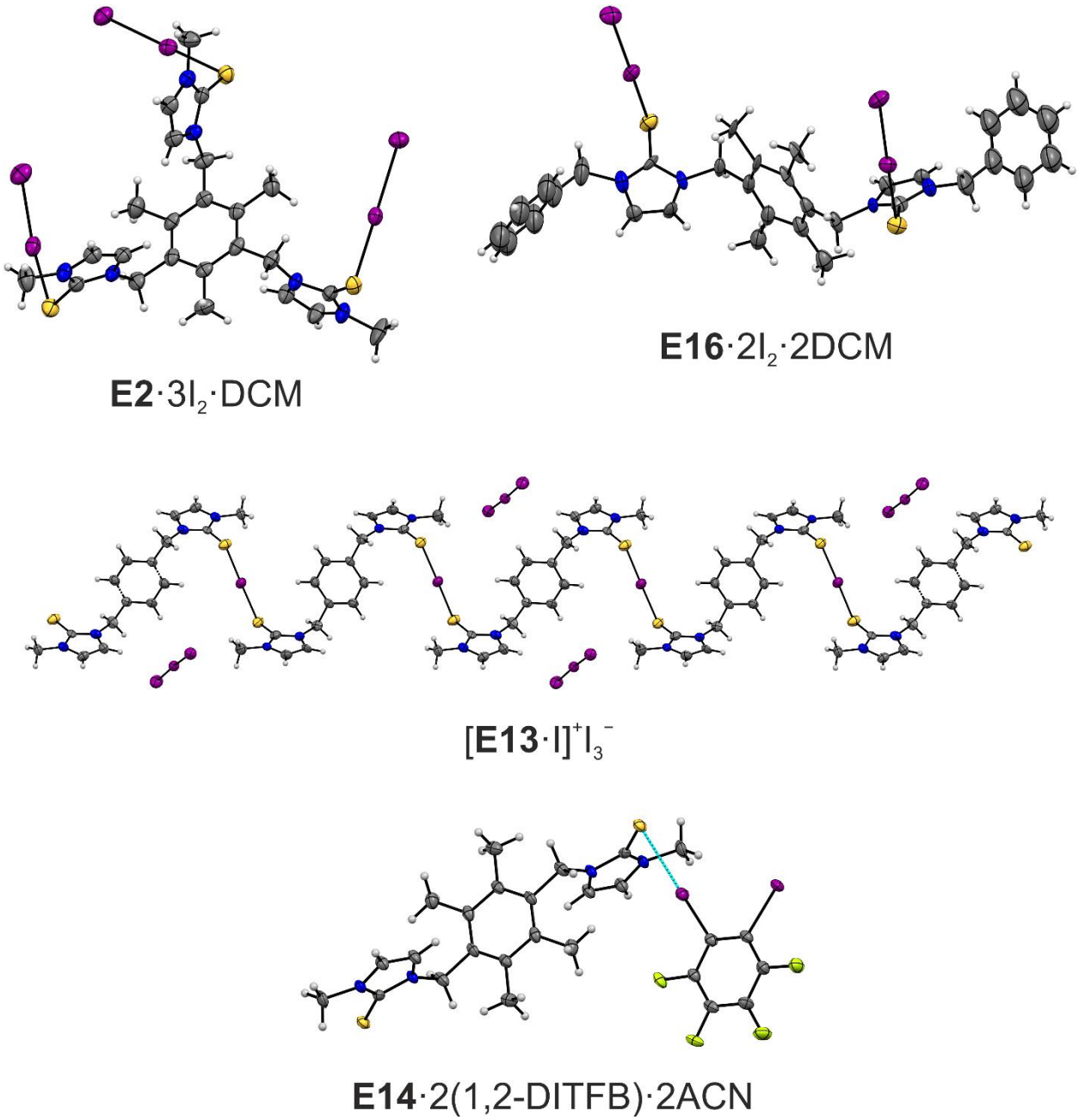


Figure 38. Crystal structures of obtained halogen-bonded complexes. Solvent molecules removed for clarity.

6. Conclusion

It is well demonstrated in this thesis that imidazoles and their derivatives have a rich chemistry. Many reactions to produce *N*-substituted imidazoles are known, but Debus-Radziszewski reaction is the most common and important way. Another substituent can be added to the *N*-substituted imidazole to form *N,N'*-substituted imidazole.

As seen in the literature review, applications for imidazole-2-thiones are wide and large. Sulphur can be added to the *N,N'*-substituted imidazole in many ways to produce imidazole-2-thiones. There are many options for catalysts, reagents and reaction conditions when trying to produce different imidazole-2-thiones. Synthesis with intermediate imidazolium salt is the most common way, but other mechanisms with different catalysts have been discovered as well. Electrochemical catalysis and ultrasound can be used as catalyst for imidazole-2-thione synthesis instead of chemical catalysts as well. This variety in ways to produce imidazole-2-thiones and in final products provides many applications for imidazole-2-thiones in many fields of chemistry, biggest ones being biochemistry and pharmaceutics.

As seen in the experimental section, reactions are not perfect. Almost every performed reaction yielded product, but most of them were mixtures and purification procedures were needed. A few crude products could not be purified at all. In general, half of the experimental reactions made were considered successful after purification. Recrystallization procedures lead in many cases to formation of distinctly crystalline material, which were directly or after further crystallization experiments analysable with single crystal x-ray diffraction method. Crystal structures of ten products were obtained. The crystallizations with halogen bond donors led to further four crystals structures of halo-bonded complexes. Mass spectrometric analyses gave a possible indication that the second step of the reactions might not happen completely. But any other used analytic method did not support that and the observed deficiency in sulphur content remained unclear.

It was noticed form MS spectra that sometimes with the original procedure, one sulphur did not attach to the imidazole on the second step, when reacting with benzylic trisbromides. This anomality might also be due unexpected cleaving of sulphur in the ionisation process (ESI), as NMR spectra does not show any deficiency in the reaction. If reaction is deficient, different alkyl halides, like alkyl chloride or iodine, different solvents, higher amount of sulphur in the second step, and longer reflux time or use of another catalyst could help sulphur bond to all of the imidazoles in second step.

In future research it could be interesting to try the same reactions done in the experimental part with different azoles, for example triazole and its derivatives, as they have many common properties with imidazole and its derivatives. Reactions with four-, five- and six-armed alkyl halides would also be interesting, but they would most likely require some kind of catalyst, as possible problems with the sulphur attaching into the imidazole were noticed with three handed alkyl bromide. Use of chemical catalyst is problematic, as they need to be removed and finding suitable catalyst can be very challenging. Ultrasound could work as catalyst for certain types of imidazole-2-thione synthesis.

7. Experimental procedures

7.1. Used materials and methods

All chemicals used in this work are listed in Table 2 with their suppliers, purities, and CAS-numbers. Products were analysed with ^{1}H-, ^{13}C-, ^{1}H,^{13}C-HMBC and ^{1}H,^{15}N HMBC NMR, ESI-MS and single-crystal X-ray data was collected from products that crystallized in appropriate way for diffraction analysis. Crystals from pure product were formed by evaporating ACN, $CDCl_3$, Ac and CH_2Cl_2. Products were also crystallized with 1,2- and 1,4-diiodotetrafluorobenzene in CH_2Cl_2 and $CHCl_3$. Used NMR-spectrometers were Bruker Avance III HD 300 MHz- and Bruker Avance III 500 MHz. Mass spectra were obtained with MicroMass LCT Premier and melting points were measured with Stuart Scientific SMP3. Crystallographic data were collected either with a Bruker-

Nonius KappaCCD or with an Agilent SuperNova single-source diffractometer using graphite or mirror monochromatized Mo Kα radiation (λ = 0.71073 Å).

Table 2. Purities, producers and CAS-numbers of solvents used in experiments.

Solvent	Producer	Purity	CAS-number
Acetone	VWR Chemicals	100%	67-64-1
Acetonitrile	VWR Chemicals	> 99.5%	75-05-8
Chloroform	Fisher Chemicals	≥99.8%	67-66-3
Dichloromethane	VWR Chemicals	100%	75-09-2
Diethyl ether	VWR Chemicals	>99.7%	60-29-7
Ethyl acetate	VWR Chemicals	>99.5%	141-78-6
Hexane	Honeywell	>97%	110-54-3
Methanol	Honeywell	>99.8	67-56-1
Pentane	Honeywell	>99%	109-66-0
Petroleum ether	Honeywell	-	-
Tetrahydrofuran	Sigma-Aldrich	>99.9	109-99-9
Toluene	Sigma-Aldrich	>99.7	108-88-3

Table 3. Purities, producers and CAS-numbers of reagents used in experiments.

Compound	Producer	Purity	CAS-number
α,α'-Dibromo-*p*-xylene	Sigma-Aldrich	97%	623-24-5
1-Benzylimidazole	TCI	>98%	4238-71-5
Benzyl bromide	Aldrich	98%	100-39-0
1,2-Diiodotetrafluorobenzene	Fluorochem	-	2708-97-6
1,4-Diiodotetrafluorobenzene	Fluorochem	99%	392-57-4
3,6-Bis(bromomethyl)durene	TCI	>98%	35168-64-0
1-*tert*-Butylimidazole	TCI	>98%	45676-04-8
Caffeine	Sigma-Aldrich	-	58-08-2

1-Ethylimidazole	Aldrich	>95%	7096-07-9
Hyflo Super-Cel	Sigma-Aldrich	-	68855-54-9
Iodine	TCI	>98%	7553-56-2
1-Methylbenzimidazole	Aldrich	99%	1632-83-3
1-Methylimidazole	Aldrich	99%	616-47-7
1,3,5-Tris(bromomethyl)-2,4,6-triethylbenzene	Aldrich	98%	181058-08-2
1,3,5-Tris(bromomethyl)-2,4,6-trimethylbenzene	TCI	>98%	21988-87-4
1-Tritylimidazole	TCI	>98%	15469-97-3
1-Phenyl-imidazole	Apollo scientific		7164-98-9
Potassium carbonate	VWR Chemicals	99%	584-08-7
Sea sand	VWR Chemicals	-	14808-60-7
Silica gel 60	VWR Chemicals	-	7631-86-9
Sulphur powder	Abcr	>99.5	7704-34-9

7.1.1. Synthesis: Method 1

Step 1: First 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene (**1**, 0.441 g, 1.0 mmol) or 1,3,5-tris(bromomethyl)-2,4,6-trimethylbenzene (**2**, 0.399 g, 1.0 mmol) was weighed into round-bottomed flask and THF (10 ml) was added. Then the appropriate imidazole (**6** − **13**, 3.0 mmol) was added into the solution. Reaction mixture was refluxed for 3 to 24 h and the white solid product was filtered, washed with ether (40 ml), and dried overnight in hood or under vacuum for 2 h. Step 2: The intermediate product was mixed with MeOH (10 ml), potassium carbonate (0.515 g, 3.7 mmol) and sulphur powder (0.100 g, 3.0 mmol) in round-bottomed flask. The reaction mixture was refluxed for 24 h and then cooled. MeOH was evaporated under reduced pressure and the residue was extracted with $CHCl_3$ (2x15 ml or 3x10 ml). The combined organic extracts were filtered through Hyflo Super-Cel and the crude product was obtained from the filtrate after evaporation. Crude product was purified by flash column chromatography or recrystallisation if needed. Reaction scheme is presented in Figure 39.

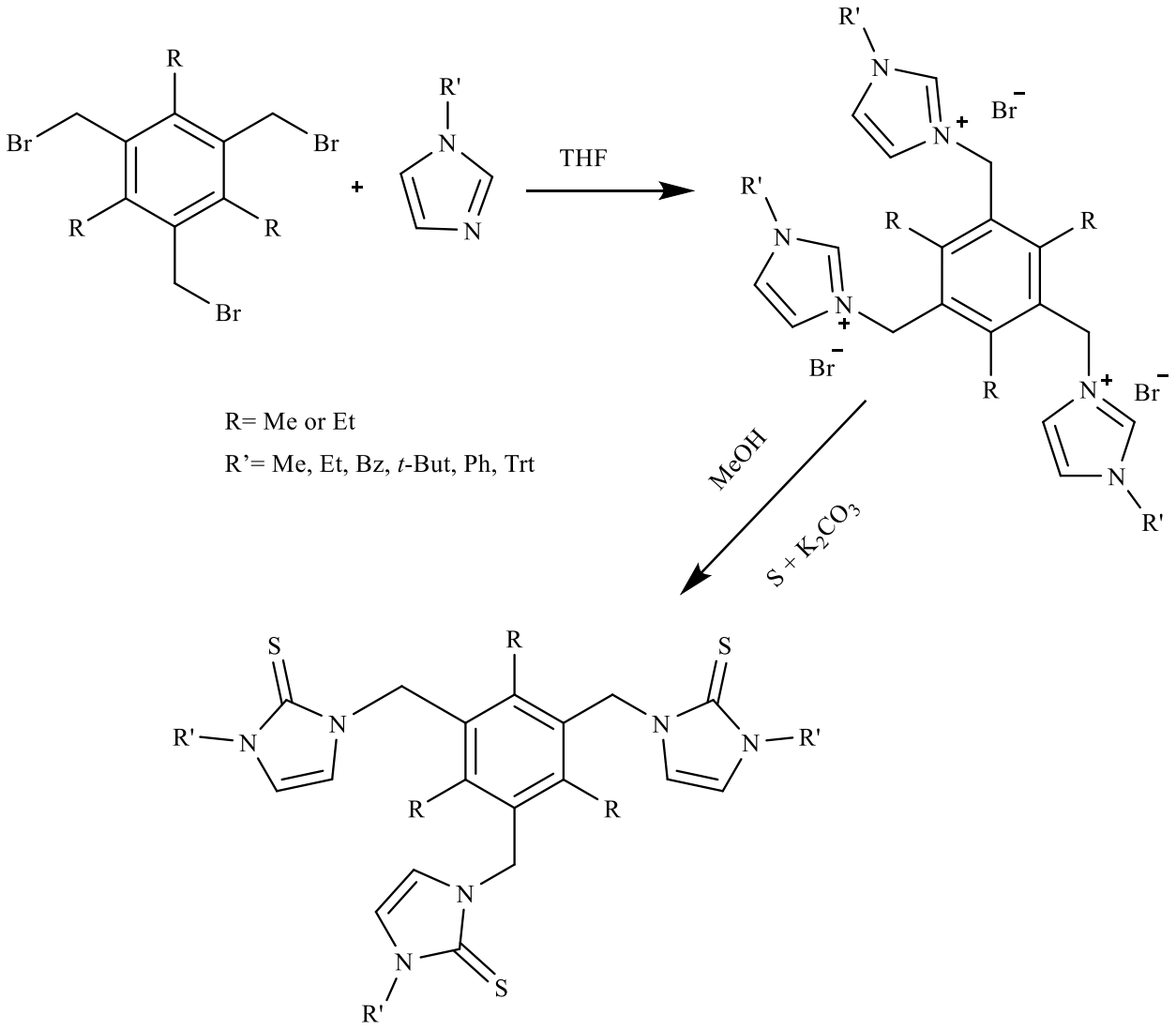


Figure 39. General reaction scheme for cores **1** and **2**. In addition to imidazoles **6** – **11** experiments also included 1-methylbenzimidazole (**12**) or caffeine (**13**).

7.1.2. Synthesis: Method 2

Step 1: First 1,4-bis(bromomethyl)benzene (**3**, 0.264 g, 1.0 mmol) or 1,4-bis(bromomethyl)-2,3,5,6-tetramethylbenzene (**4**, 0,320 g, 1.0 mmol) was weighed into round-bottomed flask and THF (10 ml) was added. Then the appropriate imidazole (**6** – **9,** 2.0 mmol) was added into the solution. Reaction mixture was refluxed for 3 to 24 h and the white solid product was filtered, washed with ether (40 ml), and dried overnight in hood or under vacuum for 2 h. Step 2: The

intermediate product was mixed with MeOH (10 ml), potassium carbonate (0.346 g, 2.5 mmol) and sulphur powder (0.067 g, 2.0 mmol) in round-bottomed flask. The reaction mixture was refluxed for 24 h and then cooled. MeOH was evaporated under reduced pressure and the residue was extracted with $CHCl_3$ (3x10 ml). The combined organic extracts were filtered through Hyflo Super-Cel and the crude product was obtained from the filtrate after evaporation. Crude product was purified by flash column chromatography or recrystallisation if needed. Reaction scheme is presented in Figure 40.

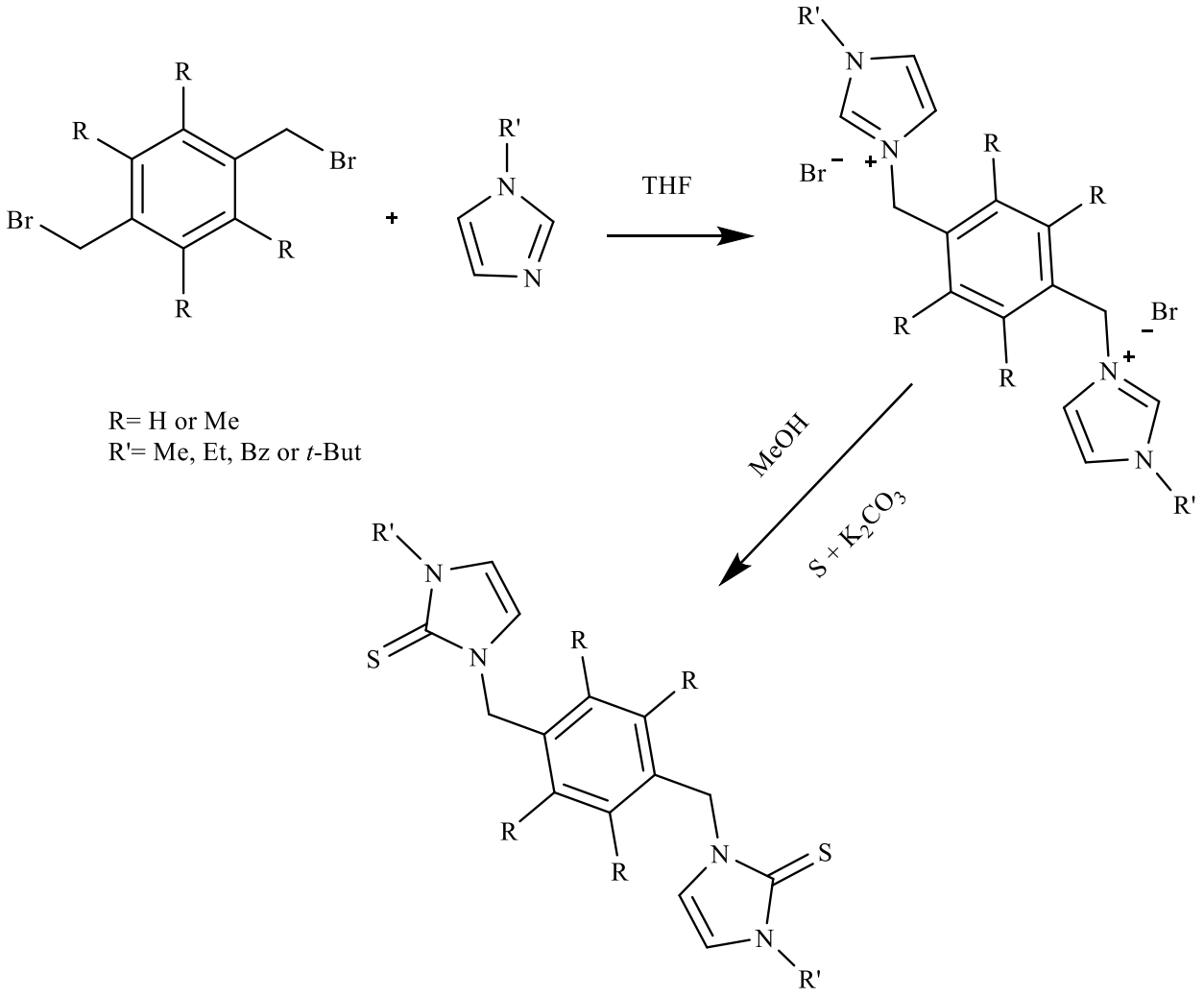


Figure 40. General reaction scheme for cores **3** and **4**.

7.1.3. Synthesis: Method 3

Step 1: First bromo(methylbenzene) (**5**, 0.171 g, 1.0 mmol) was weighed into round-bottomed flask and THF (10 ml) was added. Then the appropriate imidazole (**10-13,** 1.0 mmol) was added into the solution. Reaction mixture was refluxed for 3 to 24 h and the white solid product was filtered, washed with ether (40 ml), and dried overnight in hood or under vacuum for 2 h. Step 2: The intermediate product was mixed with MeOH (10 ml), potassium carbonate (0.187 g, 1.4 mmol) and sulphur powder (0.033 g, 1.0 mmol) in round-bottomed flask. The reaction mixture was refluxed for 24 h and then cooled. MeOH was evaporated under reduced pressure and the residue was extracted with $CHCl_3$ (2x15 ml or 3x10 ml). The combined organic extracts were filtered through Hyflo Super-Cel and the final product was obtained from the filtrate after evaporation. Reaction scheme is presented in Figure 41.

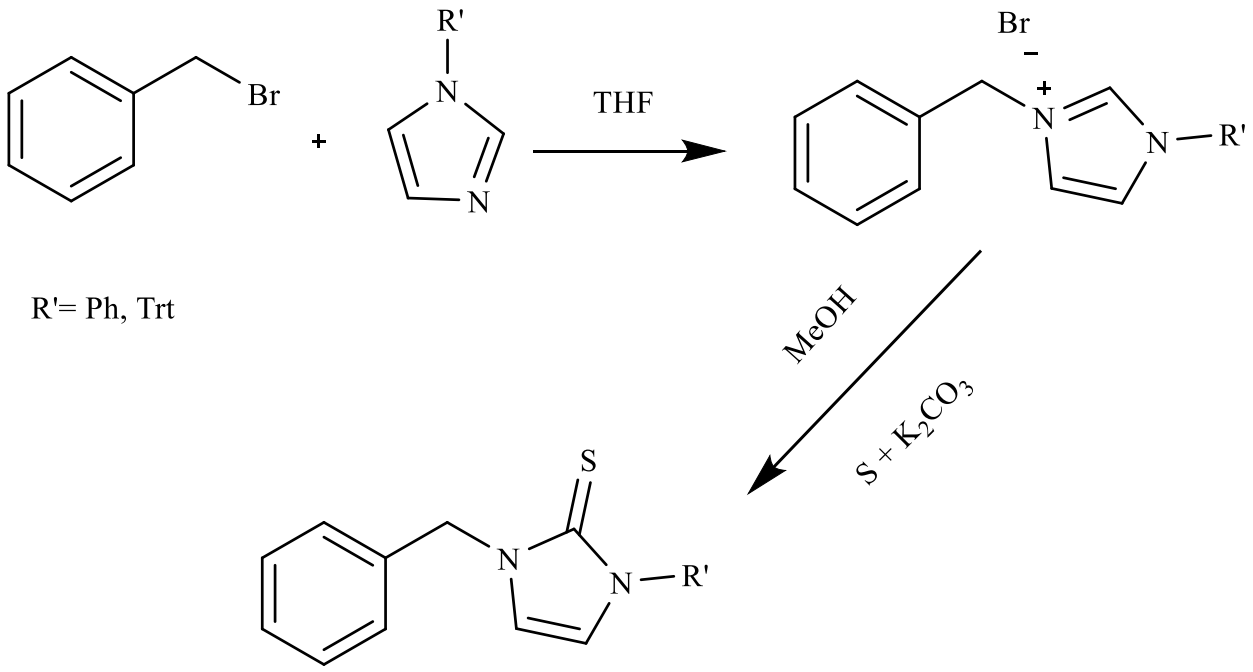


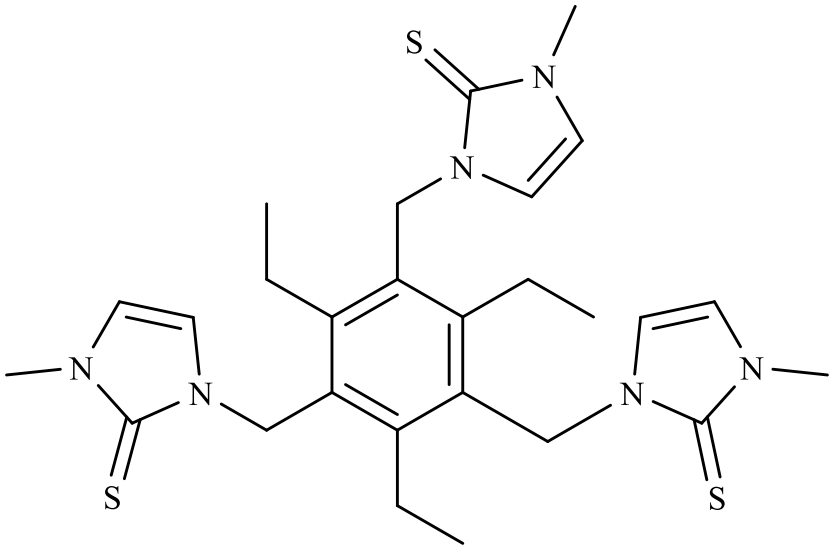
Figure 41. General reaction scheme for core **5**. Instead of imidazoles **10** and **11** experiments also included 1-methylbenzimidazole (**12**) or caffeine (**13**).

7.2. Experimental data

Deuterated chloroform ($CDCl_3$) was used as a solvent in NMR analyses. The calibration for ^1H spectra was done by setting the chemical shift of solvent residual ^1H signal to 7.26 ppm and for ^{13}C spectra the solvent signal to 77.0 ppm. Water signals were observed around 1.5-1.6 ppm. The source of water is most likely the deuterated chloroform.

7.2.1. Synthesis of E1

This experiment was successfully conducted in earlier project and in this experiment the reaction worked as expected. Reaction was made according to the Method 1 and was repeated in this work. Purification was done by dissolving the product in warm ACN and recrystallizing it from water.



^{1}H NMR (500 MHz; $CDCl_3$): δ = 6.60 (3H, d), 6.05 (3H, d), 5.21 (6H, s), 3.64 (9H, s), 2.57 (6H, q), 1.00 (9H, t) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ = 162.6, 146.4, 130.7, 117.9, 114.6, 45.7, 35.1, 23.6, 15.4 ppm.

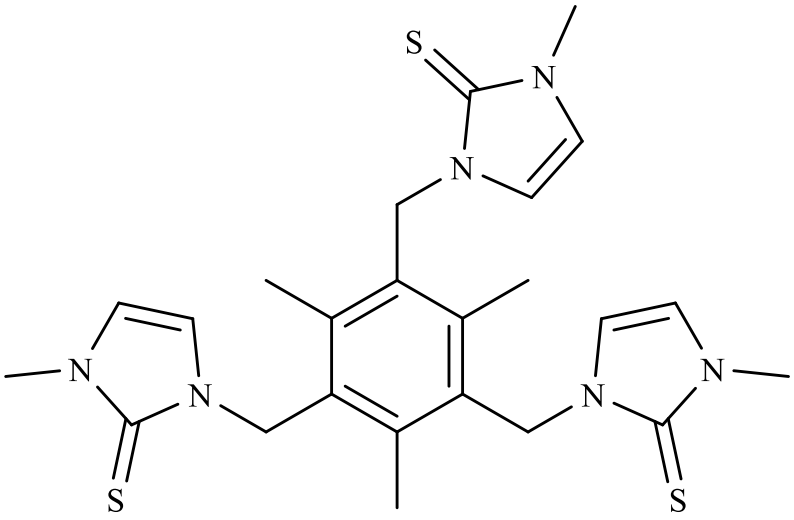
m/z for $[M-S]^+$ = 509.2182 (theoretical 509.2515), $[M-S+H]^+$ = 510.25 (theoretical 510.26), $[M-S+K]^+$ = 547.2164 (theoretical 547.2074), $[M+Na]^+$ = 563.1533 (theoretical 563.2055), $[M+K]^+$ = 579.1555 (theoretical 579.1795).

MP: 232-235°C

Raw yield: 441 mg (81.5 %). Purified yield from 77 mg of product: 22 mg (23.3 %)

7.2.2. Synthesis of E2

This experiment was conducted in earlier project with success. Reaction was made according to the Method 1 and was repeated in this work. Purified by dissolving it into ACN and then recrystallized by adding water.



^{1}H NMR (500 MHz; $CDCl_3$): δ = 6.62 (3H, d), 6.08 (3H, d), 5.21 (6H, s), 3.64 (9H, s), 2.21 (9H, q) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ = 162.5, 139.8, 131.3, 118.0, 114.4, 47.0, 35.1, 16.7 ppm

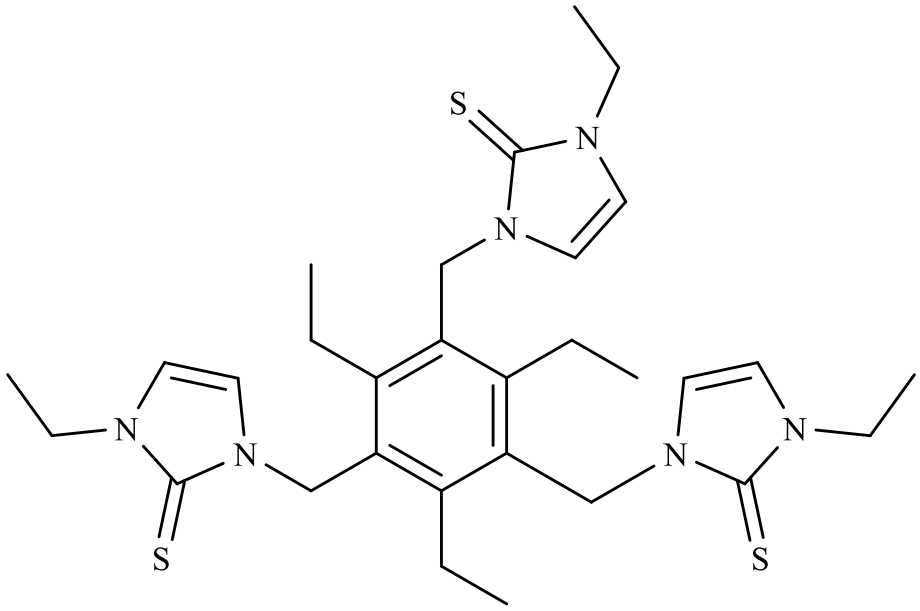
m/z for $[M+H]^+$ = 499.1821 (theoretical 499.1766), $[M+Na]^+$ = 521.1373 (theoretical 521.1586), $[M+K]^+$ = 537.0864 (theoretical 537.1325).

MP: 255-260°C

Raw yield: 347 mg (69.6 %). Purified yield from 107 mg of raw product: 55 mg (35.8 %).

7.2.3. Synthesis of E3

Reaction was made according to the Method 1. Purification by recrystallization from ACN and water.



^{1}H NMR (500 MHz; $CDCl_3$): δ = 6.62 (3H, d), 6.09 (3H, d), 5.24 (6H, s), 4.12 (6H, q), 2.60 (6H, q), 1.38 (9H, t), 0.96 (9H, t) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ = 161.7, 146.3, 130.8, 116,0, 114.9, 45.4, 42.8, 23.6, 15.3, 14.2 ppm.

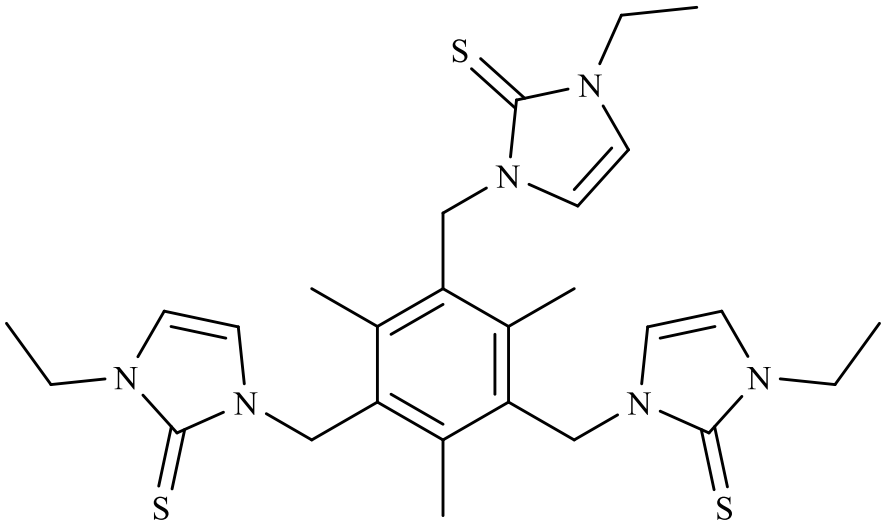
m/z for $[M-S+H]^+$ = 551.3587 (theoretical 551.2985), $[M+Na]^+$ = 605.2503 (theoretical 605.2525), $[M+K]^+$ = 621.2426 (theoretical 621.2264).

MP: 197-200°C

Yield: 248 mg (42.6 %)

7.2.4. Synthesis of E4

Reaction was made according to the Method 1. Purification by recrystallization from ACN and water.



^{1}H NMR (500 MHz; $CDCl_3$): δ = 6.64 (3H, d), 6.09 (3H, d), 5.21 (6H, s), 4.12 (6H, q), 2.30 (9H, d), 1.38 (9H, t) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ = 161.6, 139.7, 131.3, 116.1, 114.6, 46.7, 42.78, 30.8, 16.7, 14.13 ppm.

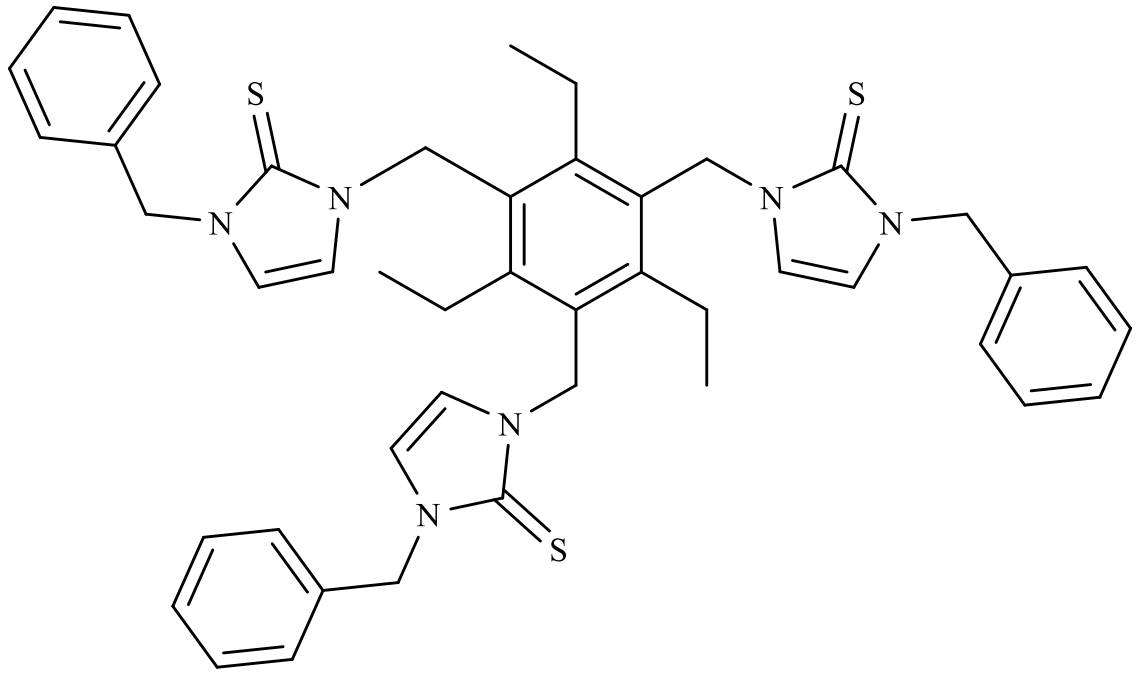
m/z for $[M-S+H]^+$ = 509.2566 (theoretical 509.2515), $[M+Na]^+$ = 563.1937 (theoretical 563.2055), $[M+K]^+$ = 579.1555 (theoretical 579.1795).

MP: 210-212°C

Yield: 286 mg (53.0 %)

7.2.5. Synthesis of E5

Reaction was made according to the Method 1. Purification by recrystallization from ACN and water.



^{1}H NMR (500 MHz; $CDCl_3$): δ = 7.35-7.29 (15H, m), 6.46 (3H, d), 6.01 (3H, d), 5.27 (12H, s), 2.62 (6H, q), 0.97 (9H, t) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ = 162.7, 146.4, 135.6, 130.7, 128.9, 128.3, 128.2, 116.6, 115.0, 51.2, 45.6, 23.6, 15.4 ppm.

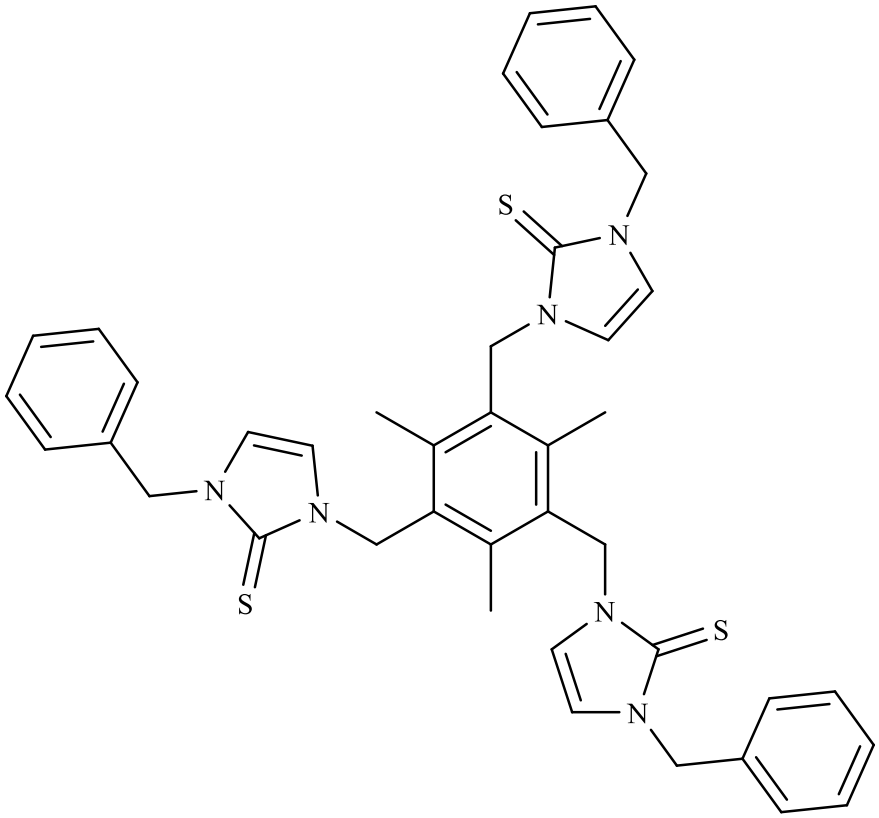
m/z for $[M-S+H]^+$ = 737.3751 (theoretical 737.3454), $[M+Na]^+$ = 791.3434 (theoretical 791.2994), $[M+K]^+$ = 807.3437 (theoretical 807.2734).

MP: 198-202°C

Yield: 590 mg (76.7 %)

7.2.6. Synthesis of E6

Reaction was made according to the Method 1. Purification by recrystallization from MeOH and water.



^{1}H NMR (500 MHz; $CDCl_3$): δ = 7.36-7.29 (15H, m), 6.48 (3H, d), 6.04 (3H, d), 5.27 (12H, d), 2.23 (9H, s), 2.17 (3H, s) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ = 162.7, 139.8, 135.7, 131.4, 128.9, 128.3, 116.7, 114.8, 51.2, 47.0, 30.9, 16.8 ppm.

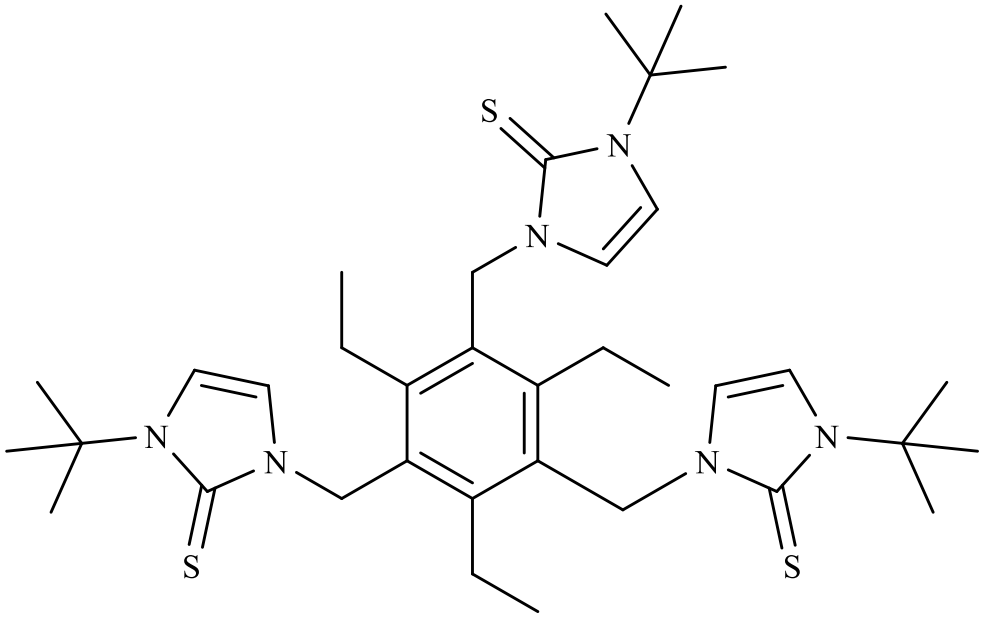
m/z for $[M-S+H]^+$ = 695.3849 (theoretical 695.2985), $[M+H]^+$ = 727.2930 (theoretical 727.2706), $[M+Na]^+$ = 749.2731 (theoretical 749.2525), $[M+K]^+$ = 765.3144 (theoretical 765.2265).

MP: 216-221°C

Raw yield: 500 mg (68.8 %). Purified yield from 97 mg of product: 50 mg (35.4 %)

7.2.7. Synthesis of E7

Reaction was made according to the Method 1. Purification by column 1:1 Hex/EtOAc.



^{1}H NMR (500 MHz; $CDCl_3$): δ = 6.76 (3H, d), 6.02 (3H, d), 5.24 (6H, s), 2.58 (6H, q), 1.82 (27H, s), 0.90 (9H, t) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ = 160.8, 146.2, 131.2, 114.5, 114.0, 59.3, 45.0, 28.1, 23.6, 15.1 ppm.

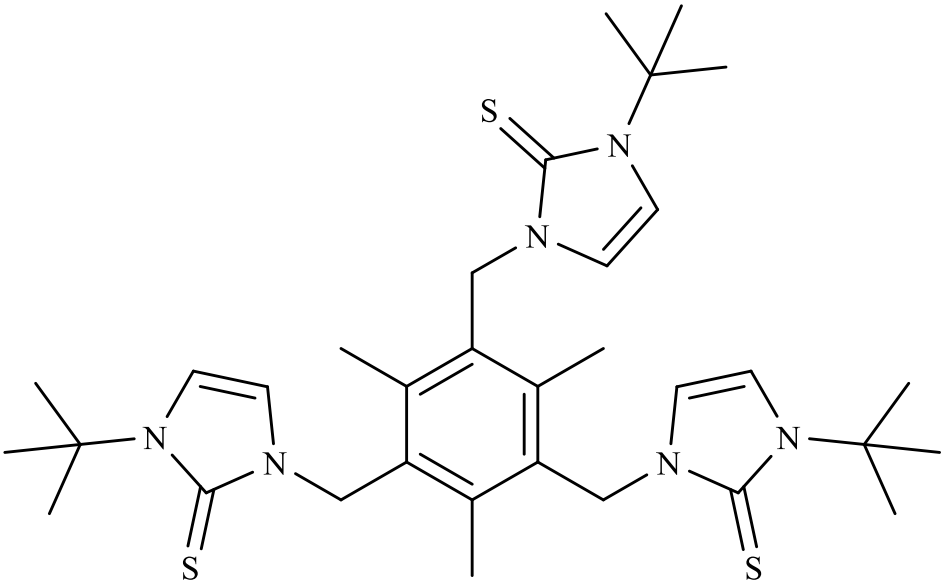
m/z for $[M-S+H]^+$ = 635.3853 (theoretical 635.3924), $[M+H]^+$ = 667.3937 (theoretical 667.3644), $[M+K]^+$ = 705.3696 (theoretical 705.3203).

MP: 306-308°C

Yield: 26 mg (3.9 %)

7.2.8. Synthesis of E8

Reaction was made according to the Method 1. Purification by column 1:2 Hex/EtOAc.



^{1}H NMR (500 MHz; $CDCl_3$): δ = 6.77 (3H, d), 6.03 (3H, d), 5.19 (6H, s), 2.16 (9H, d), 1.83 (27H, s) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ = 160.8, 139.8, 131.5, 114.6, 113.6, 59.26, 46.6, 29.7, 28.1, 16.6 ppm.

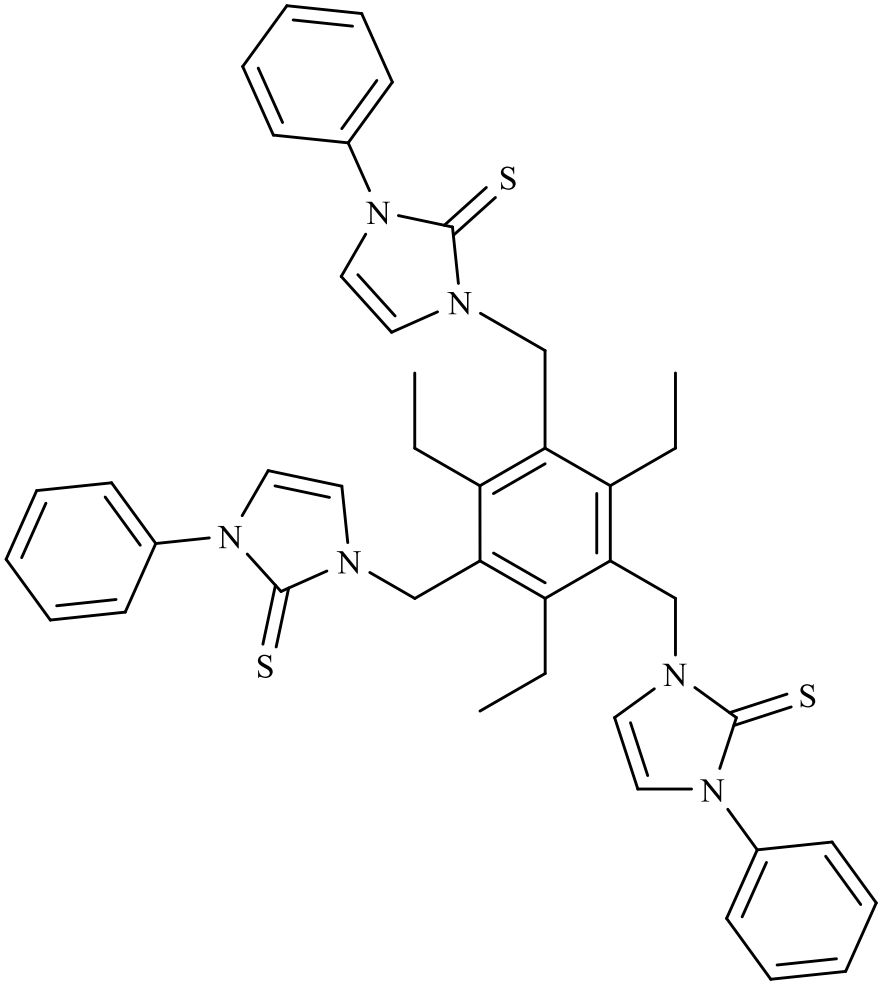
m/z for $[M+H]^+$ = 625.3582 (theoretical 625.3175), $[M+Na]^+$ = 647.3504 (theoretical 647.2994), $[M+K]^+$ = 663.3168 (theoretical 663.2734).

MP: 288-290°C

Yield: 14 mg (2.2 %)

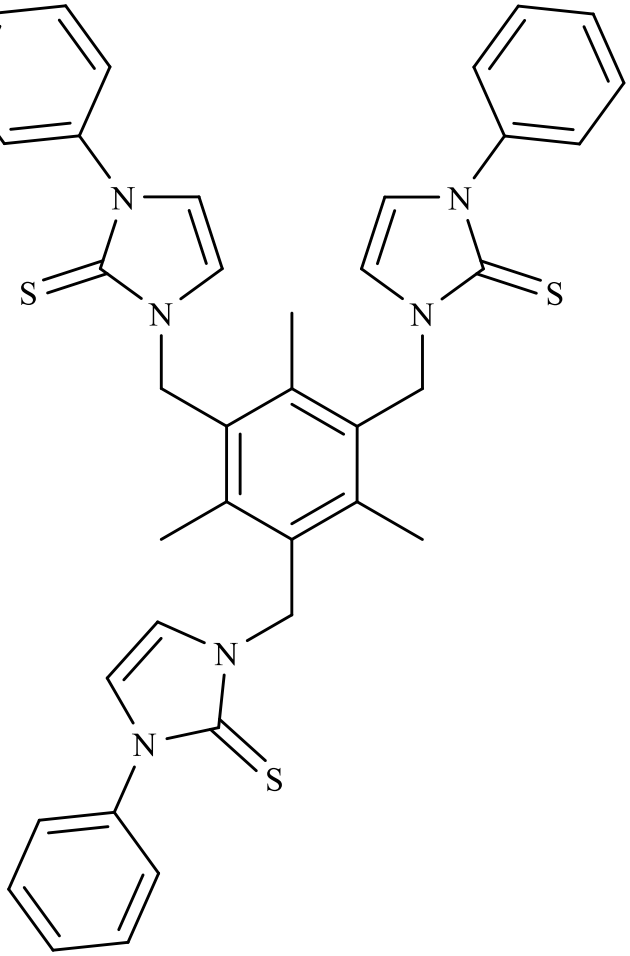
7.2.9. Synthesis of E9

Reaction was made according to the Method 1. Product was mixture, didn’t purify in column 2:1 EtOAc/Hex. No measurements done.



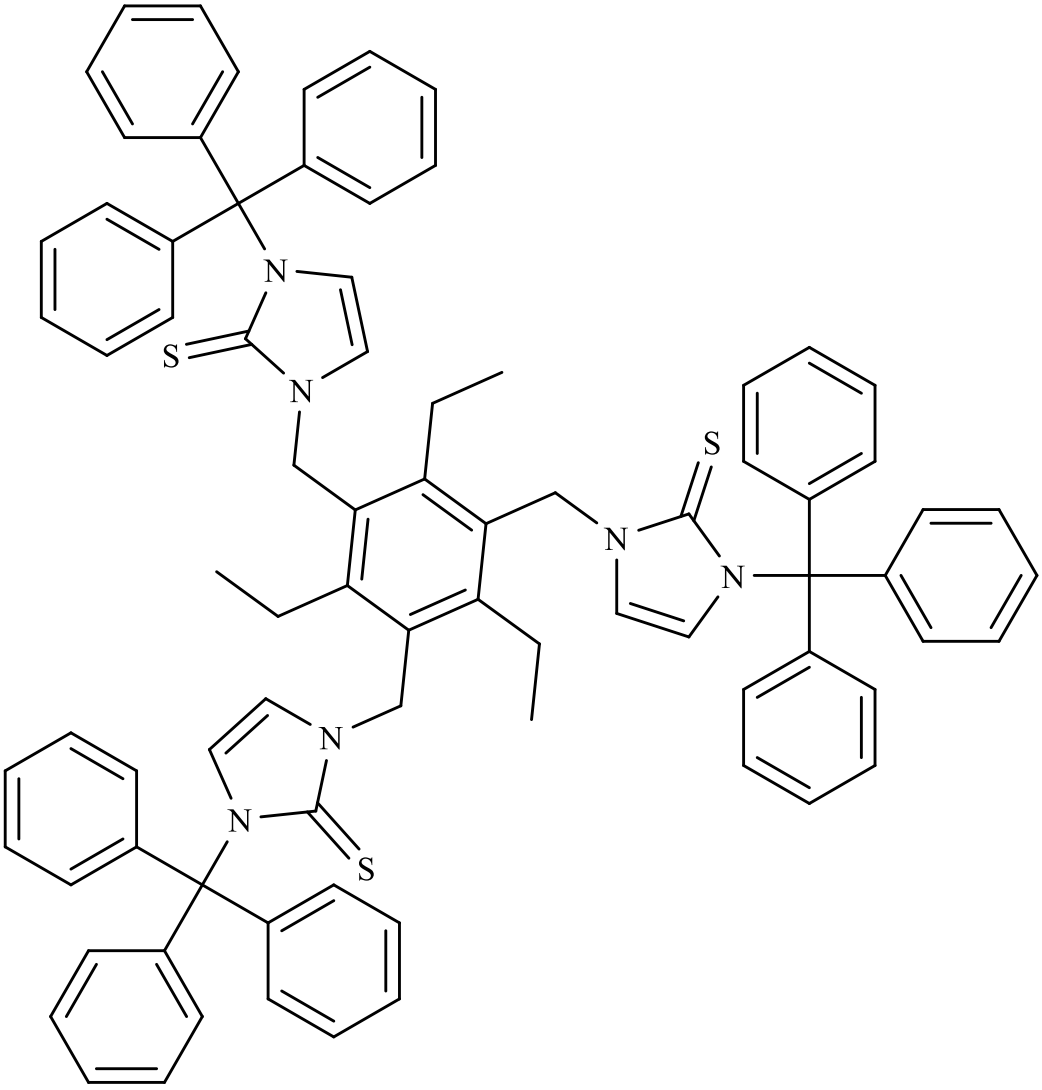
7.2.10. Synthesis of E10

Reaction was made according to the Method 1. Reaction product was goo, got lost in column/ dirty fractions 2/1 EtOAc/Hex.



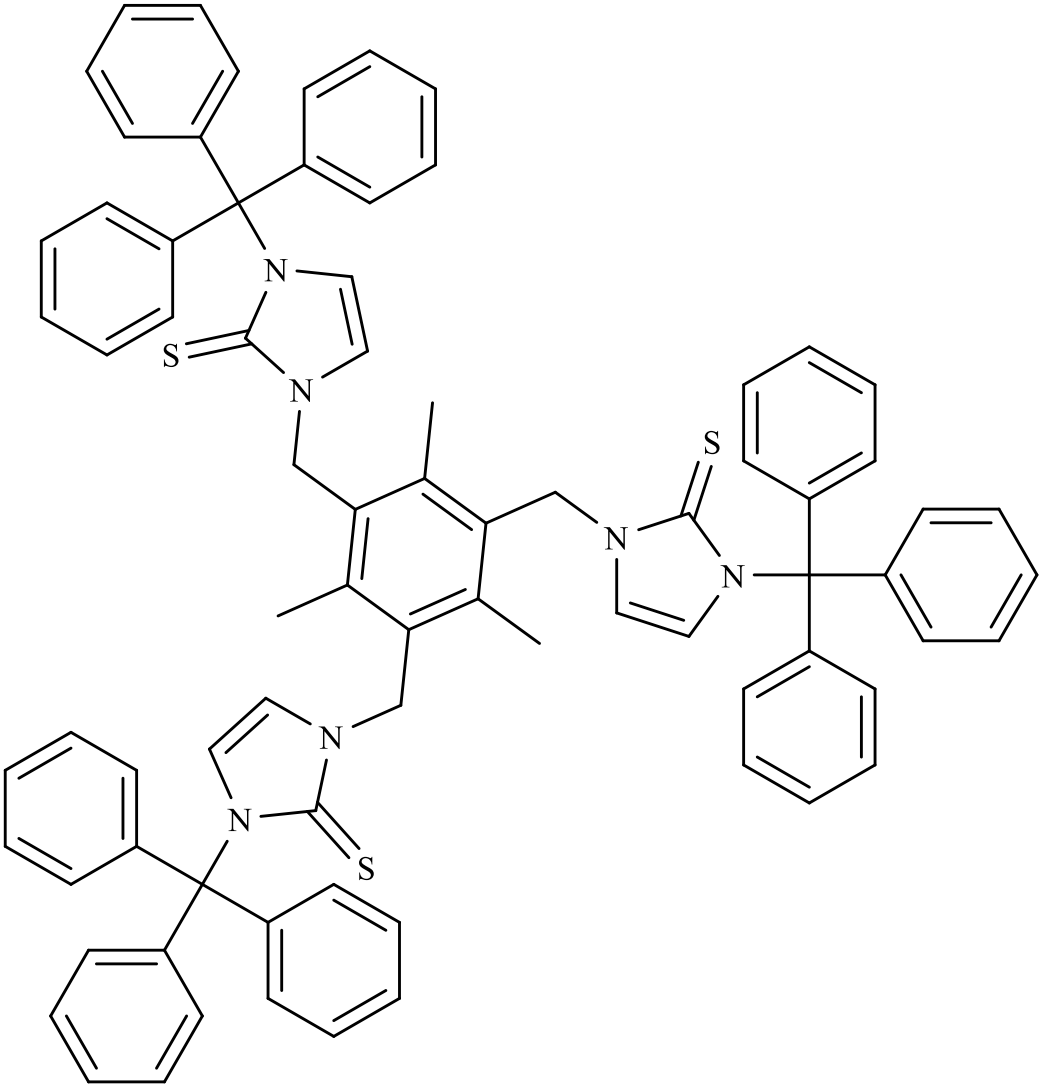
7.2.11. Synthesis of E11

Reaction was made according to the Method 1. Product was mixture. Did not move on TLC and recrystallization did not work, could not be purified.



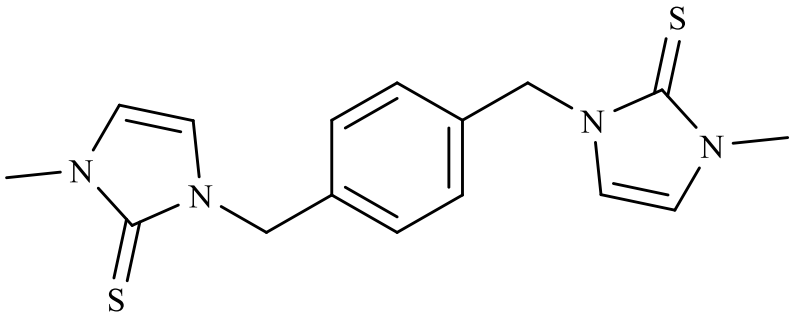
7.2.12. Synthesis of E12

Reaction was made according to the Method 1. Produced black goo that was mixture. Did not purify by recrystallization.



7.2.13. Synthesis of E13

Reaction was made according to the Method 2. Product was decently pure from reaction.



^{1}H NMR (500 MHz; $CDCl_3$): δ = 6.66 (2H, d), 6.56 (2H, d), 5.21 (4H, s), 3.61 (6H, s) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ = 162.9, 135.8, 128.6, 118.0, 116.3, 50.9, 35.2 ppm.

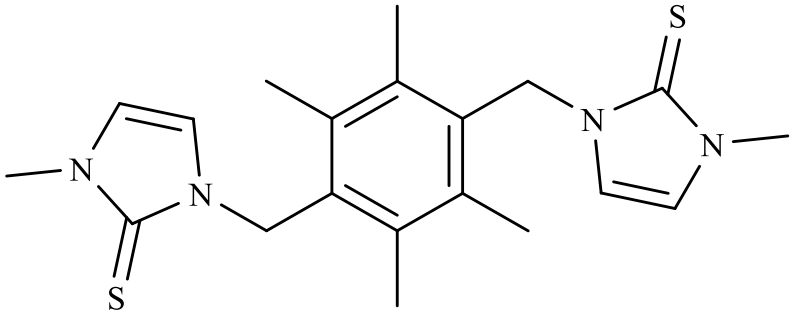
m/z for $[M+H]^+$ = 331.0483 (theoretical 331.1045), $[M+Na]^+$ = 353.0128 (theoretical 353.0865), $[M+K]^+$ = 368.9615 (theoretical 369.0604).

MP: 222-224°C

Yield: 206 mg (62.4 %)

7.2.14. Synthesis of E14

Reaction was made according to the Method 2. Decently pure product, purification by recrystallizing from ACN.



^{1}H NMR (500 MHz; $CDCl_3$): δ = 6.60 (2H, d), 6.11 (2H, d), 5.18 (4H, s), 3.66 (6H, s), 2.19 (12H, s) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ = 161.9, 135.1, 131.9, 117.6, 115.0, 47.3, 35.0, 16.7 ppm.

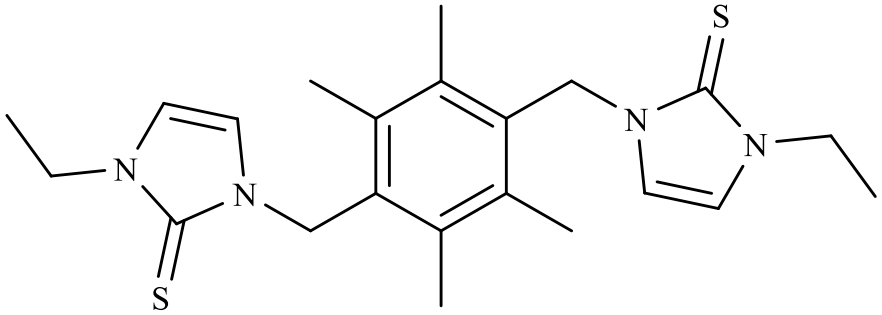
m/z for $[M+H]^+$ = 387.0996 (theoretical 387.1671), $[M+Na]^+$ = 409.0349 (theoretical 409.1491), $[M+K]^+$ = 425.0334 (theoretical 425.1230).

MP: 336-338°C

Raw yield: 185 mg (47.9 %). Purified yield from 40 mg of product: 15 mg (17.9 %)

7.2.15. Synthesis of E15

Reaction was made according to the Method 2.



Molecular Weight: 414,63

^{1}H NMR (500 MHz; $CDCl_3$): δ = 6.62 (2H, d), 6.12 (2H, d), 5.19 (4H, s), 4.14 (4H, q), 2.19 (12H, s), 1.39 (6H, t) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ = 161.1, 135.1, 132.0, 115.7, 115.3, 47.1, 42.7, 16.7, 14.2 ppm.

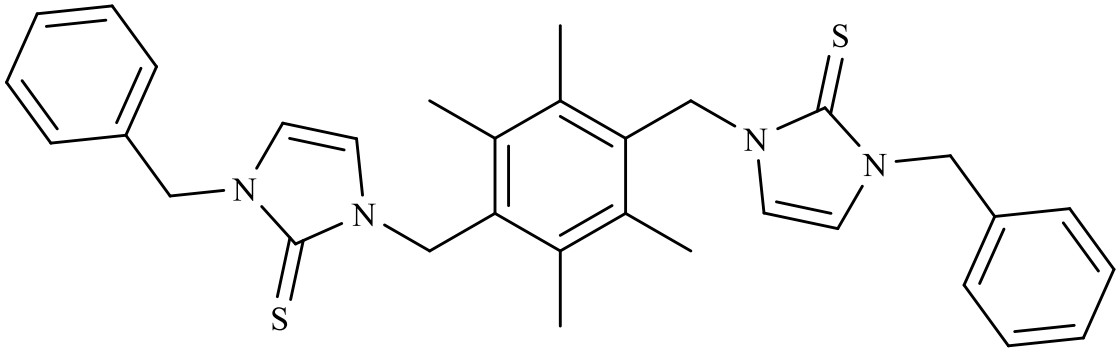
m/z for $[M+H]^+$ = 415.1065 (theoretical 415.1984), $[M+Na]^+$ = 437.1006 (theoretical 437.1804), $[M+K]^+$ = 453.0190 (theoretical 453.1543).

MP: 292-295°C

Raw yield: 215 mg (51.9 %). Purified yield from 56 mg of product: 25 mg (23.1 %)

7.2.16. Synthesis of E16

Reaction was made according to the Method 2.



^{1}H NMR (500 MHz; $CDCl_3$): δ = 7.34-7.30 (10H, m), 6.47 (2H, d) 6.09 (2H, d), 5.30 (4H, s), 5.24 (4H, s), 2.20 (12H, s) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ = 162.2, 135.8, 135.1, 132.0, 128.8, 128.2, 128.1, 116.3, 115.4, 51.0, 47.3, 16.7 ppm.

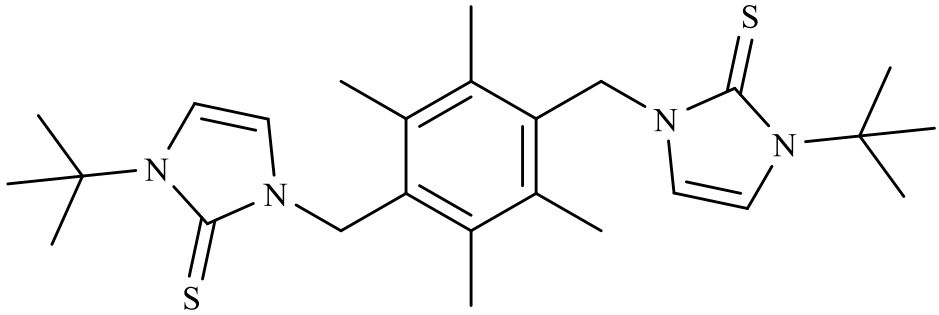
m/z for $[M+H]^+$ = 539.1320 (theoretical 539.2297), $[M+K]^+$ = 577.0698 (theoretical 577.1856).

MP: 243-244°C

Yield: 366 mg (67.9 %)

7.2.17. Synthesis of E17

Reaction was made according to the Method 2. Purified with column 1:1 Hex/EtOAc.



^{1}H NMR (500 MHz; $CDCl_3$): δ = 6.74 (2H, d), 6.06 (2H, d), 5.17 (4H, s), 2.17 (12H, s), 1.84 (18H, s) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ = 160.5, 135.1, 132.3, 114.2, 59.1, 46.9, 28.09, 16.7 ppm.

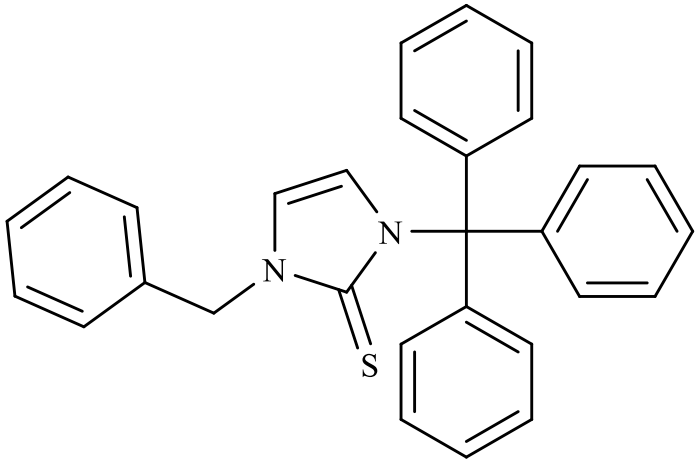
m/z for $[M+H]^+$ = 471.1757 (theoretical 471.2610), $[M+Na]^+$ = 493.1555 (theoretical 493.2430), $[M+K]^+$ = 509.0582 (theoretical 509.2169).

MP: 284-286°C

Yield: 397 mg (84.3 %)

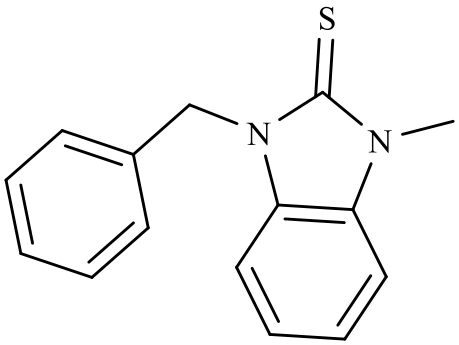
7.2.18. Synthesis of E18

Reaction was made according to the Method 2. Sticky brown goo that did not move on TLC.



7.2.19. Synthesis of E19

Reaction was made according to the Method 2. Decently pure from reaction.



^{1}H NMR (500 MHz; $CDCl_3$): δ = 7.29-7.05 (9H, m), 5.58 (2H, s), 3.83 (3H, s) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ = 171.1, 170.4, 135.6, 132.5, 131.7, 128.6, 128.2, 127.7, 127.4, 122.9, 60.0, 48.2, 31.4, 21.0, 14.1 ppm.

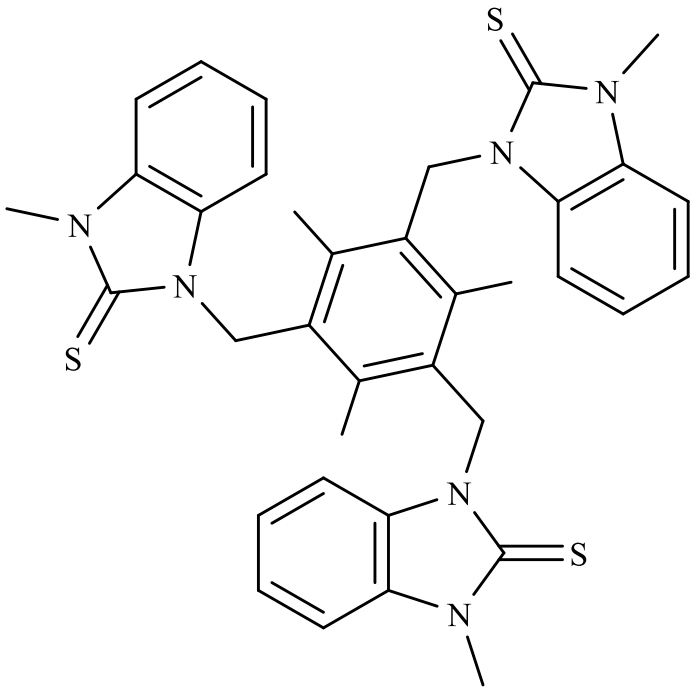
m/z for $[M+H]^+$ = 255.0560 (theoretical 255.0950), $[M+Na]^+$ = 277.0294 (theoretical 277.0769), $[M+K]^+$ = 293.0063 (theoretical 293.0509).

MP: 134-135°C

Yield: 150 mg (59.1 %)

7.2.20. Synthesis of E20

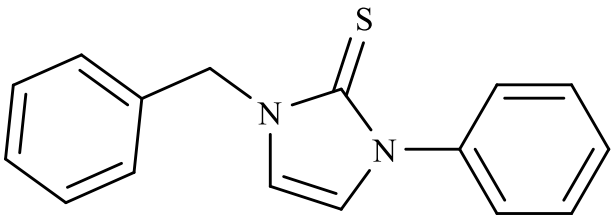
Reaction was made according to the Method 1. Purified by column. Only ^{1}H spectrum as almost all was lost in purification.



^{1}H NMR (500 MHz; $CDCl_3$): δ = 7.14-7.13 (6H, m), 6.63 (2H, s), 6.19 (4H, d) 5.70 (6H, d), 3.81 (9H, s), 2.35 (9H, d) ppm.

7.2.21. Synthesis of E21

Reaction was made according to the Method 2. First phenylimidazole reaction that produced non-mixture. Product was decently pure from reaction.



^{1}H NMR (500 MHz; $CDCl_3$): δ = 7.46-7.33 (10H, m), 6.83 (1H, d) 6.67 (1H, d), 5.32 (2H, s) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ = 163.3, 138.2, 135.5, 129.8, 129.0, 128.8, 128.4, 128.2, 128.1, 125.9, 121.3, 118.0, 117.0, 51.3 ppm.

m/z for $[M+H]^+$ = 267.0527 (theoretical 267.0950), $[M+K]^+$ = 304.9935 (theoretical 305.0509)

MP: 120-122°C

Yield: 264 mg (99.2 %)

References

1. Randic, M., Aromaticity and conjugation, *J. Am. Chem. Soc.*, **1977**, *99*, 444–450.

2. Faraday, M., Isolation of benzene, *Phil. Trans. R. Soc. London*, **1825**, 440.

3. Schleyer, P. von R., Introduction: Aromaticity, *Chem. Rev.*, **2001**, *101*, 1115–1118.

4. Aihara, J., Unified theory of aromaticity and London diamagnetism, *J. Am. Chem. Soc.*, **1981**, *103*, 5704–5706.

5. Filler, A., The History, Development and Impact of Computed Imaging in Neurological Diagnosis and Neurosurgery: CT, MRI, and DTI, *Nat. Preced.*, **2009**.

6. Lee, D., *From X-rays to DNA : How Engineering Drives Biology*, The MIT Press, USA, 2014. pp. 163-165.

7. Flygare, W. H. and Benson, R. C., Molecular Zeeman effect of cyclopentadiene and isoprene and comparison of the magnetic susceptibility anisotropies, *J. Am. Chem. Soc.*, **1970**, *92*, 7523–7529.

8. von Schleyer, P. R. and Jiao, H., What is aromaticity?, *Pure Appl. Chem.*, **1996**, *68*, 209–218.

9. Chen, Z.; Puchata, R.; Corminboeuf, C.; Wannere, C. S. and von Ragué Schleyer, P., Nucleus-Independent Chemical Shifts (NICS) as an Aromaticity Criterion, *Chem. Rev.*, **2005**, *105*, 3842–3888.

10. Schleyer, P. von R.; Maerker, C.; Dransfeld, A.; Jiao, H. and van Eikema Hommes, N. J. R., Nucleus-Independent Chemical Shifts: A Simple and Efficient Aromaticity Probe, *J. Am. Chem. Soc.*, **1996**, *118*, 6317–6318.

11. Mitchell, R. H., Measuring Aromaticity by NMR, *Chem. Rev.*, **2001**, *202*, 1301–1316.

12. Günther, H., *NMR Spectroscopy*, John Wiley & Sons, Incorporated, Germany, 2013. pp. 13-39.

13. Ebel, K.; Koehler, H.; Gamer, A. O. and Jäckh, R., *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA, 2000.

14. Debus, H., Ueber die Einwirkung des Ammoniaks auf Glyoxal, *Ann. Chem. Pharm.*, **1858**, *107*, 199–208.

15. Saxer, S.; Marestin, C.; Mercier, R. and Dupuy, J., The multicomponent Debus–Radziszewski reaction in macromolecular chemistry, *Polym. Chem.*, **2018**, *9*, 1927–1933.

16. Bouchakour, M.; Daaou, M. and Duguet, N., Synthesis of Imidazoles from Fatty 1,2-Diketones, *Eur. J. Org. Chem.*, **2021**, *2021*, 1647–1652.

17. Qiu, S.; Sun, H.; Zhang, A.-H.; Xu, H.-Y.; Yan, G.-L.; Han, Y. and Wang, X.-J., Natural alkaloids: basic aspects, biological roles, and future perspectives, *Chin. J. Nat. Med.*, **2014**, *12*, 401–406.

18. Liu, H. and Du, D.-M., Recent Advances in the Synthesis of 2-Imidazolines and Their Applications in Homogeneous Catalysis, *Adv. Synth. Catal.*, **2009**, *351*, 489–519.

19. Imyanitov, N. S., Is This Reaction a Substitution, Oxidation-Reduction, or Transfer?, *J. Chem. Educ.*, **1993**, *70*, 14.

20. Smith, M. and March, J., *March's Advanced Organic Chemistry*, 7. edition, John Wiley & Sons, Incorporated, USA, 2013. pp. 373-442.

21. Theophil Eicher, *The Chemistry of Heterocycles*, 3. edition, John Wiley & Sons, USA Incorporated, Germany, 2013. pp. 227-273.

22. Mrozek, A.; Karolak-Wojciechowska, J. and Kieć-Kononowicz, K., Five-membered heterocycles. Part III. Aromaticity of 1,3-imidazole in 5+n hetero-bicyclic molecules, *J. Mol. Struct.*, **2003**, *655*, 397–403.

23. Yuan, Y.; Jiang, Z.-L.; Yan, J.-M.; Gao, G.; Chan, A. S. C. and Xie, R.-G., A Convenient and Effective Synthesis of Tris-Bridged Tricationic Azolophanes, *Synth. Commun.*, **2000**, *30*, 4555–4561.

24. Laus, G.; Kahlenberg, V.; Wurst, K.; Müller, T.; Kopacka, H. and Schottenberger, H., Synthesis and Crystal Structures of New 1,3-Disubstituted Imidazoline-2-thiones, *Z. Naturforsch. B*, **2013**, *68*, 1239–1252.

25. Roy, G.; Andyaram, P. N. and Mugesh, G., Inhibition of lactoperoxidase-catalyzed oxidation by imidazole-based thiones and selones: a mechanistic study., *Chem. - Asian J.*, **2013**, *8*, 1910–21.

26. Jia, W.-G.; Gao, L.-L.; Wang, Z.-B.; Sun, L.-Y. and Han, Y.-F., Synthesis, Characterization, and Catalytic Activities of Palladium Complexes with Phenylene-Bridged Bis(thione) Ligands, *Organometallics*, **2019**, *38*, 1946–1954.

27. Das, D.; Roy, G. and Mugesh, G., Antithyroid Drug Carbimazole and Its Analogues: Synthesis and Inhibition of Peroxidase-Catalyzed Iodination of <scp>l</scp> -Tyrosine, *J. Med. Chem.*, **2008**, *51*, 7313–7317.

28. Bhabak, K. P. and Mugesh, G., Antithyroid Drugs and their Analogues Protect Against Peroxynitrite-Mediated Protein Tyrosine Nitration-A Mechanistic Study, *Chem. – Eur. J.*, **2010**, *16*, 1175–1185.

29. Renier, O.; Bousrez, G.; Baryshnikov, G. v.; Paterlini, V.; Smetana, V.; Ågren, H.; Rogers, R. D. and Mudring, A.-V., Shape Preserving Single Crystal to Amorphous to Single Crystal Polymorphic Transformation Is Possible, *J. Am. Chem. Soc.*, **2021**, *143*, 20202–20206.

30. Spicer, M. D. and Reglinski, J., Soft Scorpionate Ligands Based on Imidazole-2-thione Donors, *Eur. J. Inorg. Chem.*, **2009**, *2009*, 1553–1574.

31. Wang, L.-J.; Li, X.; Bai, S.; Wang, Y.-Y. and Han, Y.-F., Self-Assembly, Structural Transformation, and Guest-Binding Properties of Supramolecular Assemblies with Triangular Metal–Metal Bonded Units, *J. Am. Chem. Soc.*, **2020**, *142*, 2524–2531.

32. Matsuda, K.; Yanagisawa, I.; Isomura, Y.; Mase, T. and Shibanuma, T., One-Pot Preparation of 1-Substituted Imidazole-2-thione from Isothiocyanate and Amino Acetal, *Synth. Commun.*, **1997**, *27*, 3565–3571.

33. Deng, J.-C.; Chen, J.-H.; Zhang, J.-R.; Lu, T.-T. and Tang, R.-Y., Sulfite-Induced *N* -Alkylation and Thioketonization of Azoles Enable Access to Diverse Azole Thiones, *Adv. Synth. Catal.*, **2018**, *360*, 4795–4806.

34. Deng, J.-C.; Gao, Y.-C.; Zhu, Z.; Xu, L.; Li, Z.-D. and Tang, R.-Y., Sulfite-Promoted Synthesis of *N* -Difluoromethylthioureas via the Reaction of Azoles with Bromodifluoroacetate and Elemental Sulfur, *Org. Lett.*, **2019**, *21*, 545–548.

35. Xu, W.; Abboud, K. A.; Ghiviriga, I.; Dolbier, W. R.; Rapp, M. and Wnuk, S. F., An Unexpected Reaction of Trimethylsilyl Fluorosulfonyldifluoroacetate (TFDA) with Imidazoles. Formation of *N* -Difluoromethylthioureas, *Org. Lett.*, **2006**, *8*, 5549–5551.

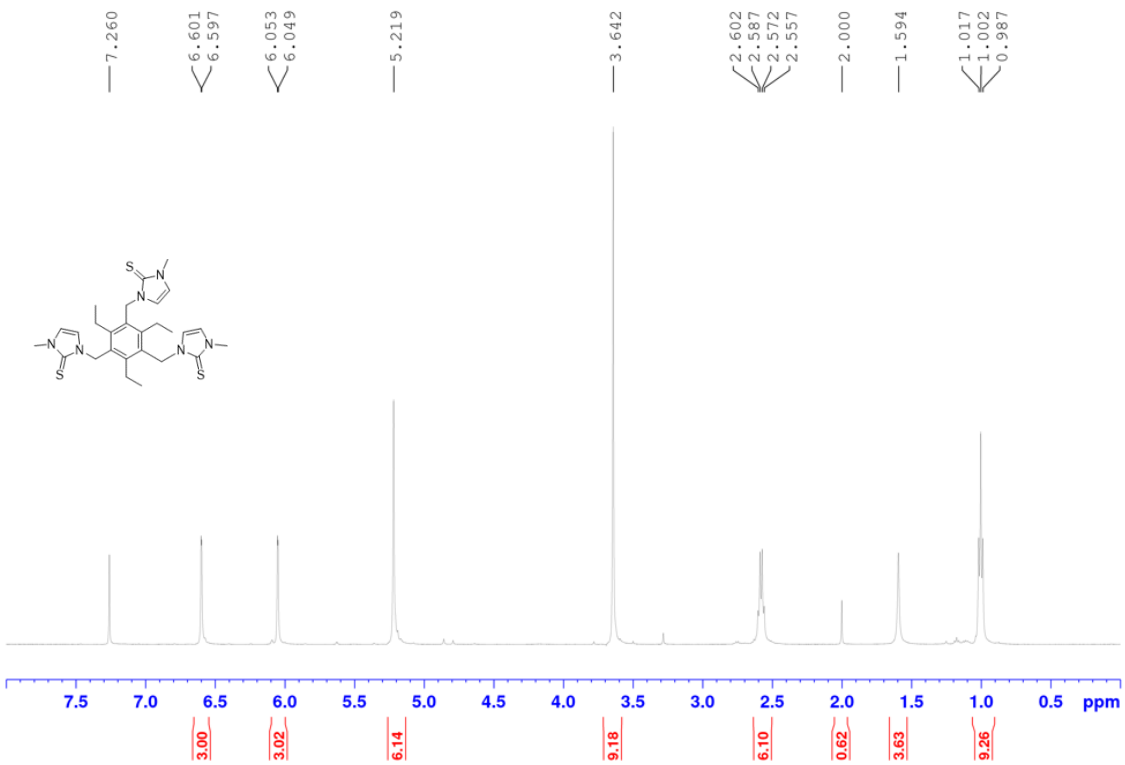
36. Belyaeva, K. v.; Andriyankova, L. v.; Nikitina, L. P.; Mal'kina, A. G.; Afonin, A. v.; Ushakov, I. A.; Bagryanskaya, I. Yu. and Trofimov, B. A., Three-component reaction of imidazoles, cyanophenylacetylene, and chalcogens: stereoselective synthesis of 3-alkenyl-2-imidazolethiones and -selones, *Tetrahedron*, **2014**, *70*, 1091–1098.

37. Petrov, V. A.; Marshall, W. and Dooley, R., One step synthesis of 1,3-dihydro-1-alkyl(aryl)-3-(hexafluoro-iso-propyl)-2H-imidazole-2-thiones, *J. Fluorine Chem.*, **2014**, *167*, 159–165.

38. Feroci, M.; Orsini, M. and Inesi, A., An Efficient Combined Electrochemical and Ultrasound Assisted Synthesis of Imidazole-2-Thiones, *Adv. Synth. Catal.*, **2009**, *351*, 2067–2070.

List of Appendices

APPENDIX 1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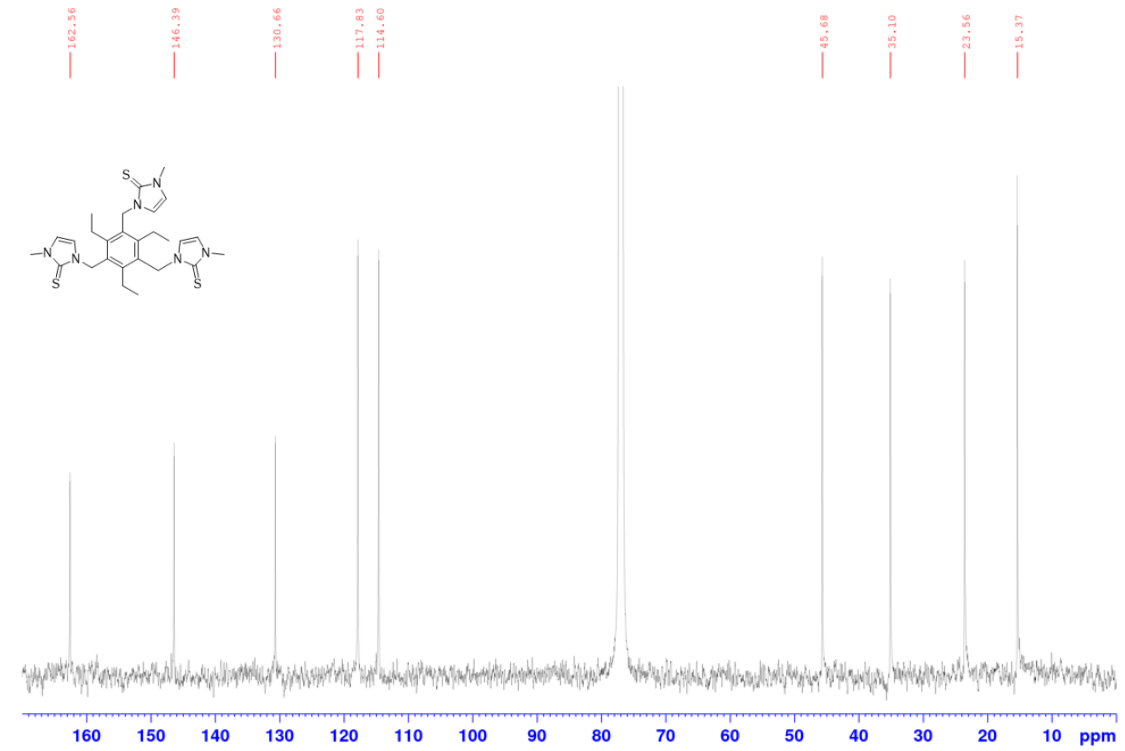
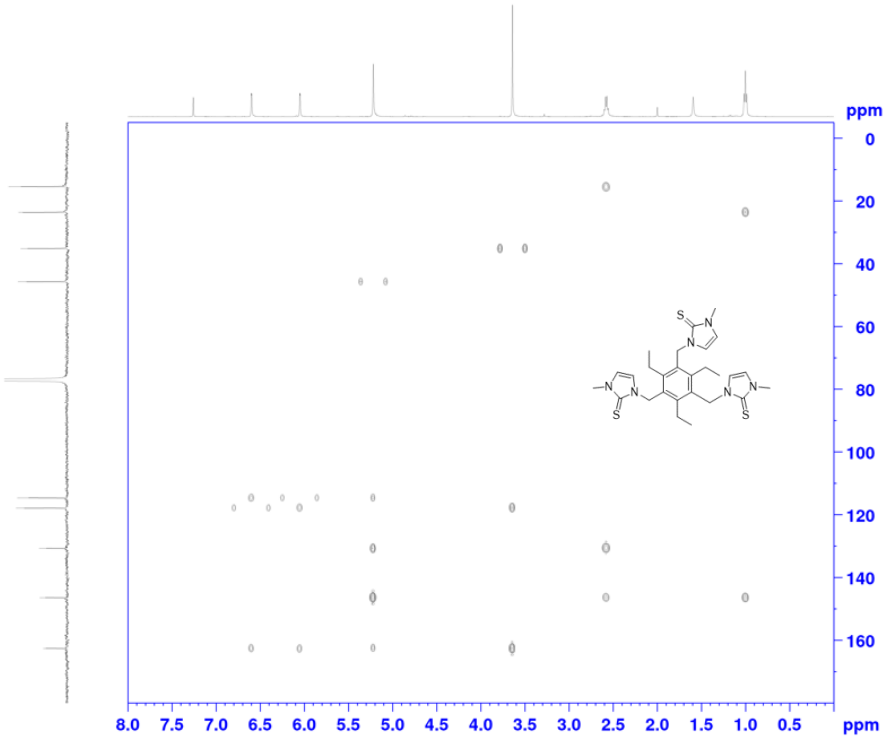
6.601
6.597
6.053
6.049
5.219
3.642
2.602
2.587
2.572
2.557
2.000
1.594
1.017
1.002
0.987
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
3.00
3.02
6.14
9.18
6.10
0.62
3.63
9.26


162.56
146.39
130.66
117.83
114.60
45.68
35.10
23.56
15.37
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

APPENDIX 2


ppm
0
20
40
60
80
100
120
140
160
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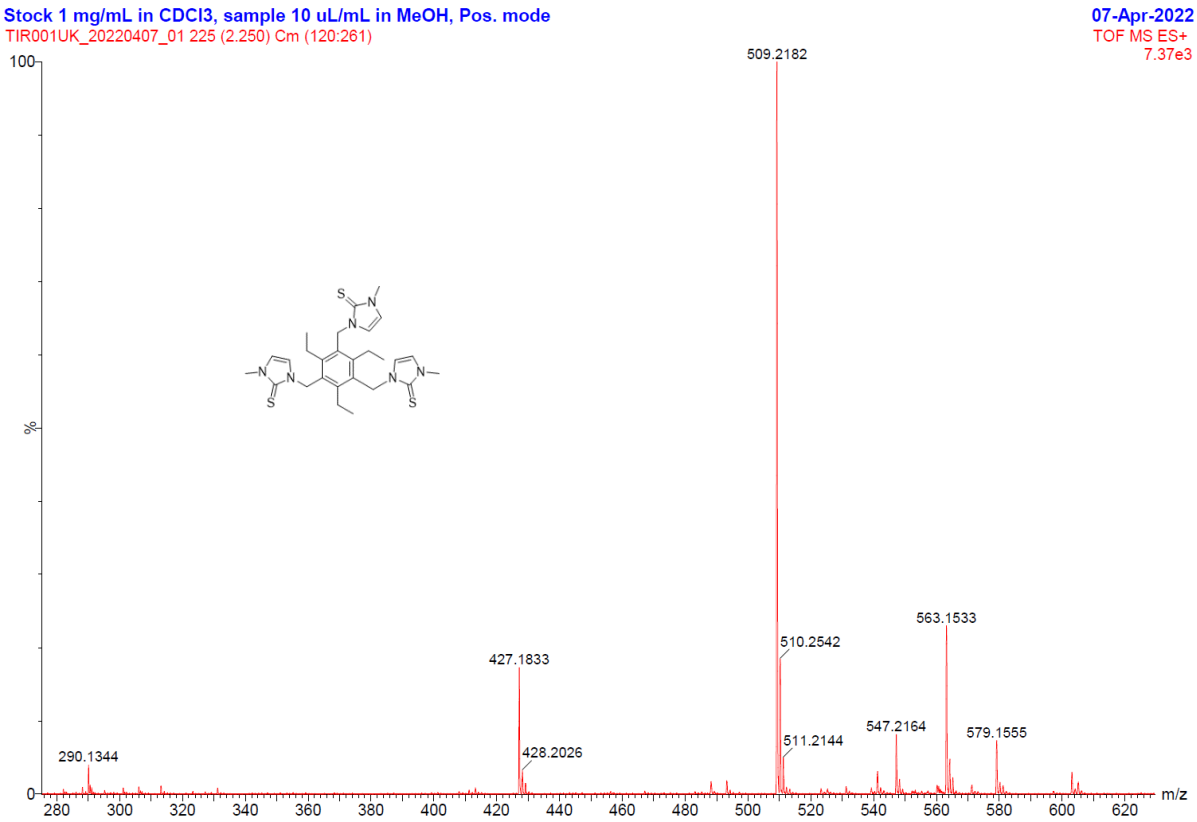
ppm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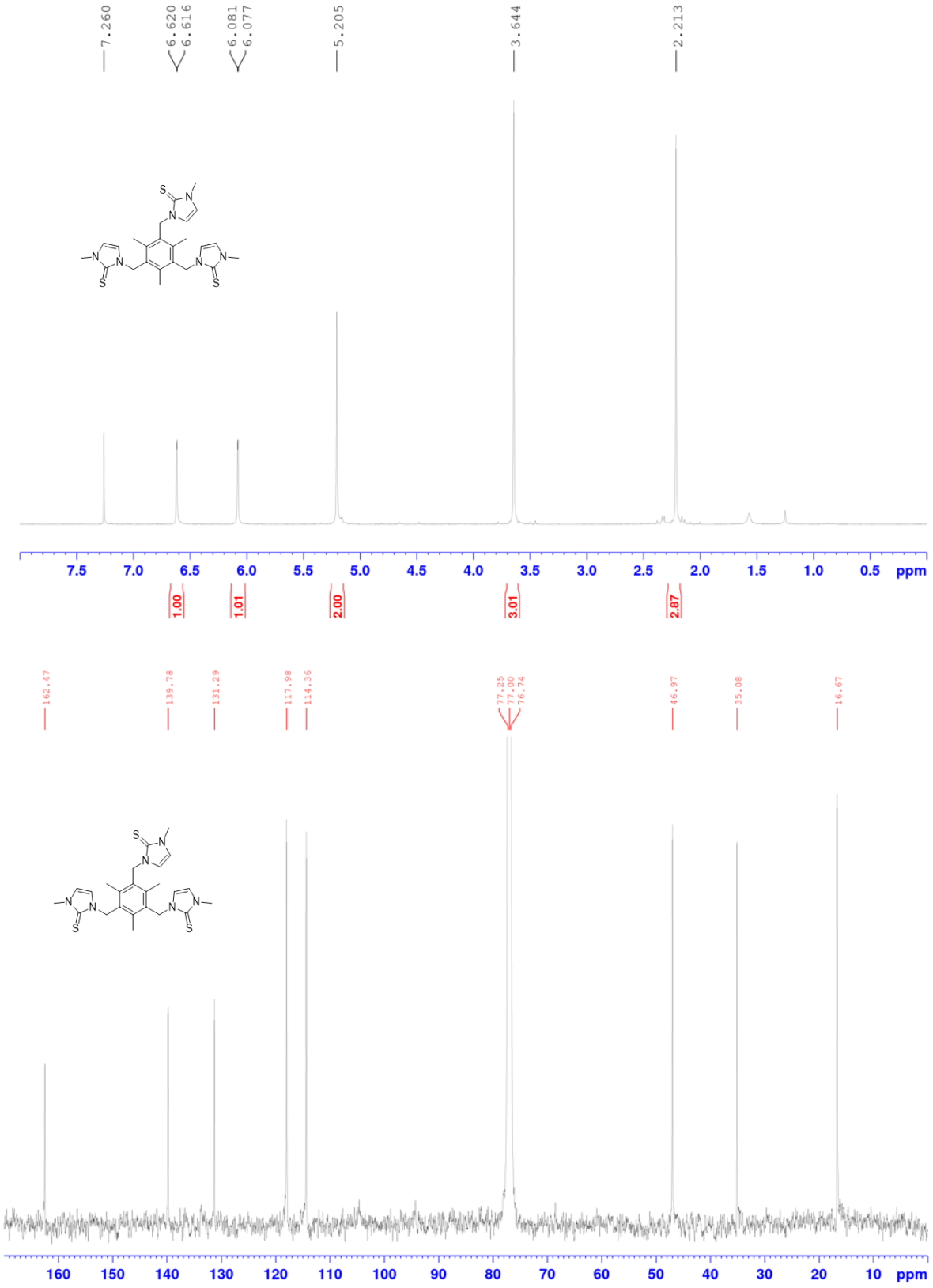
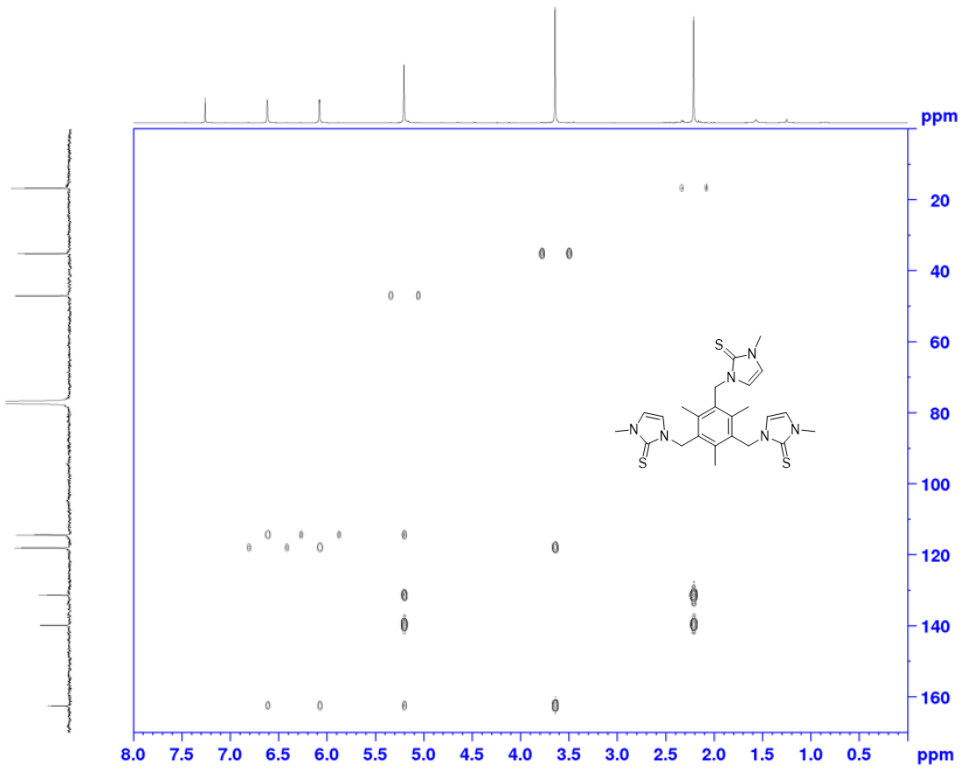
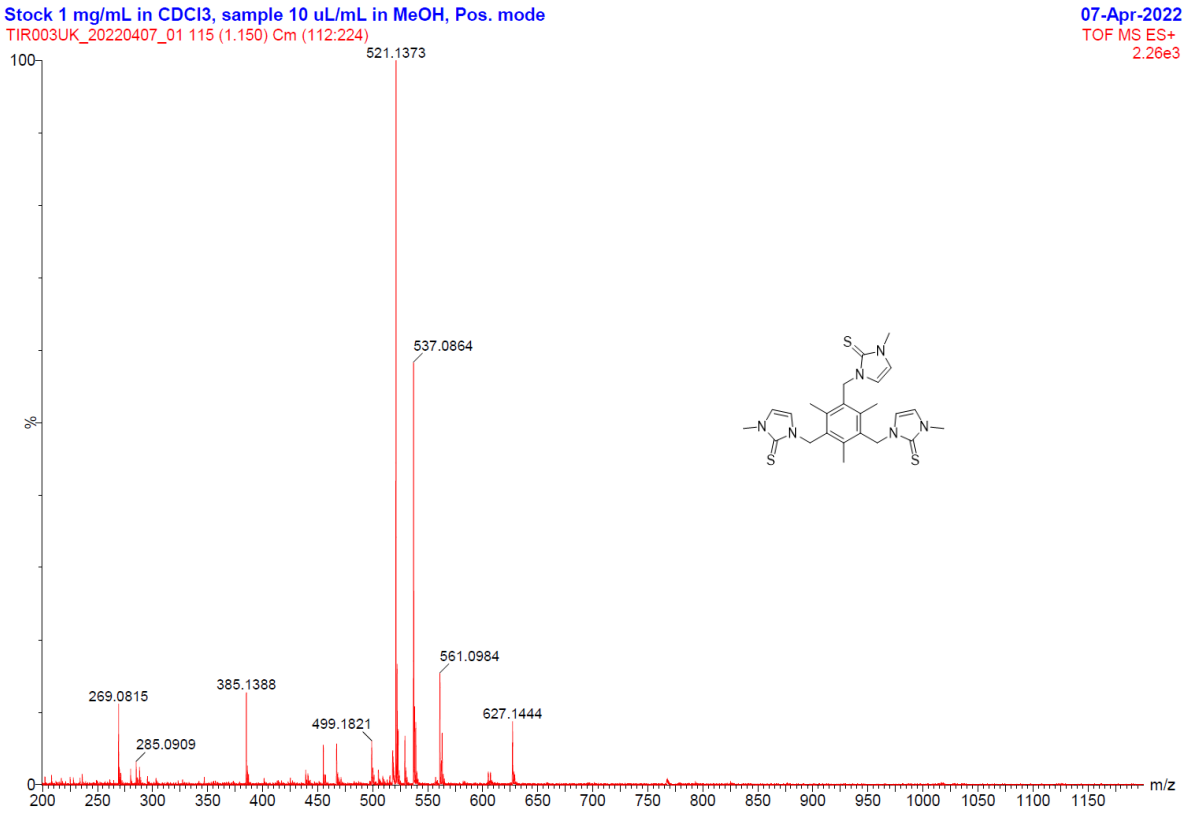
07-Apr-2022
TOF MS ES+
7.37e3
100
%
0
509.2182
563.1533
510.2542
427.1833
547.2164
579.1555
511.2144
290.1344
428.2026
280 300 320 340 360 380 400 420 440 460 480 500 520 540 560 580 600 620
m/z

APPENDIX 3


7.260
6.620
6.616
6.081
6.077
5.205
3.644
2.213
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
1.01
2.00
3.01
2.87
162.47
139.78
131.29
117.98
114.36
77.25
77.00
76.74
46.97
35.08
16.67
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

APPENDIX 4


ppm
20
40
60
80
100
120
140
160
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm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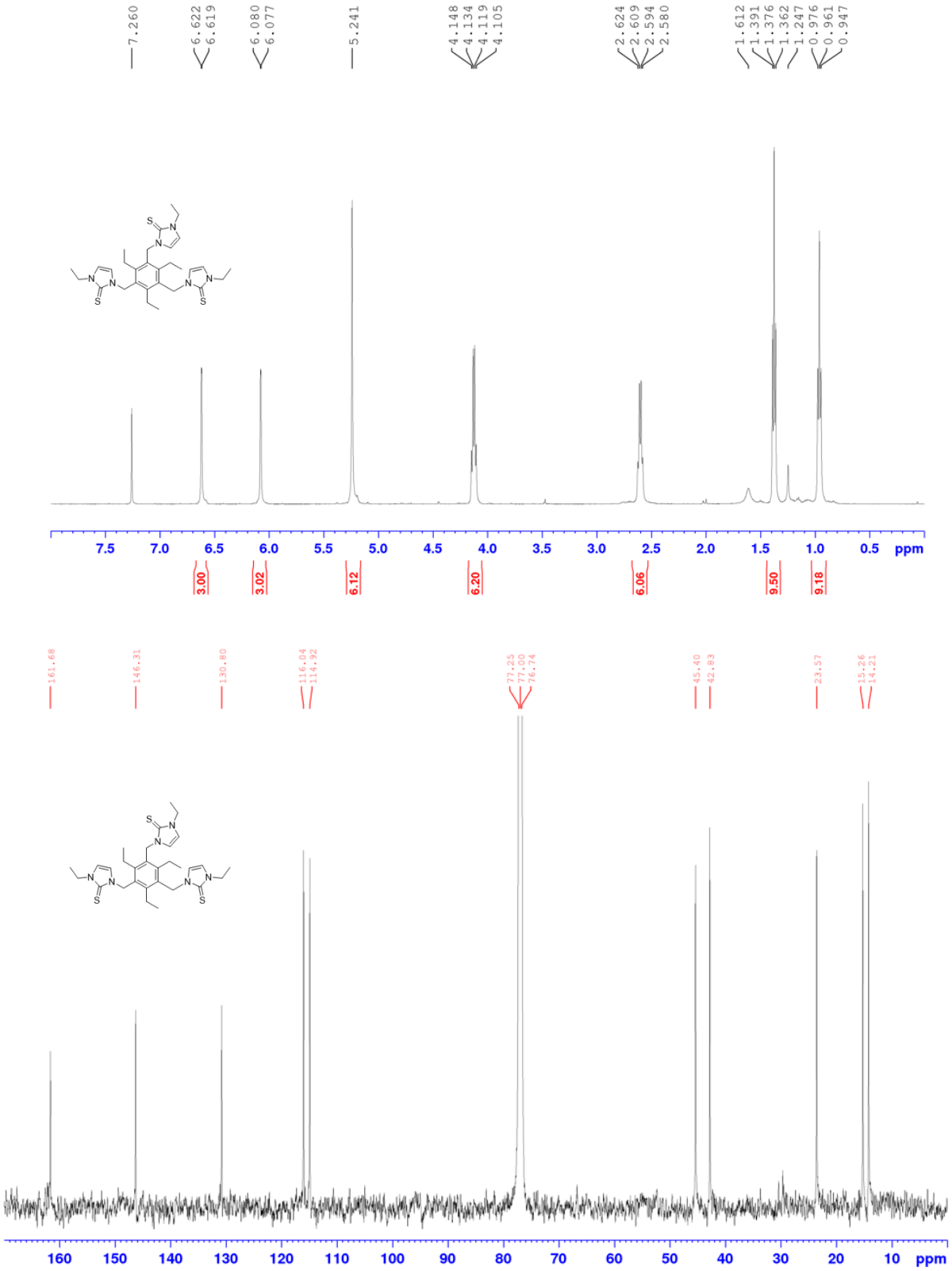
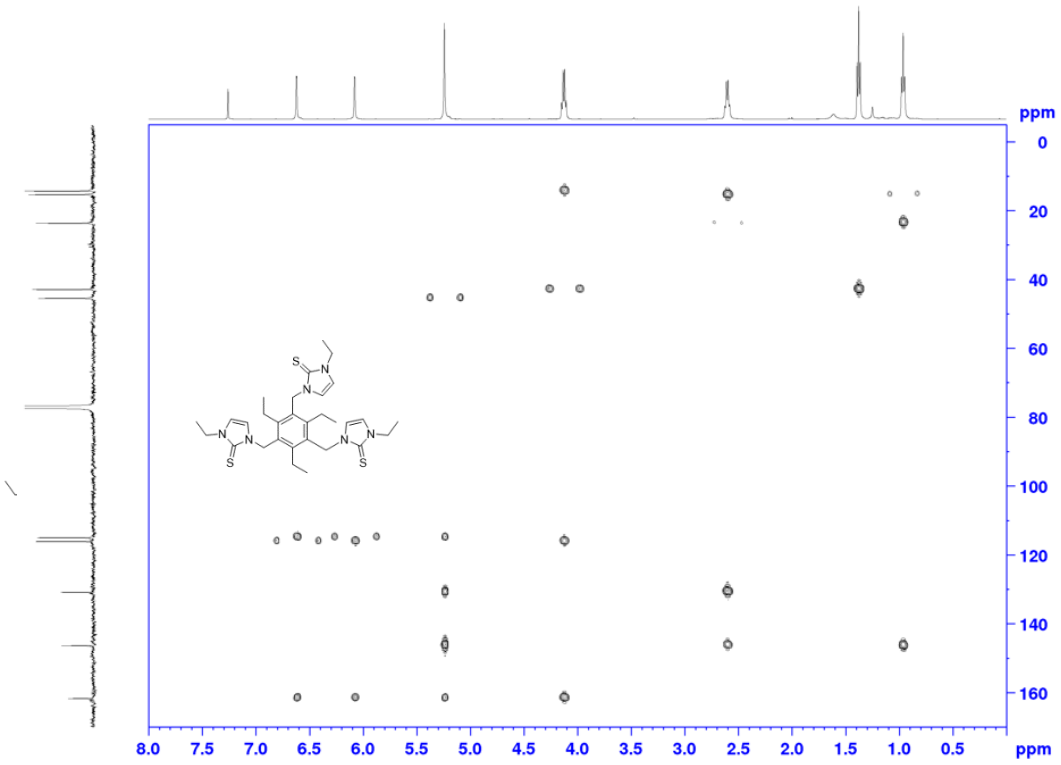
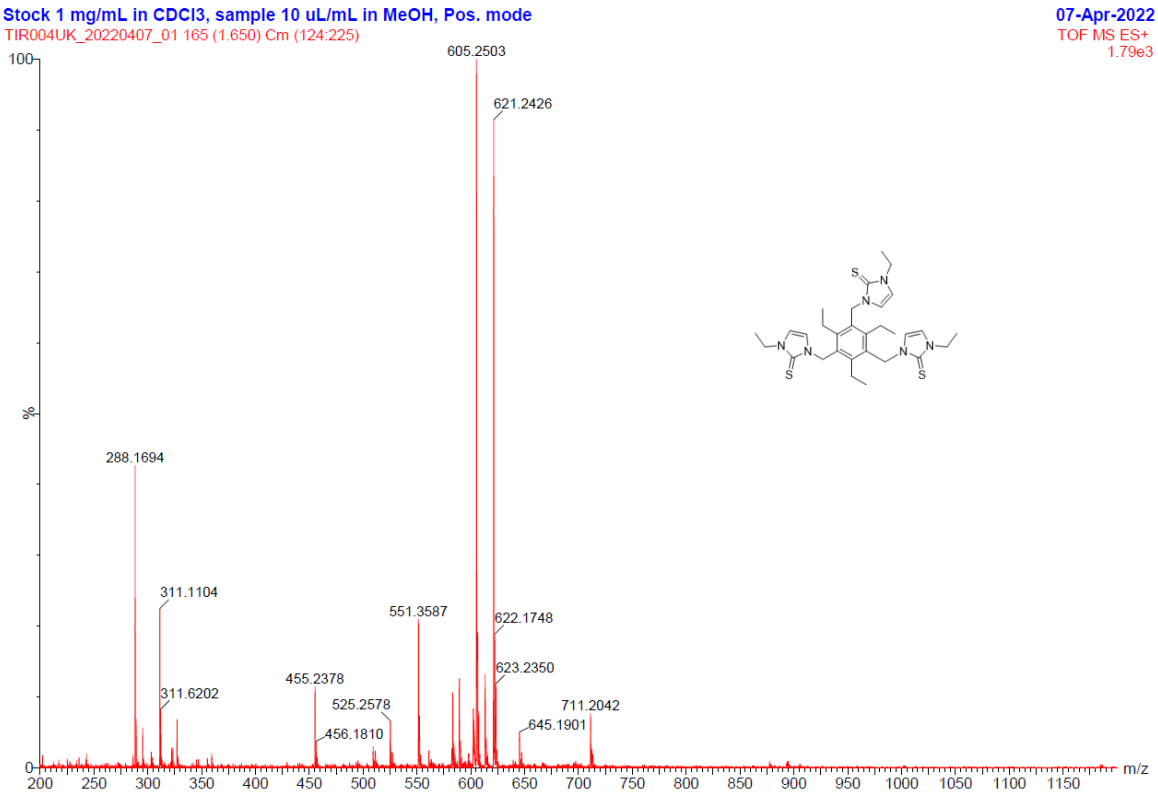
07-Apr-2022
TOF MS ES+
2.26e3
100
%
0
521.1373
537.0864
561.0984
269.0815
285.0909
385.1388
499.1821
627.1444
200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950 1000 1050 1100 1150
m/z

APPENDIX 5


7.260
6.622
6.619
6.080
6.077
5.241
4.148
4.134
4.119
4.105
2.624
2.609
2.594
2.580
1.612
1.391
1.376
1.362
1.247
0.976
0.961
0.947
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
3.00
3.02
6.12
6.20
6.06
9.50
9.18
161.68
146.31
130.80
116.04
114.92
77.25
77.00
76.74
45.40
42.83
23.57
15.26
14.21
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

APPENDIX 6


ppm
0
20
40
60
80
100
120
140
160
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm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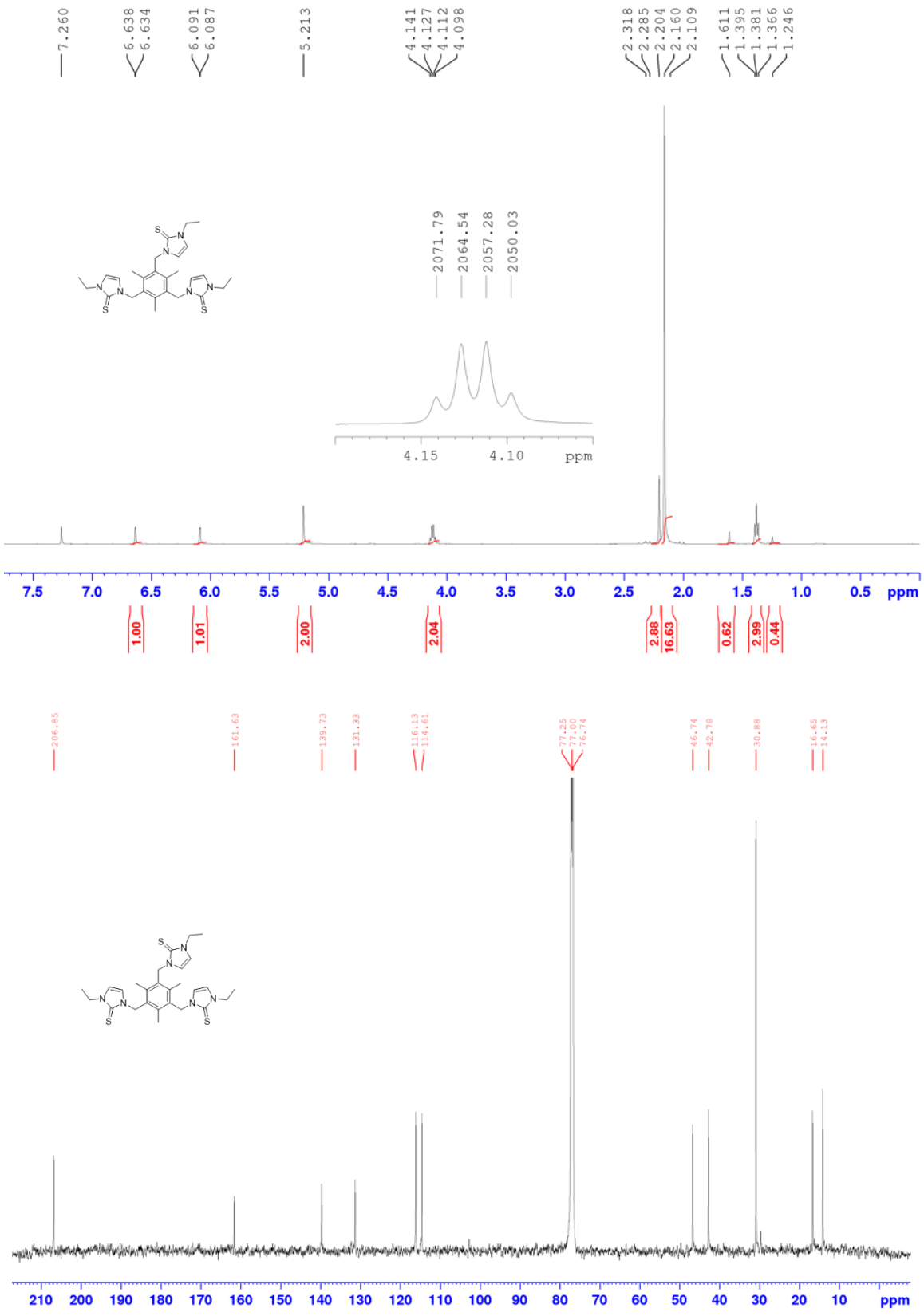
TIR004UK_20220407_01 165 (1.650) Cm (124:225)
07-Apr-2022
TOF MS ES+
1.79e3
605.2503
621.2426
288.1694
311.1104
311.6202
455.2378
525.2578
456.1810
551.3587
622.1748
623.2350
645.1901
711.2042
%
m/z

APPENDIX 7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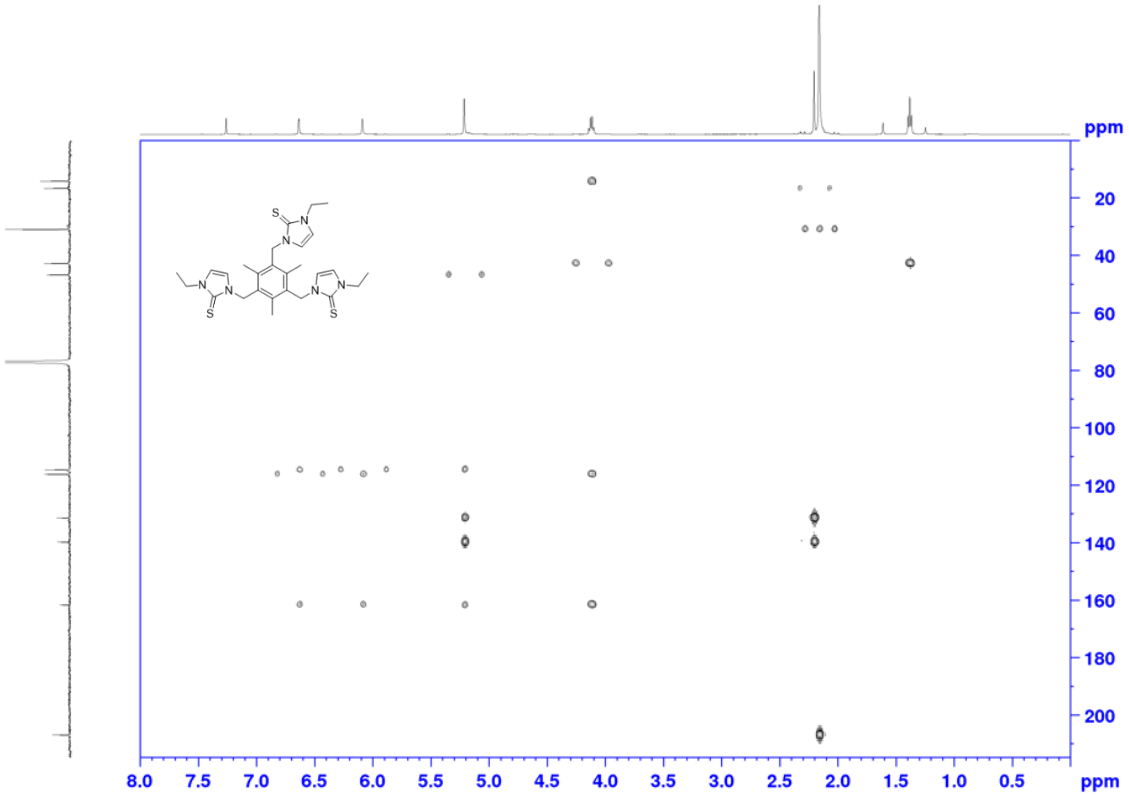
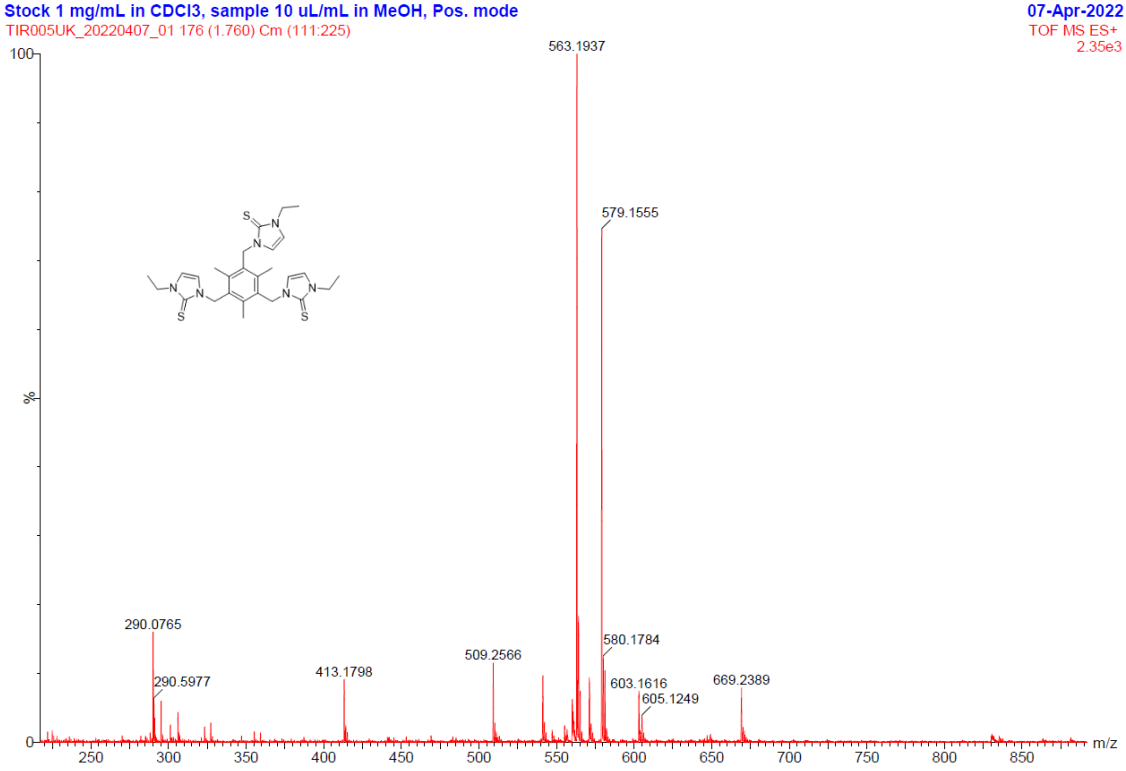
6.638
6.634
6.091
6.087
5.213
4.141
4.127
4.112
4.098
2.318
2.285
2.204
2.160
2.109
1.611
1.395
1.381
1.366
1.246
2071.79
2064.54
2057.28
2050.03
4.15
4.10
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.01
2.00
2.04
2.88
16.63
0.62
2.99
0.44
206.85
161.63
139.73
131.33
116.13
114.61
77.25
77.00
76.74
46.74
42.78
30.88
16.65
14.13
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

APPENDIX 8


ppm
20
40
60
80
100
120
140
160
180
200
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm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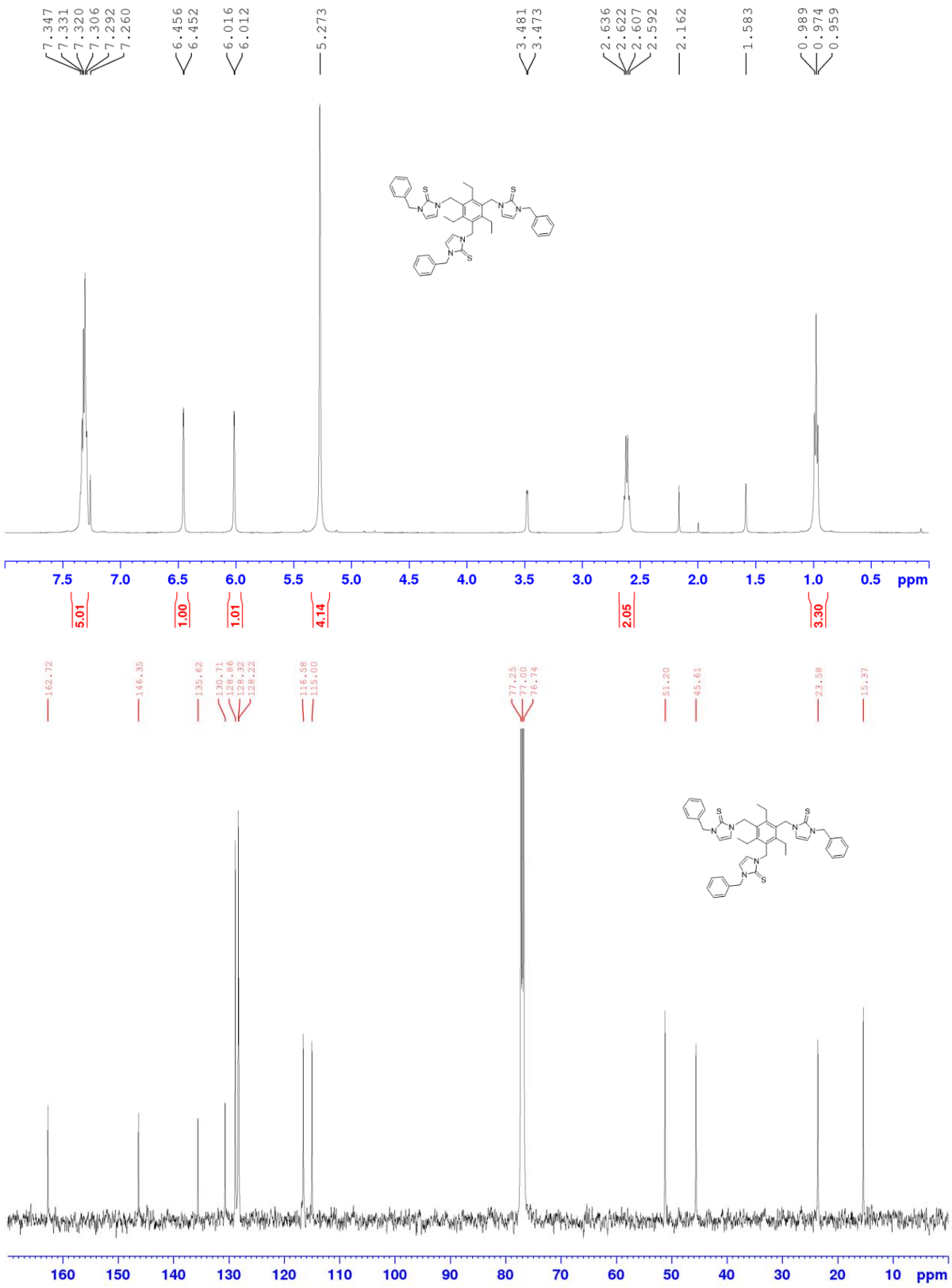
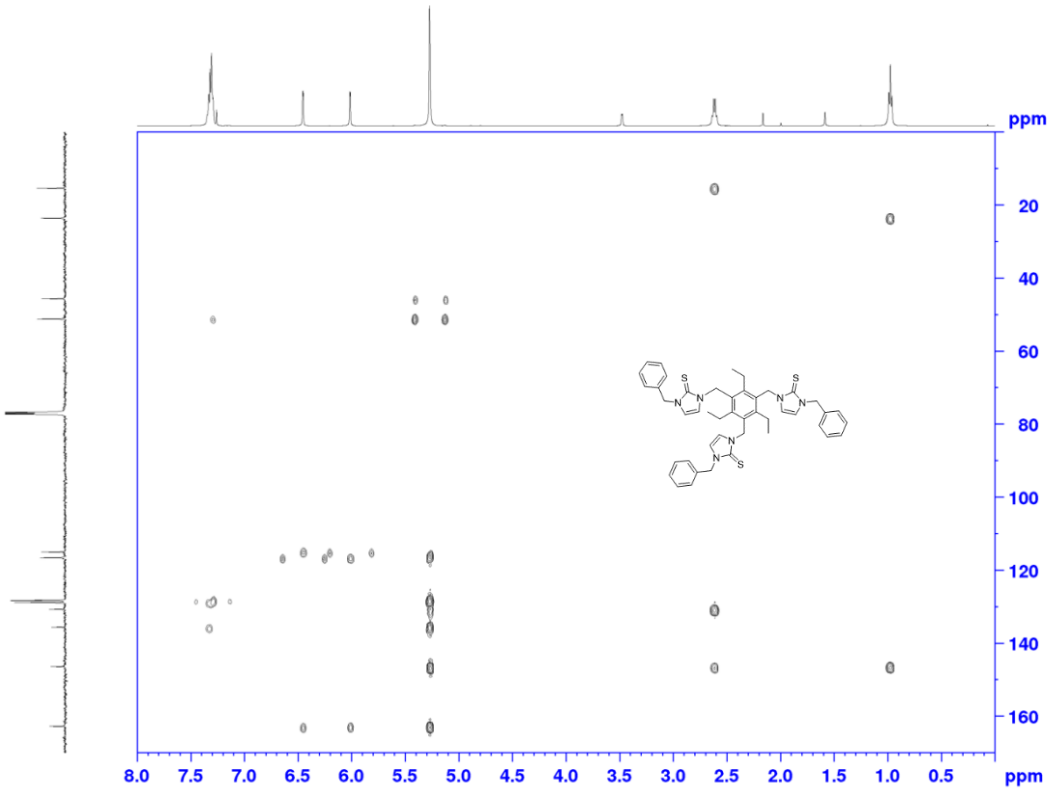
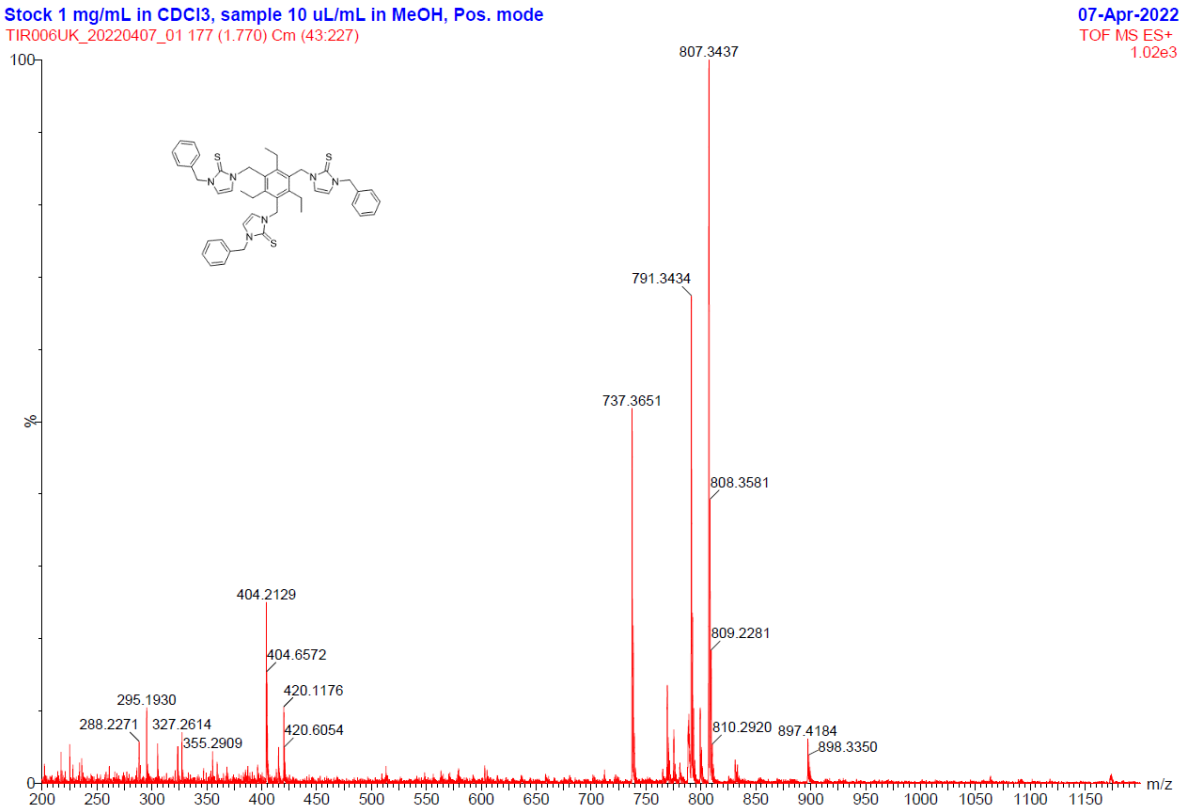
TIR005UK_20220407_01 176 (1.760) Cm (111:225)
07-Apr-2022
TOF MS ES+
2.35e3
100
%
0
563.1937
579.1555
580.1784
290.0765
290.5977
413.1798
509.2566
603.1616
605.1249
669.2389
250
300
350
400
450
500
550
600
650
700
750
800
850
m/z

APPENDIX 9


7.347
7.331
7.320
7.306
7.292
7.260
6.456
6.452
6.016
6.012
5.273
3.481
3.473
2.636
2.622
2.607
2.592
2.162
1.583
0.989
0.974
0.959
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
5.01
1.00
1.01
4.14
2.05
3.30
162.72
146.35
135.62
130.71
128.86
128.32
128.22
116.58
115.00
77.25
77.00
76.74
51.20
45.61
23.58
15.37
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

APPENDIX 10


ppm
20
40
60
80
100
120
140
160
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm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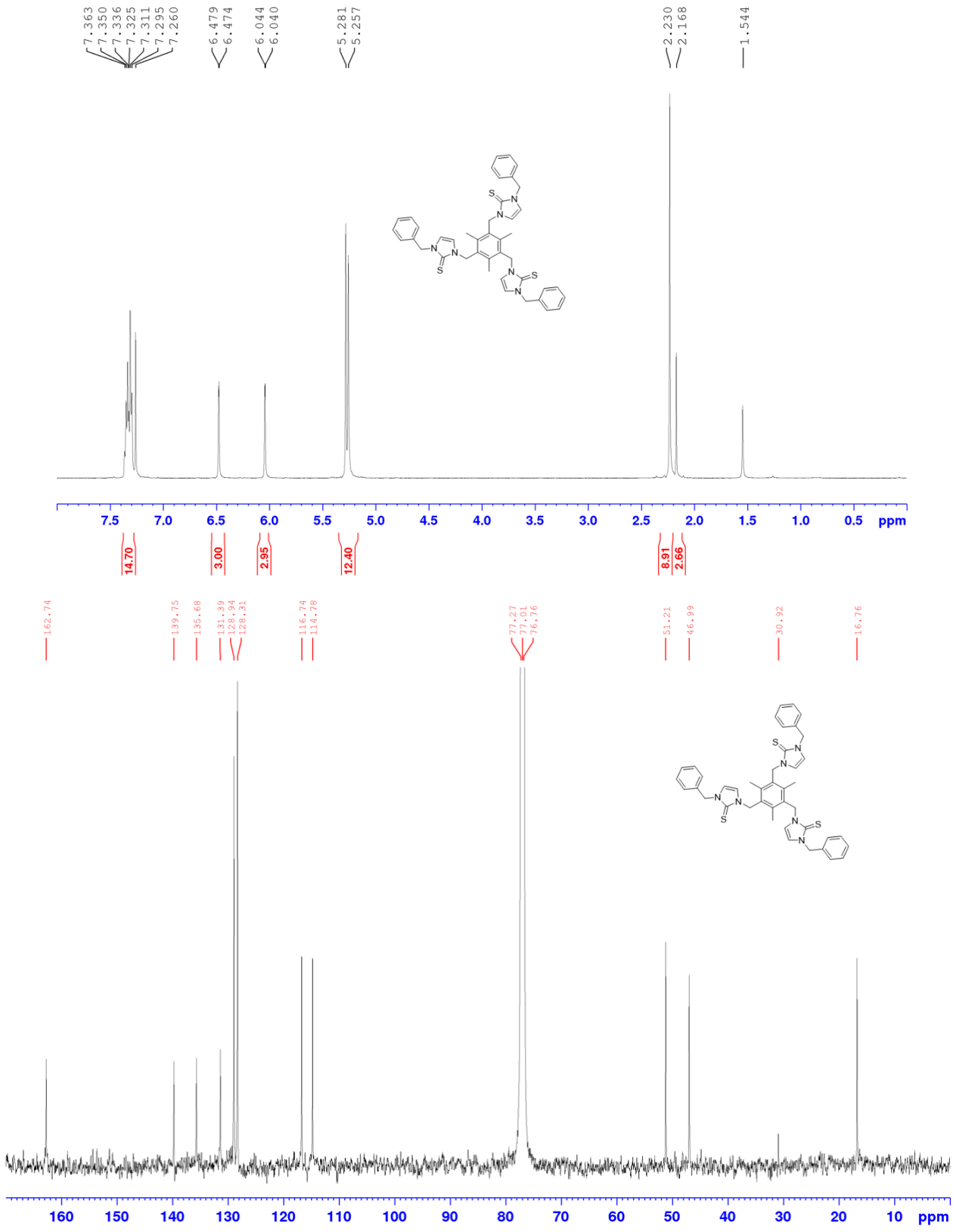
TIR006UK_20220407_01 177 (1.770) Cm (43:227)
07-Apr-2022
TOF MS ES+
1.02e3
100
%
0
807.3437
791.3434
737.3651
808.3581
809.2281
404.2129
404.6572
420.1176
420.6054
295.1930
288.2271
327.2614
355.2909
810.2920
897.4184
898.3350
200
250
300
350
400
450
500
550
600
650
700
750
800
850
900
950
1000
1050
1100
1150
m/z

APPENDIX 11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7.336
7.325
7.311
7.295
7.260
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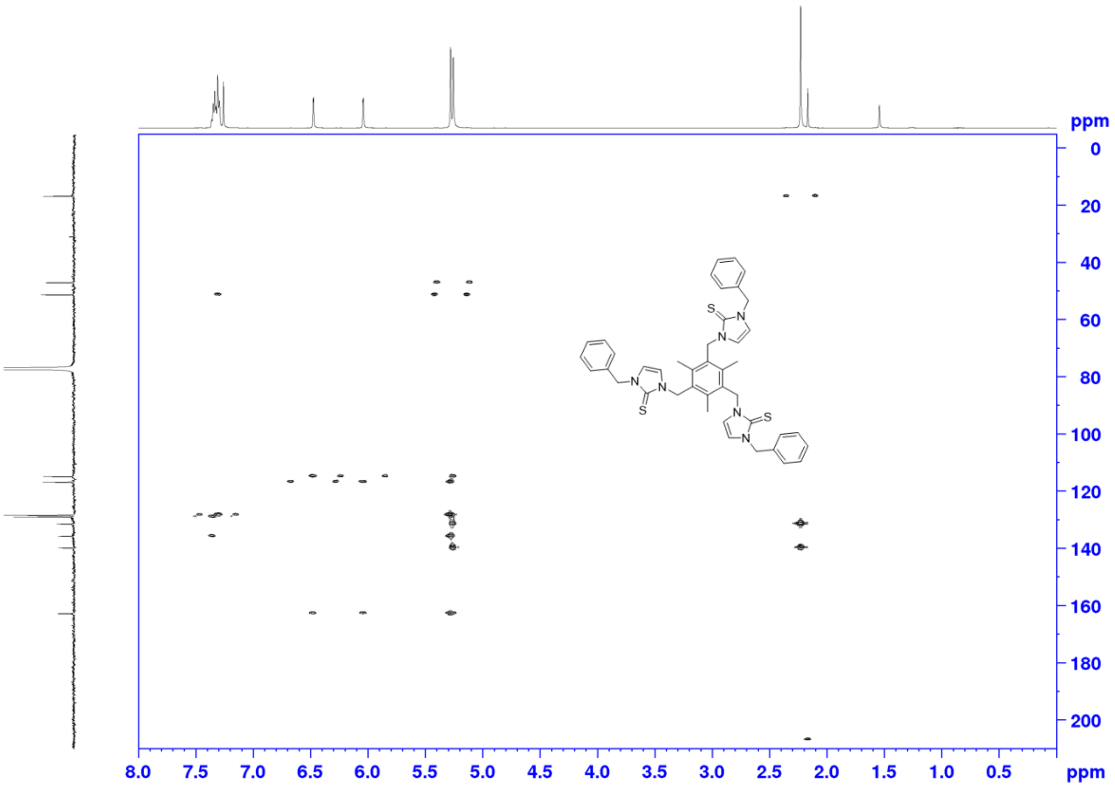
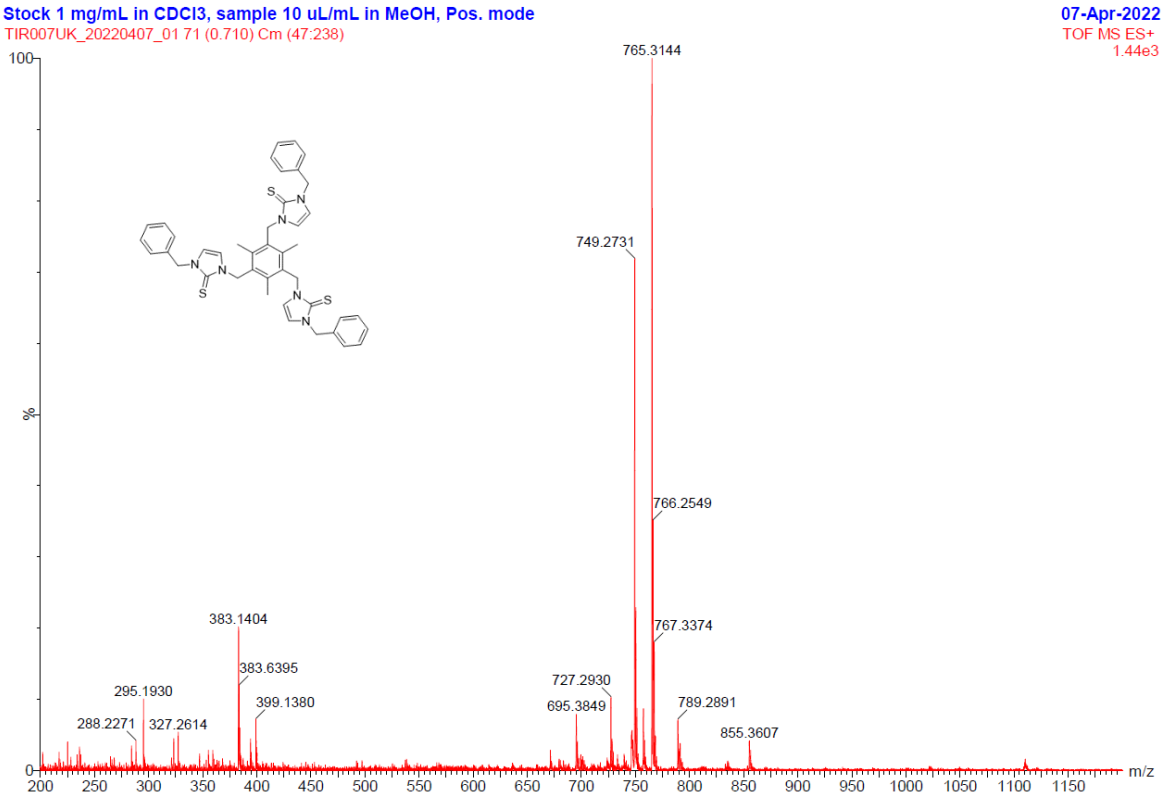
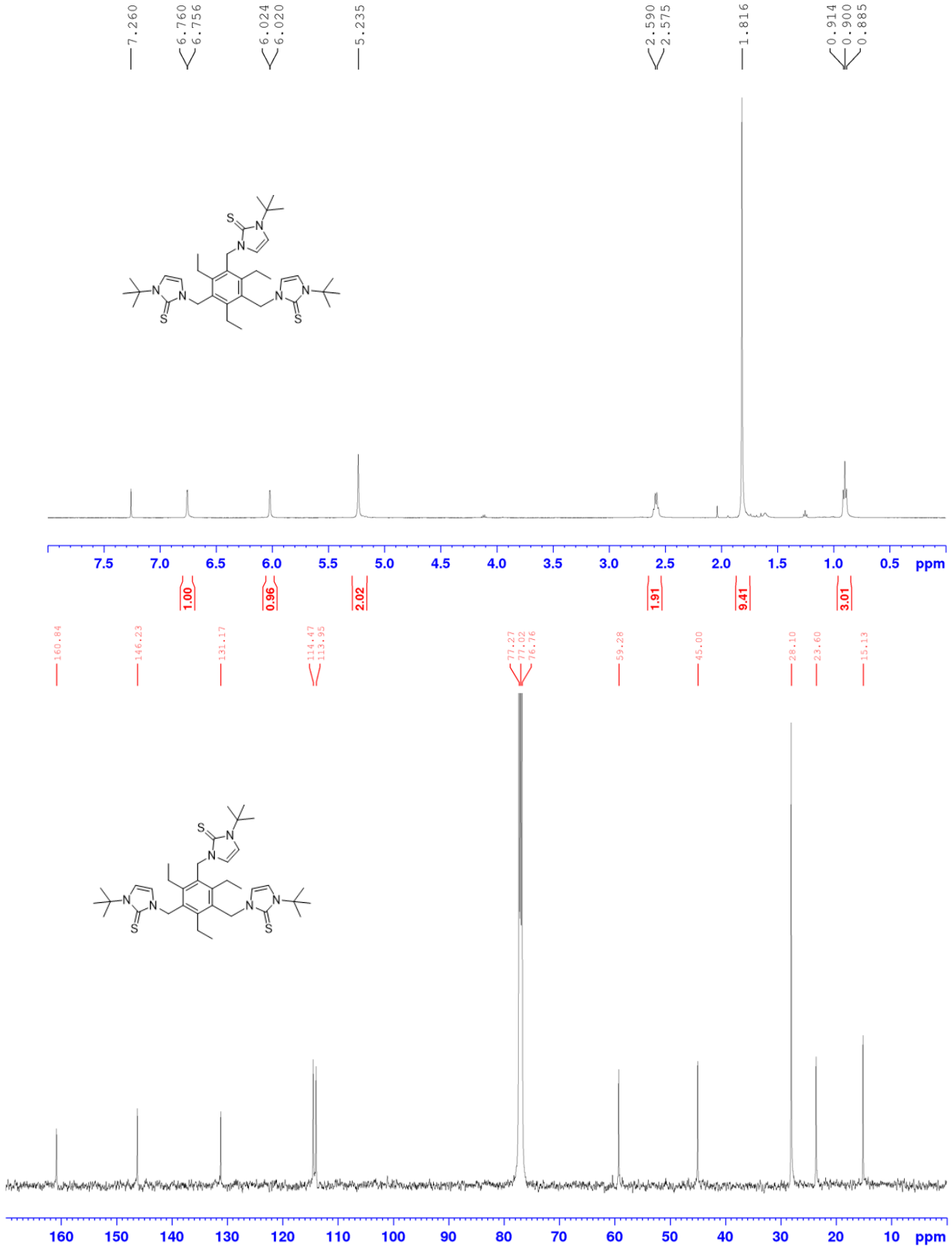
6.474
6.044
6.040
5.281
5.257
2.230
2.168
1.544
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
14.70
3.00
2.95
12.40
8.91
2.66
162.74
139.75
135.68
131.39
128.94
128.31
116.74
114.78
77.27
77.01
76.76
51.21
46.99
30.92
16.76
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

APPENDIX 12

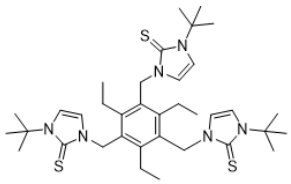

ppm
0
20
40
60
80
100
120
140
160
180
200
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

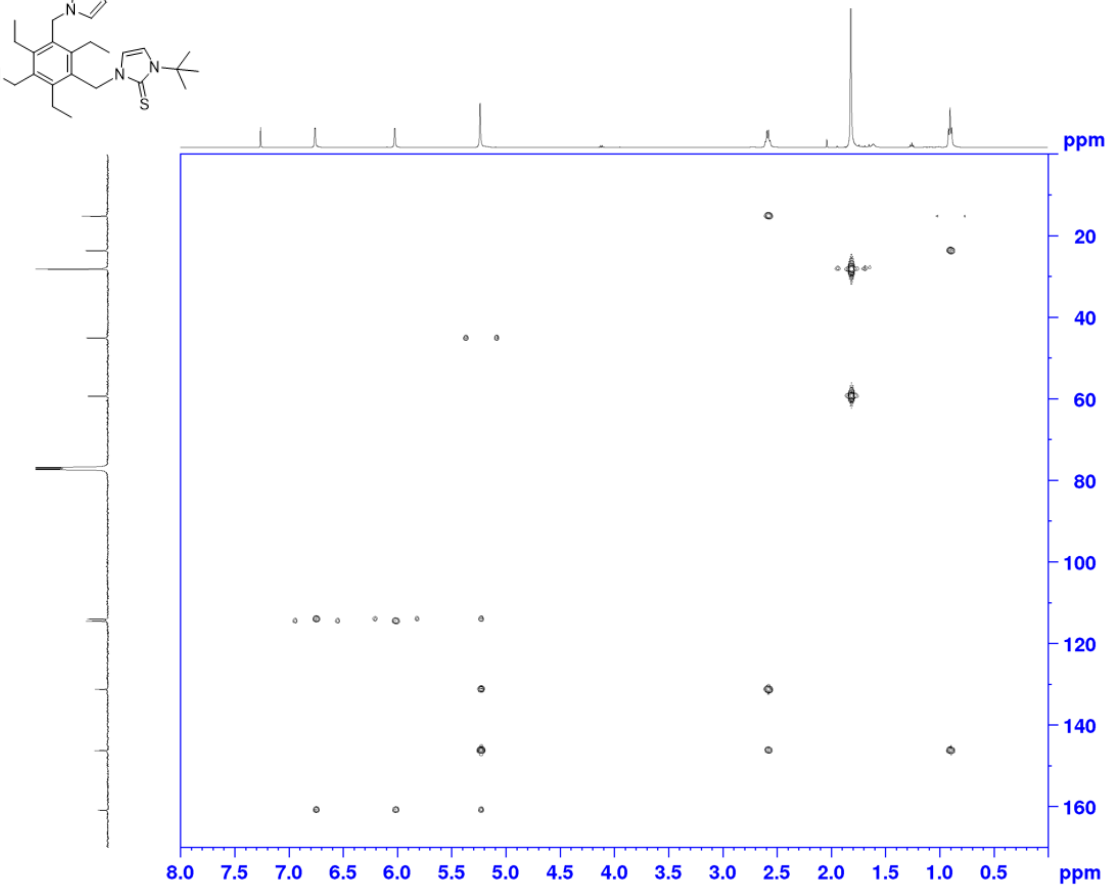

Stock 1 mg/mL in CDCl3, sample 10 uL/mL in MeOH, Pos. mode
TIR007UK_20220407_01 71 (0.710) Cm (47:238)
07-Apr-2022
TOF MS ES+
1.44e3
100
%
0
765.3144
749.2731
766.2549
767.3374
789.2891
855.3607
727.2930
695.3849
383.1404
383.6395
399.1380
295.1930
288.2271
327.2614
200
250
300
350
400
450
500
550
600
650
700
750
800
850
900
950
1000
1050
1100
1150
m/z

APPENDIX 13


7.260
6.760
6.756
6.024
6.020
5.235
2.590
2.575
1.816
0.914
0.900
0.885
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
0.96
2.02
1.91
9.41
3.01
160.84
146.23
131.17
114.47
113.95
77.27
77.02
76.76
59.28
45.00
28.10
23.60
15.13
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

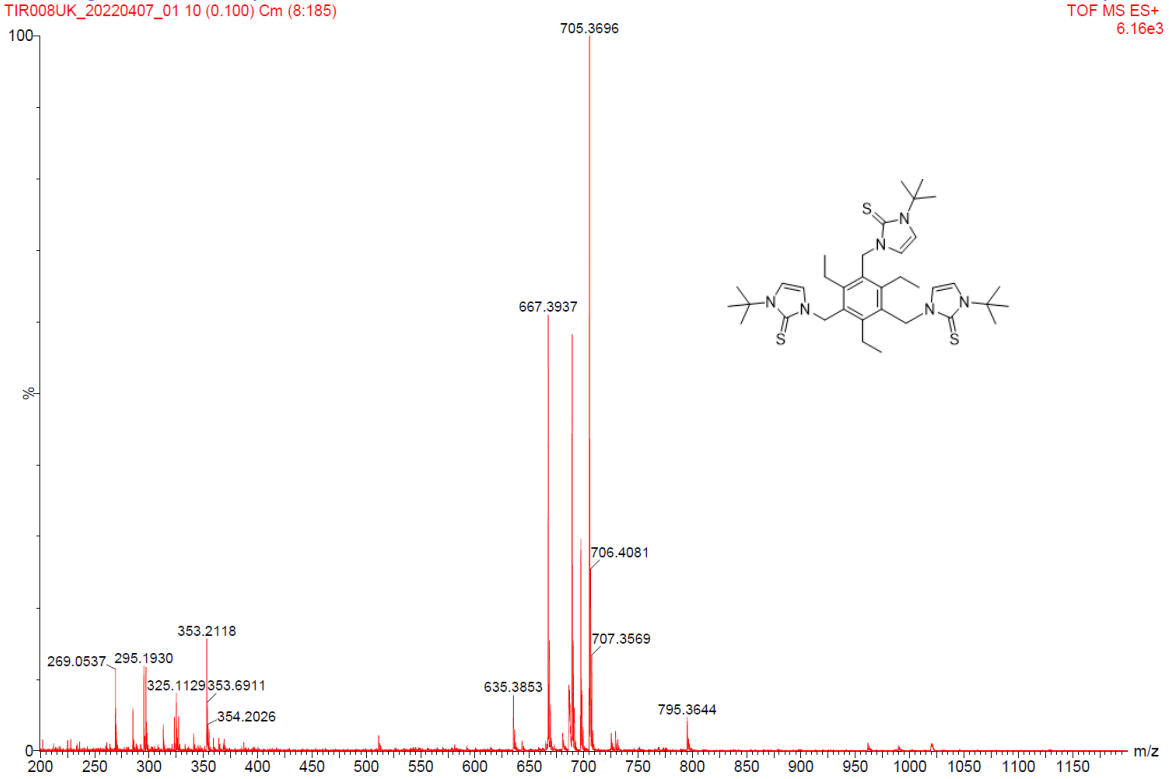
APPENDIX 14



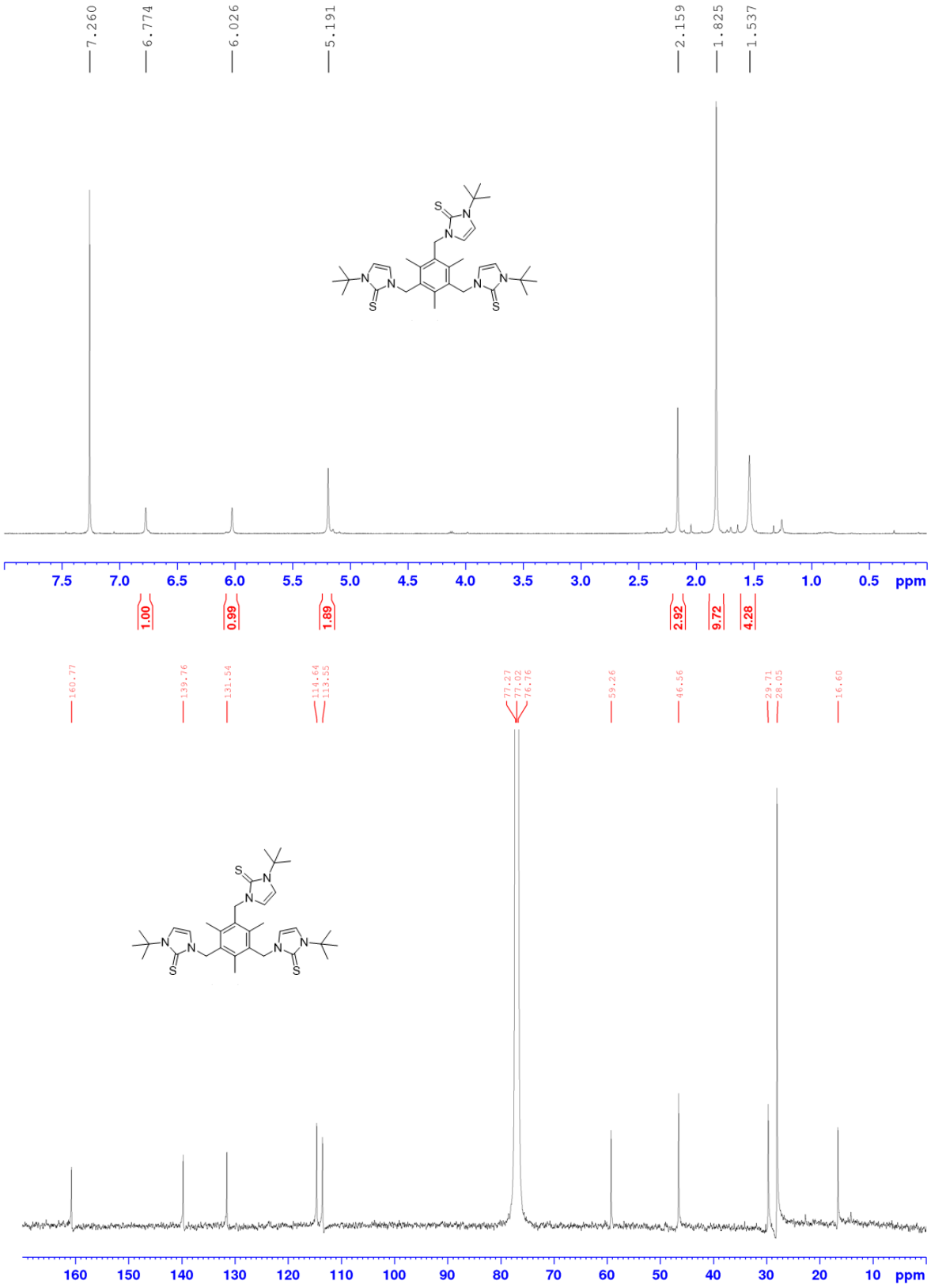


Stock 1 mg/mL in CDCl3, sample 10 uL/mL in MeOH, Pos. mode
TIR008UK_20220407_01 10 (0.100) Cm (8:185)

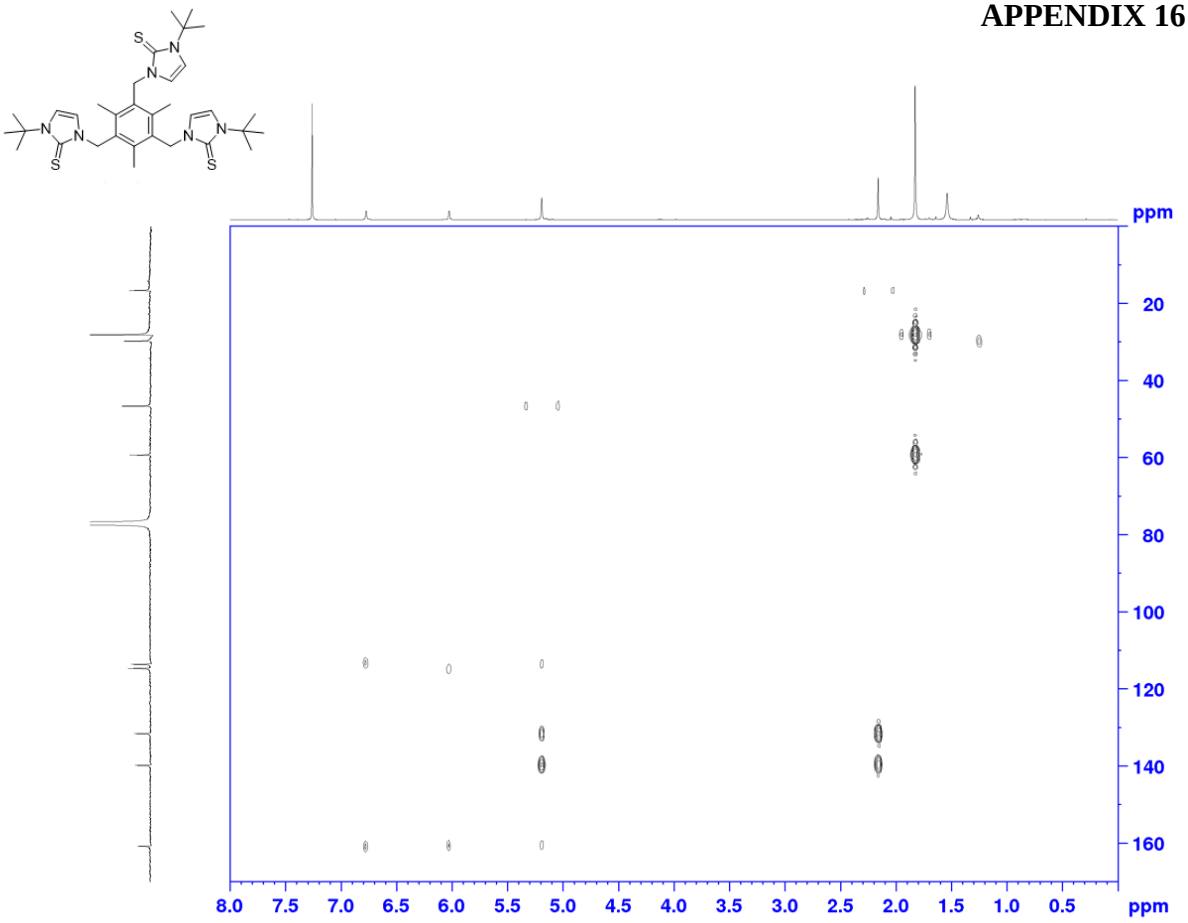
07-Apr-2022
TOF MS ES+
6.16e3

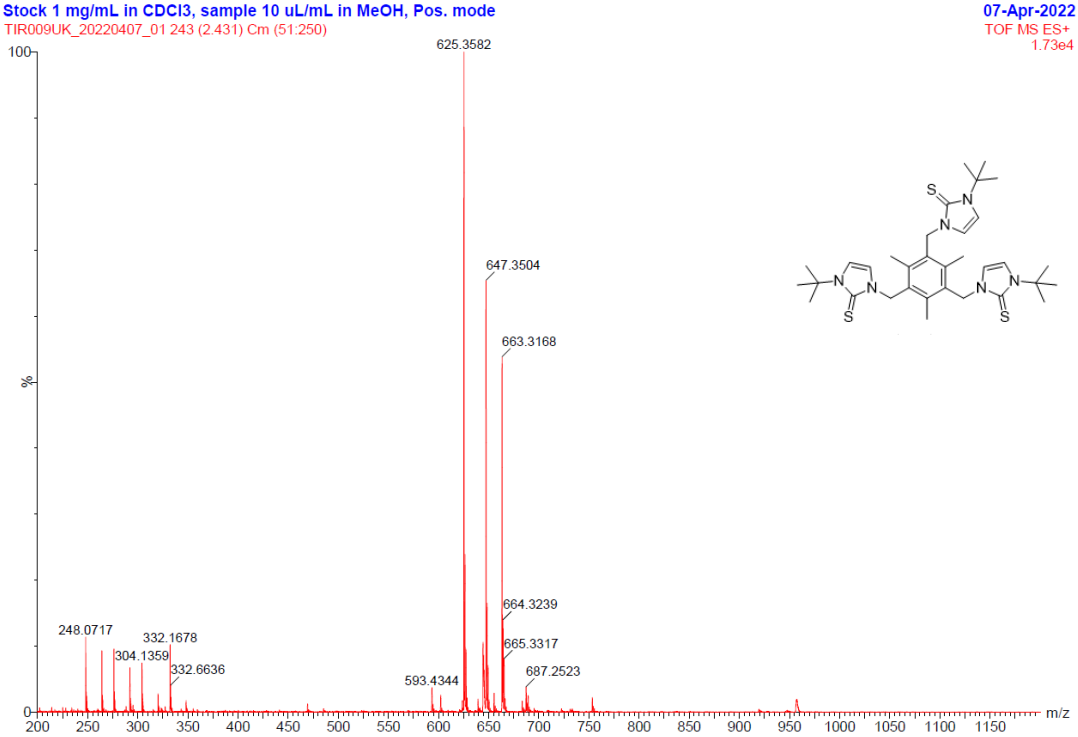


APPENDIX 15

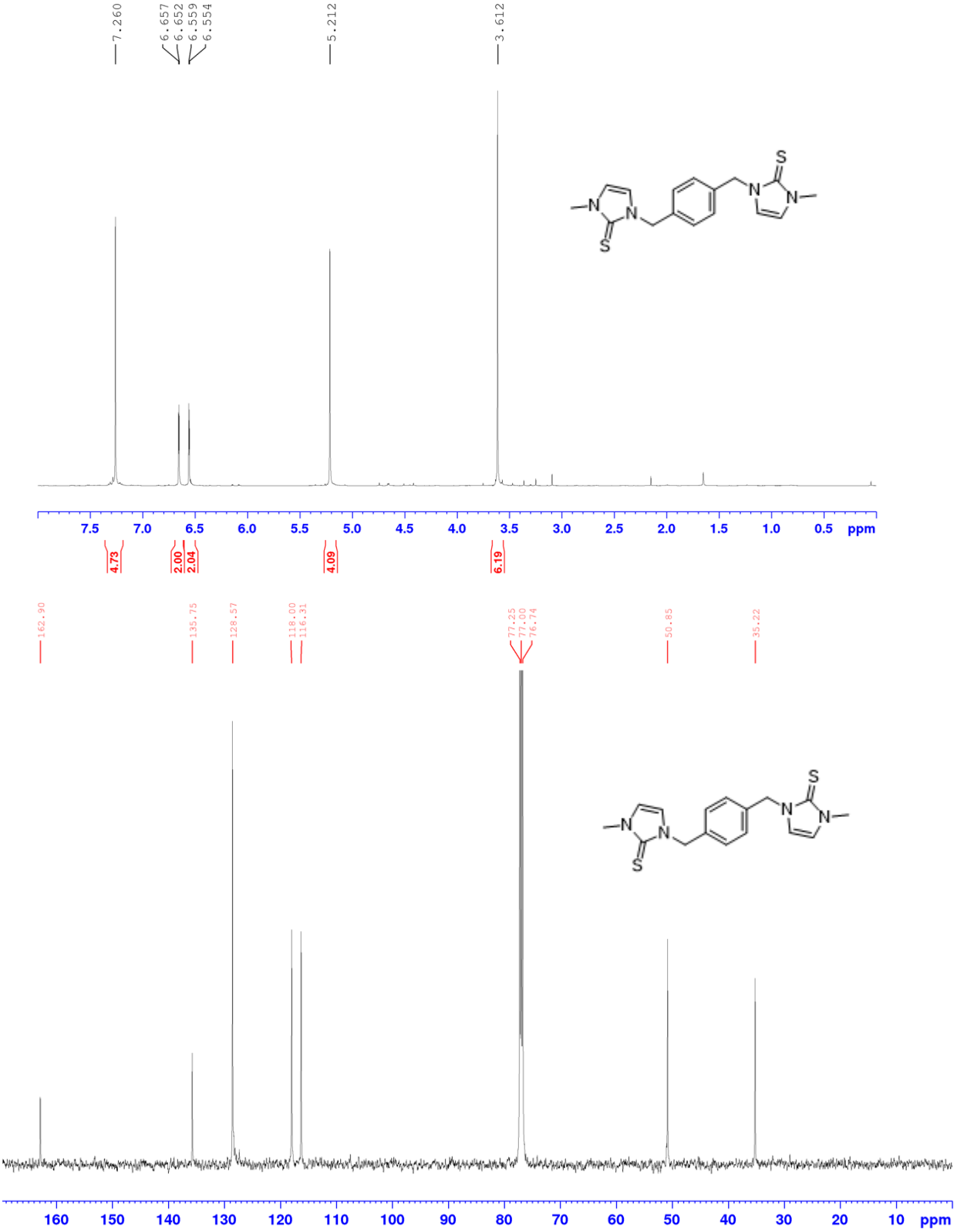

7.260
6.774
6.026
5.191
2.159
1.825
1.537
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
0.99
1.89
2.92
9.72
4.28
160.77
139.76
131.54
114.64
113.55
77.27
77.02
76.76
59.26
46.56
29.71
28.05
16.60
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

APPENDIX 16

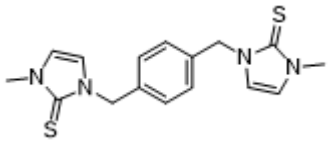

ppm
20
40
60
80
100
120
140
160
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

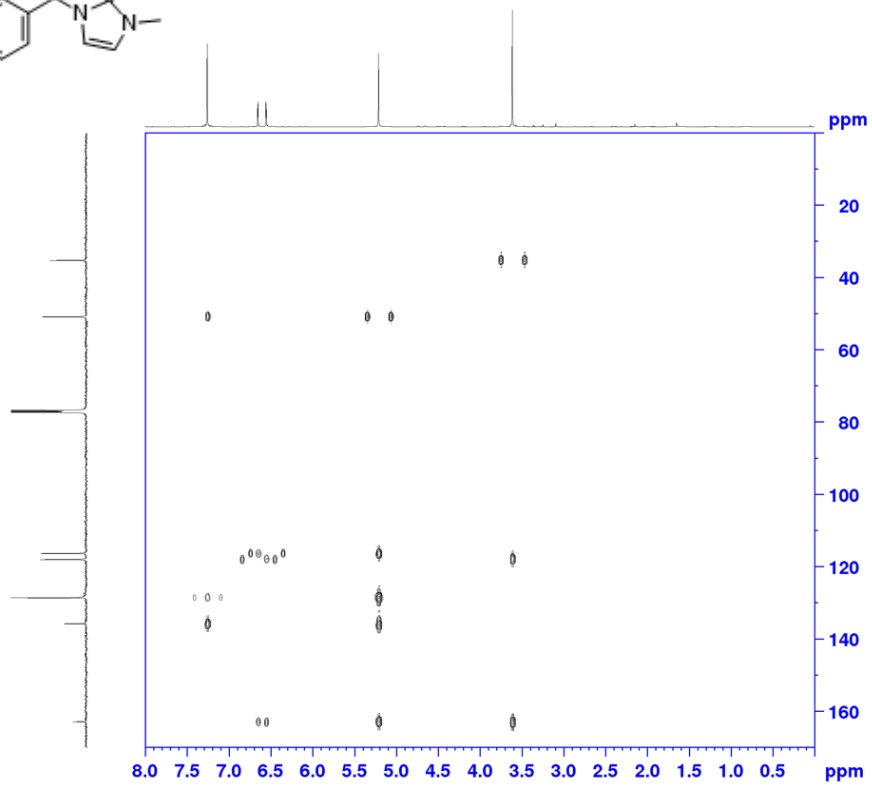

Stock 1 mg/mL in CDCl3, sample 10 uL/mL in MeOH, Pos. mode
TIR009UK_20220407_01 243 (2.431) Cm (51:250)
07-Apr-2022
TOF MS ES+
1.73e4
625.3582
647.3504
663.3168
664.3239
665.3317
687.2523
593.4344
248.0717
304.1359
332.1678
332.6636
100
%
0
200
250
300
350
400
450
500
550
600
650
700
750
800
850
900
950
1000
1050
1100
1150
m/z

APPENDIX 17


7.260
6.657
6.652
6.559
6.554
5.212
3.612
S
N
N
N
N
S
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
4.73
2.00
2.04
4.09
6.19
162.90
135.75
128.57
118.00
116.31
77.25
77.00
76.74
50.85
35.22
S
N
N
N
N
S
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

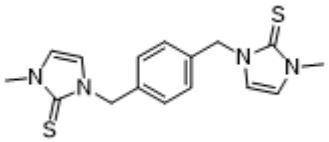
APPENDIX 18



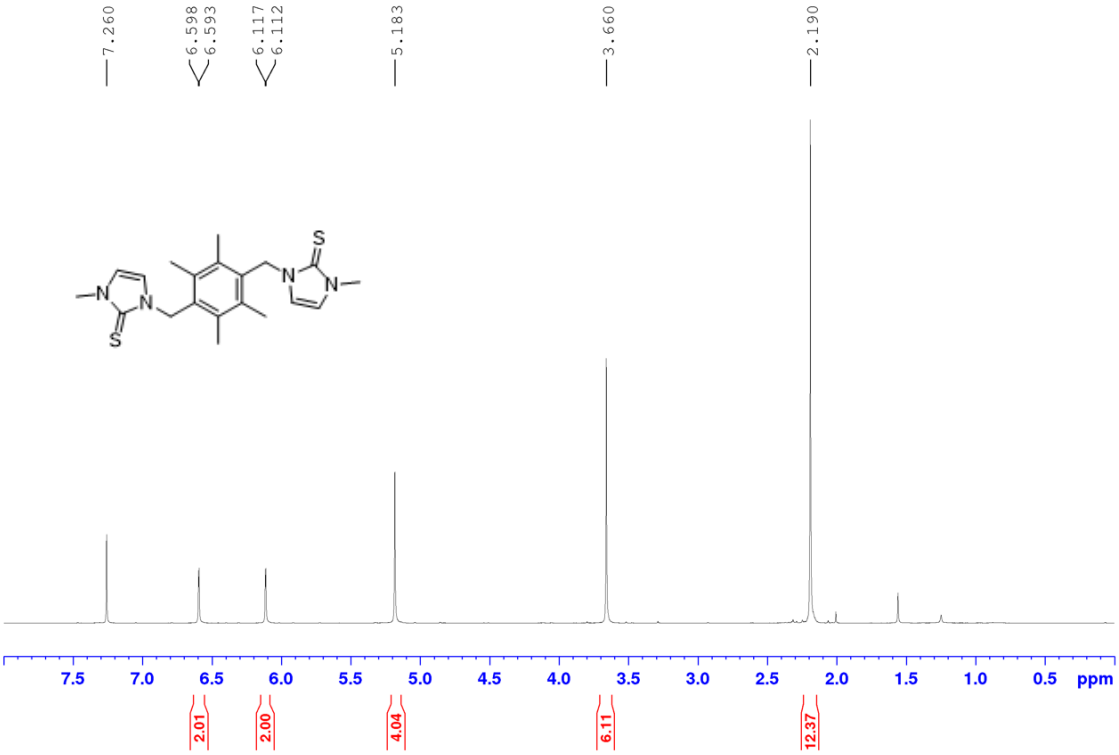


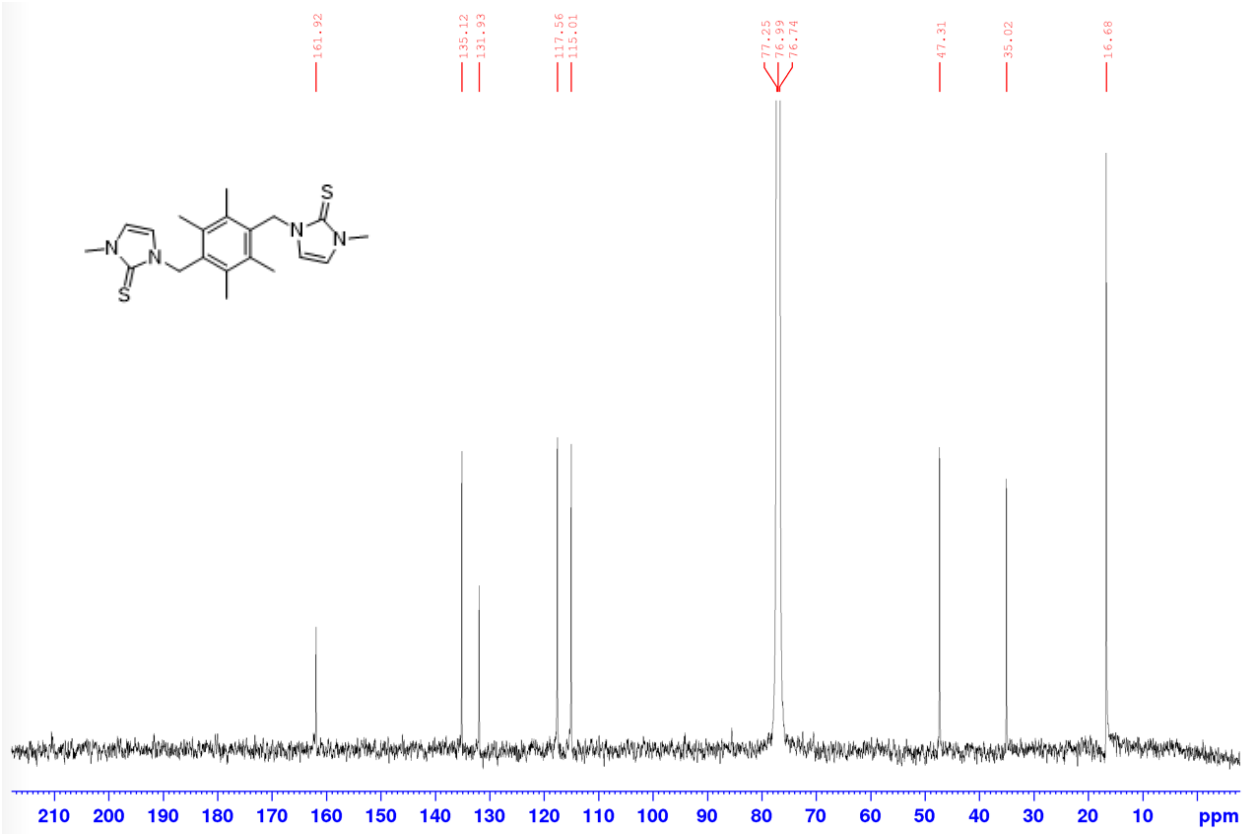
Stock 1 mg/ml in CHCl3, sample 10uM in MeOH
TIR-016_20220603 45 (0.449) Cm (12:174)

03-Jun-2022
TOF MS ES+
1.21e5

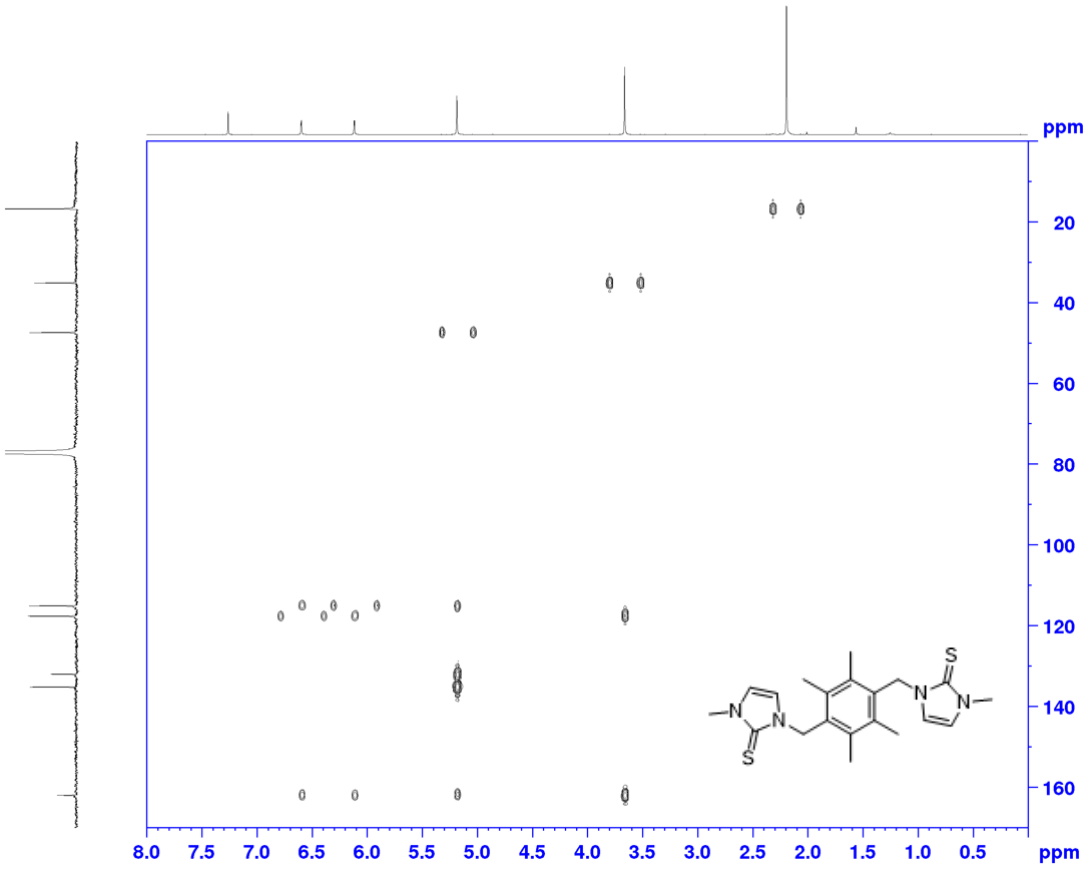


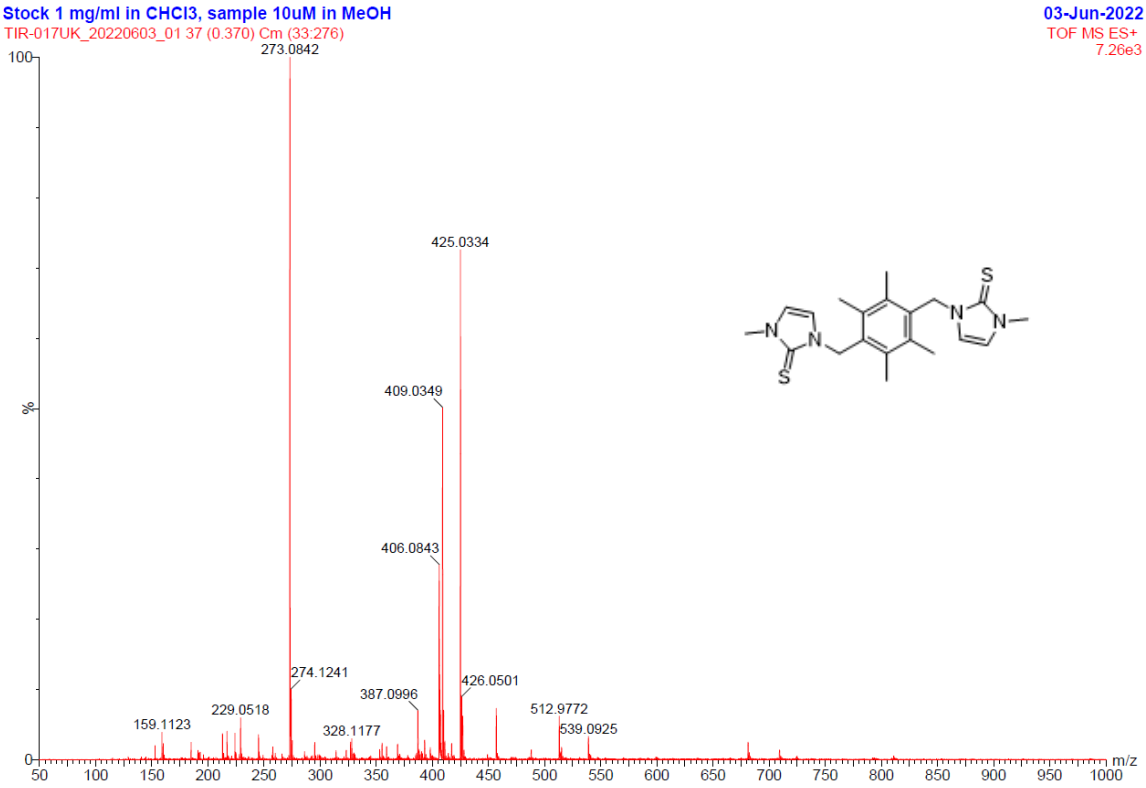
APPENDIX 19


7.260
6.598
6.593
6.117
6.112
5.183
3.660
2.190
S
N
N
N
S
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.01
2.00
4.04
6.11
12.37

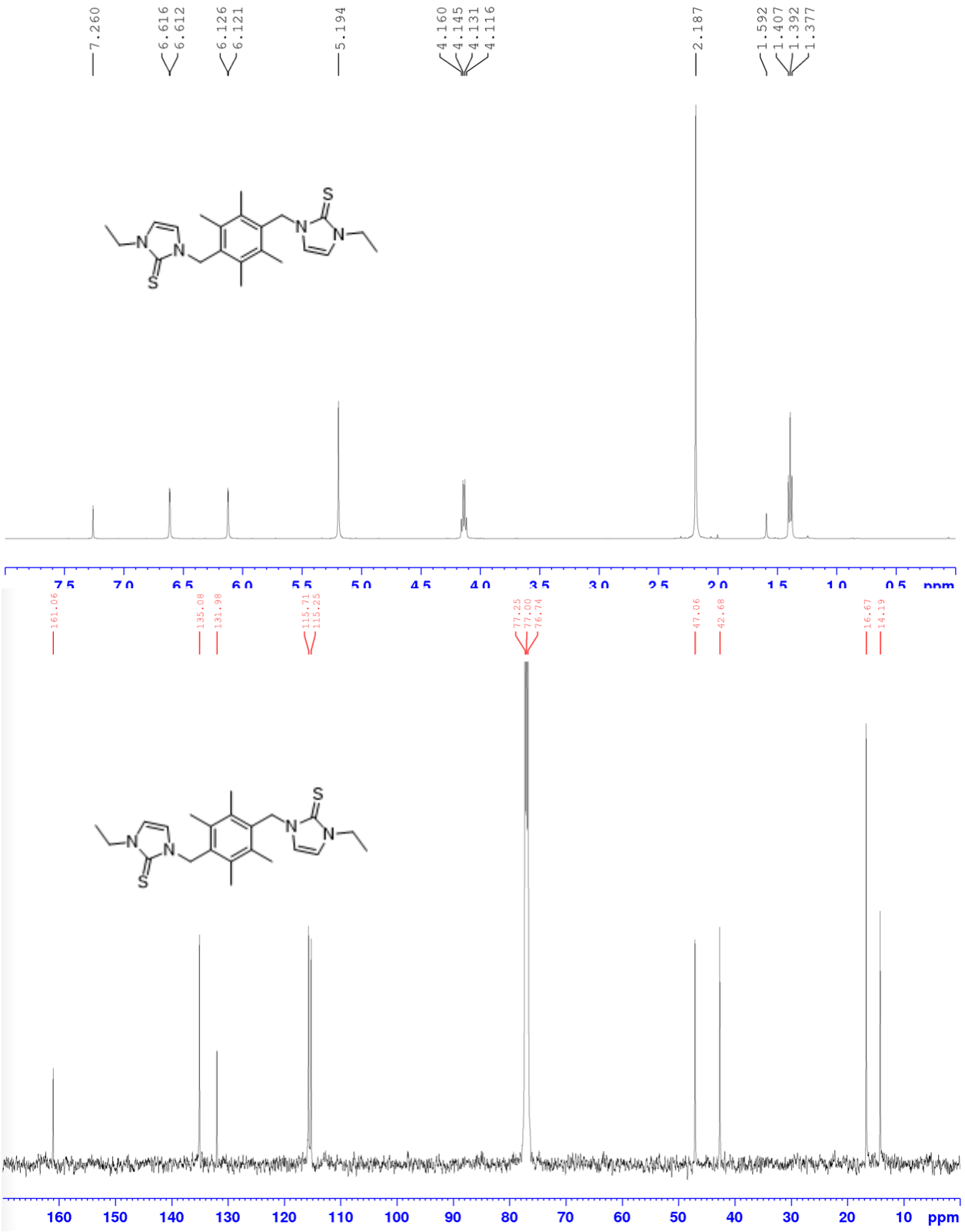

161.92
135.12
131.93
117.56
115.01
77.25
76.99
76.74
47.31
35.02
16.68
S
N
N
N
S
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

APPENDIX 20

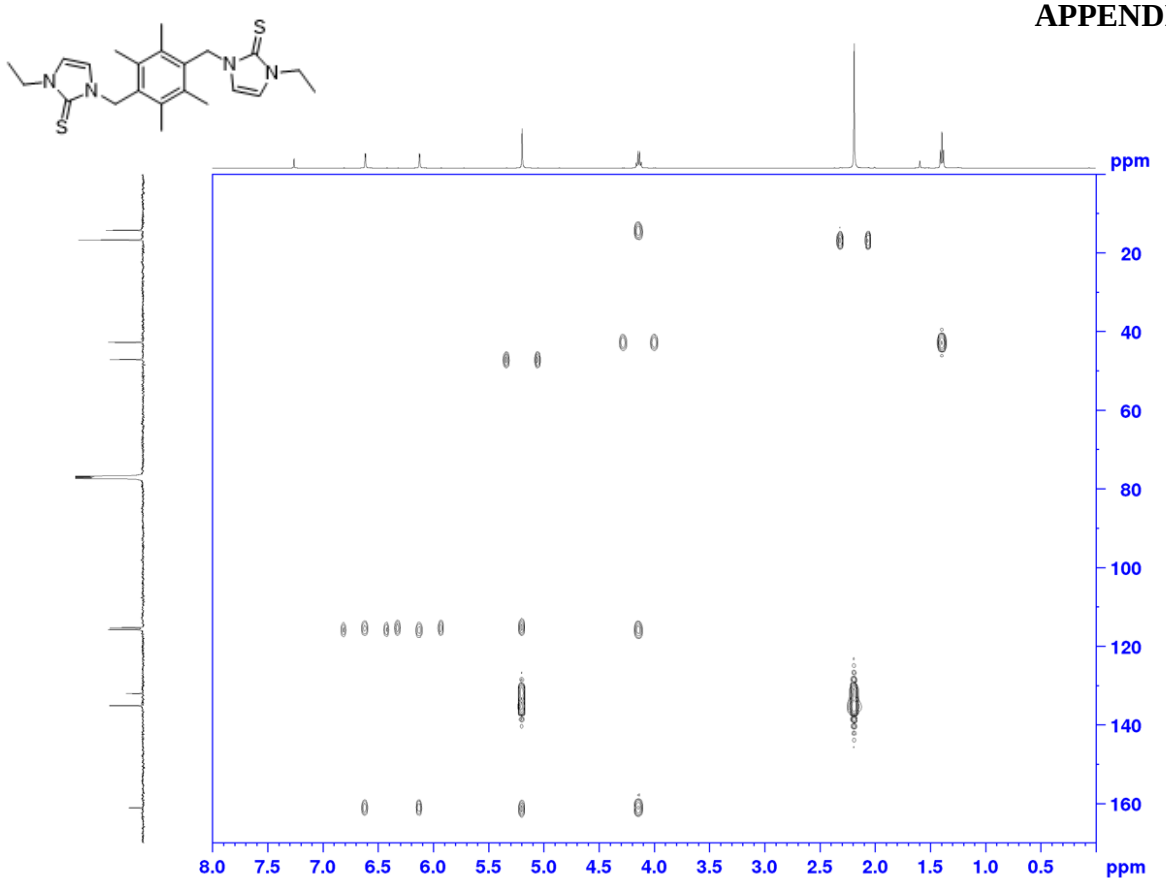

ppm
20
40
60
80
100
120
140
160
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm

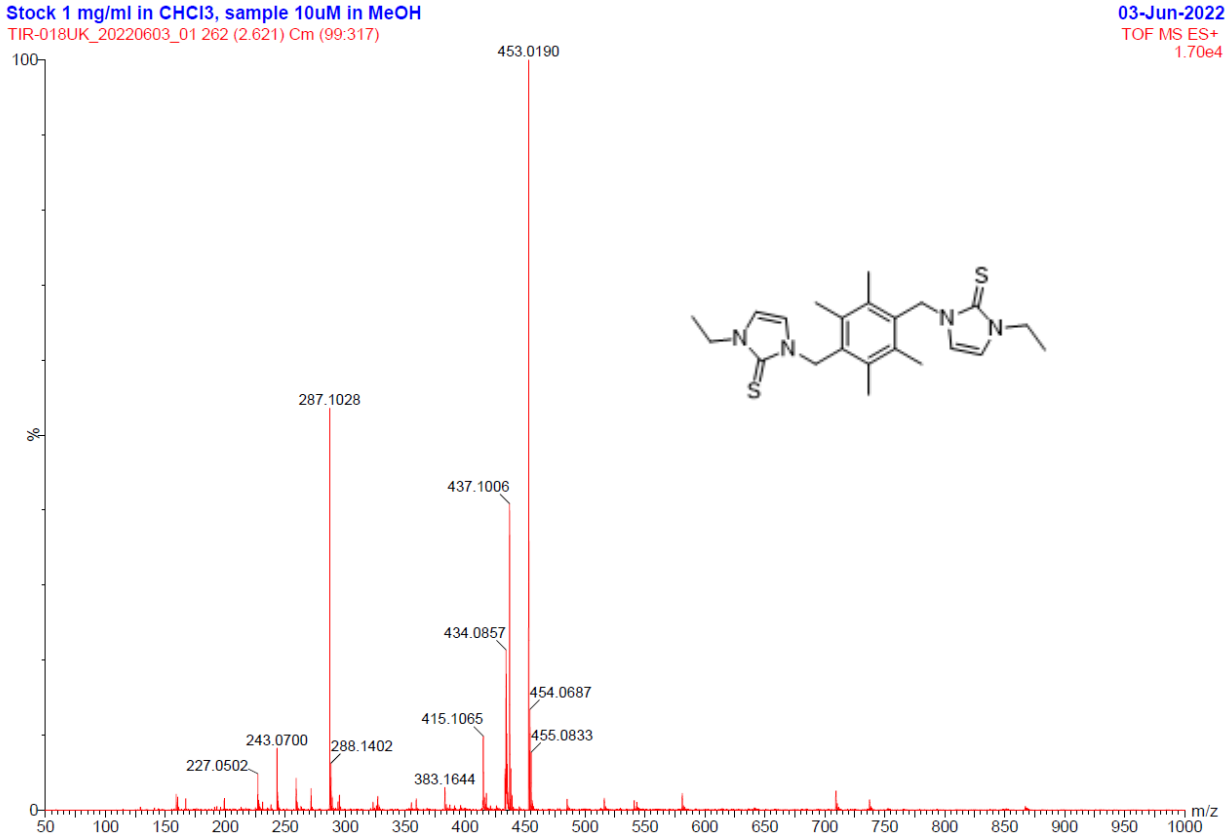

Stock 1 mg/ml in CHCl3, sample 10uM in MeOH
TIR-017UK_20220603_01 37 (0.370) Cm (33:276)
03-Jun-2022
TOF MS ES+
7.26e3
273.0842
425.0334
409.0349
406.0843
274.1241
426.0501
387.0996
512.9772
229.0518
159.1123
328.1177
539.0925
100
%
0
50 100 150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950 1000
m/z

APPENDIX 21

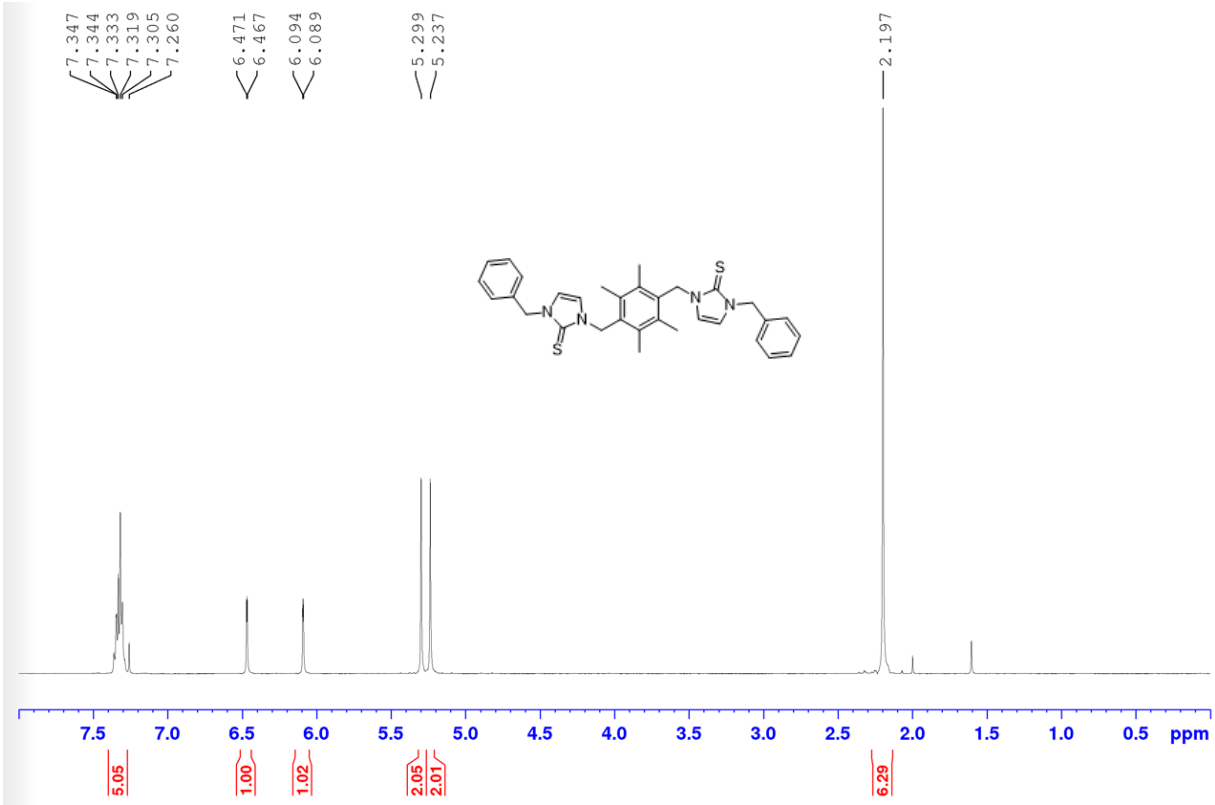

7.260
6.616
6.612
6.126
6.121
5.194
4.160
4.145
4.131
4.116
2.187
1.592
1.407
1.392
1.377
ppm
161.06
135.08
131.98
115.71
115.25
77.25
77.00
76.74
47.06
42.68
16.67
14.19
ppm

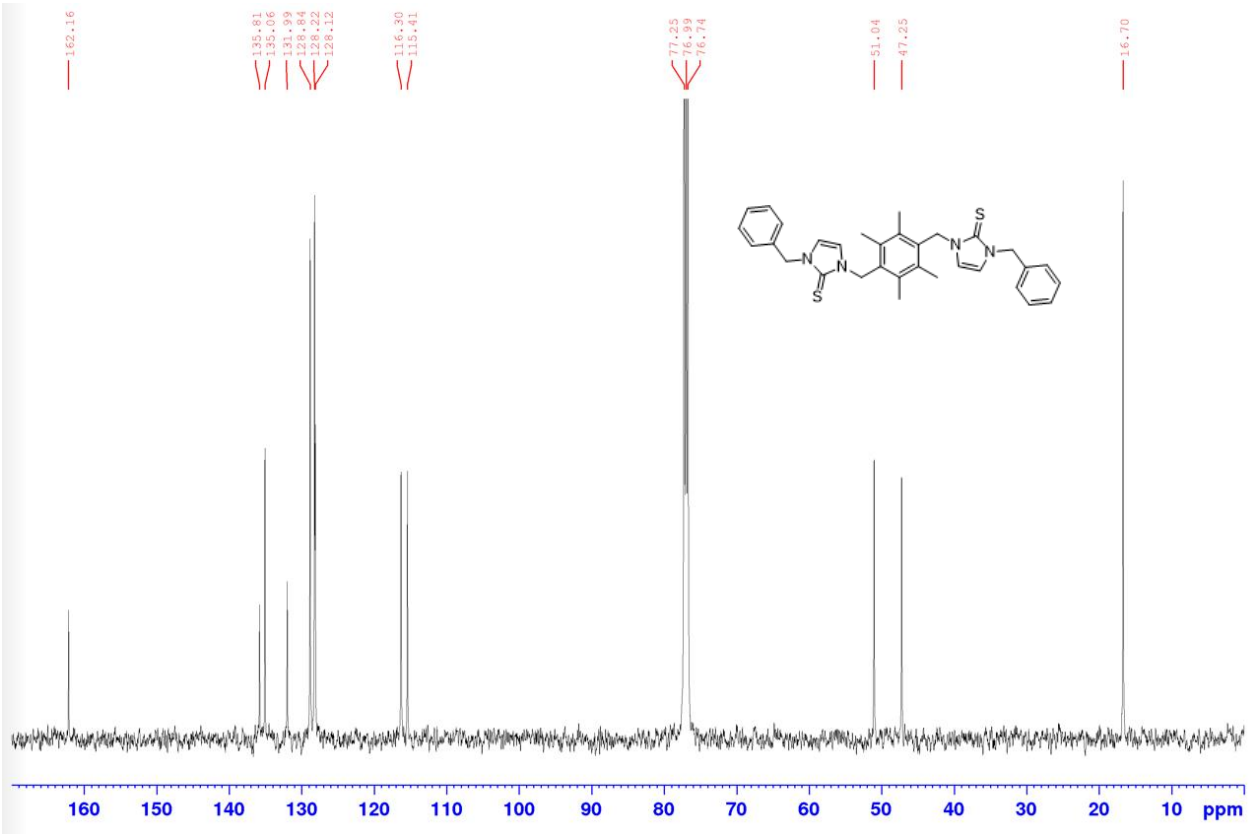
APPENDIX 22


S
N
N
S
N
N
ppm
20
40
60
80
100
120
140
160
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

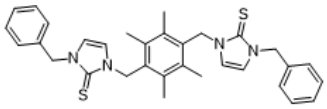

Stock 1 mg/ml in CHCl3, sample 10uM in MeOH
TIR-018UK_20220603_01 262 (2.621) Cm (99:317)
03-Jun-2022
TOF MS ES+
1.70e4
100
%
0
453.0190
287.1028
437.1006
434.0857
454.0687
415.1065
455.0833
243.0700
288.1402
227.0502
383.1644
50
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800
850
900
950
1000
m/z

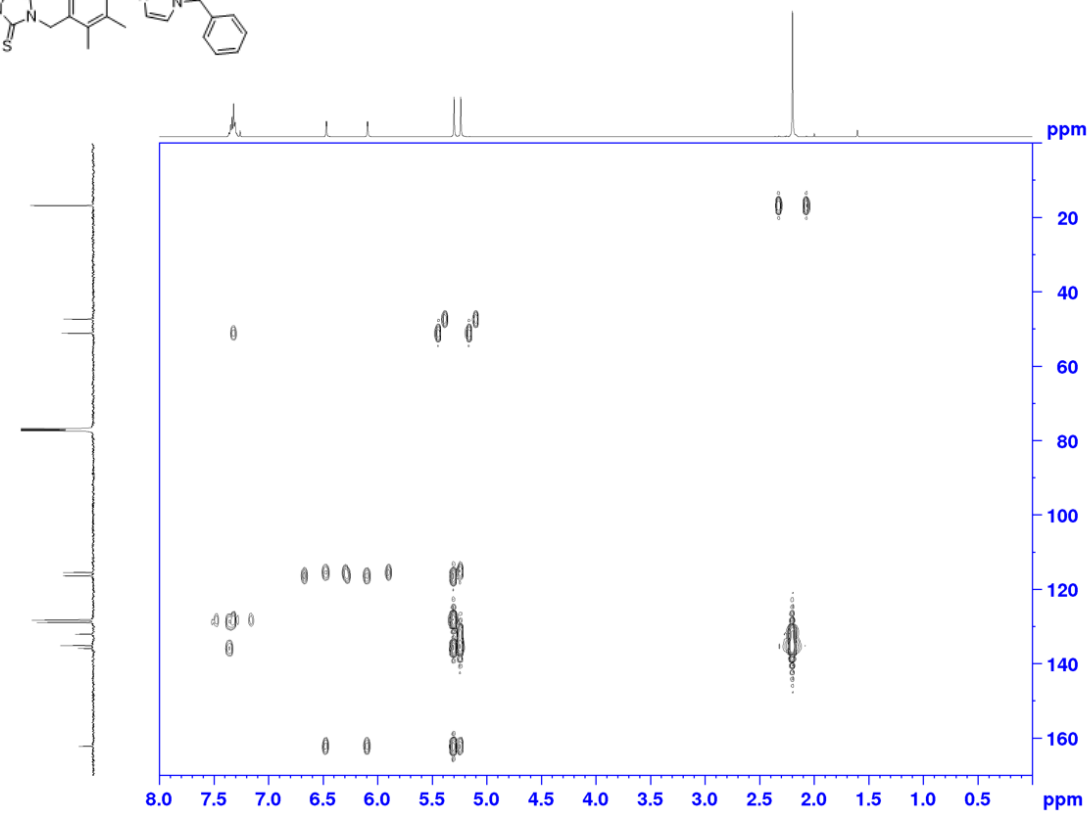
APPENDIX 23

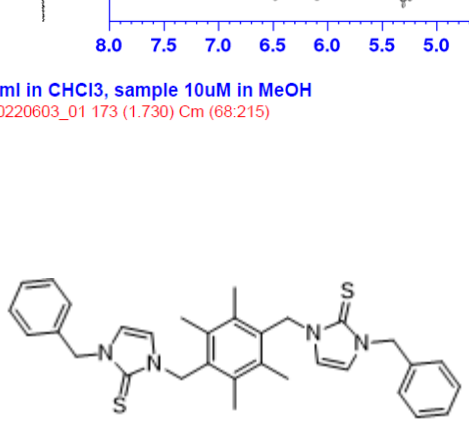

7.347
7.344
7.333
7.319
7.305
7.260
6.471
6.467
6.094
6.089
5.299
5.237
2.197
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
5.05
1.00
1.02
2.05
2.01
6.29


162.16
135.81
135.06
131.99
128.84
128.22
128.12
116.30
115.41
77.25
76.99
76.74
51.04
47.25
16.70
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

APPENDIX 24

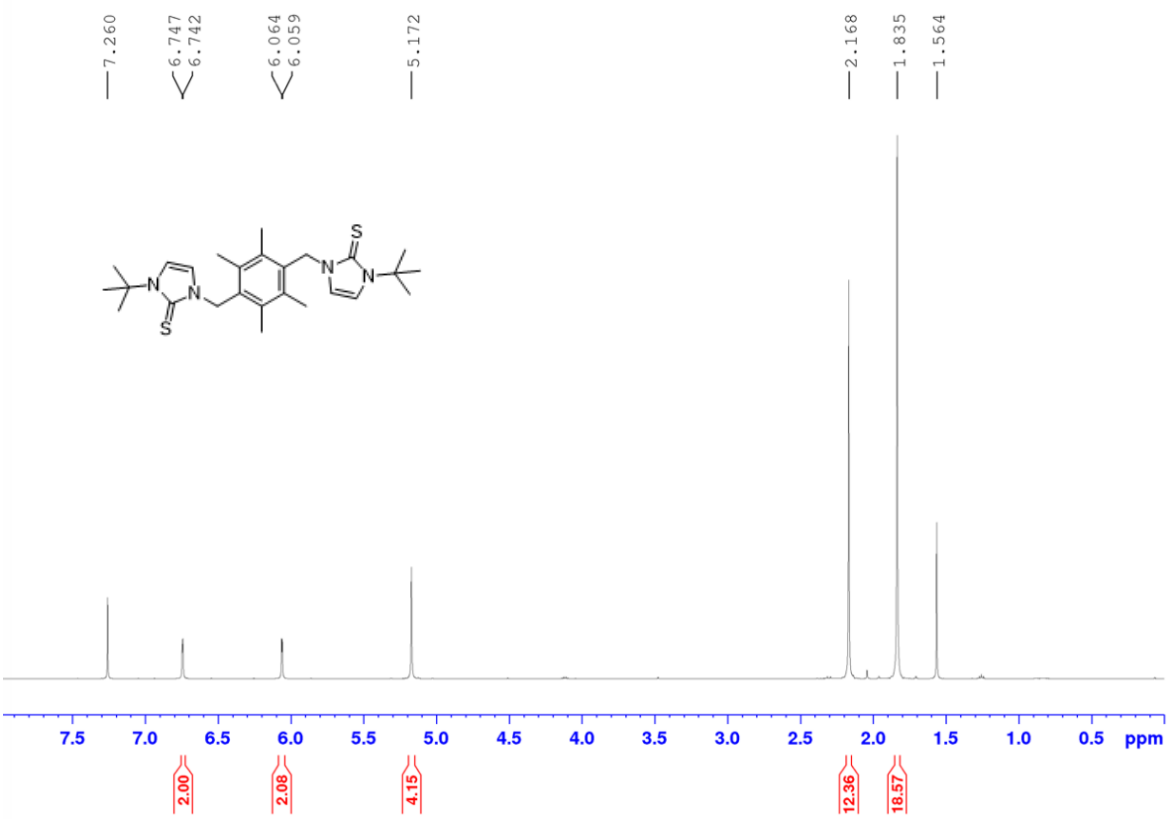


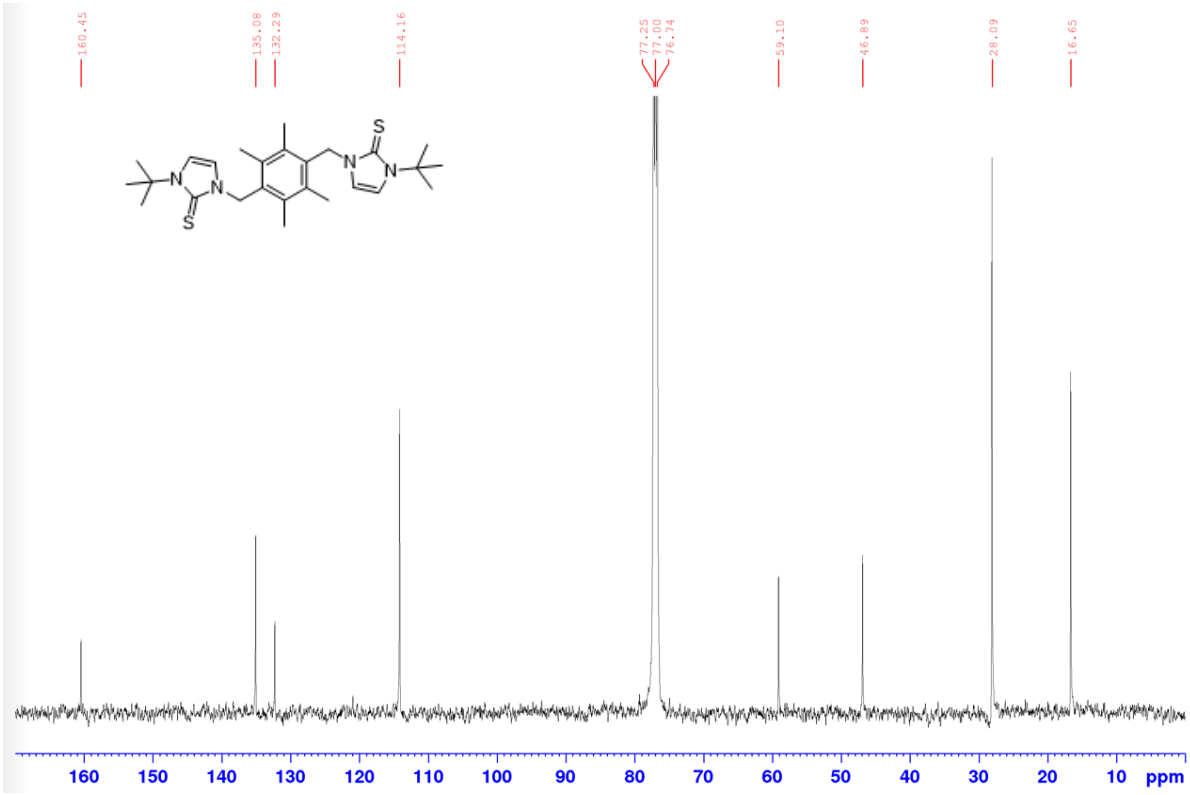

ppm
20
40
60
80
100
120
140
160
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm



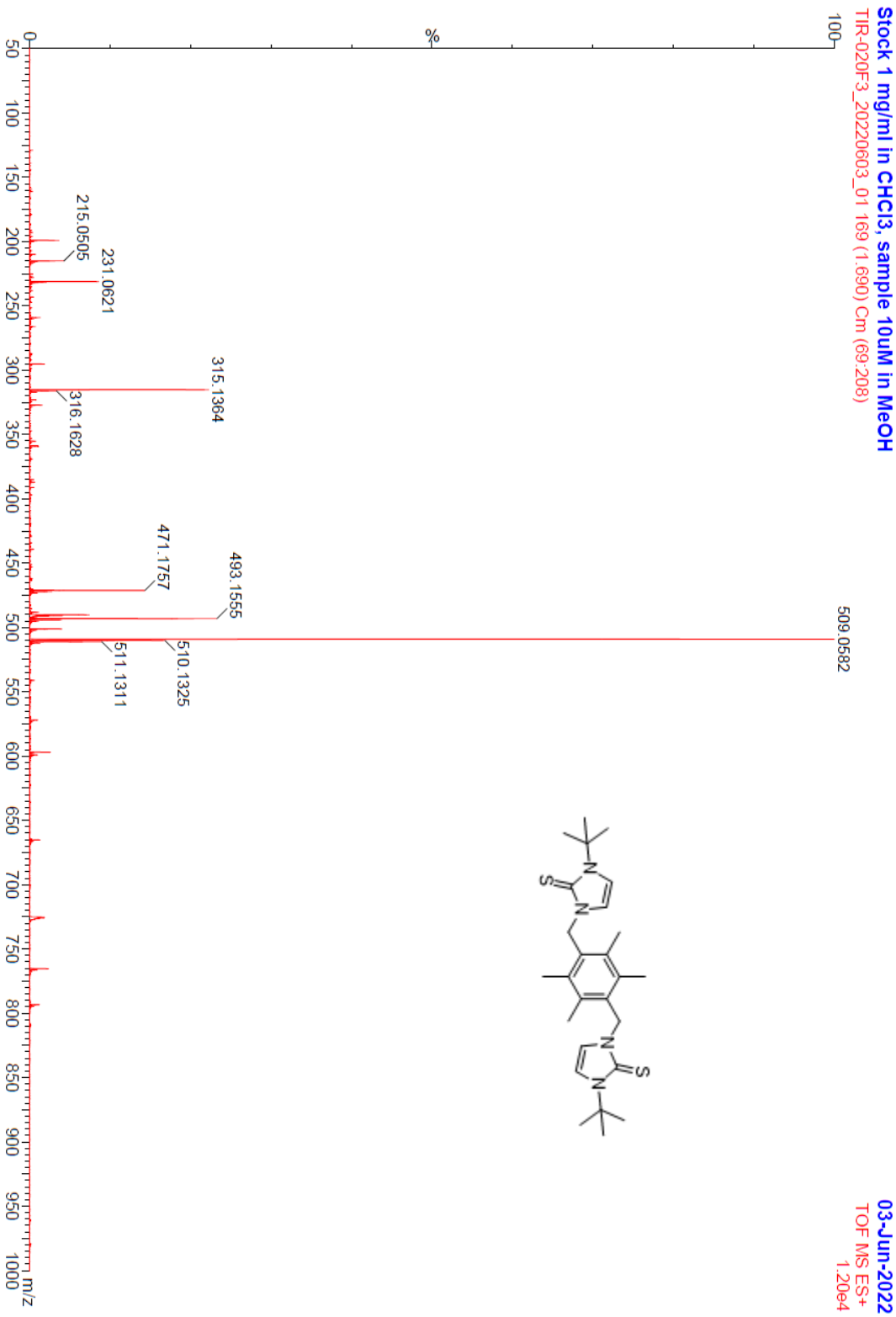
Stock 1 mg/ml in CHCl3, sample 10uM in MeOH
TIR-019UK_20220603_01 173 (1.730) Cm (68:215)
03-Jun-2022
TOF MS ES+
4.96e3
100
%
0
577.0698
349.0966
578.1320
295.1625
539.1320
289.0351
359.2018
579.0722
287.1316
387.1665
640.1083
665.0714
50
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800
850
900
950
1000
m/z

APPENDIX 25

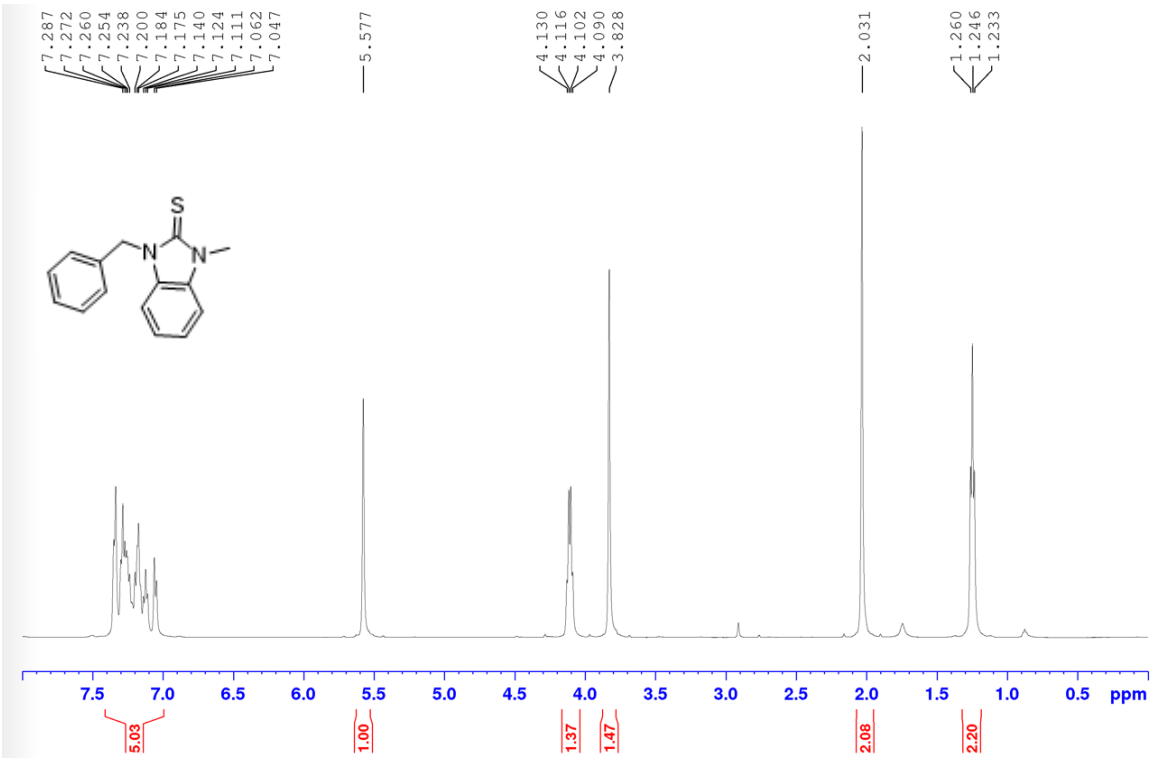

7.260
6.747
6.742
6.064
6.059
5.172
2.168
1.835
1.564
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.00
2.08
4.15
12.36
18.57

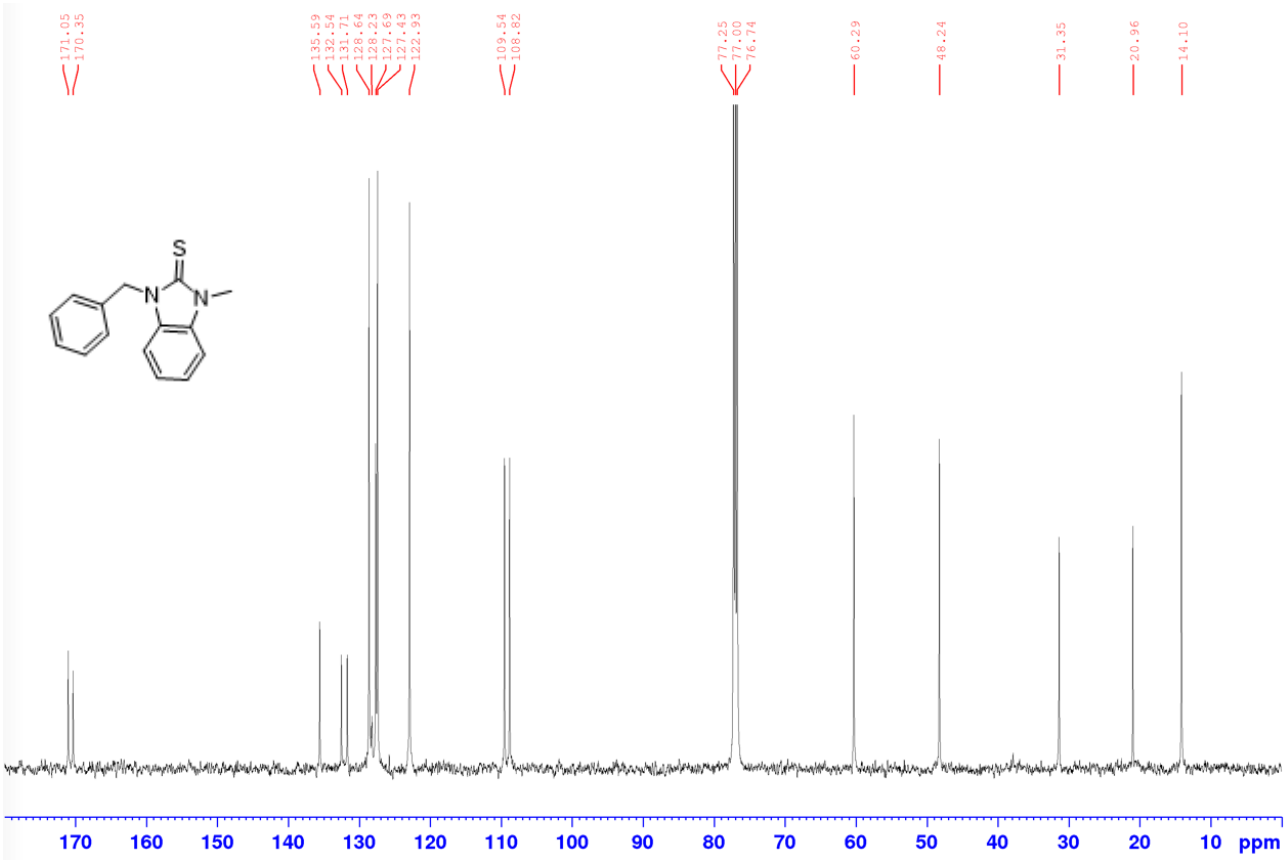

160.45
135.08
132.29
114.16
77.25
77.00
76.74
59.10
46.89
28.09
16.65
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

APPENDIX 26

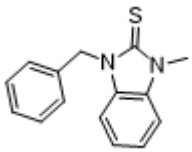

Stock 1 mg/ml in CHCl3, sample 10uM in MeOH
TIR-020F3_20220603_01 169 (1.690) Cm (69:208)
03-Jun-2022
TOF MS ES+
1.20e4
%
m/z
509.0582
493.1555
315.1364
471.1757
231.0621
215.0505
316.1628
510.1325
511.1311

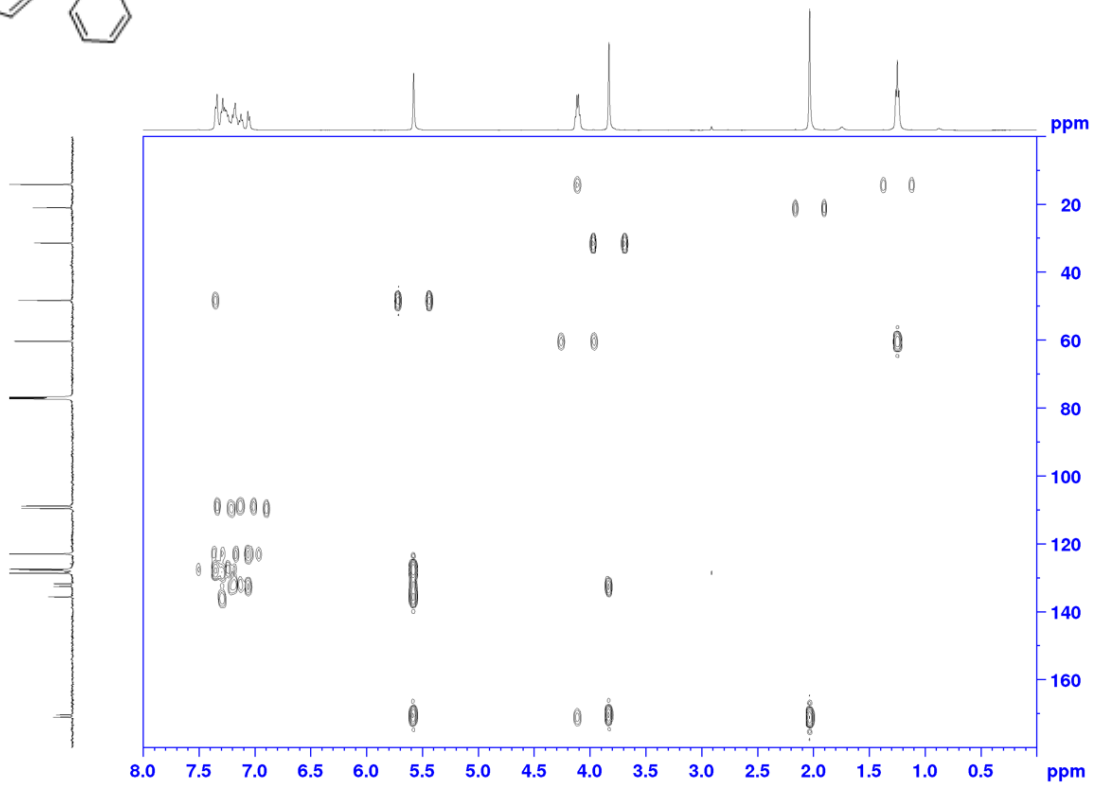
APPENDIX 27

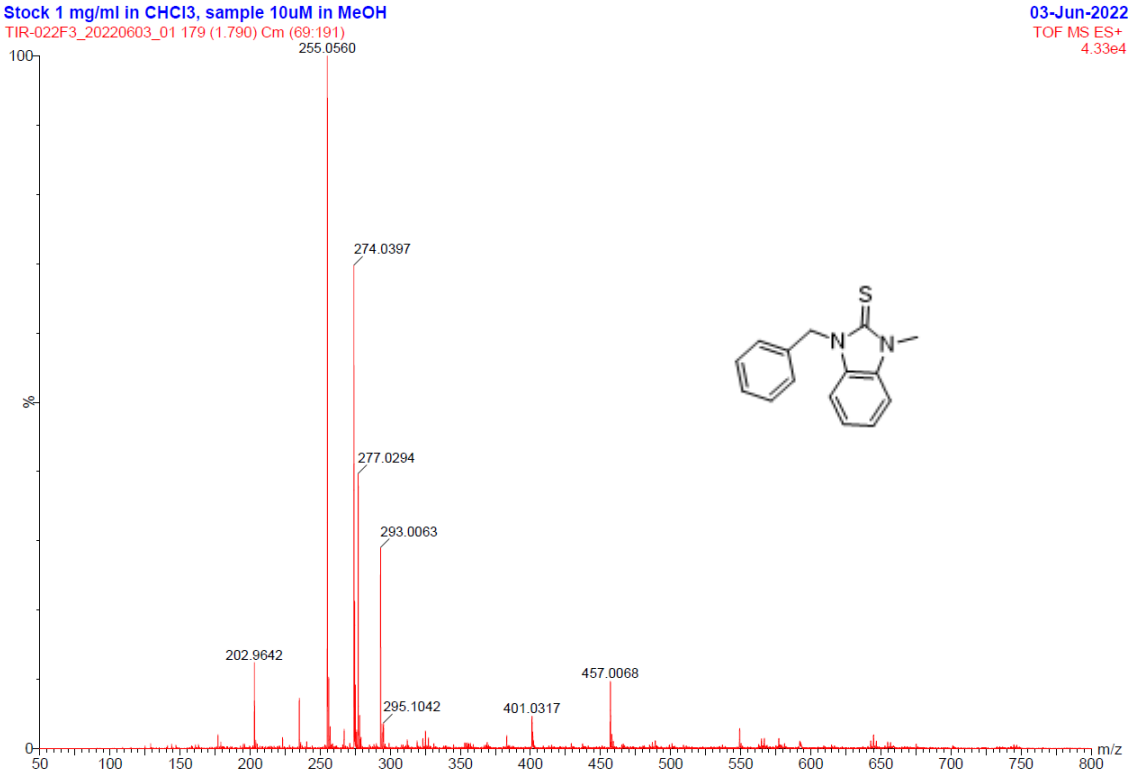

7.287
7.272
7.260
7.254
7.238
7.200
7.184
7.175
7.140
7.124
7.111
7.062
7.047
5.577
4.130
4.116
4.102
4.090
3.828
2.031
1.260
1.246
1.233
S
N
N
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
5.03
1.00
1.37
1.47
2.08
2.20


171.05
170.35
135.59
132.54
131.71
128.64
128.23
127.69
127.43
122.93
109.54
108.82
77.25
77.00
76.74
60.29
48.24
31.35
20.96
14.10
S
N
N
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

APPENDIX 28

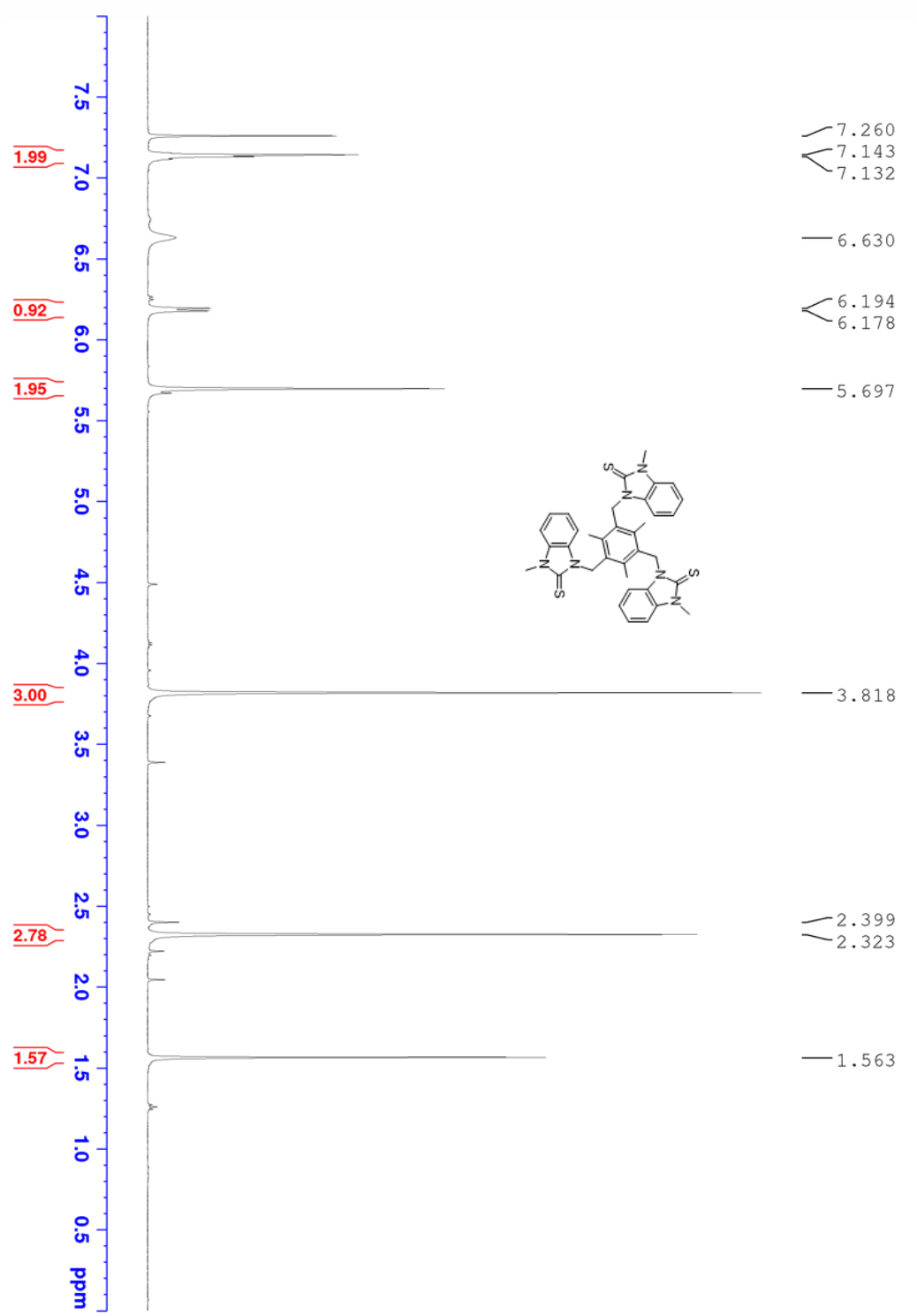

S
N
N


ppm
20
40
60
80
100
120
140
160
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

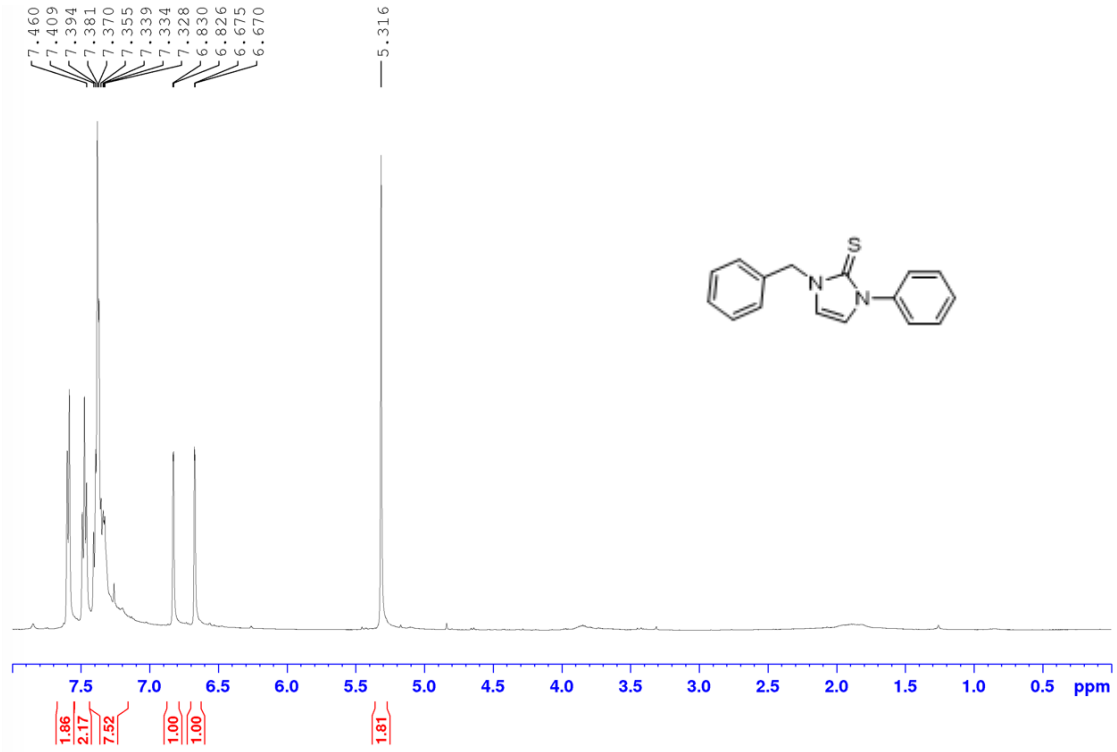

Stock 1 mg/ml in CHCl3, sample 10uM in MeOH
TIR-022F3_20220603_01 179 (1.790) Cm (69:191)
03-Jun-2022
TOF MS ES+
4.33e4
100
%
0
255.0560
274.0397
277.0294
293.0063
202.9642
295.1042
401.0317
457.0068
50
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800
m/z

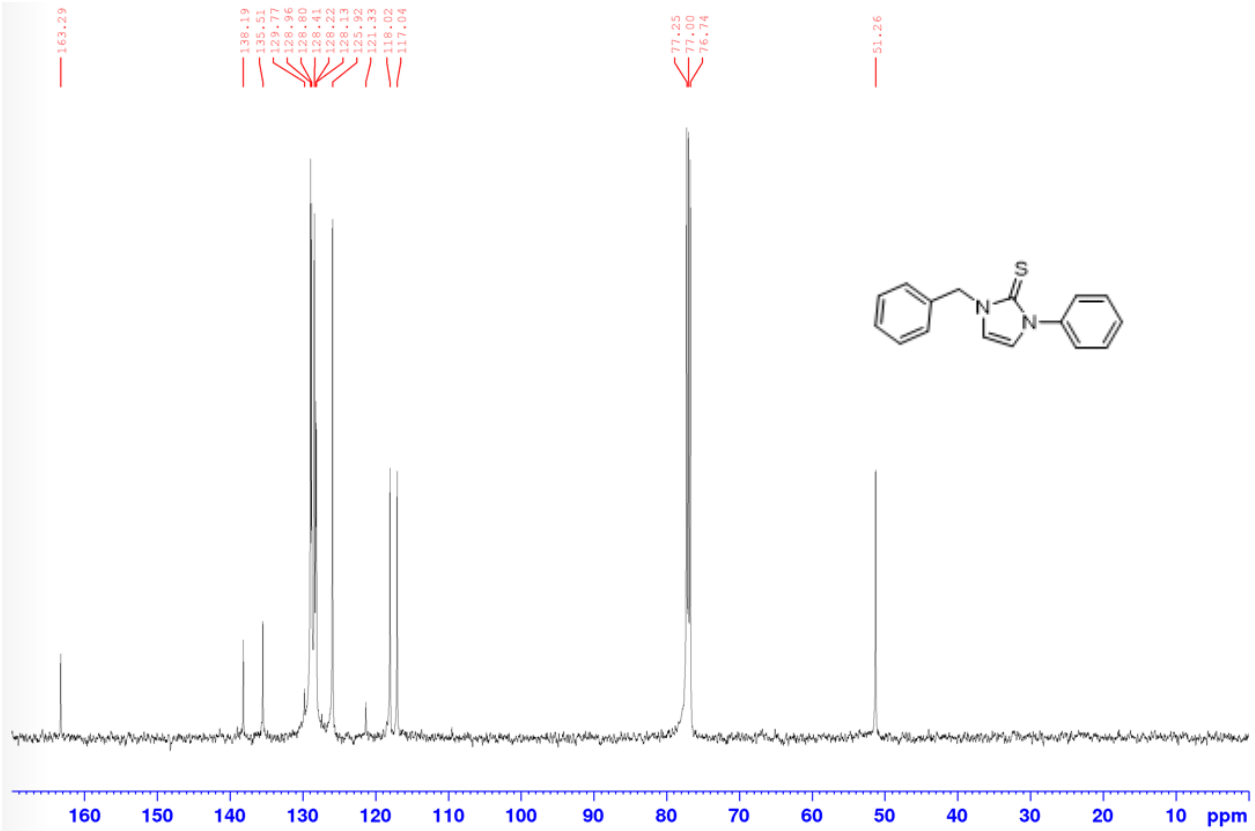
S
N
N

APPENDIX 29

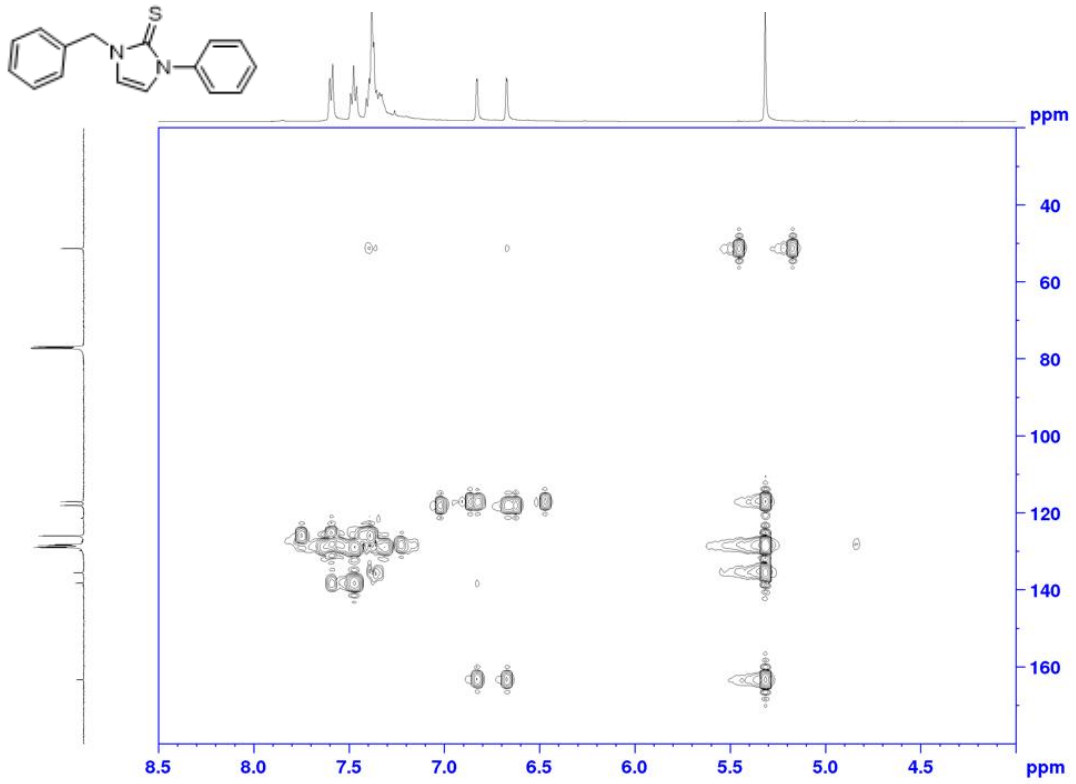

7.260
7.143
7.132
6.630
6.194
6.178
5.697
3.818
2.399
2.323
1.563
1.99
0.92
1.95
3.00
2.78
1.57
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

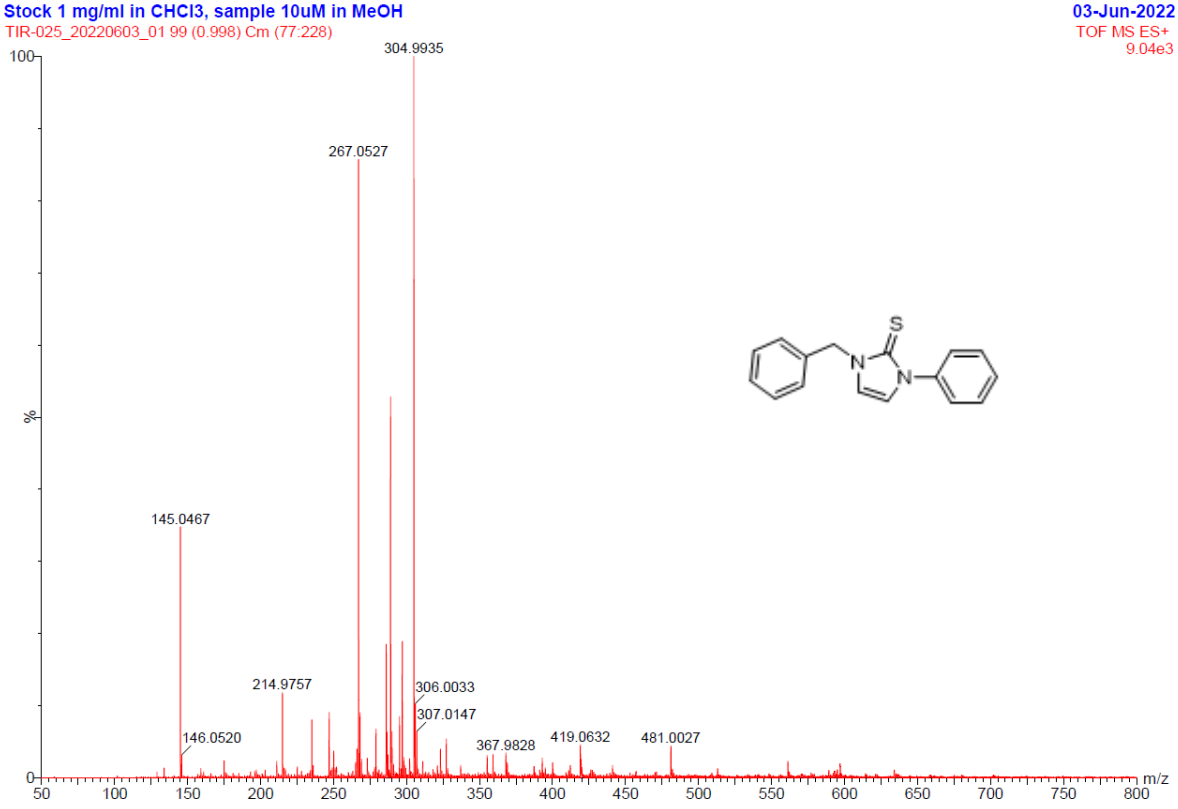
APPENDIX 30


7.460
7.409
7.394
7.381
7.370
7.355
7.339
7.334
7.328
6.830
6.826
6.675
6.670
5.316
S
N
N
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.86
2.17
7.52
1.00
1.00
1.81


163.29
138.19
135.51
129.77
128.96
128.80
128.41
128.22
128.13
125.92
121.33
118.02
117.04
77.25
77.00
76.74
51.26
S
N
N
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

APPENDIX 31


S
N
N
ppm
40
60
80
100
120
140
160
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
ppm


Stock 1 mg/ml in CHCl3, sample 10uM in MeOH
TIR-025_20220603_01 99 (0.998) Cm (77:228)
03-Jun-2022
TOF MS ES+
9.04e3
100
%
0
304.9935
267.0527
145.0467
214.9757
306.0033
307.0147
146.0520
367.9828
419.0632
481.0027
S
N
N
50
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800
m/z

APPENDIX 32

Crystal data and structure refinement parameters for **E1**·2H_2O, **E3**, 2**E5**·3MeOH, **E7** and **E20**·2$CHCl_3$

		E1·**2H_2O**	E3	**2**E5·**3MeOH**	E7	E20·**2$CHCl_3$**
Formula		$C_{27}H_{40}N_6O_2S_3$	$C_{30}H_{42}N_6S_3$	$C_{96}H_{108}N_{12}O_3S_6$	$C_{36}H_{54}N_6S_3$	$C_{38}H_{38}Cl_6N_6S_3$
F_w		576.83	582.87	1634.27	667.03	887.62
T **[K]**		170(2)	120(2)	170(2)	120(2)	170(2)
Crystal system		Orthorhombic	Monoclinic	Monoclinic	Tetragonal	Triclinic
Space group		*Pnma*	$P2_1/n$	$C2/c$	$P4_2/n$	$P\bar{1}$
Unit cell dimensions						
a **[Å]**		13.6872(3)	11.9417(3)	55.1014(11)	22.7360(8)	11.9877(7)
b **[Å]**		18.3567(7)	19.2428(5)	8.0515(2)	22.7360(8)	13.0390(4)
c **[Å]**		11.4697(5)	14.4945(4)	19.6507(3)	14.886(2)	14.9104(9)
α **[°]**		90	90	90	90	65.100(3)
β **[°]**		90	109.716(3)	92.5950(10)	90	74.645(2)
γ **[°]**		90	90	90	90	80.907(4)
V **[Å^3]**		2881.78(18)	3135.46(15)	8709.1(3)	7695.1(14)	2035.62(19)
Z		4 (Z' = 0.5)	4	4	8	2
ρ_{calc} **[Mg/m^3]**		1.330	1.235	1.246	1.152	1.448
μ **[mm^{-1}]**		0.293	0.266	0.214	0.225	0.613
F_{000}		1232	1248	3480	2880	916
θ **range [°]**		2.09 − 28.85	2.10 − 29.86	2.22 − 28.78	2.25 − 25.22	2.07 − 25.25
Reflections		7101	16273	21363	40462	13613
Independent refl.		3878	7876	11261	6956	7368
Reflections [*I*>2*σ*(*I*)]		2572	6032	7797	2795	3296
R_{int}		0.0474	0.0360	0.0307	0.1328	0.0978
Completeness to *θ* [%]		99.9	99.8	99.8	99.8	99.8
Restraints/parameters		2 / 196	0 / 352	59 / 534	521 / 573	19 / 491
Goodness-of-fit on F^2		1.012	1.037	1.032	1.202	1.012
R **indices**	*R*1	0.0514	0.0474	0.0546	0.1491	0.0754
[*I*>2*σ*(*I*)]	w*R*2	0.1120	0.1106	0.1251	0.2758	0.1102
R **indices**	*R*1	0.0918	0.0665	0.0870	0.2743	0.1973
(all data)	w*R*2	0.1294	0.1239	0.1407	0.3320	0.1453
Largest diff.	peak	0.350	0.346	0.348	1.052	0.359
[e.Å^{-3}]	hole	−0.332	−0.363	−0.420	−0.516	−0.319

APPENDIX 33

Crystal data and structure refinement parameters for **E15** – **E17**, **E19** and **E21**

		E15	E16	E17	E19	E21
Formula		$C_{22}H_{30}N_4S_2$	$C_{32}H_{34}N_4S_2$	$C_{26}H_{38}N_4S_2$	$C_{15}H_{14}N_2S$	$C_{16}H_{14}N_2S$
F_w		414.62	538.75	470.72	254.34	266.35
***T* [K]**		120(2)	120(2)	120(2)	120(2)	173(2)
Crystal system		Orthorhombic	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group		*Pbca*	$P2_1/n$	$P2_1/c$	*Ia*	$P2_1/c$
Unit cell dimensions						
***a* [Å]**		16.3421(5)	9.32541(11)	16.8673(11)	7.4349(2)	12.0062(3)
***b* [Å]**		10.5771(2)	14.20633(17)	6.7405(3)	12.4932(3)	10.5169(3)
***c* [Å]**		25.0168(6)	20.8536(2)	11.1789(6)	13.7079(5)	21.7938(7)
***α* [°]**		90	90	90	90	90
***β* [°]**		90	96.4822(11)	98.785(6)	92.130(2)	101.564(2)
***γ* [°]**		90	90	90	90	90
***V* [Å^3]**		4324.20(19)	2745.02(5)	1256.06(12)	1272.39(7)	2696.00(14)
Z		8	4	2	4	8
ρ_{calc} **[Mg/m^3]**		1.274	1.304	1.245	1.328	1.312
μ **[mm^{-1}]**		0.262	0.223	0.233	0.237	0.227
F_{000}		1776	1144	508	536	1120
***θ* range [°]**		2.43 − 29.86	2.30 − 29.91	2.44 − 29.73	2.21 − 29.93	1.73 − 28.81
Reflections		13640	24263	5378	3046	8900
Independent refl.		5526	7269	3120	2067	6939
Reflections [*I*>2*σ*(*I*)]		4285	6123	2420	2009	5002
R_{int}		0.0318	0.0245	0.0331	0.0144	0.0218
Completeness to *θ* [%]		99.7	100.0	99.7	99.7	99.7
Restraints/parameters		0 / 253	0 / 349	0 / 147	2 / 163	0 / 343
Goodness-of-fit on F^2		1.038	1.037	1.080	1.093	1.045
***R* indices**	*R*1	0.0448	0.0379	0.0598	0.0278	0.0496
[*I*>2*σ*(*I*)]	w*R*2	0.1052	0.0960	0.1287	0.0655	0.1120
***R* indices**	*R*1	0.0623	0.0469	0.0803	0.0294	0.0764
(all data)	w*R*2	0.1158	0.1019	0.1408	0.0668	0.1245
Largest diff.	peak	0.307	0.354	0.464	0.191	0.284
[e.Å^{-3}]	hole	−0.289	−0.230	−0.360	−0.162	−0.254

APPENDIX 34

Crystal data and structure refinement parameters for **E2**·3I_2·DCM, **E16**·2I_2·2DCM, [**E13**·I]$^+I_3^-$ and **E14**·2(1,2-DITFB)·2ACN

		E2·**3I_2·DCM**	E16·**2I_2·2DCM**	[E13·**I]$^+$I$_3^-$**	E14·**2(1,2-DITFB)·2ACN**
Formula		$C_{25}H_{32}Cl_2I_6N_6S_3$	$C_{34}H_{38}Cl_4I_4N_4S_2$	$C_{16}H_{18}I_4N_4S_2$	$C_{36}H_{32}F_8I_4N_6S_2$
F_w		1345.04	1216.20	838.06	1272.39
***T* [K]**		170(2)	170(2)	170(2)	120(2)
Crystal system		Triclinic	Monoclinic	Triclinic	Triclinic
Space group		*P*−1	*P*2/*c*	*P*−1	*P*−1
Unit cell dimensions					
***a* [Å]**		11.3284(8)	16.5425(11)	9.4173(8)	7.9817(4)
***b* [Å]**		13.0286(9)	9.1313(6)	10.8321(8)	11.4633(5)
***c* [Å]**		15.9100(12)	14.3071(9)	13.5410(8)	12.4553(6)
***α* [°]**		104.653(4)	90	74.592(5)	98.700(4)
***β* [°]**		106.113(3)	95.489(4)	71.088(5)	99.213(4)
***γ* [°]**		104.302(4)	90	79.241(4)	104.344(4)
***V* [Å^3]**		2051.5(3)	2151.2(2)	1252.09(17)	1067.91(9)
Z		2	2	2	1
ρ_{calc} [Mg/m^3]		2.177	1.878	2.223	1.979
μ [mm^{-1}]		4.851	3.272	5.153	3.085
F_{000}		1248	1164	772	606
θ range [°]		2.50 − 28.96	2.23 − 25.25	1.63 − 28.90	2.26 − 29.95
Reflections		18405	7493	11532	9347
Independent refl.		10431	3891	6483	5372
Reflections [$I>2\sigma(I)$]		7747		3406	4412
R_{int}		0.0252	0.0690	0.0589	0.0208
Completeness to θ [%]		98.9	99.9	99.9	99.9
Restraints/parameters		63 / 410	73 / 207	0 / 235	0 / 255
Goodness-of-fit on F^2		1.051	1.168	1.023	1.048
***R* indices**	*R*1	0.0418	0.1703	0.0653	0.0290
[$I>2\sigma(I)$]	w*R*2	0.0923	0.4024	0.1284	0.0531
***R* indices**	*R*1	0.0660	0.2023	0.1516	0.0403
(all data)	w*R*2	0.1031	0.4189	0.1607	0.0578
Largest diff.	peak	0.984	5.686	2.409	0.621
[e.Å^{-3}]	hole	−1.477	−5.404	−0.919	−0.487