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The use of Acetic Anhydride in Annulations onto Benzimidazoles to give Novel Reducible *p*-Dione Adducts

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Thesis presented for the PhD degree

of the

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School of Chemistry

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Abstract

Chapter 1: Introduction to the reactive intermediates used in this thesis, namely acyl radicals and N-heterocyclic carbenes (NHC) is presented, along with an assessment of the anti-cancer activity of literature bioreductive heterocyclic quinones.

Chapter 2: Acyl radicals are shown to undergo photochemical intramolecular homolytic aromatic substitution onto the 2-position of benzimidazoles from readily accessible phenyl selenoesters using chemical initiator-free conditions. The addition of acetic anhydride (Ac_2O) can improve the yields of cyclized products by increasing the electrophilicity of the benzimidazole towards the nucleophilic radical. However many *p*-dione targets are found to absorb UV-light very efficiently leading to extra reactions, which lower yields.

Chapter 3: Ac_2O behaves as a traceless activating agent allowing thermal intramolecular condensation of (benzimidazol-1-ylmethyl) benzoic and nicotinic acids. Aerial oxidation gives benzimidazo[1,2-*b*]isoquinoline-6,11-diones and benzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-diones in a facile one-pot transformation. 1,4-Dimethoxy analogue of the former is converted to benzimidazo[1,2-*b*]isoquinoline-1,4,6,11-tetrone (**1**) using cerium(iv) ammonium nitrate (CAN). The 1,7-naphthyridine-5,12-dione system readily ring-opens, and X-ray crystal structure of the MeOH-adduct was obtained. Ac_2O mediated thermal condensation of 4-(1*H*-benzimidazol-1-yl)butanoic acid led to fully aromatic pyrido[1,2-*a*]benzimidazole, and intermediates in its formation were characterized.

Chapter 4: Ac_2O mediates a facile and rapid condensation of benzimidazole with aromatic *o*-diacid dichlorides to precipitate *p*-dione adducts in excellent yields. Condensation with pyridine-3,4-dicarbonyl dichloride produced a 1:1 mixture of isomeric *p*-diones. The X-ray crystal structure of one of the latter isomers revealed unusual high density and inter-layer separation similar to graphite. Cyclic voltammetry demonstrated the *p*-dione is capable of two consecutive one electron reductions with formal potentials influenced by the fused (hetero)aromatic and substituent effects. Cytotoxicity analysis showed benzimidazo[1,2-*b*]isoquinoline-6,11-dione was more cytotoxic towards the human prostate cancer cells (DU145) than its tetrone derivative **1**, with lesser cytotoxicity towards the human normal cancer cells (GM00637).

Chapter 5: All experimental detail is described for Chapters 2, 3, and 4.

Acknowledgements

Firstly, I would like to sincerely thank Dr. Fawaz Aldabbagh for all the guidance, advice and help he has given me over the course of my research.

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Abbreviations

Ac	acetyl
ACCN	1,1′-azobis(cyclohexanecarbonitrile)
Ac_2O	acetic anhydride
AcOH	acetic acid
AIBN	2,2′-azobis(isobutyronitrile)
ATR	universal attenuated total reflectance
BPO	benzoyl peroxide
Br_2	dibromine
Bu	butyl
Bu_3P	tributyl phosphine
Bu_3SnH	tributyltin hydride
°C	degrees celsius
Calcd	calculated
CAN	cerium(iv) ammonium nitrate
CCDC	Cambridge crystallographic data centre
CSA	camphorsulfonic acid
DCM	dichloromethane
DCVC	dry column vacuum chromatography
Dec.	decomposed
DEPT	distortionless enhancement by polarization transfer
DIPEA	diisopropylethylamine
DMF	*N*,*N*-dimethyl formamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
Et	ethyl
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
Equiv	equivalents
E_{redox}	formal potential
ESI	electrospray ionization

EWG	electron withdrawing group
FA	fanconi anemia
FAD	flavin adenine dinucleotide
FBS	fetal bovine serum
Fc	ferrocene
FT-IR	fourier transform infrared
h	hours
HMQC	heteronuclear multiple quantum coherence
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectra
hv	planks constant (*h*) by frequency (*v*)
Hz	hertz
IC_{50}	50% inhibition concentration
i-Pr	*iso*-propyl
IR	infrared
IUPAC	international union of pure and applied chemistry
M	molar
Me	methyl
MEM	minimum essential media
MeOH	methanol
MHz	megahertz
min	minutes
MMC	mitomycin C
µM	micromolar
mM	millimolar
mp	melting point
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
m/*z*	mass to charge ratio
NADH	nicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate
NBS	*N*-bromosuccinimide
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance
NQO1	NAD(P)H:quinone oxidoreductase 1

o-	*ortho-*
Ph	phenyl
pH	power/potential of hydrogen
ppm	parts per million
R	carbon side chain
R_f	retention factor
RNA	ribonucleic acid
rt	room temperature
SET	single electron transfer
t-	tertiary-
tert-	tertiary-
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
UV	ultraviolet
V	volts

Chapter 1

General Introduction

1.1 Thesis reactive intermediates

1.1.1 Acyl radicals

1.1.1.1 Structure of acyl radicals

The unpaired electron in acyl radicals occupies an orbital with substantial 2s character, and is considered a σ-radical (Figure 1.01).[1] The orbital of the unpaired electron of σ-radicals lies in the plane of the local molecular framework. Such radicals are more reactive than π-radicals, due to a lack of resonance stabilization. A selection of radicals is shown in Figure 1.02. In 1996 Guerra in a theoretical study found the average bond angle (θ) for a range of acyl radicals was essentially constant at 128°, which is slightly larger than that expected for sp^2 hybridized carbon.[2]

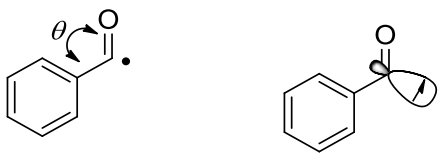


Figure 1.01: Benzoyl radical (acyl type radical)

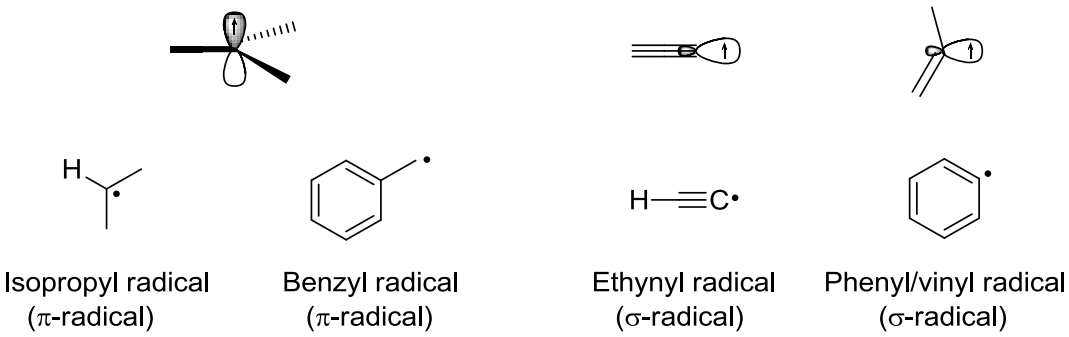
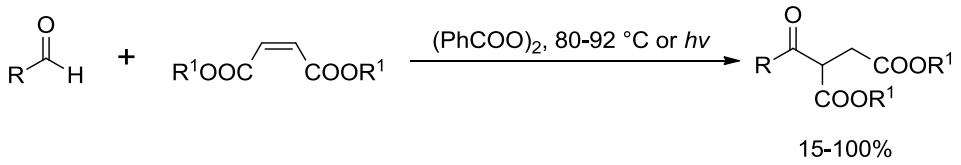


Figure 1.02: Examples of π-radicals and σ-radicals

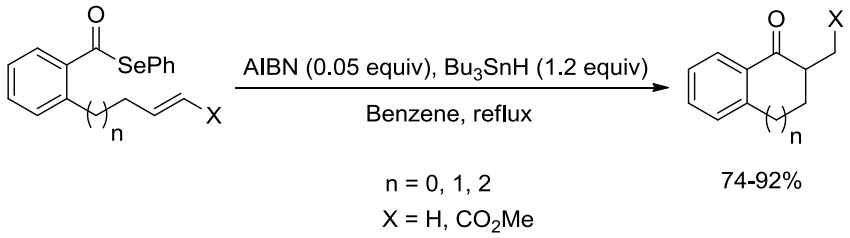
1.1.1.2 Reactions of acyl radicals

In the 1950s, Patrick Jr. used aldehydes to generate reactive acyl radicals capable of addition onto a range of maleates in 15-100% yield (Scheme 1.01).[3] Benzoyl peroxide (0.1-1.7 weight %) heated to 80-92 °C or UV light was used to initiate the radical chain reaction.



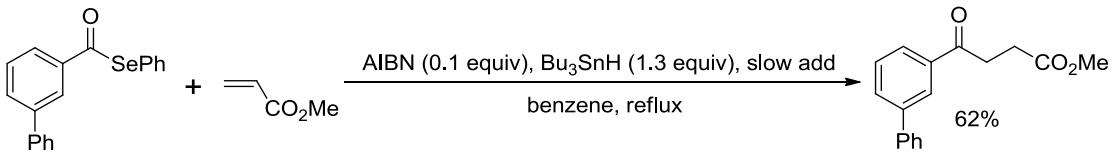
Scheme 1.01: Aldehydes as sources of acyl radicals

In 1988 Boger and Mathvink demonstrated the use of phenyl selenoesters as substrates for acyl radicals under mild Bu_3SnH/AIBN conditions.[4] Five to seven-membered *exo*-cyclizations went in 74-92% yield under chain reaction conditions (Scheme 1.02).



Scheme 1.02: Phenylselenides as sources of acyl radicals

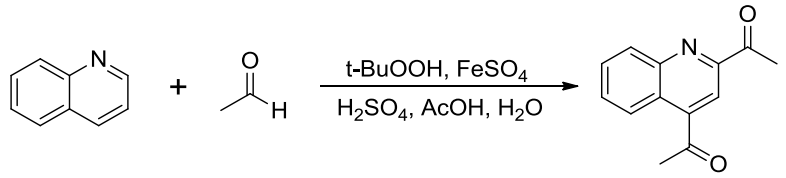
The same workers generated acyl radicals that underwent intermolecular addition onto alkenes with electron-withdrawing and radical stabilizing groups as well as electron rich alkenes.[5] One of the best yielding intermolecular additions reported was onto methyl acrylate supporting the perceived nucleophilic character of the radical (Scheme 1.03). Additions onto electron-rich alkenes provided low yields of the addition products accompanied by substantial amounts of direct phenyl selenoester reduction products.



Scheme 1.03: Intermolecular addition of acyl radicals

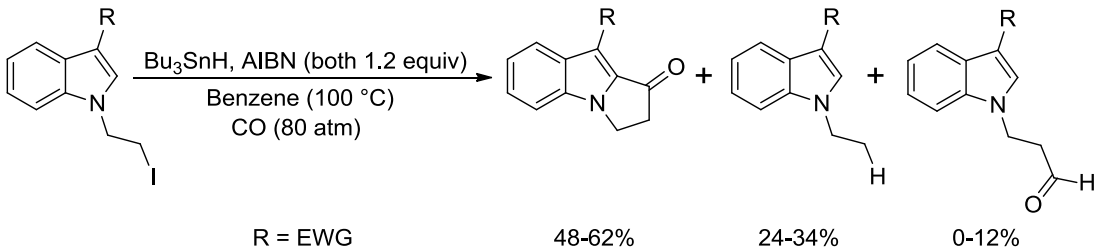
1.1.1.2.1 Homolytic aromatic substitutions

The first homolytic aromatic substitution of acyl radicals was carried out by Minisci in 1969 onto protonated quinolines using a t-BuOOH/Fe^{2+} redox system in the presence of aldehydes to give 2,4-diacetylquinoline[6] (Scheme 1.04).



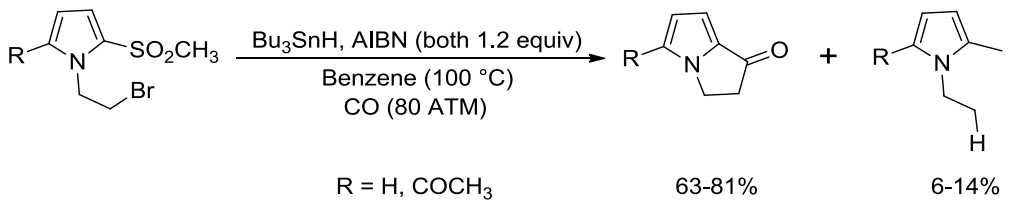
Scheme 1.04: Homolytic acylation of protonated quinoline

Miranda and co-workers reported the Bu_3SnH-mediated radical reaction of 1-(2-iodoethyl)indoles under 80 atm pressure of carbon monoxide.[7] CO was efficiently trapped by the alkyl radical generating an acyl radical, which underwent homolytic aromatic substitution to give the tricyclic aromatic ketones as well as, the reduced alkyl and acyl radical products (Scheme 1.05). The substitution at C-2 of indole was more facile when there was an electron-withdrawing group at the 3-position (e.g. ester or CN). More than full equivalents of radical initiators were required for this substitution supporting a non-chain reaction for the oxidative cyclization.[8-10] Later Bowman inferred that the azo-initiator was responsible for the hydrogen atom abstraction to give aromatized pyrroles by isolation of hydrazine adducts of the azo-initiator.[11]



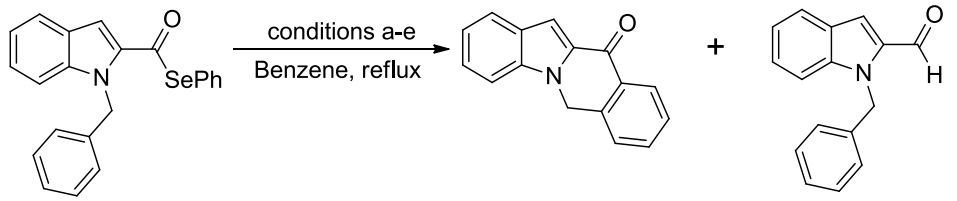
Scheme 1.05: Cyclization of acyl radicals onto indoles via CO trapping

In Scheme 1.06 the acyl radical was generated as described above, but was shown to undergo an *ipso*-substitution[12,13] of 2-methylsulfonyl group on pyrrole in yields of 63-81%.[14]



Scheme 1.06: Methylsulfonyl derivatives in selective acyl radical attack

Bennasar and co-workers generated a 2-indolylacyl radical from the corresponding selenoester under both reductive (Bu_3SnH-AIBN) and non-reductive (hexabutylditin (Bu_6Sn_2), 300 W) conditions (Scheme 1.07).[15] Under reductive conditions the aldehyde was isolated as the only product, generated from simple reduction. When the weaker hydrogen atom donor tris(trimethylsilyl)silane [$(TMS)_3SiH$] and excess AIBN were used, the cyclization did occur, although the reduced compound also formed was not separated. The cyclized tetracycle was however isolated in 65% yield under non-reductive conditions. All attempts to synthesize five or seven-membered annulated ring analogues proved unsuccessful.

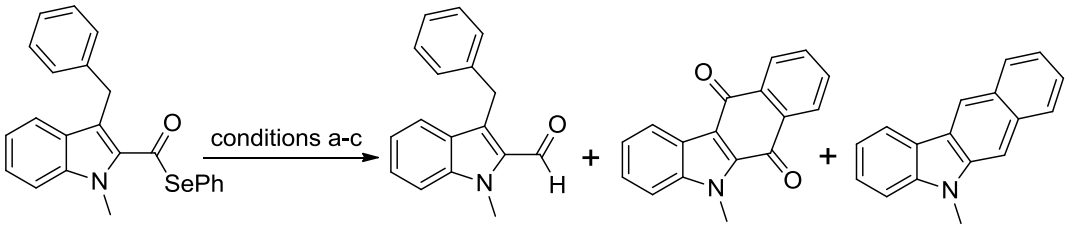


a: Bu_3SnH (1.5 equiv), AIBN (0.1 equiv)	none	90%
b: Bu_3SnH (1.8 equiv), AIBN (1.8 equiv)	none	90%
c: $(TMS)_3SiH$ (1.2 equiv), AIBN (2.0 equiv)	not isolated	not isolated
d: Bu_6Sn_2 (0.2 equiv), 300 W	40%	10%
e: Bu_6Sn_2 (2.2 equiv), 300 W	65%	none

Scheme 1.07: 2-Indolyacyl radical cyclization onto benzene attached at the indole nitrogen

Subsequently the synthesis of 2,3-ring fused indole derivatives was carried out (Scheme 1.08). Small quantities (5-10%) of the fully aromatized tetracycle were isolated under the Bu_6Sn_2-mediated reactions. It is postulated that re-aromatization under non-reductive conditions occurs via hydrogen abstraction by the peroxy radical $Bu_3SnOO\cdot$ coming from the reaction of tin radicals with oxygen that was not rigorously excluded from the reaction mixture. The formation of the fully aromatized tetracycle is postulated to occur through reduction of the cyclohexadienyl radical,

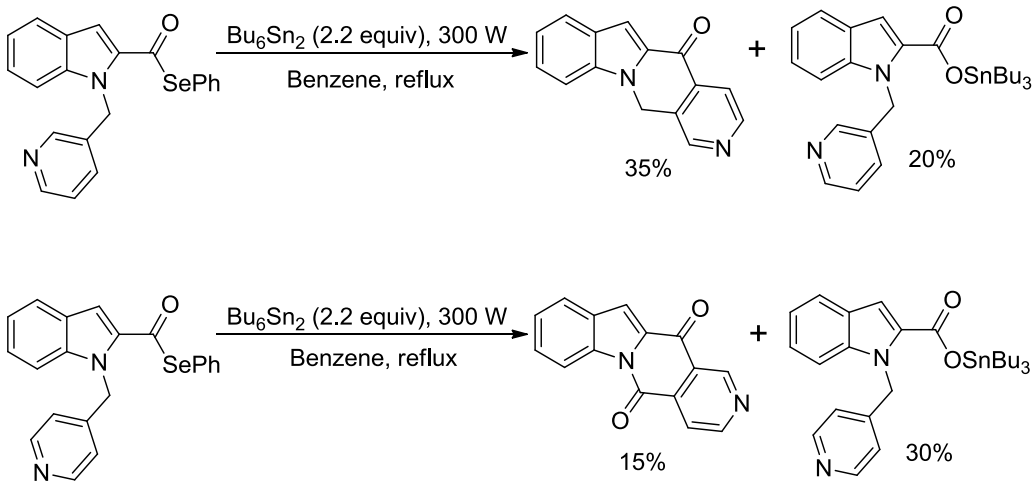
probably by phenylselenol produced from the reaction. The *p*-dione was formed by autoxidation of the methylene group.



a: Bu_3SnH, AIBN (both 1.8 equiv)	50%	40%	none
b: Bu_6Sn_2 (0.2 equiv), 300 W	14%	30%	5%
c: Bu_6Sn_2 (2.2 equiv), 300 W	none	50%	10%

Scheme 1.08: 2-Indolyacyl radical cyclization onto benzene attached at the indole 3 ring position

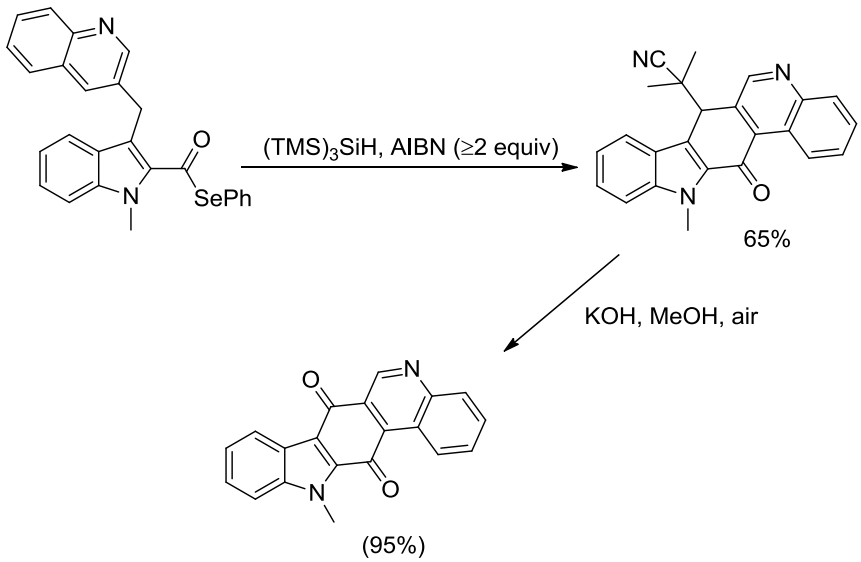
Reduction of the intermediate acyl radical to aldehyde was observed under reductive ($(TMS)_3SiH$ or Bu_3SnH-AIBN) conditions for pyridine derivatives attached at the indole nitrogen (Scheme 1.09).[16] The desired cyclization did take place upon treatment with Bu_6Sn_2-mediated conditions, although the yields were lower than in the phenyl series, and significant amounts of non-cyclized tin ester compounds were also isolated (20-30%).



Scheme 1.09: 2-Indolyacyl radical cyclization onto 3-*N*/4-*N* pyridines

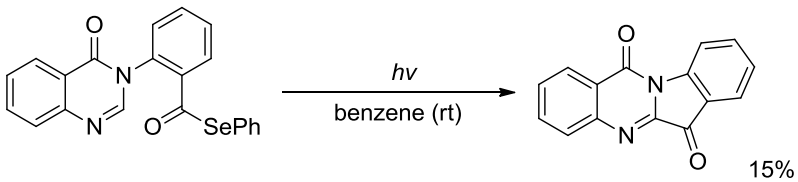
Bennasar and co-workers cyclized an acyl radical onto a quinoline derivative (Scheme 1.10) using reductive ($(TMS)_3SiH$ and AIBN) conditions producing a

cyclized product incorporating the 2-cyano-2-propyl fragment of AIBN.[17] The breakdown of AIBN leads to two 2-cyano-2-propyl radicals, the first abstracting a hydrogen atom from the benzylic position of the pentacycle followed by reaction of the second 2-cyano-2-propyl radical with the benzylic radical generated. Treatment of the latter adduct with potassium hydroxide in methanol in the presence of air through a process involving a gramine-type nucleophilic substitution followed by oxidation of the resulting alcohol, generated the expected dione.



Scheme 1.10: Acyl radical cyclization onto quinoline derivatives

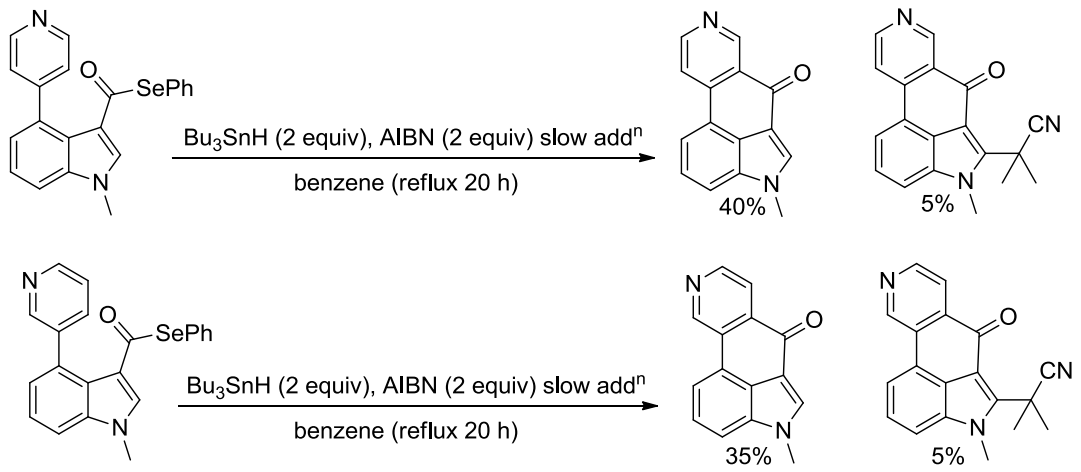
Bowman and co-workers performed 5-*exo* and 6-*exo* acyl radical cyclizations onto quinazolin-4-one analogues (Scheme 1.11) with the highest yield for the 5-*exo* cyclization obtained by simple photolysis of the selenoester at room temperature in benzene.[18]



Scheme 1.11: 5-*exo* Acyl radical cyclization onto quinazolin-4-one analogues

More recently reaction of 4-pyridyl substituted indolyl-3-selenoester under reductive conditions led to the target 4-methylindolo[4,3-*fg*]isoquinolin-6-one in 40% yield,

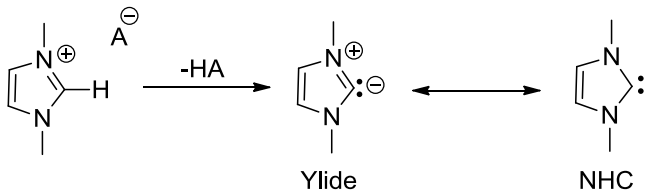
along with minor amounts of a tetracycle incorporating the 2-cyano-2-propyl moiety of the initiator at the indole 2-position (Scheme 1.12).[19] An entirely parallel cyclization course was observed in the 3-pyridyl series. It was assumed that AIBN hydrogen atom abstraction from the intermediate cyclized radical generated the re-aromatized products,[11,9,20] however this mechanism does not account for the observed 2-cyano-2-propyl by-products. The latter is assumed to be formed by a coupling of the 2-cyano-2-propyl radical with the delocalized cyclohexadienyl radical at the indole-2-position followed by rearomatization. Motherwell et al,[21] and Aldabbagh et al[8] have previously reported 2-cyano-2-propyl products, when excess amounts of AIBN are added to non-chain radical reactions.



Scheme 1.12: 3-Indolylacyl radical cyclizations onto 4- or 3-pyridyl moieties

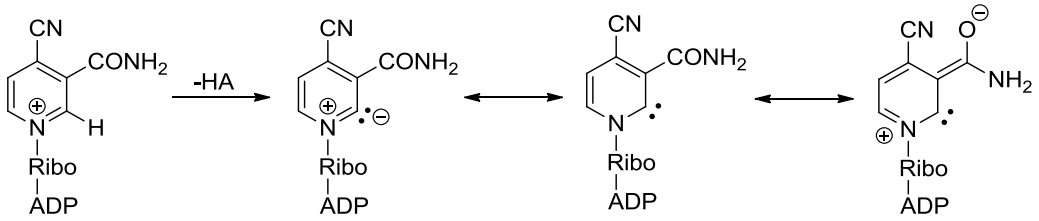
1.1.2 N-Heterocyclic Carbenes (NHCs)

1,3-Dialkylated imidazolium salts are weakly acidic, and can readily loose a proton at the 2-position to give an imidazolium ylide species. Resonance stabilization makes this ylide isoelectronic with the imidazolin-2-ylidene (N-heterocyclic carbene, NHC)[22] (Scheme 1.13). A review on NHCs by Cavell and McGuinness[23] reports that NHCs have been known for many years since the pioneering work done by Wanzlick in the 1960s and 1970s.[24-30] Lappert and co-workers[31] and Hill and Nile[32] in the 1970s discovered the application of transition metal-carbene complexes in catalysis. However these carbene ligands had to be generated in situ and no further advances were made until 1991 when the first synthesis of a stable free imidazolin-2-ylidene was reported by Arduengo.[33,34] The background to the development of stable carbenes as ligands has been reviewed on separate occasions by Regitz,[35] Hermann and Köcher[36] and Bertrand et al.[37]



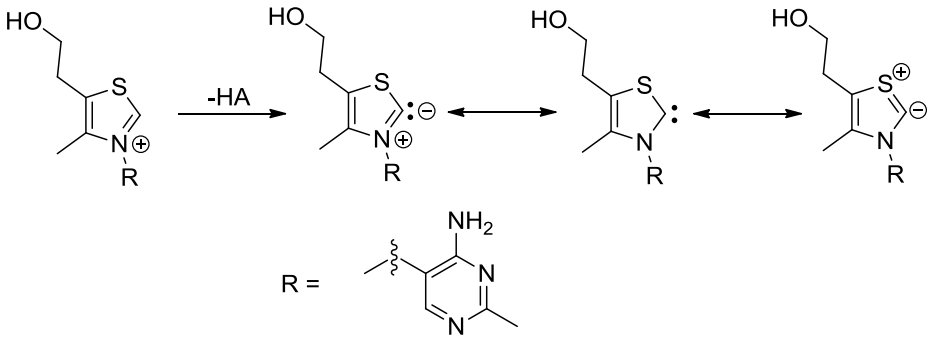
Scheme 1.13: The acidity of 1,3-dimethylimidazolium salt

Pietro in 1955[38] proved that deuterium swapping at the 2-position was possible for diphosphopyridine nucleotide-cyanide complex. However he concluded that the mechanism was uncertain at the time. Breslow in 1958 reported the formation of a thiazolium salt as an ylide.[39] He proposed the generation of an NHC on the diphosphopyridine nucleotide-cyanide complex carried out by Pietro (Scheme 1.14). It was reported that the NHC was formed selectively at C-2 but not at C-6 on standing at room temperature for two hours at pH 11.0. The carboxamide group is creating an inductive effect with stabilization provided by resonance.



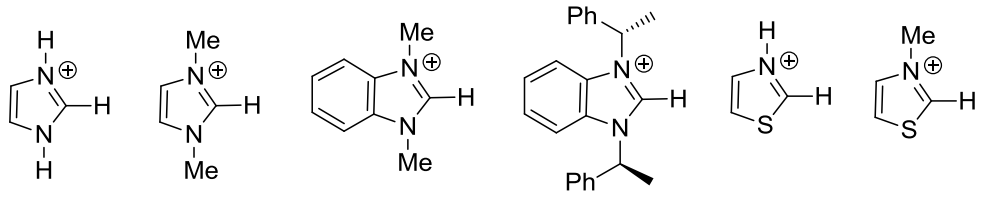
Scheme 1.14: NHC formation on a diphosphopyridine nucleotide-cyanide complex

The thiazolium ring of thiamine is acidic due to resonance stabilization, and involvement of S atom empty d-orbitals (Scheme 1.15).[40]



Scheme 1.15: Generation and stabilization of thiazolium NHC

Olofson reported the first observed deuterium exchange at the 2-position of the 1,3-dimethylimidazolium cation.[40] Amyes in 2004 evaluated the pK_a for the ionization of imidazolium cations at the 2-position to give the corresponding singlet imidazolin-2-ylidene in water.[22] The pK_a values for some imidazolium and thiazolium salts are shown in Figure 1.03. The addition of the extra benzene ring increases the rate of formation of the ylide by stabilizing the intermediate through resonance. Steric bulk also helps stabilize the NHC formed, hence the use of bulkier substituents at positions 1 and 3 lowers the pK_a.



pK_a	23.8	23.0	21.6	21.2	19.9	19.5

Figure 1.03: pK_a values of some 1,3-dialkylated imidazolium/thiazolium salts

1.1.2.1 Structure of carbenes

Carbenes are neutral with a divalent carbon atom with six electrons in its valence shell. The carbon atom can be either linear or bent, each geometry describable by a certain degree of hybridization.[37] The linear geometry implies an sp-hybridized carbene center with two nonbonding degenerate orbitals (p_x and p_y). An example of a linear carbene is propadienylidene ($H_2C{=}C{=}C{:}$). Bending the molecule breaks this degeneracy and the carbon atom adopts an sp^2-type hybridization: the p_y-orbital remains unchanged (called p_π) while the orbital that starts as the pure p_x-orbital is stabilized since it acquires some s character (it is called σ). Most carbenes are not linear and their frontier orbitals are the σ and p_π orbitals. The two electrons can be located in the same orbital (singlet state) or different orbitals (triplet state) (Figure 1.04).

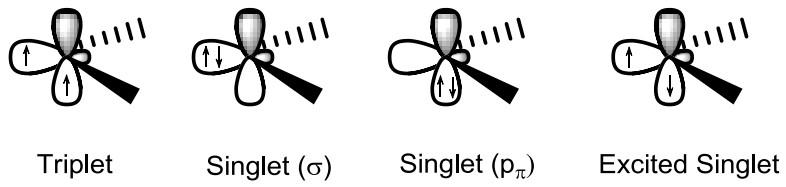


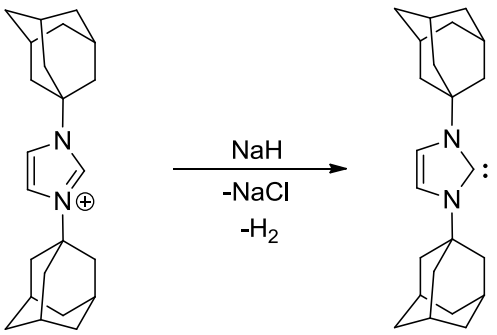
Figure 1.04: Possible electronic configurations of sp^2-hybridized carbenes

Inductive electron withdrawing groups favor the singlet carbene[41,42] as opposed to inductive electron donating groups which favor the triplet state. Electron withdrawing substituents increase the s character of the σ-orbital and leave the p_π orbital unchanged, thus increasing the σ–p_π energy gap. Carbenes with adjacent π electron donating groups such as F, Cl, Br, I, NR_2, PR_2, OR, and SR donate into the vacant p_π orbital thus increasing the σ-p_π energy gap, again making the σ-singlet the more favored state. Imidazoles and thiazoles have two substituents that are both

inductively electron withdrawing and electron donating via resonance (lone pair on the N atom).[37] This means that NHCs have to be singlet carbenes occupying the σ-orbital. Imidazole NHCs are also stabilized by resonance due to aromaticity independently demonstrated by Apeloig et al[43] and Frenking et al[44] in 1996, however the major stabilizing affect for imidazole NHCs is still the π-donating, σ-attracting amino groups.

1.1.2.2 Generation and isolation of NHCs

Previous work carried out by Wanzlick in the 1960s generated 1,3-diphenylimidazolidin-2-ylidene by thermal loss of chloroform but only the dimeric electron rich olefin was isolated.[24-26] In 1970 Wanzlick deprotonated imidazolium salts using potassium *tert*-butoxide to generate imidazolin-2-ylidenes which were trapped but not isolated.[28,30] Arduengo prepared the first stable NHC by deprotonation of the 1,3-di-1-adamantylimidazolium chloride with sodium or potassium hydride (Scheme 1.16).[33] The crystals are thermally stable and melted above 200 °C without decomposition.



Scheme 1.16: Generation of the first isolable NHC

Herrmann used liquid ammonia as the solvent and sodium hydride as base to characterize the stable NHCs in Figure 1.05.[45,46] The use of liquid ammonia is advantageous as no common organic solvent is inert towards free carbenes under conditions that allow a smooth and rapid deprotonation. In addition imidazolium salts are much more soluble in mixtures containing liquid ammonia than in organic solvents alone.

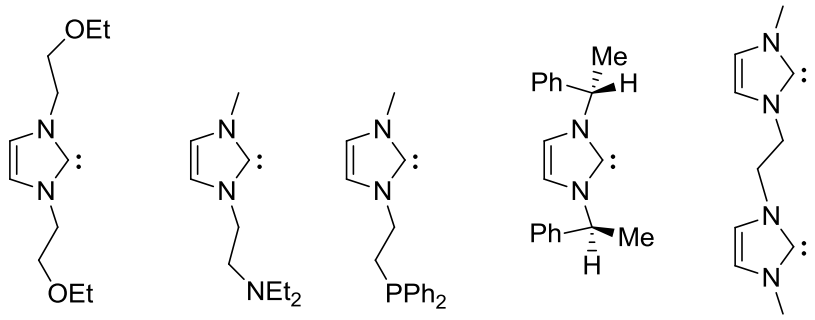
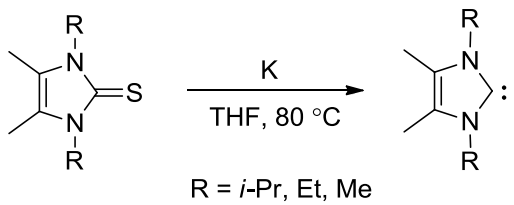


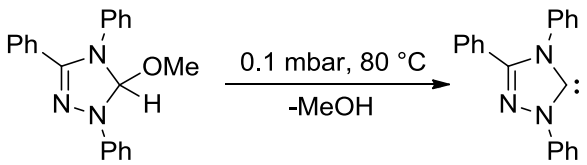
Figure 1.05: Isolable NHCs generated using liquid ammonia

In 1993 Kuhn and co-workers developed a new and versatile approach to the alkyl-substituted N-heterocyclic carbenes. Kuhn reduced imidazole-2(3*H*)thiones with potassium in THF under reflux to generate the NHCs shown (Scheme 1.17).[47]



Scheme 1.17: Reduction of imidazole-2(3*H*)-thiones with potassium

Enders and co-workers in 1995 generated the first commercially available NHC by thermal methanol elimination under vacuum (0.1 mbar) from 1,2,4-triazol-5-ylidene in quantitative yield (Scheme 1.18).[48]

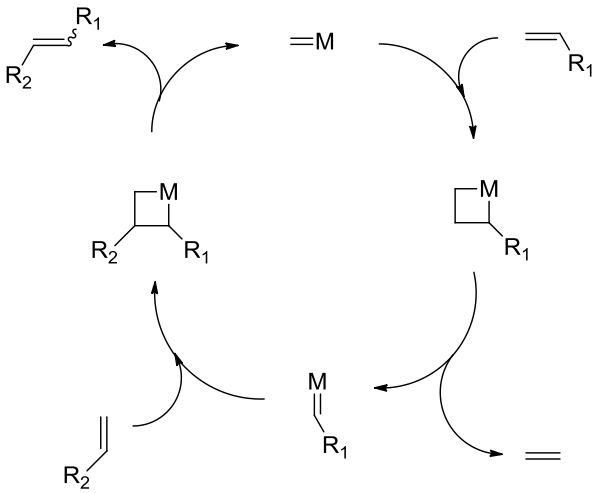


Scheme 1.18: Synthesis of the first commercial NHC

1.1.2.3 Uses in catalysis

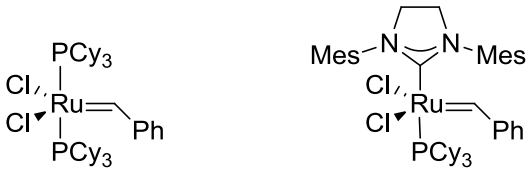
The electron-rich (nucleophilic) nature of the singlet NHC has led to a wide-range of applications in transition metal-catalyzed, and organocatalyzed reactions. NHCs are a very common ligand in transition metal-catalyzed metathesis reactions (Scheme 1.19). Catalyst activity is directly related to the electron-donating ability of the

ligands as well as their steric bulk. The use of NHCs is attractive because of ease of preparation, and their tendency to act as strong σ-donors but poor π-acceptors. Therefore, NHC's bind strongly to important metal centers such as Ru, Rh, Pd, Cu, Ag, Au, etc. with little tendency to dissociate.[49]



Scheme 1.19: General metathesis mechanism

Two of the most famous catalysts in transition metal-catalysis are the Grubbs 1 and Grubbs 2 catalysts. (Figure 1.06)



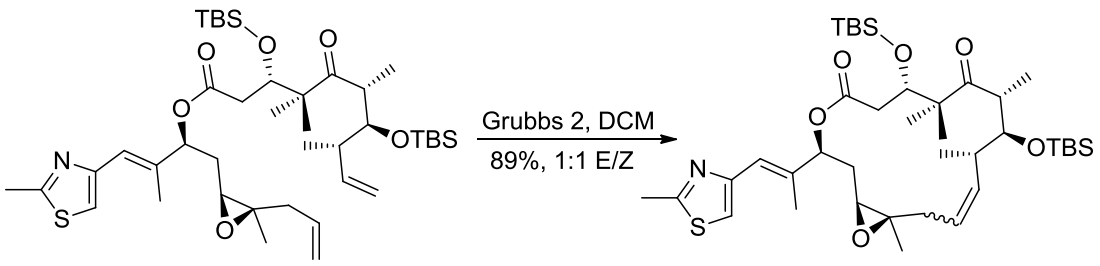
Grubbs 1 Grubbs 2

Cy = Cyclohexyl, Ph = Phenyl, Mes = Mesitylene

Figure 1.06: Grubbs 1 and 2

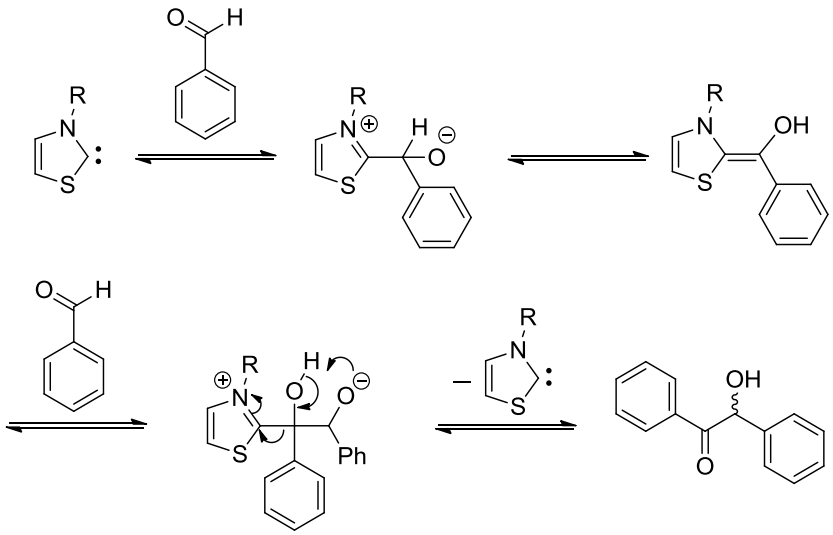
Scheme 1.20 shows a Metathesis reaction carried out by Sun and Sinha, Grubbs 1 did not catalyze the reaction but Grubbs 2 formed the desired product in 89% yield.[50] Phosphine dissociation from Grubbs 1 is two orders of magnitude faster than that for Grubbs 2, making the Grubbs 2 a slower initiator. The increase in reactivity on using Grubbs 2 is due to increased σ-donor character of NHCs in comparison to phosphines, this increases the preference for coordination of olefinic substrates

relative to phosphines. Hence Grubbs 2 stays longer in the catalytic cycle even if it initiates slower. The strong donor ability of the NHC leads to an overall faster rate of catalysis.



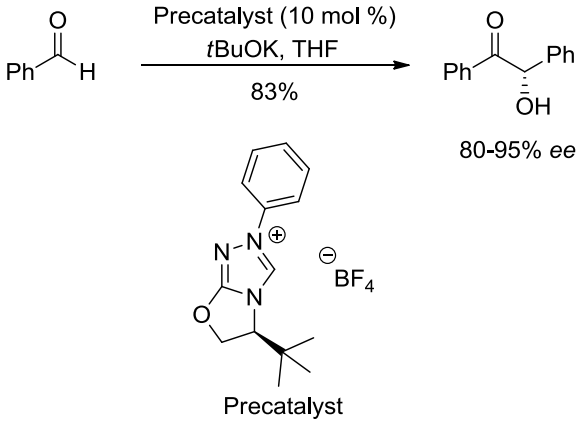
Scheme 1.20: The use of Grubbs 2 in metathesis

NHC is used to catalyze benzoin condensations such as the self-condensation of benzaldehyde. This reaction was already reported in 1832 using cyanide anions as catalysts. In 1943 thiazol-2-ylidenes were used as catalysts instead of the cyanide anions (Scheme 1.21).[51] Formoin condensation can be catalyzed by NHCs which is the autocondensation of formaldehyde. The mechanism is the same as below but due to competition between formaldehyde starting material and other aldehyde products of the reaction, complex mixture of adducts are usually observed.



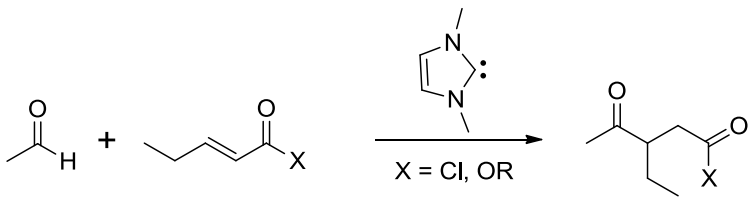
Scheme 1.21: NHC-catalyzed benzoin condensation

Enders and Kallfass accomplished the first high-yield and highly enantioselective intermolecular benzoin condensation using a nucleophilic carbene catalyst generated from an enantiopure bicyclic triazolium salt, which allowed an in situ deprotonation with potassium *tert*-butoxide (Scheme 1.22).[52]



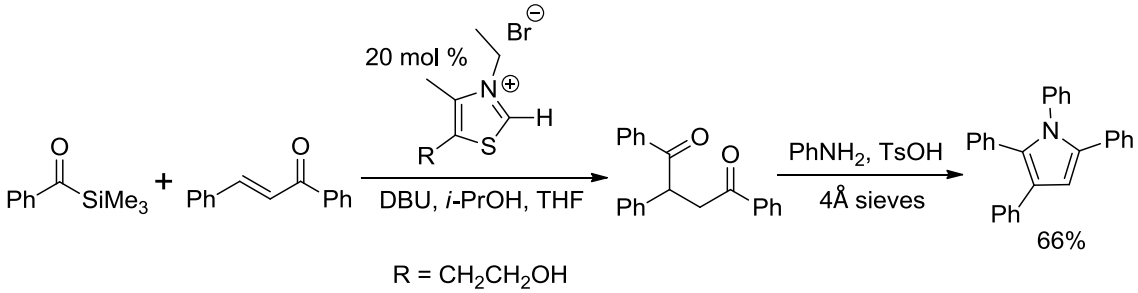
Scheme 1.22: NHC-catalyzed benzoin condensation

The Stetter reaction is a conjugate addition of an aldehyde to an α,β-unsaturated carbonyl compound competing with the corresponding benzoin condensation. However, the benzoin-condensation is reversible, and since the Stetter reaction leads to more stable products, the main product will be the 1,4-dicarbonyl. The NHC (Scheme 1.23) activates the aldehyde in the form of an enol which can subsequently undergo nucleophilic attack at the β-position of the electron poor olefin.[49]

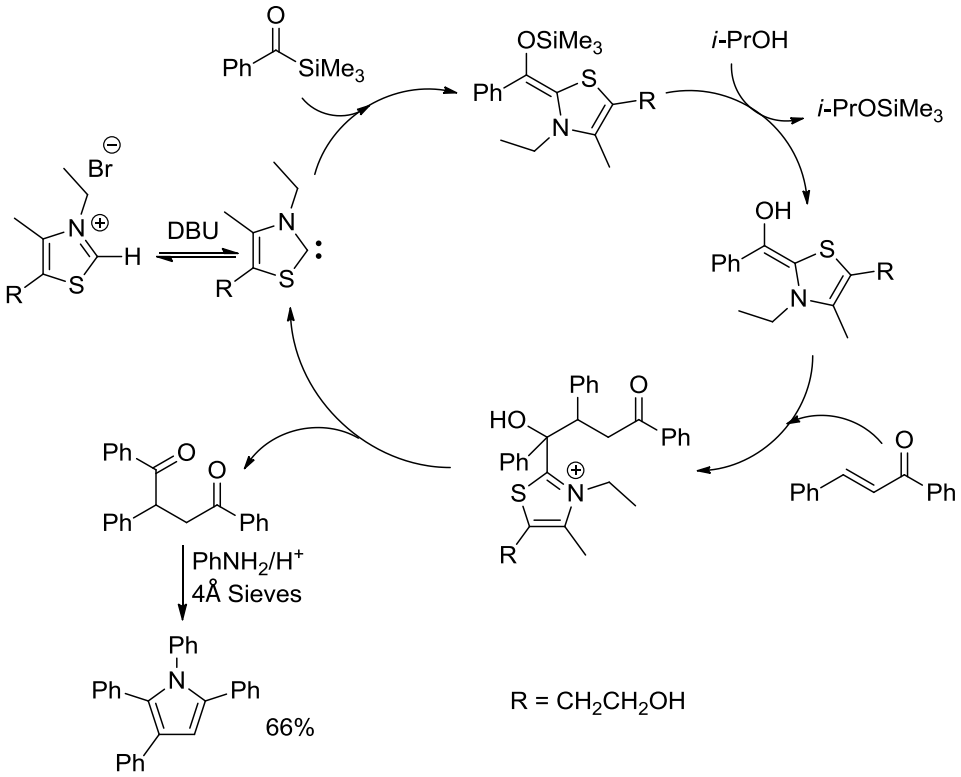


Scheme 1.23: The Stetter reaction

Scheidt and co-workers carried out a pyrrole-forming reaction sequence involving a thiazolium NHC and acylsilane (aldehyde avoided due to problematic dimerization reactions e.g. benzoin reactions) in a Stetter type reaction, followed by a Paal-Knorr reaction (1,4-diketone condensation) with a primary amine (Scheme 1.24).[53] The proposed catalytic cycle is shown in Scheme 1.25.



Scheme 1.24: One pot Sila–Stetter/Paal-Knorr synthesis of pyrroles

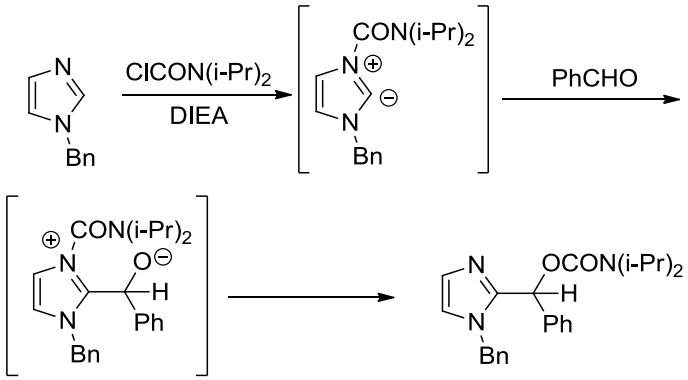


Scheme 1.25: Sila–Stetter/Paal-Knorr mechanism

1.1.2.4 Uses as reagents

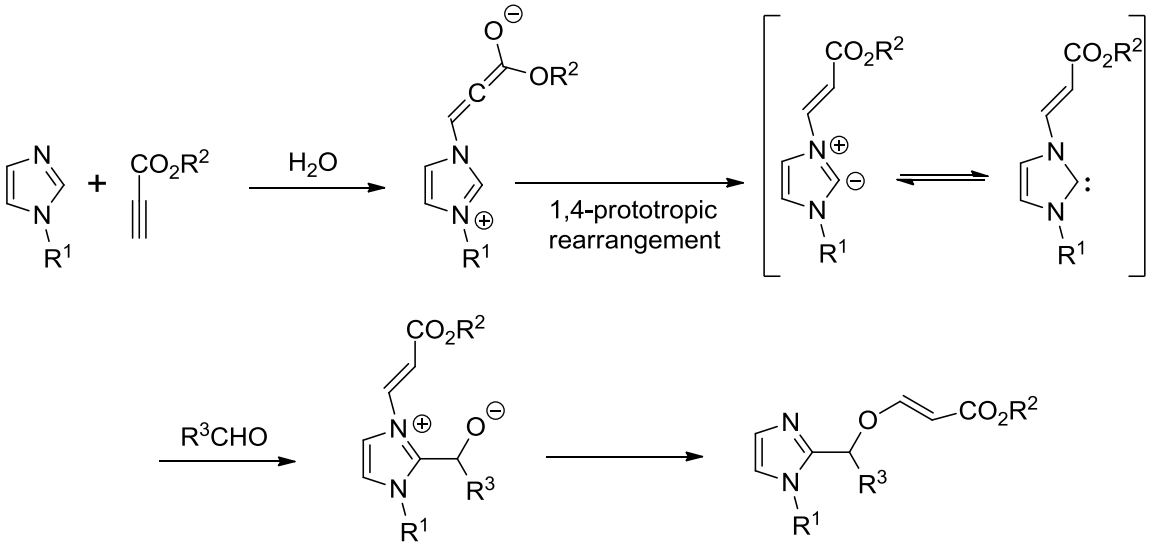
As reagents NHCs are generated in situ upon quaternization of the 3-*N* lone pair of imidazoles to give an acidic salt intermediate.[54] The NHC-generated in the presence of base undergoes nucleophilic attack onto an electrophilic atom. For example, Hlasta used DIPEA (diisopropylethylamine) to deprotonate the acidic imidazolium chloride generated upon reaction with diisopropylcarbamyl chloride, which

condensed with benzaldehyde to give functionality at the imidazole-2-position (Scheme 1.26).



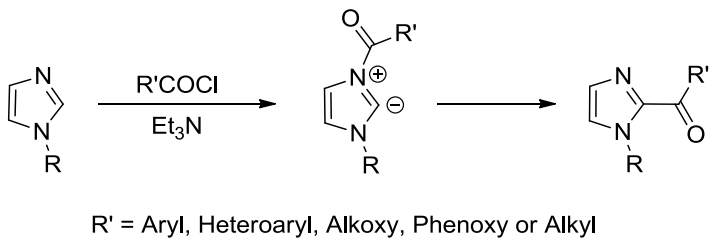
Scheme 1.26: Generation and reaction of NHC (ylide)

NHCs can be formed by quaternization of imidazoles with alkynes followed by a 1,5-prototropic rearrangement. Condensation with an aldehyde gives imidazoles incorporating functionality at the 2-position (Scheme 1.27).[55] Trofimov also reacted 1-substituted imidazoles with electron-withdrawing acetylenes again generating NHCs in the presence of trace amounts of water, which led to similar reactions to that of Scheme 1.27.[56]



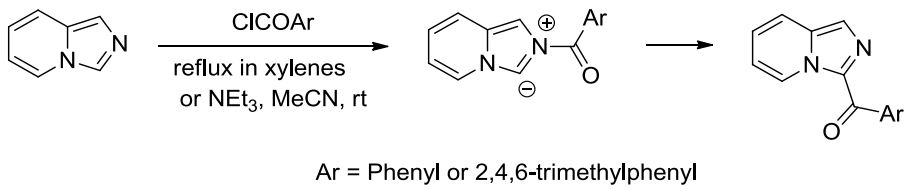
Scheme 1.27: Alkynoate used in generation of NHC

More than thirty years earlier, Regel and Büchel established substitution of ketone and ester functionality onto the imidazole (and benzimidazole) 2-position using imidazolium ylide species (Scheme 1.28).[57,58]



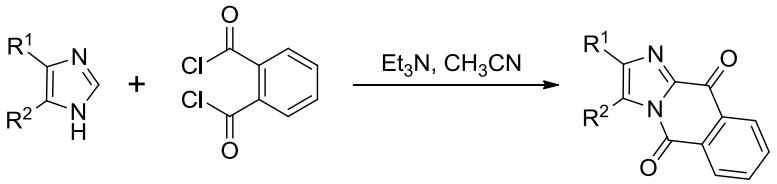
Scheme 1.28: NHC-generation with electrophilic migration to the 2-position

These reactions used various acid chlorides or chloroformic esters in the presence of triethylamine in polar solvents hence utilizing the migration to the 2-position without the use of a second electrophile for trapping. The protocol gave regioselective acylation of the electron-deficient position of imidazopyridines using benzoyl chloride under thermal or triethylamine-mediated conditions (Scheme 1.29).[59,60]



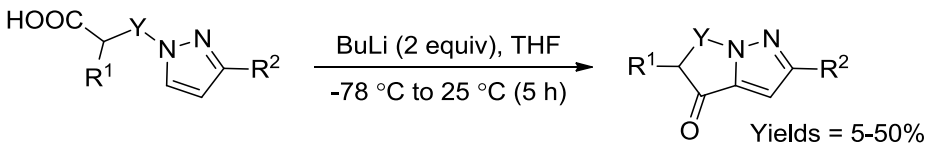
Scheme 1.29: Thermal and base-mediated functionalization of imidazopyridine

Imidazole (and benzimidazole) reacted with phthaloyl dichlorides in the presence of two equivalents of triethylamine in acetonitrile to give imidazo[1,2-*b*]isoquinolinediones[57,61](Scheme 1.30) and an ylide intermediate was proposed.[57]



Scheme 1.30: Base-mediated intermolecular annulation

Larsen reported five to seven-membered base-induced intramolecular acylations of 1*H*-pyrazole-1-alkanoic acids, although no carbene intermediate is described, it is conceivable that the anion generated by lithiation at the C-5 position may be stabilized as a carbene intermediate using resonance (Scheme 1.31).[62] The reaction is described as being a Parham-type cycloacylation. Parham cyclization describes the generation by halogen-lithium exchange of aryllithiums and their subsequent intramolecular cyclization onto an electrophilic site.



Y = CH_2, $(CH_2)_2$, $(CH_2)_3$ R^1 = H, Me, Ph, *t*-Bu R^2 = H, Ph, *p*-Tol

Scheme 1.31: Parham-type cycloacylations of 1*H*-pyrazole-1-alkanoic acids

1.2 Heterocyclic quinones and anti-tumour activity

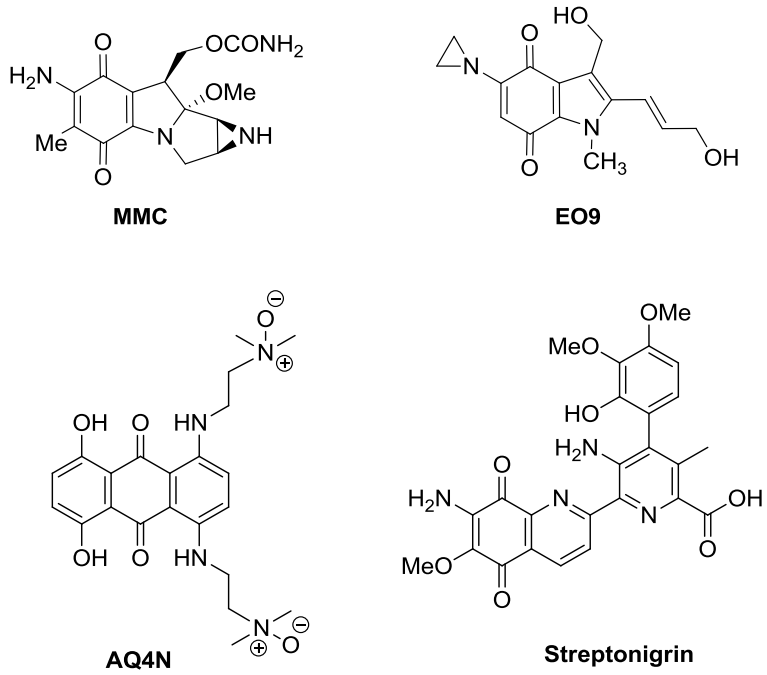
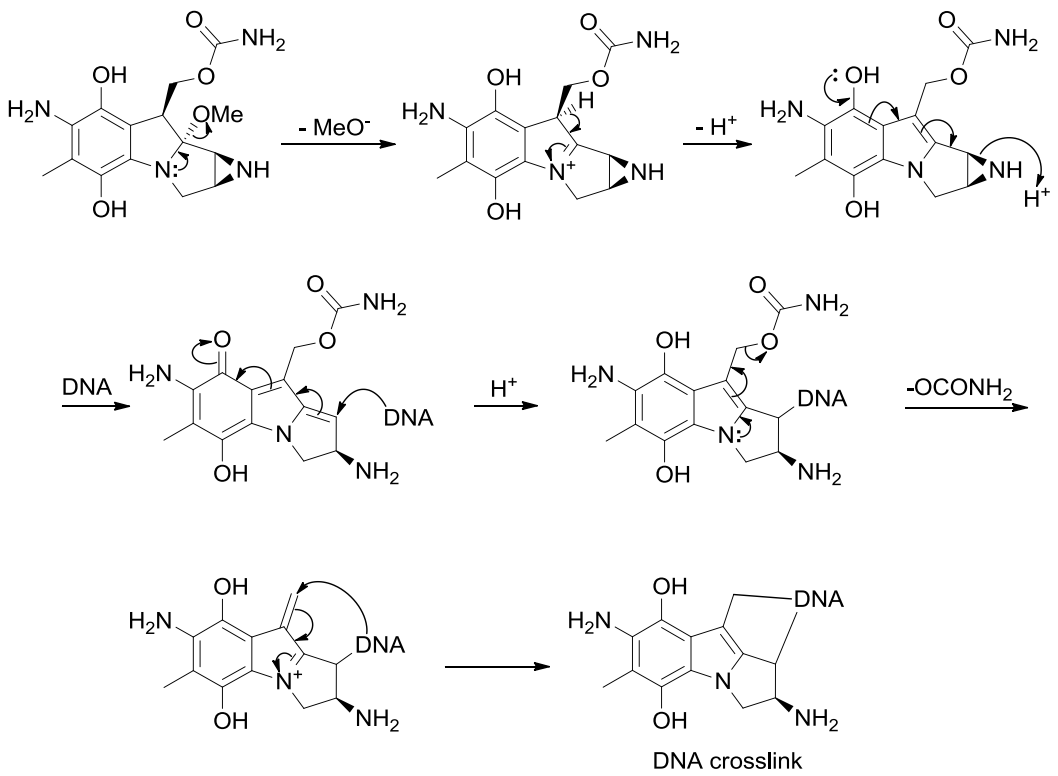


Figure 1.07: Anti-tumour heterocyclic quinones

Quinonoid heterocyclic compounds have long been known to have the potential to act as bioreductively–activated alkylating agents. Quinones are reduced by reductase enzymes in a biological system. Many tumour cells have been shown to over-express reductase enzymes such as NQO1 (NAD(P)H quinone oxidoreductase 1)[63] (e.g. human cervical cancer cell line[64] [HeLa] and human prostate cancer cell line[65] [DU145]) making bioreductive activation more efficient in the cancer cells, giving rise to tumour selective toxicity. The compounds in Figure 1.07 are examples of heterocyclic quinones that have been identified as anti-tumour compounds. Mitomycin C (MMC) is an indolequinone anti-tumour agent which has been used as a chemotherapeutic agent for over five decades. MMC is referred to as a bioreductive prodrug that requires intra-cellular reductive activation. MMC can be reduced to the semiquinone radical via single electron transfer (SET) or to the hydroquinone via a two electron reduction. SET is catalysed by cellular oxidoreductase enzymes which are very common in hypoxic (low pO_2) environments similar to those found in solid tumours.[66,67] The re-oxidation of the semiquinone radical to the nontoxic quinone occurs much more efficiently in well-oxygenated cells as opposed to hypoxic tissues

(solid tumours) leading to tumour-selective therapy. The semiquinone radical can disproportionate to give the hydroquinone, which can alternatively be generated by direct two electron reduction of the quinone. Upon hydroquinone formation, a cascade of spontaneous transformations takes place. An iminium ion is produced upon expulsion of the tertiary methoxy group due to release of the *N*-4 lone pair from conjugation with the quinone. Proton elimination with subsequent tautomerism of the hydrogen from the hydroquinone leads to aziridine ring opening, generating an electrophilic alkylation centre which can bind DNA. Loss of the carbamate group, again initiated by the lone pair of the N-4, generates a second electrophile that can also bind DNA. Double alkylation leads to cross linking of DNA and ultimately cell death (Scheme 1.32).[68-70]



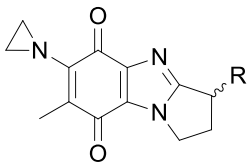
Scheme 1.32: Mechanism of action of reductively activated MMC

EO9 has been shown to undergo reductive activation to give three reactive centres (allylic and benzylic hydroxyls as well as the aziridine ring).[71] AQ4N is a di-*N*-oxide prodrug that undergoes a two-step enzymatic reduction followed by DNA binding. Streptonigrin is a quinoline-5,8-dione anti-tumour antibiotic isolated from

Streptomyces flocculas.[72] It was shown to exert a cytotoxic effect by several cellular mechanisms, such as inhibition of DNA and RNA synthesis, strand breaks and induction of unscheduled DNA synthesis.

1.2.1 Benzimidazolequinones

Skibo and co-workers reported pyrrolo[1,2-*a*]benzimidazolequinones (PBIs), which possess an aziridine substituent at the 6-position, to be powerful cytotoxic agents (Figure 1.08).[73-75] A substituent at the 3-position on the pyrrolo[1,2-*a*] fused ring which is capable of hydrogen bonding contributes considerably to the potency. It is also suggested that the substituent at the 3-position can increase cytotoxicity by improving the molecules ability to pass through cellular membranes.[74,75] Bioreduction to the hydroquinone allows DNA to hydrogen bond to 6-aziridylpyrrolo[1,2-*a*]benzimidazolequinones[76] resulting in nucleophilic attack at the aziridine ring by the DNA phosphate backbone or by DNA bases resulting in DNA damage and cell death.[73,74]



PBI

R = OAc, $OCONH_2$, $NHCOCH_3$, NH_2, $NHCONH_2$

Figure 1.08: 6-Aziridinylpyrrolo[1,2-*a*]benzimidazolequinones

Aldabbagh and co-workers reported the synthesis of a library of alicyclic ring-fused [1,2-*a*]benzimidazolequinones with and without an additional fused cyclopropane ring (Figure 1.09). These compounds were found to be significantly more cytotoxic than indolequinone analogues with selectivity towards hypoxic conditions.[9,77-79] The higher cytotoxicity of benzimidazolequinones was correlated with their reductive potentials obtained using cyclic voltammetry. One electron-reductive potentials (-1.052 to -1.168 V versus ferrocene in DMF) were less negative than that of MMC (-1.421 V versus ferrocene in DMF), indicating a more facile reduction of the quinone to the radical-anion intermediate, which was used to explain their higher cytotoxicity

towards hypoxic conditions in which single-electron reductase enzymes are prevalent. This increase in reducibility can be attributed to the extra electron-withdrawing effect of the 3-*N* of the fused-imidazole.[9,78] There was no evidence of possible ring-opening of the cyclopropane influencing cytotoxicity for cyclopropane-fused compounds.

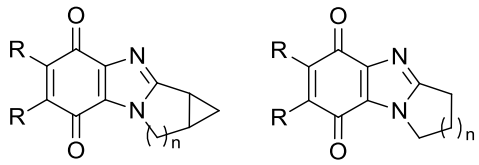


Figure 1.09: Alicyclic ring-fused [1,2-*a*]benzimidazolequinones with and without a fused cyclopropane ring

Fanconi anemia (FA) is a rare human genetic disease, leading to a high incidence of cancer in early adulthood. FA cells lack a protein known as FANCD2 (repairs damaged DNA) which leads to hypersensitive toxicity to DNA-cross-linking agents, including MMC.[80] Aldabbagh and co-workers reported the synthesis of 4,7-dimethoxy-*N*-[(aziridin-2*S*-yl)methyl]benzimidazole and *N*-[(aziridinyl)methyl]benzimidazolequinone (Figure 1.10) both of which induced hypersensitive killing of a FA cell line (PD20i) despite only having one site for DNA alkylation (no cross-linking).[80] The hypersensitive killing of the FA cells by the dimethoxy derivative implies the aziridine and not the quinone is responsible for the hypersensitive toxicity towards the FA cells. That is bioreductive activation is unnecessary for a cytotoxic response. The hypersensitivity for both the 4,7-dimethoxy-*N*-aziridinyl benzimidazole and benzimidazolequinone was partially corrected upon introduction of the missing FANCD2 protein in an isogenic FA cell line (PD20:RV) expressing wild-type FANCD2 protein from an inserted transgene.

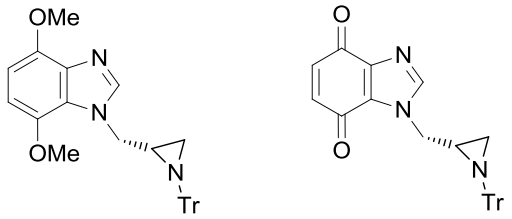


Figure 1.10: 4,7-Dimethoxy-*N*-aziridinyl benzimidazole and benzimidazolequinone

Aldabbagh and co-workers later reported methoxy and aziridine analogues of alicyclic ring-fused [1,2-*a*]benzimidazolequinones, and found that increasing the size of the fused alicyclic ring to six or seven membered decreased potency (Figure 1.11).[81,82] The role of the aziridine was investigated by comparing the response of a (FA) cell line (PD20i) to the 6-methoxy and 6-aziridinyl anologues of pyrrolo[1,2-*a*]benzimidazolequinone. The aziridine analogue was found to be cytotoxic in the nanomolar range (10^{-9} M) similar to MMC whereas the methoxy analogue had negligible toxicity at the same concentrations, implicating the aziridinyl group in the hypersensitivity of FA cells lacking FANCD2.[82] The toxicity of the aziridinyl analogue was significantly reduced upon introduction of the missing FANCD2 protein (PD20:RV cell line) again implicating the FANC complex in cellular repair of DNA-damage.[82]

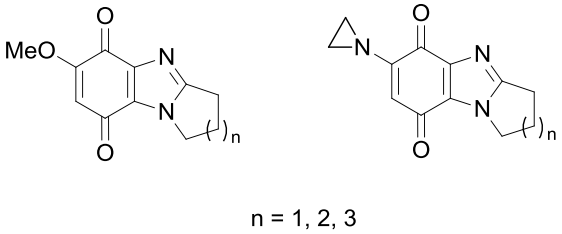


Figure 1.11: 6-Methoxy and aziridinyl analogues of alicyclic ring-fused [1,2-a]benzimidazolequinones

Aldabbagh and co-workers reported ring-fused and non-ring fused pyrrolo[1,2-*a*]benzimidazoles (Figure 1.12) to be significantly more cytotoxic towards the human breast cancer cell lines MCF-7 and HCC1937 than towards human normal fibroblasts cells (GM00637).[83] The fused compound was found to be less toxic to all cell lines

compared to the non-fused compound. The HCC1937 cell line (derived from a primary breast cancer carcinoma, from a patient with germ-line mutation in the breast cancer susceptibility gene BRCA1)[84] has been reported to be hypersensitive to MMC. The BRCA1 protein plays a key role in repair of DNA-strand breaks arising as a result of intrastrand and interstrand DNA-crosslinks induced by chemotherapeutic agents. The BRCA1-defecient breast cancer cell line (HCC1937) showed a significantly greater response towards MMC than ring-fused and non-ring fused aziridinylpyrrolo[1,2-*a*]benzimidazoles. This indicates that different pathways may mediate cellular response to benzimidazole-containing aziridine compounds compared to MMC. This is not surprising as the benzimidazole derivatives in Figure 1.12 do not allow for the formation of cross-links, because there is only one position for DNA-alkylation (at the aziridine). The lack of a quinone moiety indicates that bioreductive activation is not required for the cytotoxic response.

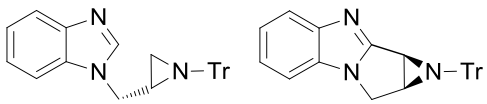


Figure 1.12: Non-fused and fused aziridinylpyrrolo[1,2-*a*]benzimidazoles

Aldabbagh and co-workers reported the synthesis of a series of aromatic ring-fused benzimidazolequinones that possess anticancer activity despite lacking reactive sites that upon reductive activation can undergo DNA alkylation (Figure 1.13). The naphthalene analogue showed the highest specificity towards human cervical (HeLa) and prostate (DU145) cancer cell lines with little toxicity towards a human normal (GM00637) cell line. This is presumably attributed to resonance stabilization of the chemically reduced intermediates formed, since this was the most conjugated quinone system prepared. The requirement of the quinone moiety to induce a cytotoxic response was highlighted in the negligible cytotoxic response of its benzimidazole derivative.[85]

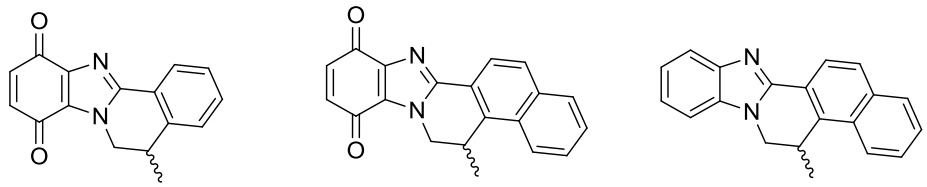


Figure 1.13: Aromatic ring-fused benzimidazolequinones/benzimidazole

Garuti et al., reported the synthesis of 2-(pyridinyl)benzimidazolequinones and showed that the location of the *N*-heteroatom in the pyridine ring had a considerable impact on the activity (Figure 1.14). Shifting the nitrogen from the 4-position to the 3- and 2-position resulted in the progressive increase of anti-proliferation activity towards human erythroleukemia and colon carcinoma cell lines.[86]

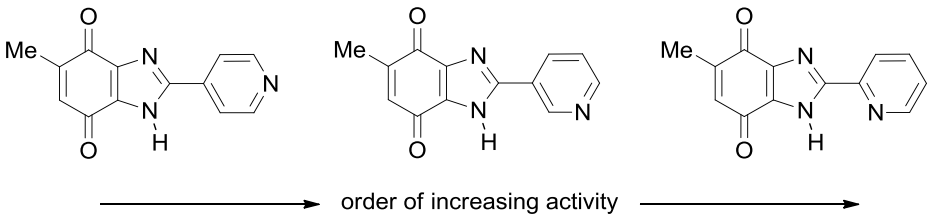


Figure 1.14: Effect of *N*-heteroatom position in 2-(pyridinyl)benzimidazolequinones

More recently Aldabbagh and co-workers reported the synthesis of dialicyclic ring fused imidazobenzimidazolequinones (Figure 1.15). Selective toxicity towards human cervical (HeLa) and prostate (DU145) cancer cell lines with negligible toxicity towards a normal human cell line, GM00637 was reported for the imidazo[5,4-*f*]benzimidazolequinones. The iminoquinone analogue showed a particularly high specificity towards the prostate cancer cell line, being up to twelve times more toxic towards this cell line than to normal cells.[20]

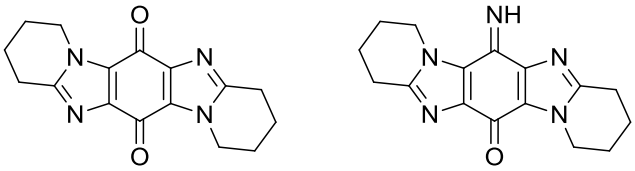


Figure 1.15: Imidazo[5,4-*f*]benzimidazolequinones

1.3 Thesis aims and objectives

The aim of this thesis is to synthesize a novel series of *p*-diones fused between two aromatic systems, where one is a diazole (Figure 1.16). This would result in the development of new synthetic methodology for annulation of diazoles, as well as the development of new potential bioreductive antibiotics, which may act as alternatives to widely studied bioreductive quinone anti-tumour agents.

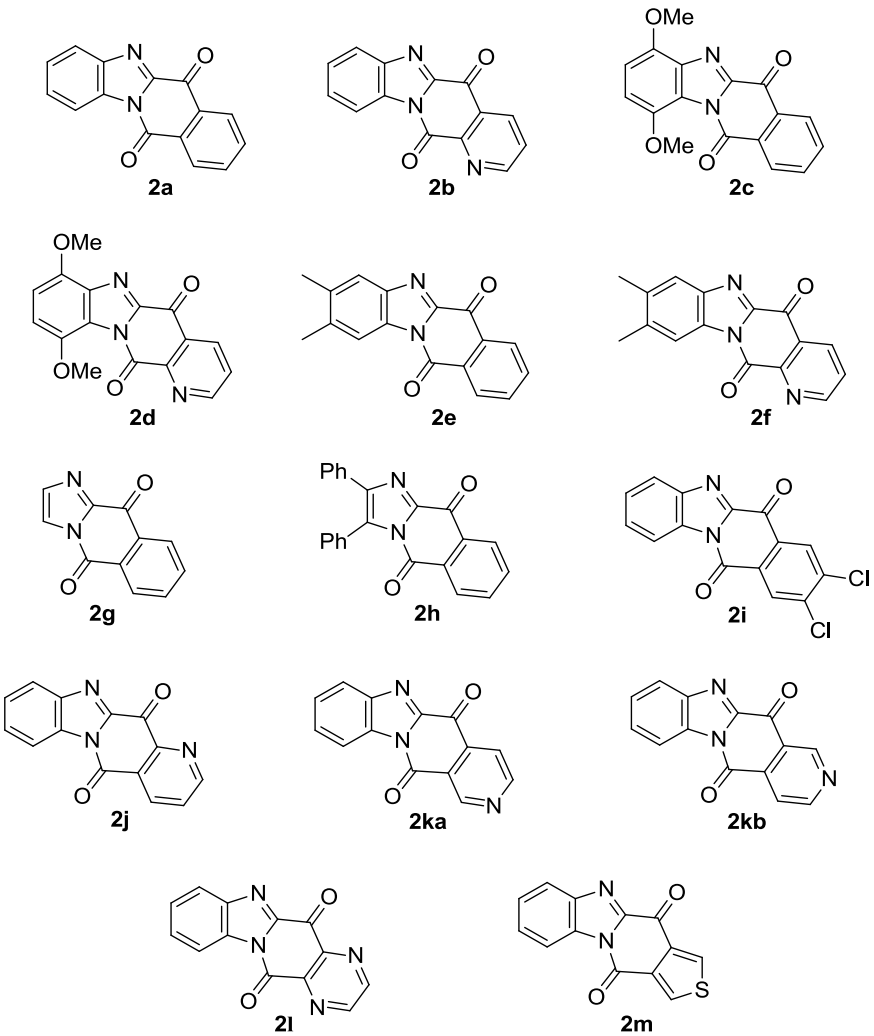


Figure 1.16: Structure of *p*-dione targets

Once synthesized the library of compounds above will undergo cyclic voltammetry analysis, as well as cytotoxicity evaluation against a human cancer and normal cell line. Chapters 2, 3 and 4 present the results and discussion of these investigations, and chapter 5 details the experimental carried out.

Chapter 2

Acyl Radical Cyclizations onto the Benzimidazole-2-position to give Aromatic *p*-Dione Adducts

2.1 Introduction

The target compounds for this thesis are aromatic ring-fused *p*-diones of general structure in Figure 2.01. Targets have an electro-reducible *p*-dione moiety, as an alternative to the widely reported quinone moiety.[9,20,66,73-81,87-90] The preparation of these compounds is part of a program to investigate *p*-diones and derivatives as potential new bioreductive anti-tumour agents.

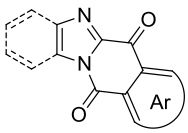
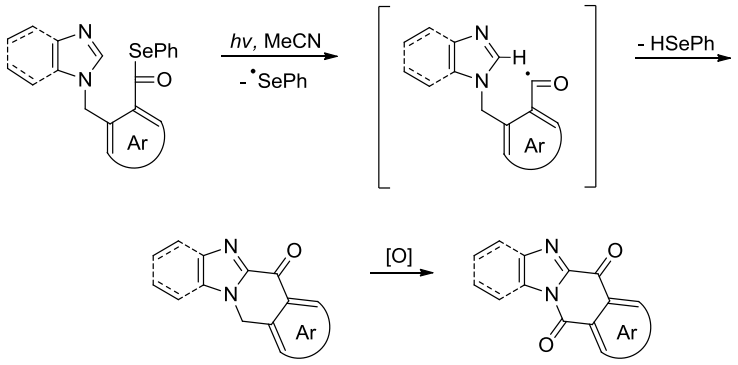


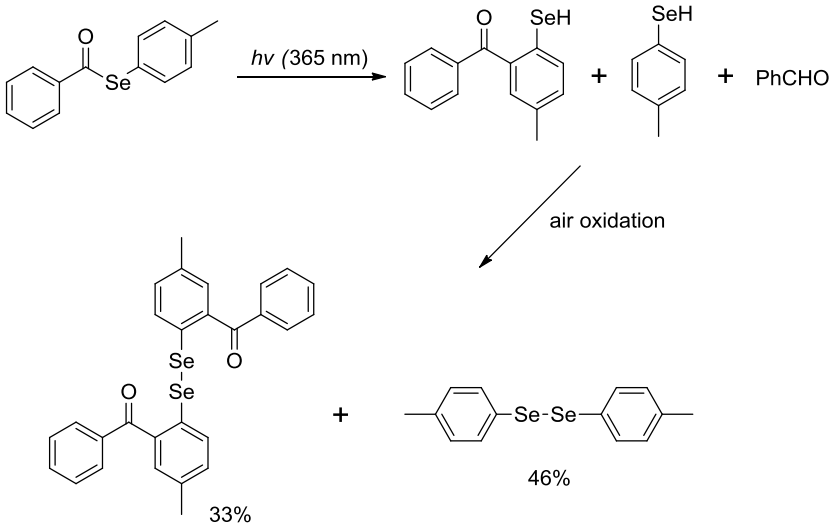
Figure 2.01: General structure of target compounds

The following chapter investigates photochemical homolytic aromatic substitutions of acyl radicals onto the benzimidazol-2-yl position, as a route to target compounds. There are few examples of acyl radicals generated under photochemical conditions undergoing homolytic aromatic substitution. Most reports of acyl radicals used in aromatic substitutions are mediated by organotin or organosilicon radical initiators.[15-19] Given the limited research using metal-free photochemical methods, we decided to investigate this intramolecular radical substitution with benzimidazoles. Acyl radicals can be generated from phenyl selenoesters, which are readily prepared from the corresponding carboxylic acid.[91-93] Related phenyl selenides have been shown to be excellent alkyl radical precursors in diazole reactions because of their efficient radical, but poor S_N2 leaving group ability.[9,12,20,94-97] Our aim is to decompose the phenyl selenoesters into acyl radicals using UV-light, and proceed with the oxidative substitution at the benzimidazole-2-position, as shown in Scheme 2.01. Although phenyl selenol (PhSeH) is produced it is not expected to be observed, as it is known to give diphenyl diselenide in the presence of air.[13,14,98,99] Further oxidation to the *p*-diones is expected, since derivatives benzimidazo[1,2-*b*]isoquinoline-6,11-dione (**2a**), imidazo[1,2-*b*]isoquinoline-5,10-dione (**2g**) and 2,3-diphenylimidazo[1,2-*b*]isoquinoline-5-10-dione (**2h**) (Figure 1.16) are well-known stable compounds.[57,61,100-102]



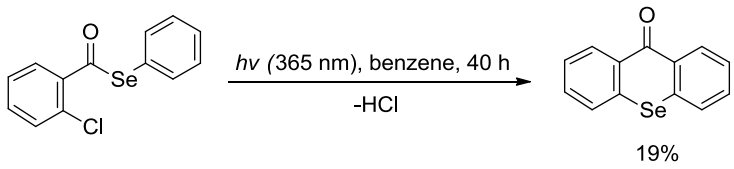
Scheme 2.01: The proposed UV-mediated oxidative annulations

Selenoesters and telluroesters are known to be easily homolyzed using UV-light, generating reactive acyl radicals. Moreover photochemical homolytic aromatic substitutions using phenyl selenoesters were first reported over 30 years ago.[98,99] The reaction in Scheme 2.02 involves the homolysis of the carbonyl selenium bond followed by acyl radical homolytic aromatic substitution to give the seleno-photo-Fries product as well as selenocresol and benzaldehyde. The reactive selenols were detected by NMR spectroscopy of the crude degassed reaction mixture. In air the selenols were oxidized to the diselenides in 33 and 46% yield.



Scheme 2.02: Seleno-photo-Fries

Scheme 2.03 shows another photo-Fries reaction followed by a second homolytic aromatic substitution, this time by the selenium radical. The loss of the chlorine substituent gives the seleno-xanthone shown in 19% yield.[98,103]

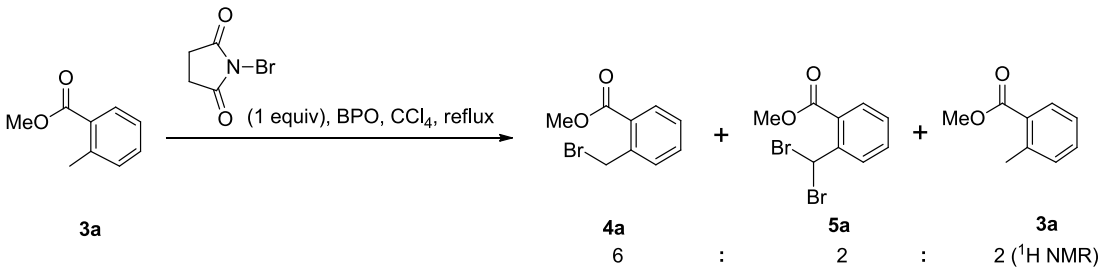


Scheme 2.03: Formation of seleno-xanthone

2.2 Synthesis of photochemical precursors

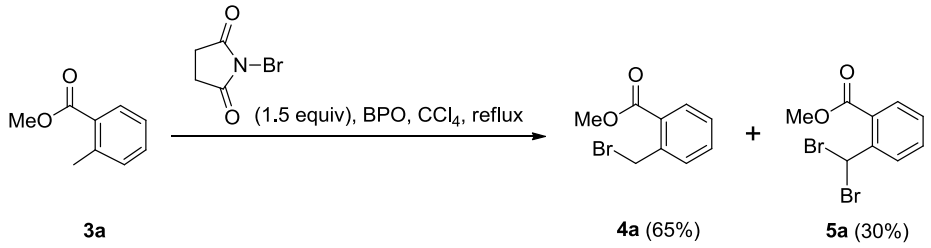
2.2.1 Synthesis of methyl 2-(halomethyl)benzoates and nicotinates

Initially the synthesis of methyl 2-(bromomethyl)benzoate (**4a**) was carried out using the literature procedure reported by Schwan,[104] involving reacting stoichiometric equivalents of methyl 2-methylbenzoate (**3a**) with *N*-bromosuccinimide (NBS) in carbon tetrachloride in the presence of benzoyl peroxide (BPO) (0.001 equiv) as the radical initiator. In our hands this gave a mixture of **4a**, methyl 2-(dibromomethyl)benzoate (**5a**) and non-reacted starting material **3a** by ^{1}H NMR (NMR ratios shown in Scheme 2.04).



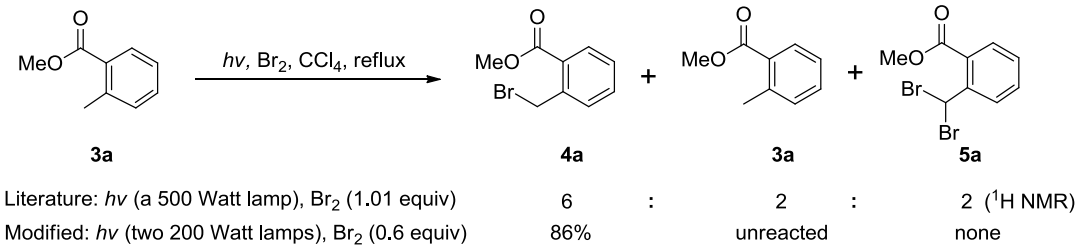
Scheme 2.04: Synthesis of 4a using conditions of Schwan[104]

We therefore increased the equivalents of NBS in order to achieve complete consumption of the starting material **3a**. This gave a mixture of the required benzyl mono-brominated adduct **4a** in 65% yield, along with benzyl di-brominated adduct **5a** in 30% yield, which were separated by vacuum distillation (Scheme 2.05).



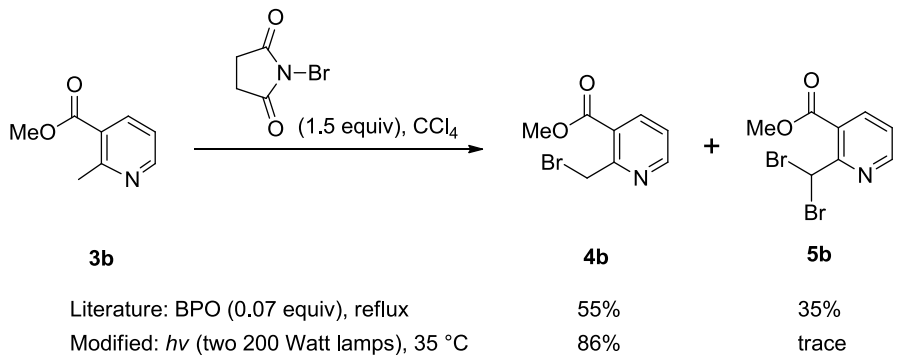
Scheme 2.05: Synthesis of 4a using excess NBS

Scrowston and Shaw claimed the quantitative conversion of **3a** into mono-brominated adduct **4a** by irradiating a solution containing bromine (1.01 equiv) in carbon tetrachloride under reflux (Scheme 2.06).[105] However, attempts to repeat this procedure produced a mixture of monobrominated **4a**, dibrominated **5a** and unreacted starting material **3a** by ^{1}H NMR. Reduction in the amount of bromine (from 1.01 equiv to 0.6 equiv) led to elimination of the dibromination, and gave **4a** in high yield, once separated from non-reacted **3a** by vacuum distillation (Scheme 2.06).



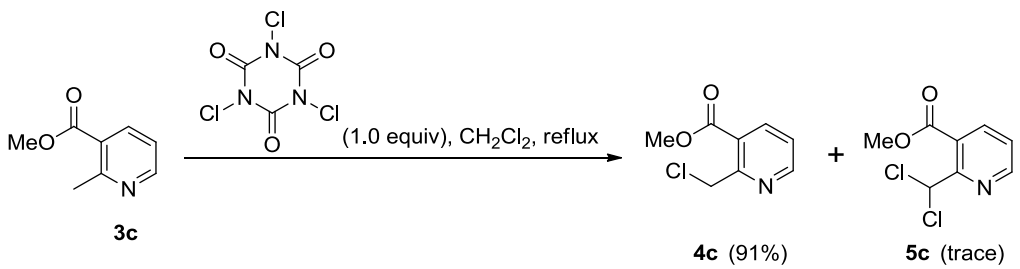
Scheme 2.06: Photochemical synthesis of 4a

Attempts to convert methyl 2-methylnicotinate (**3b**) into methyl 2-(bromomethyl)nicotinate (**4b**) with 0.6 equiv of bromine using tungsten lamps proved difficult, because the distillation to remove the excess starting material **3b** required high temperatures, which degraded **4b**. Terpstra and Van Leusen[106] reported the synthesis of **4b** following a procedure reported by Hurst and Wibberley for the bromination of ethyl 2-methylnicotinate.[107] This procedure in our hands led to the formation of mono and di-brominated products **4b** and **5b** separated by preparative TLC (Scheme 2.07). The irradiation of NBS (1.5 equiv) and **3b** in carbon tetrachloride at 35 °C gave **4b** in high yield (86%) with only trace amounts of the di-brominated product **5b** observed (Scheme 2.07).



Scheme 2.07: Synthesis of methyl 2-(bromomethyl)nicotinate (4b)

Methyl 2-(chloromethyl)nicotinate (**4c**) was synthesized using a procedure previously reported by Russell and co-workers using 0.4 equiv of trichloroisocyanuric acid and methyl 2-methylnicotinate (**3c**) in dichloromethane under reflux.[108] The use of 0.4 equiv of trichloroisocyanuric acid meant the reaction did not go to completion therefore we modified the reaction by increasing the amount of trichloroisocyanuric acid from 0.4 equiv to 1.0 equiv (Scheme 2.08).

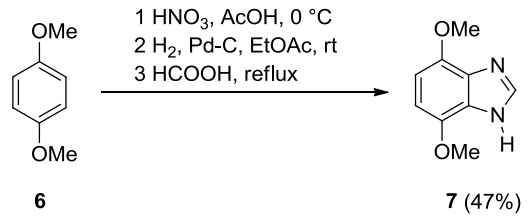


Scheme 2.08: Synthesis of methyl 2-(chloromethyl)nicotinate (4c)

Only trace amounts of dibrominated **5b** or dichlorinated **5c** products were produced using our modifications in Schemes 2.07 and 2.08. This is because NBS (at lower temperatures) and trichloroisocyanuric acid produce low concentrations of molecular bromine and chlorine as the reaction proceeds. This low concentration and milder conditions allows for the selective formation of the mono-halogenated product without the formation of the di-halogenated side-product.

2.2.2 Synthesis of phenyl selenoesters

The required 4,7-dimethoxy-1*H*-benzimidazole (**7**) was prepared by modification of previous literature and Aldabbagh group modified procedures.[9,109,110] 1,4-Dimethoxybenzene (**6**) was nitrated in the presence of concentrated acetic acid and nitric acid to give a 4:1 isomeric mixture of 1,4-dimethoxy-2,3-dinitrobenzene and 1,4-dimethoxy-2,5-dinitrobenzene determined by ^{1}H NMR. Reduction of the mixture of the dinitro-compounds was achieved using Parr hydrogenation under 5 bar hydrogen pressure in the presence of palladium catalyst and ethyl acetate to give 3,6-dimethoxy-1,2-diaminobenzene and 2,5-dimethoxy-1,4-diaminobenzene. The resultant diamine mixture was stirred at reflux in formic acid followed by neutralization using sodium carbonate. 4,7-Dimethoxy-1*H*-benzimidazole (**7**) was isolated upon precipitation in an overall yield of 47% over the three steps (Scheme 2.09).

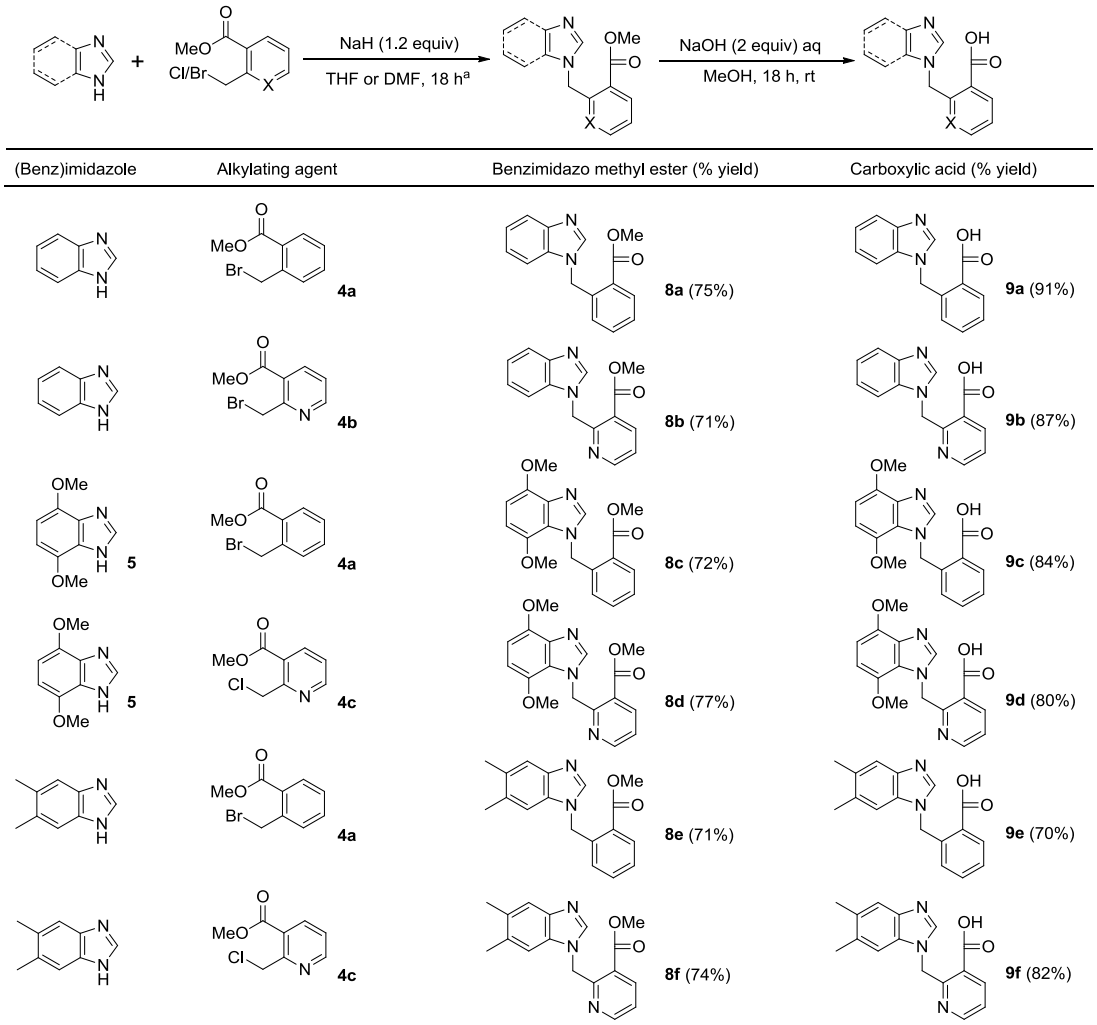


Scheme 2.09: Preparation of 4,7-dimethoxy-1*H*-benzimidazole (7)

The benzimidazoles in Table 2.01 were reacted with sodium hydride in DMF at 80 °C or THF under reflux prior to addition of the methyl 2-(halomethyl)benzoates and nicotinates **4a**-**4c** yielding the benzimidazol-1-ylmethyl benzoates and nicotinates **8a**-**8f** shown. 4,7-Dimethoxy-1*H*-benzimidazole (**7**) was not sufficiently soluble in THF and thus DMF was used as the reaction solvent, all other alkylation reactions were in THF. For the synthesis of **8b** the nicotinate **4b** had to be added at 5 °C to benzimidazole and sodium hydride in THF, so as not to decompose **4b**. Methyl 2-[(4,7-dimethoxy-1*H*-benzimidazol-1-yl)methyl]nicotinate (**8d**) was prepared using methyl 2-(chloromethyl)nicotinate (**4c**) in DMF at 80 °C, since the bromo analogue **4b** decomposed at this reaction temperatrure.

The methyl esters **8a-8f** were hydrolyzed using aqueous sodium hydroxide (2 equiv) in methanol to give the corresponding carboxylic acids **9a-9f** (Table 2.01). On reaction completion the methanol was evaporated under reduced pressure and the

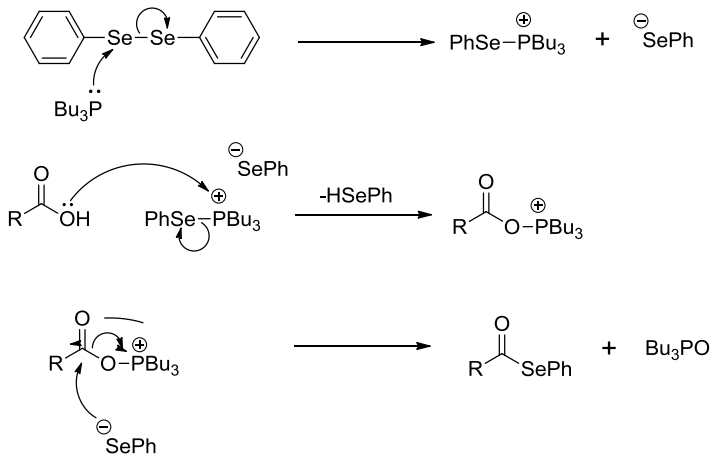
remaining aqueous solution was neutralized using dilute hydrochloric acid. The carboxylic acids were obtained by precipitation, and required no further purification.



[a] See experimental chapter for exact experimental conditions

Table 2.01: Preparation of benzoic and nicotinic acids 9a-9f

Conversion of carboxylic acids to phenyl selenoesters can be carried out reacting tributyl phosphine with phenyl selenenyl halides (PhSeX),[91] or with N-phenylselenophthalimide (NPSP)[92] or with diphenyl diselenide.[93] We synthesized the phenyl selenoesters in 68-78% yield (Table 2.02) using diphenyl diselenide and tributyl phosphine following a procedure reported by Bowman and co-workers.[18] The reaction mechanism (Scheme 2.10) is presumed to occur in a similar manner to that of the mechanism proposed by Nicolaou and co-workers for the conversion of alcohols into selenides.[92,93]



Scheme 2.10: Proposed mechanism for phenyl selenoester formation

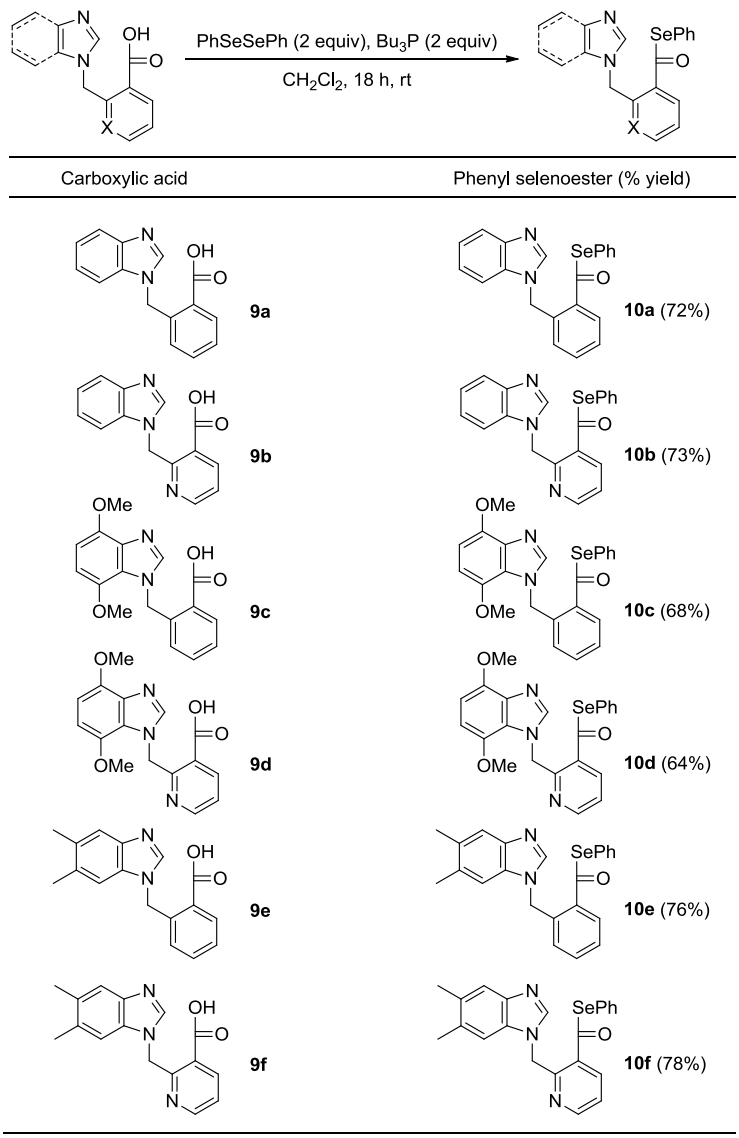
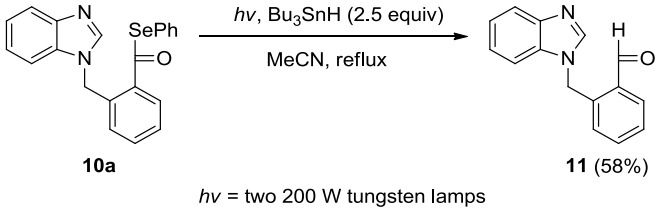


Table 2.02: Synthesis of benzimidazol-1-ylmethyl benzene and pyridine phenyl selenoesters 10a-10h

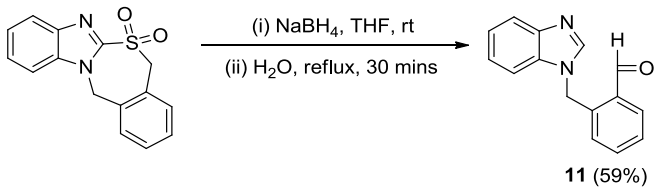
2.3 Synthesis of 2-(1*H*-benzimidazol-1-ylmethyl)benzaldehyde and its photochemical cyclizations

The reduction of the phenyl selenoester **10a** to the corresponding aldehyde **11** was possible using excess Bu_3SnH in acetonitrile under reflux, and in the presence of two 200 watt tungsten lamps (Scheme 2.11). It was noted that no reaction was observed in the absence of the light source.



Scheme 2.11: Synthesis of aldehyde 11

Aldehyde **11** was previously synthesized by Yoon and Kim via reaction of the sulfinate shown in Scheme 2.12 with sodium borohydride and water.[111]

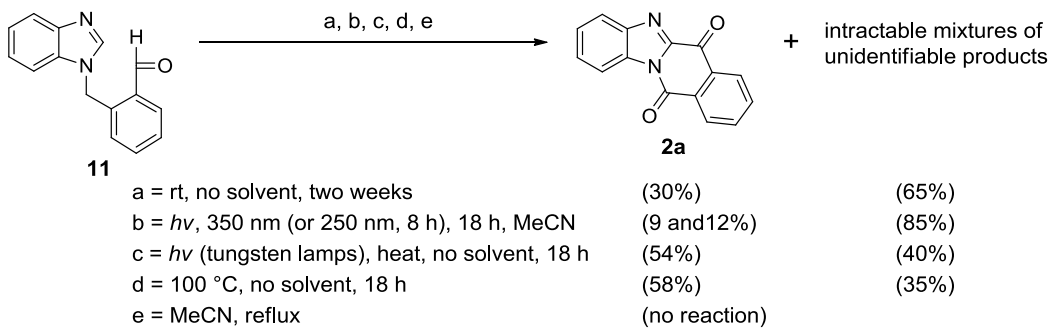


Scheme 2.12: Synthesis of aldehyde 11 reported by Yoon and co-workers[111]

Previous reported conversions of phenyl selenoesters into aldehydes by radical pathways involve the use of an azo-initiator and organotin or organosilicon hydrides.[5,15,112] Attempts to convert phenyl selenoester **10b** into the corresponding aldehyde under the same conditions led to formation of an intractable mixture of unidentifiable products.

Unexpectedly aldehyde **11** was converted at room temperature on standing for two weeks to the *p*-dione **2a** in air in 30% yield (Scheme 2.13). The aldehyde **11** was subsequently subjected to several different reaction conditions in order to improve yields of the required *p*-dione **2a**. Disappointingly irradiation of aldehyde **11** using Rayonet reactor conditions of 350 nm (18 h) and 250 nm (8 h) in acetonitrile (17 mmol) produced the *p*-dione **2a** in yields of only 9 and 12% along with a mixture of unidentifiable products. Irradiation of aldehyde **11** without any solvent using two 200 W tungsten lamps (also generating heat) for 18 hours led to isolation of the desired *p*-dione **2a** in 54% yield. In order to investigate if the reaction could be initiated by thermolysis, aldehyde **11** was heated at 100 °C in air without a solvent or light source giving the *p*-dione in 58% yield. Heating aldehyde **11** in acetonitrile (17 mmol) under reflux for prolonged periods gave unreacted starting material. Thus the

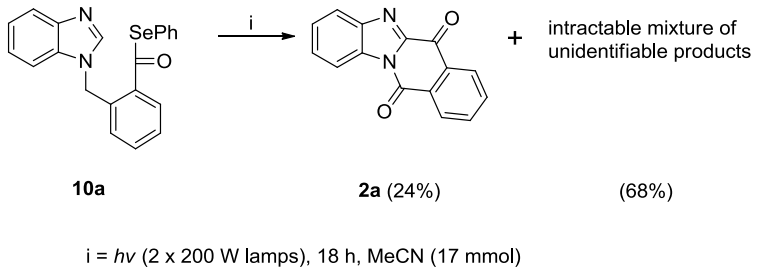
reaction is most likely proceeding by an aerial oxidation initiated more strongly by heat rather than light.



Scheme 2.13: Aldehyde cyclization reactions

2.4 Photochemical mediated acyl radical cyclizations

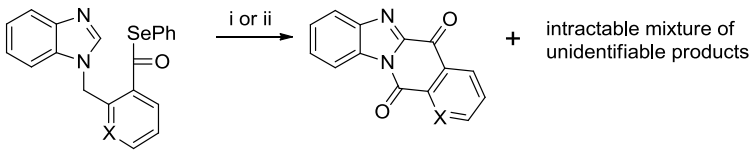
Irradiating phenyl selenoester **10a** in acetonitrile with light from two 200 W tungsten lamps produced the *p*-dione **2a** in 24% yield (Scheme 2.14). Reaction time was 18 hours and it was postulated that light of a shorter wavelength would increase the efficiency and decrease the reaction time required.



Scheme 2.14: Photochemical acyl radical cyclizations of 10a

Phenyl selenoesters **10a** and **10b**, in low concentrations of 17 mmol, were irradiated in two separate experiments using a Rayonet photochemical reactor with light of 350 nm and 250 nm. All experiments were carried out in acetonitrile at estimated temperatures for the Rayonet reactor of 30-40°C. Reactions of wavelength 250 nm and 350 nm proceeded in an identical manner apart from the length of reaction time required (8 hours and 18 hours, respectively). Phenyl selenoester **10a** was irradiated in acetonitrile giving 35% yield of the desired *p*-dione **2a** for both wavelengths. Phenyl selenoester **10b** under the same conditions gave 50% of the *p*-dione **2b** for

both wavelengths (Scheme 2.15). Trace amounts of carboxylic acids **9a** and **9b** were also detected by TLC, but for both compounds significant amounts of unidentifiable products were also isolated.

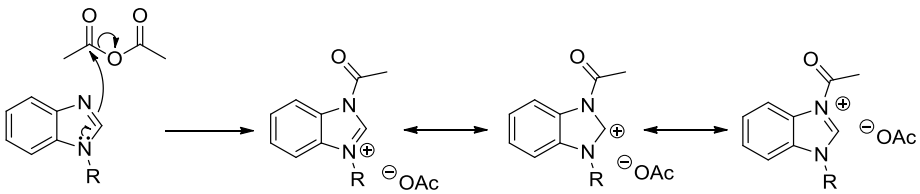


i	X = CH, **10a**	**2a** (35%)	(42%)
i	X = N, **10b**	**2b** (50%)	(31%)
ii	X = CH, **10a**	**2a** (68%)	(12%)
ii	X = N, **10b**	**2b** (63%)	(15%)

i = *hv* [250 nm (8 h) or 350nm (18 h)], MeCN (17 mmol)
ii = *hv* [250 nm (8 h) or 350nm (18 h)], MeCN (17 mmol), Ac_2O (2.5 equiv)

Scheme 2.15: Photochemical acyl radical cyclizations of 10a and 10b

Quaternization of the N-3 of imidazole has previously been shown to increase efficiency of alkyl radical cyclizations onto the 2-position of imidazole.[9,20] The quaternization of the 3-*N* lone pair makes the 2-position of imidazole more electrophilic, as indicated using resonance structures (Scheme 2.16). Several different quaternizing agents were evaluated in our photochemical reactions including acetic acid, camphorsulfonic acid and acetic anhydride. The use of acetic anhydride (Ac_2O) gave cleaner and higher yielding reactions.



Scheme 2.16: Quaternization of the 3-*N* of imidazole

The addition of 2.5 equivalents of Ac_2O in the photochemical reactions of phenyl selenoesters **10a** and **10b** boosted the yields of *p*-dione **2a** and **2b** from 35% to 68% and 50% to 63%, respectively (Scheme 2.15).

There are two reasons for the addition of Ac_2O increasing yields, firstly it makes the bezimidazole more electrophilic and secondly eliminates potential competing side reactions involving the 3-*N* lone pair. Acyl radicals have been

recognized as nucleophilic in their reactions with electron-poor alkenes[1,5,7] however it has been shown that acyl radicals exhibit an ambiphilic nature and can also act as electrophilic radicals in their reactions with electron rich alkenes. Reaction of acyl radicals with electron poor alkenes have a SOMO to π^*_{alkene} interaction that is greater than the π_{alkene} to SOMO interaction meaning the acyl radical is nucleophilic in nature (strong SOMO-LUMO interaction).[113] The ambiphilic nature is similar to aromatic σ-radicals, which react according to substrate substituent effects, but can have dual philicity.[8] It has also been suggested that the quaternization of the 3-*N* lone pair of benzimidazole also eliminates the possibility of the 3-*N* lone pair reacting with the acyl radical as shown in the literature, and given in Figure 2.02.

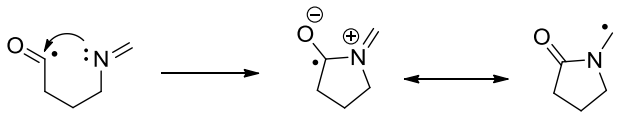
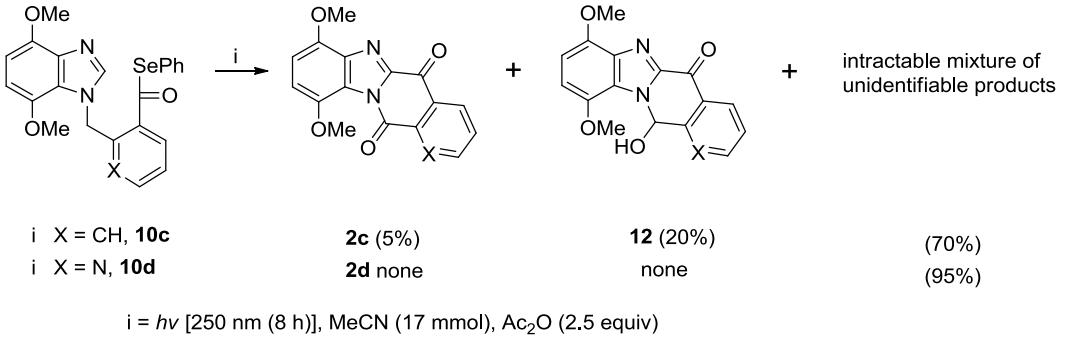


Figure 2.02: Nitrogen-philic nature of acyl radicals[114]

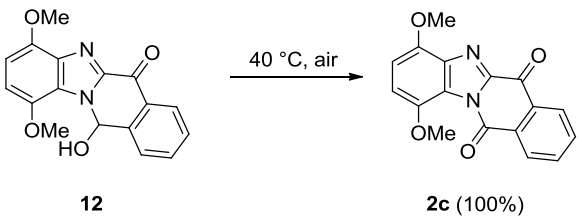
It is proposed that the expelled phenylselenyl radical ($PhSe^{\bullet}$) abstracts the hydrogen atom at the imidazole-2-position, thus regenerating aromaticity (see Scheme 2.01). Formation of diphenyl diselenide was observed in each reaction by TLC, as expected based on literature oxidation of PhSeH. [13,14,98,99] The methylene CH_2 was never observed in any cyclization product, since it is believed to be easily oxidized to give the *p*-dione moiety via autoxidation (as air was not rigorously excluded). Nevertheless for all *hv*-mediated cyclizations, a considerable amount of intractable material was isolated.

Irradiating dimethoxy substituted benzimidazole phenyl selenoester **10c** in acetonitrile (17 mmol) with Ac_2O (2.5 equiv) in a Rayonnet photochemical reactor at 250 nm (8 h) and 350 nm (18 h) produced the *p*-dione **2c** in only 5% yield, the autoxidation intermediate alcohol **12** was also found in 20% yield, along with trace amounts of carboxylic acid **9c**. Irradiating pyridine analogue **10d** under the same conditions produced no isolable *p*-dione yielding instead an intractable mixture of unidentifiable products (95%) and trace amounts of carboxylic acid **9d** (Scheme 2.17).



Scheme 2.17: Acyl radical cyclizations of dimethoxy derivatives

The autoxidation intermediate 11-hydroxy-1,4-dimethoxybenzimidazo[1,2-*b*]isoquinolin-6(11*H*)-one (**12**) was quantitatively converted to the desired *p*-dione **2c** on heating in air at 40 °C (Scheme 2.18).



Scheme 2.18: Oxidation of alcohol intermediate

The poor yields of *p*-diones **2c** and **2d** as well as the significant quantities of intractable mixtures produced for all the photochemical reactions can be tentatively rationalized by analysis of the UV-absorption spectrum of the *p*-diones (Figures 2.03-2.08) (a sample of **2d** was obtained from an alternative procedure discussed later in Chapter 3).[115] It was found that all the target *p*-dione products absorbed UV-light, some very efficiently and were therefore suspected to have undergone decomposition under the reaction conditions. For example, the UV spectra of dimethoxy *p*-diones **2c** and **2d** (Figures 2.05, 2.06) clearly show greater light absorption by the *p*-dione adduct compared to the starting materials **10c** and **10d**, moreover phenyl selenoester **10d** hardly absorbs in comparison to **2d** at the wavelengths used. Therefore, it is not surprising that no *p*-dione **2d** was isolated by irradiating phenyl selenoester **10d** with UV-light.

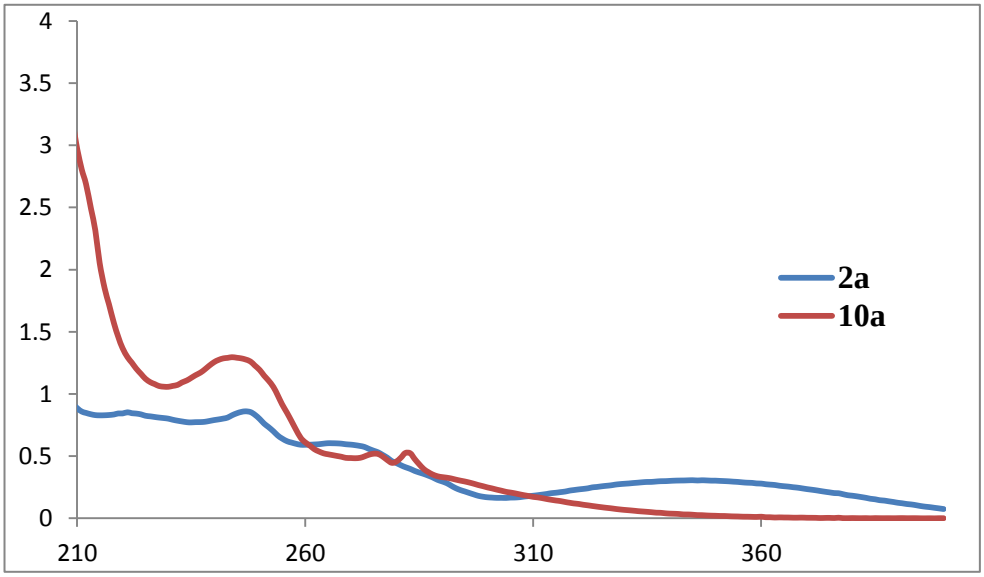


Figure 2.03: UV-spectrum of benzimidazo[1,2-*b*]isoquinoline-6,11-dione (2a) and 2-(1*H*-benzimidazol-1-ylmethyl)benzenecarbophenylselenoate (10a) (6.25 x 10^{-5} M in MeCN)

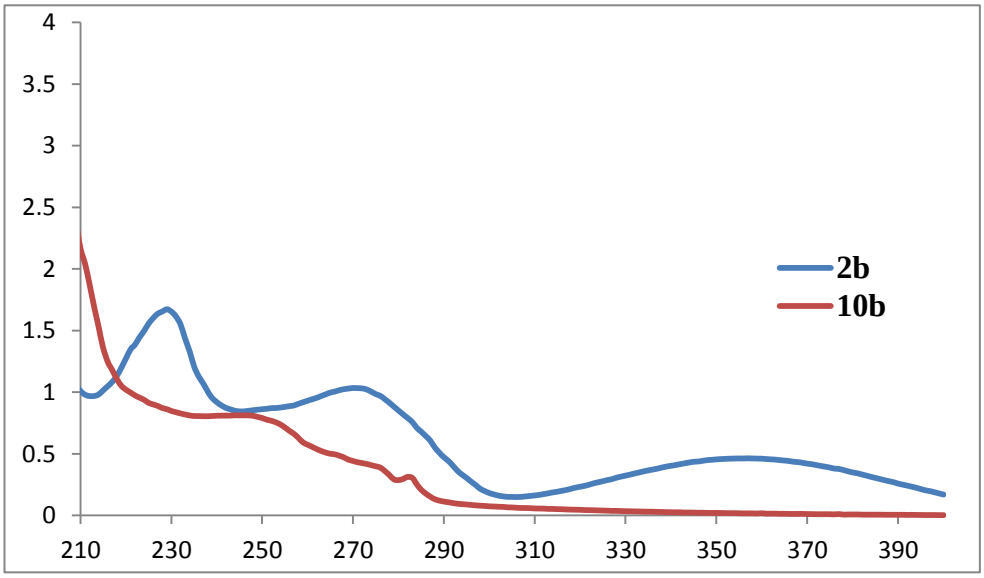


Figure 2.04: UV-spectrum of benzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-dione (2b) and 2-(1*H*-benzimidazol-1-ylmethyl)pyridine-3-carbophenylselenoate (10b) (6.25 x 10^{-5} M in MeCN)

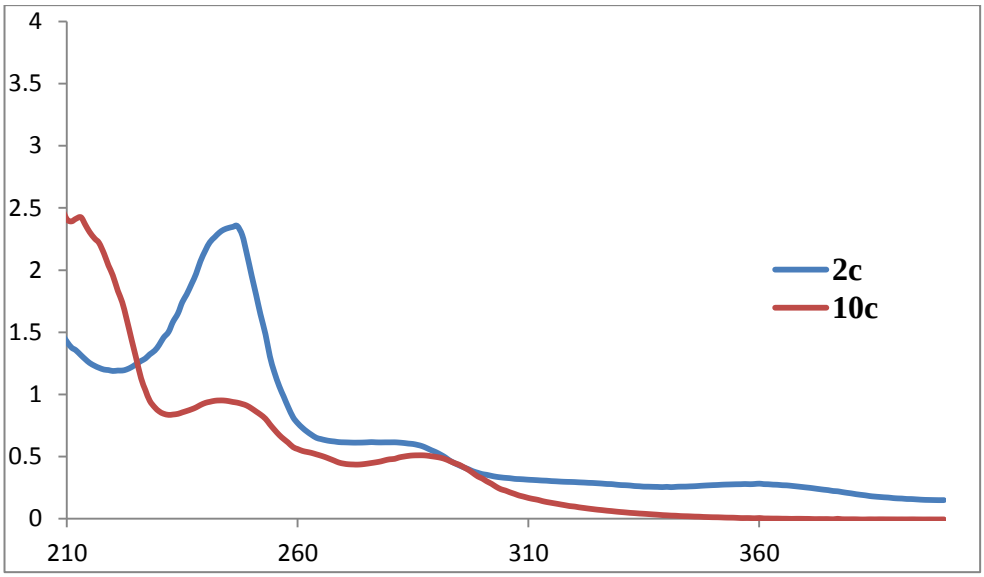


Figure 2.05: UV-spectrum of 1,4-dimethoxybenzimidazo[1,2-*b*]isoquinoline-6,11-dione (2c) and 2-[(4,7-dimethoxy-1*H*-benzimidazol-1-yl)methyl]benzenecarbophenylselenoate (10c) (6.25 x 10^{-5} M in MeCN)

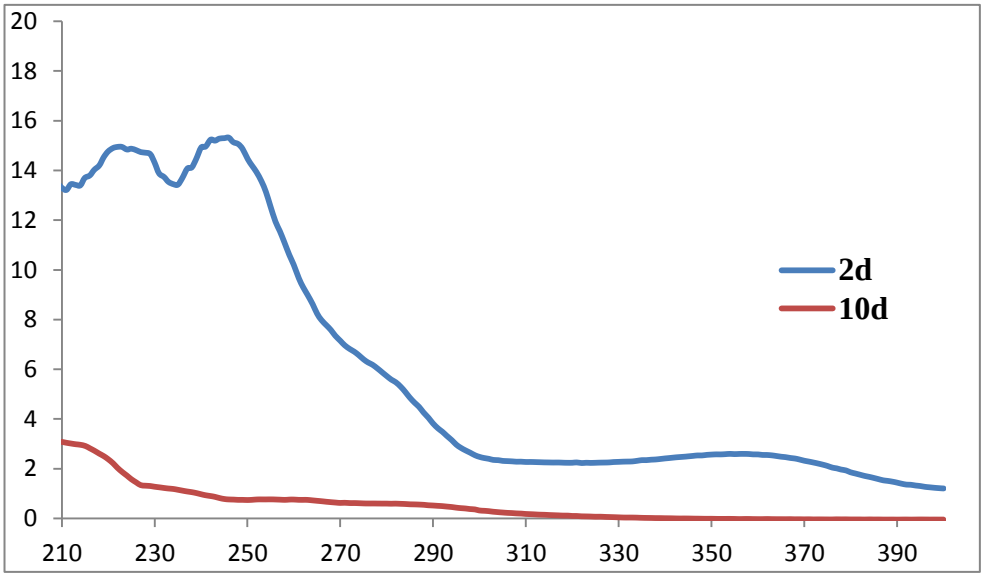
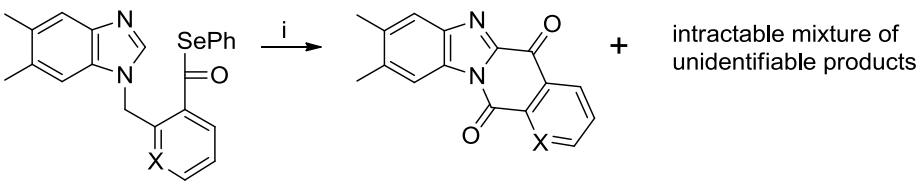


Figure 2.06: UV-spectrum of 7,10-dimethoxybenzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-dione (2d) and 2-[(4,7-dimethoxy-1*H*-benzimidazol-1-yl)methyl]pyridine-3-carbophenylselenoate (10d) (6.25 x 10^{-5} M in MeCN)

Irradiation of 5,6-dimethyl benzimidazole derivative phenyl selenoesters **10e** and **10f** in acetonitrile (17 mmol) in a Rayonet photochemical reactor at 250 nm (8 h) and 350 nm (18 h) with Ac_2O (2.5 equiv) gave *p*-diones **2e** and **2f** in 50% and 54% yield, respectively with trace amounts of carboxylic acids **9e** and **9f** also observed (Scheme 2.19). For dimethyl phenyl selenoesters **10e** and **10f**, the UV spectra (Figures 2.07, 2.08) show comparable absorption to the *p*-dione adducts **2e** and **2f**, thus rationalizing the moderate product yields obtained. The trace amounts of acid formed in all photochemical reactions is probably due to hydrolysis of phenyl selenoesters or intermediates.



i X = CH, **10e**	**2e** (50%)	(45%)
i X = N, **10f**	**2f** (54%)	(41%)

i = *hv* [250 nm (8 h)], MeCN (17 mmol), Ac_2O (2.5 equiv)

Scheme 2.19: Acyl radical cyclizations of dimethyl derivatives 10e and 10f

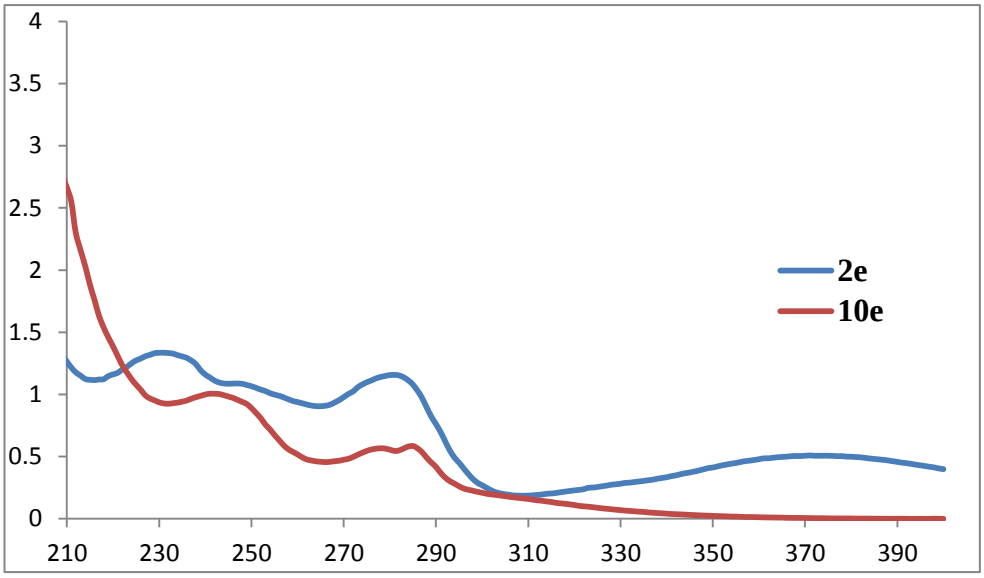


Figure 2.07: UV-spectrum of 2,3-dimethylbenzimidazo[1,2-*b*]isoquinoline-6,11-dione (2e) and 2-[(5,6-dimethyl-1*H*-benzimidazol-1-yl)methyl]benzenecarbophenylselenoate (10e) (6.25 x 10^{-5} M in MeCN)

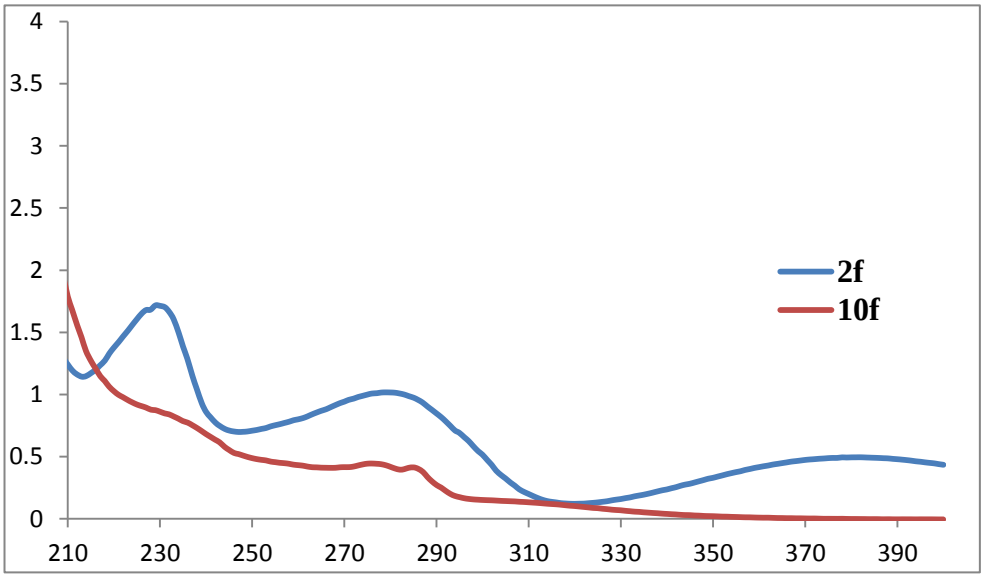


Figure 2.08: UV-spectrum of 8,9-dimethylbenzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-dione (2f) and 2-[(5,6-dimethyl-1*H*-benzimidazol-1-yl)methyl]pyridine-3-carbophenylselenoate (10f) (6.25 x 10^{-5} M in MeCN)

2.5 Nomenclature of *p*-dione adducts

All compounds were named according to International Union of Pure and Applied Chemistry (IUPAC) rules.[116] The nomenclature of benzimidazo[1,2-*b*]isoquinoline-6,11-dione (**2a**) is explained in detail to illustrate the procedure for naming such fused ring systems. The parent component (red) was identified as isoquinoline (Figure 2.09) and the benzimidazole ring was identified as the first order component. Benzimidazole is of lesser priority as it contains a smaller ring than isoquinoline as the preferred component contains the larger ring at the first point of difference.[116]

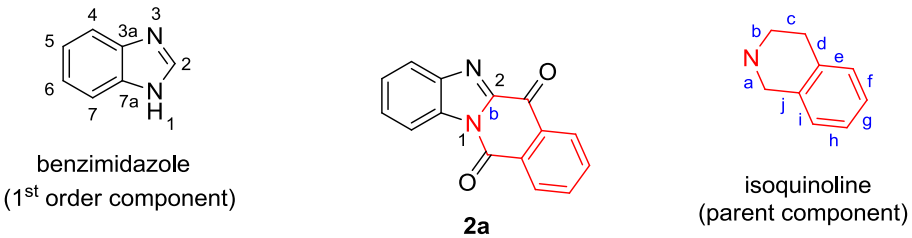


Figure 2.09: Parent and first order component assignments

The outer bonds of the parent component are labeled with letter locants (a-j) and the atoms of the first order component are labeled with numerical locants (1-7a). Incorporating the shown numbering, we can assign the fusion name as benzimidazo[1,2-*b*]isoquinoline. This is derived using the fusion face of isoquinoline (a) and fusion face -1,2- of benzimidazole. The two faces are separated by a hyphen and cited within square brackets [1,2-*b*].

The molecule is drawn with the maximum number of rings in a horizontal line using the available shapes allowed in order to assign peripheral numbers (Figure 2.10). Numbering begins with the most counter-clockwise non-fusion atom of the ring furthest to the right in the upper right hand quadrant and proceeds clockwise. If more than one orientation is equally allowed then the following rules are applied, in order, until one orientation is preferred;

(1) Give low numbers to heteroatoms as a set.

(2) Give low numbers to heteroatoms when considered in the order: 0, S, Se, Te, N, P, As, Sb, Bi, Si, Ge, Sn, Pb, B, Hg

(3) Give low numbers to fusion carbons as a set.

(4) Give low numbers to fusion rather than non-fusion atoms of the same heteroelement.

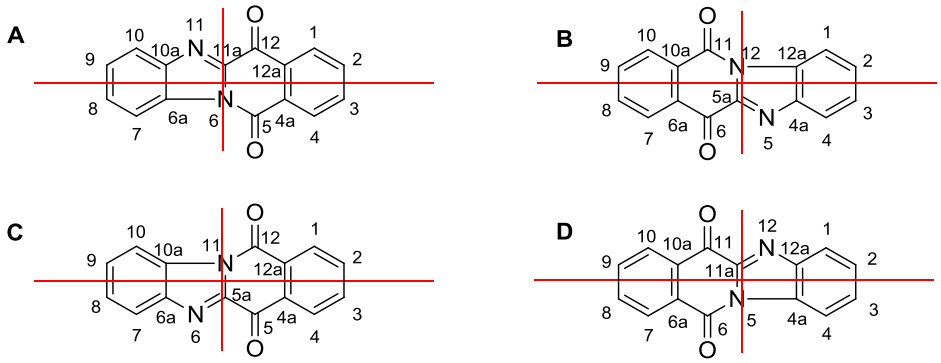


Figure 2.10: Peripheral numbering

Application of rule (1) still leaves four possible orientations (all heteroatom numbers add to 17) (Figure 2.10).

Application of rule (2) eliminates **A** and **C** (Figure 2.10) which both have the first nitrogen numbered as 6 compared to 5 for **B** and **D**.

Considering therefore only **B** and **D** and applying rule (3) we can eliminate **D** which has a sum of 43a for fusion carbons as opposed to 37a for **B**).

Rule (4) is not required.

Finally the peripheral numbering of **B** identifies the location of the two ketone functional groups (numbered 6 and 11 in Figure 2.10) (principle groups) thus completing the name; benzimidzo[1,2-*b*]isoquinoline-6,11-dione.

2.6 Conclusions

Improvements on literature reactions have resulted in high yielding procedures for the synthesis of methyl 2-(halomethyl)benzoates and nicotinates used to react with various benzimidazoles generating benzimidazol-1-ylmethyl benzoates and nicotinates in 71-77% yields. The hydrolysis of the methyl esters to the corresponding carboxylic acids occurred in 70-91% yields. Reaction of these benzoic and nicotinic acids with tributyl phosphine and diphenyl diselenide produced the phenyl selenoester radical precursors in 64-78% yields.

The formation of 2-(1*H*-benzimidazol-1-ylmethyl)benzaldehyde on irradiation of 2-(1*H*-benzimidazol-1-ylmethyl)benzenecarbophenylselenoate in the presence of excess tributyltin hydride showed the acyl radical could be generated using UV-light by homolysis of the carbonyl selenium bond. The first photochemical mediated acyl radical substitutions onto benzimidazoles were then performed. Unexpectedly 2-(1*H*-benzimidazol-1-ylmethyl)benzaldehyde was found to convert to benzimidazo[1,2-*b*]isoquinoline-6,11-dione on standing for two weeks in air in 30% yield. In attempts to investigate the mechanism 2-(1*H*-benzimidazol-1-ylmethyl)benzaldehyde was irradiated or heated with and without solvent and results showed the reaction was most likely proceeding by an aerial oxidation initiated more strongly by heat (54-58%) rather than light (9-12%).

Irradiation of 2-(1*H*-benzimidazol-1-ylmethyl)benzenecarbophenylselenoate and 2-(1*H*-benzimidazol-1-ylmethyl)pyridine-3-carbophenylselenoate in a Rayonet photochemical reactor produced the corresponding *p*-diones in 35 and 50% yields respectively. Quaternization of the 3-*N* of benzimidazole with Ac_2O was shown to increase yileds of these *p*-dione from 35 to 68% and 50 to 63% respectively. Quaternization makes the benzimidazole more electrophilic and more susceptible to substitution by the nucleophilic acyl radical. The irradiation of the 4,7-dimethoxy-phenylselenoate analogues produced little isolable *p*-dione due to UV-mediated decomposition, as indicated from analysis of UV-spectra. An autoxidation intermediate, 11-hydroxy-1,4-dimethoxybenzimidazo[1,2-*b*]isoquinolin-6(11*H*)-one was isolated, which was quantitatively converted to the corresponding *p*-dione on heating in air. Irradiation of 2-[(5,6-dimethyl-1*H*-benzimidazol-1-yl)methyl]benzenecarbophenylselenoate and its pyridine derivative produced the *p*-

diones in 50 and 54% yields respectively. Yields were rationalized by phenylselenoesters and *p*-dione adducts giving similar UV-absorption spectra.

Chapter 3

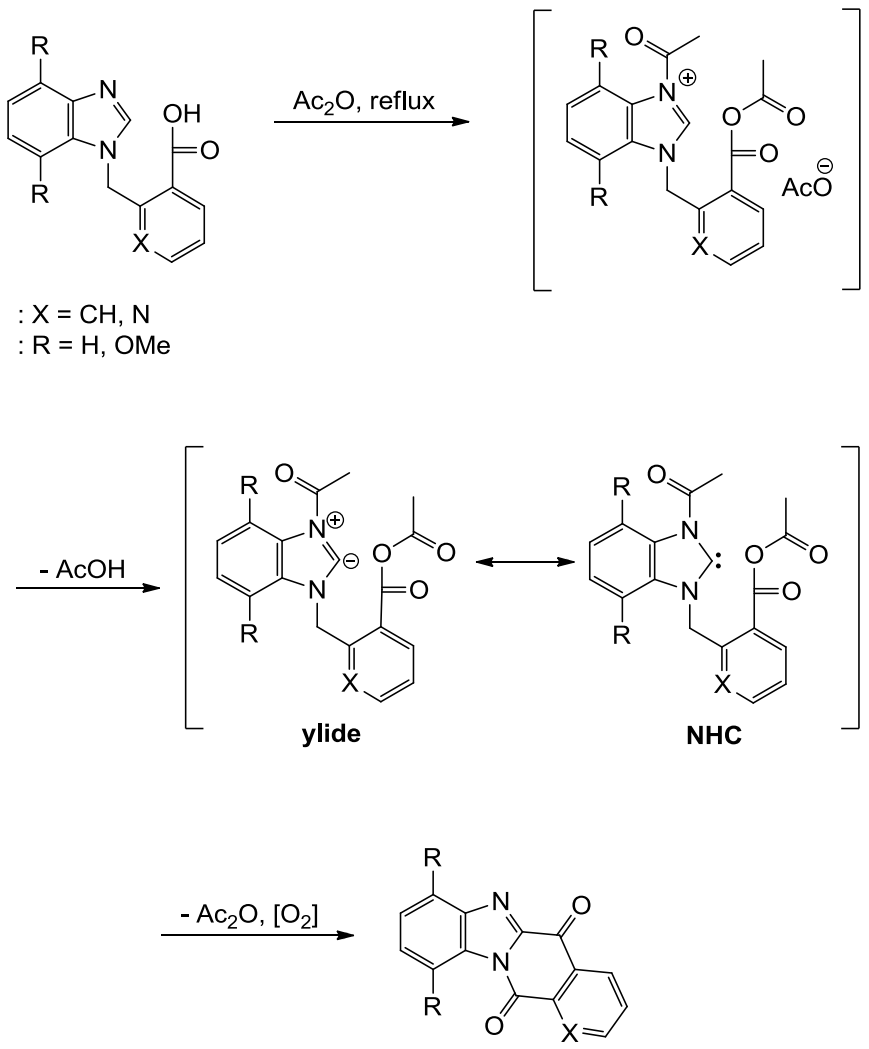
Acetic Anhydride Generated Imidazolium Ylide in Ring Closures onto Carboxylic Acids

3.1 Introduction

1,3-Dialkylated imidazolium salts are weakly acidic, and will readily form an imidazolium ylide species, which is isoelectronic with the imidazolin-2-ylidene (N-heterocyclic carbene, NHC).[22,39,40] The electron-rich (nucleophilic) nature of the singlet NHC has led to a wide-range of applications in transition metal catalyzed, and organocatalyzed reactions (incl. benzoin condensation and acyl transfer).[49] Moreover, the reactive intermediates have been used to trap electrophiles, and functionalize imidazoles at the 2-position.[54-56,117-119] In 1977, seminal work by Regel and Büchel established substitution of ketone and ester functionality onto the imidazole (and benzimidazole) 2-position using imidazolium ylide species.[57,58] These reactions used various acid chlorides or chloroformic esters in the presence of triethylamine in polar solvents. Some years later, the protocol gave regioselective acylation of the electron-deficient position of imidazopyridines using benzoyl chloride under thermal or triethylamine-mediated conditions.[59,60] Imidazole (and benzimidazole) reacted with phthaloyl dichlorides in the presence of triethylamine giving imidazo[1,2-*b*]isoquinolinediones[57,61] and an ylide intermediate was proposed.[57]

3.1.1 Mechanism of reaction

Considering the above literature reactions and the limitations of the acyl radical cyclizations described in Chapter 2, we attempted the annulation of benzimidazoles directly onto carboxylic acids using acetic anhydride (Ac_2O) under reflux. Ac_2O is the solvent with a dual role of mediating *in situ* the formation of the reactive intermediates and the derived leaving group from carboxylic acids (Scheme 3.01). Deprotonation at the imidazole-2-position of the salt occurs thermally possibly via the acetate counter ion (releasing AcOH). The ylide and NHC are now primed for six-membered annulation, and the required aromatic *p*-diones form upon air oxidation of the *N*-benzyl methylene of intermediates.



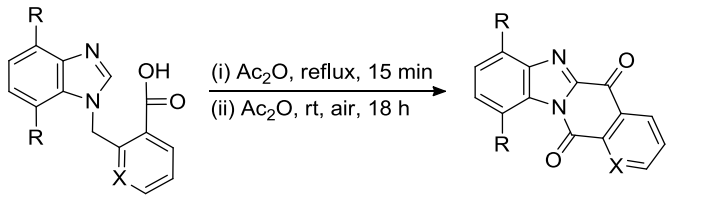
Scheme 3.01: Proposed mechanism for intramolecular condensation of (benzimidazol-1-ylmethyl) benzoic and nicotinic acids

3.2 Preparation of precursors

The carboxylic acid precursors **9a-9d** were prepared in two synthetic steps as outlined in Chapter 2.

3.3 NHC annulations onto carboxylic acids

Annulations via the proposed reactive intermediates required heating carboxylic acids **9a-9d** in Ac_2O under reflux for 15 minutes. TLC (except for **9c**) indicated the complete consumption of acids, and the generation of a complex mixture of products. After overnight stirring in Ac_2O at room temperature, benzimidazo[1,2-*b*]isoquinoline-6,11-dione (**2a**) was isolated in 80% yield, and benzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-diones **2b** and **2d** were isolated in 91 and 71% yield respectively (Scheme 3.02).

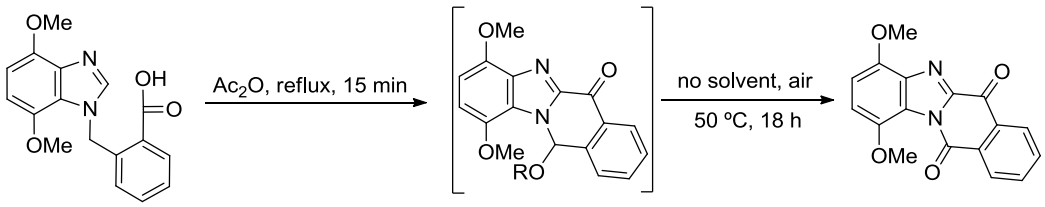


9a: X = CH, R = H
9b: X = N, R = H
9d: X = N, R = OMe

2a: X = CH, R = H (80%)
2b: X = N, R = H (91%)
2d: X = N, R = OMe (71%)

Scheme 3.02: Ac_2O mediated intramolecular annulations

The reaction of **9c** was evaporated after the initial reflux, and part of the residue purified by chromatography to yield unstable alcohol **12** (slowly changing to **2c**) and acetate derivative **13** (Scheme 3.03). Intermediates **12** and **13** were combined with the derived residue, and converted to the required *p*-dione **2c** in 78% yield (from **9c**) upon further heating in air at 50 ºC for 18 hours.



9c

12: R = H **13**: R = Ac

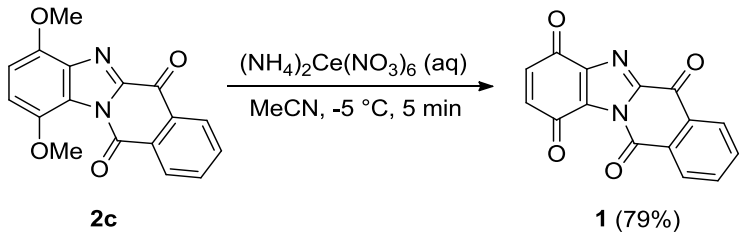
2c (78%)

Scheme 3.03: Ac_2O mediated annulation allowing detection of intermediates

It should be noted that methyl esters **8a-8d** remained unchanged when heated in Ac_2O under reflux for prolonged times, and no annulations were observed when replacing Ac_2O by AcOH under reflux for acids **9a-9d**.

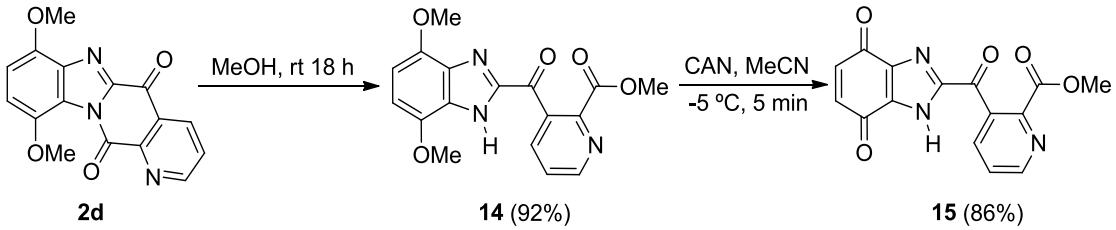
3.4 Tetrone synthesis

The dimethoxy groups provide a route to the synthesis of a tetrone incorporating reductive *p*-dione and quinone moieties in a single molecule. Cerium(iv) ammonium nitrate (CAN) readily converted **2c** into the target tetrone **1** in 79% yield (Scheme 3.04). CAN in aqueous solution was added drop-wise to a solution of **2c** dissolved in acetonitrile at -5 °C. The solution was stirred vigorously in air for 5 minutes followed by extraction into DCM.



Scheme 3.04: Synthesis of tetrone 1

The reaction of CAN with the dimethoxy-naphthyridine-5,12-dione analogue **2d** under the same conditions as Scheme 3.04 gave no isolable product. We presume that the more strained benzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-dione system was being hydrolytically ring-opened in attempted oxidations. This was supported by isolation of ring-opened adduct **14** in 92% yield, when **2d** was stirred in methanol (Scheme 3.05). X-ray crystallography confirmed the structure of **14** (Figure 3.01), with the site of opening analogous to that previously reported on **2a**.[61] The dimethoxy-substituted compound **14** was readily converted to the corresponding benzimidazolequinone **15** in 86% yield using CAN under the same conditions as **2c** (Scheme 3.04).



Scheme 3.05: Ring-opening of 7,10-dimethoxybenzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-dione and oxidation to the quinone

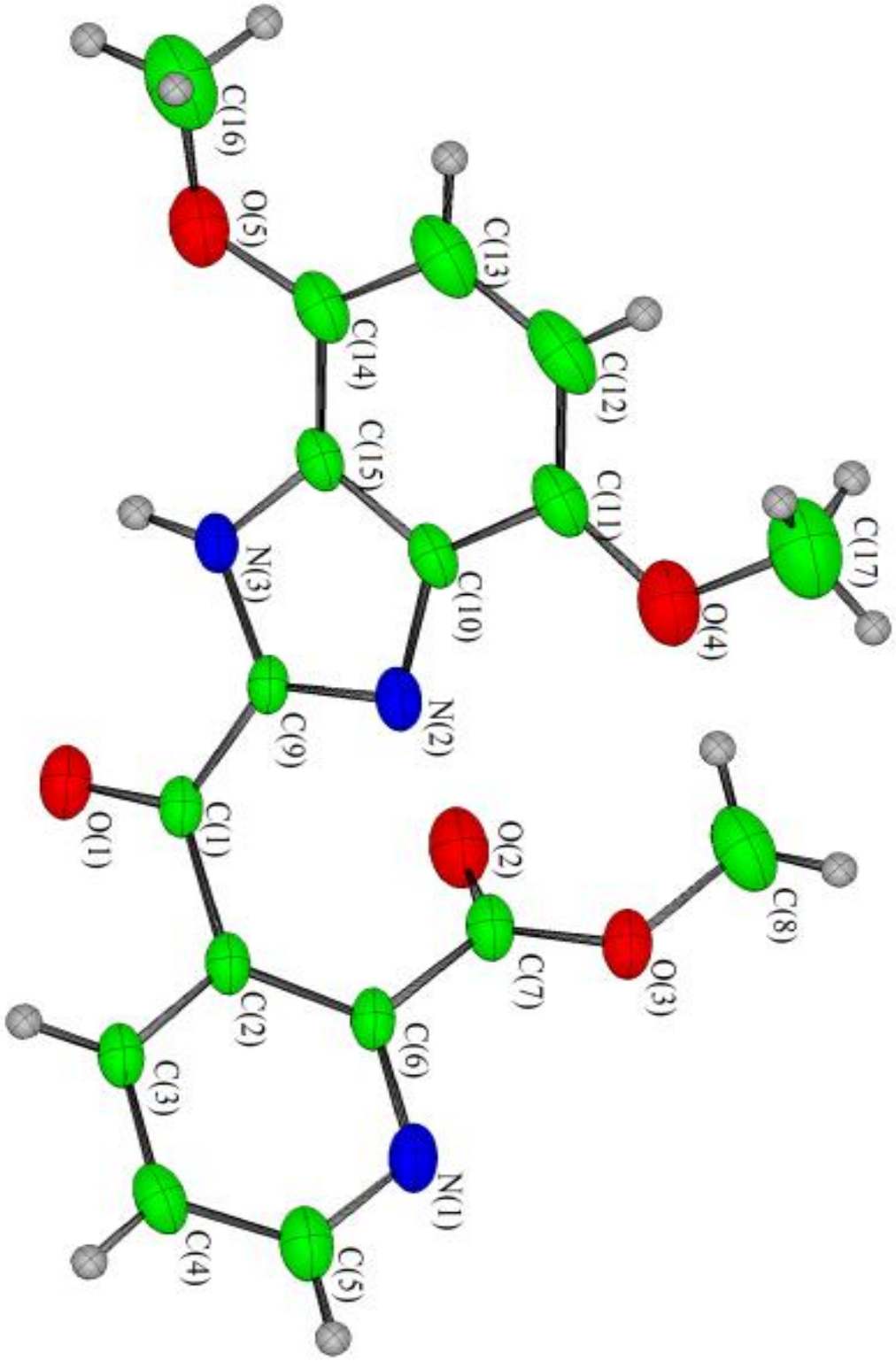
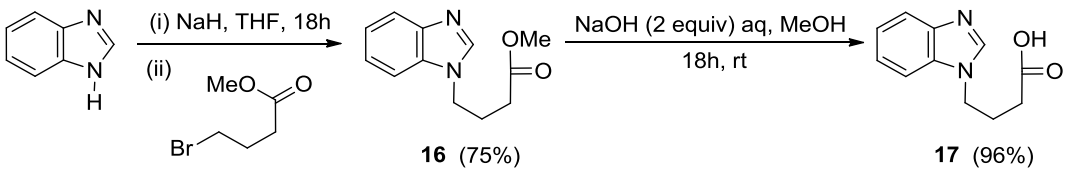


Figure 3.01: X-ray crystal structure of methyl 3-[(4,7-dimethoxy-1*H*-benzimidazol-2-yl)carbonyl]pyridine-2-carboxylate (14)

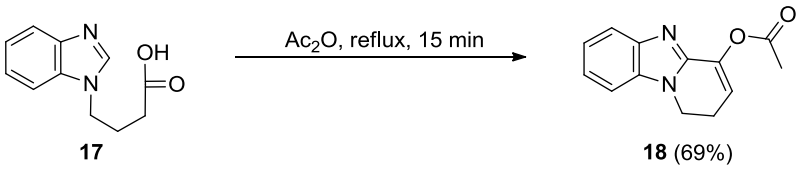
3.5 NHC annulations onto aliphatic carboxylic acids

The imidazolium ylide annulation onto aliphatic carboxylic acids was subsequently investigated. Methyl 4-bromobutyrate was alkylated onto benzimidazole using NaH as base in THF under reflux to give the aliphatic ester **16**. Methyl 4-(1*H*-benzimidazol-1-yl)butanoate (**16**) was hydrolyzed as per the previously described procedure using sodium hydroxide to give the corresponding carboxylic acid **17** (Scheme 3.06).

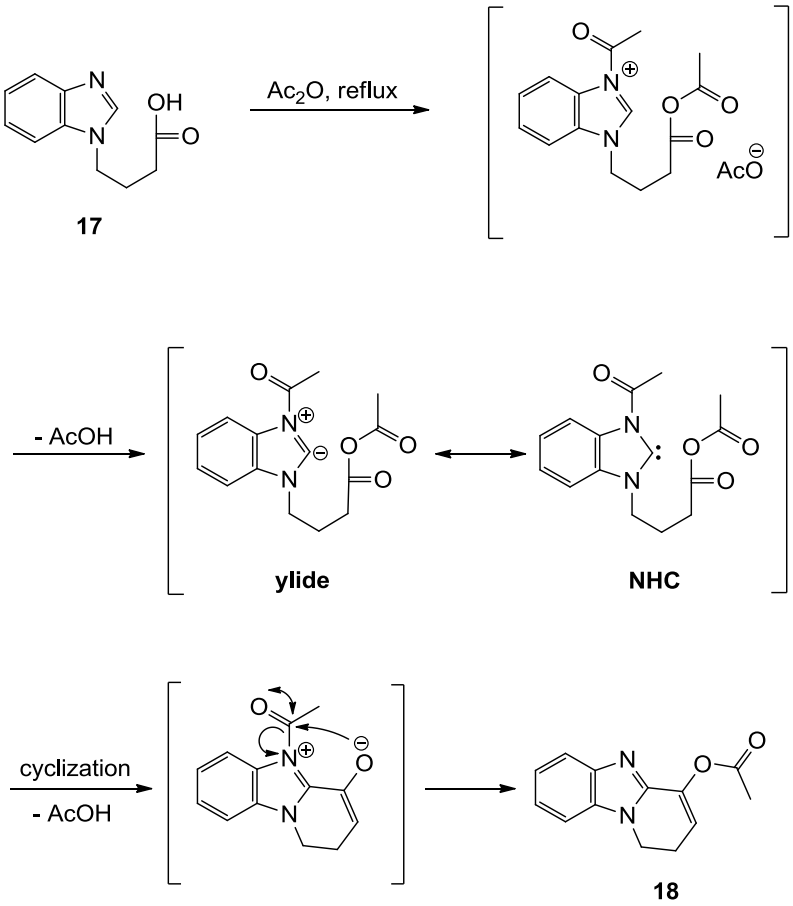


Scheme 3.06: Preparation of aliphatic carboxylic acid

Treatment of carboxylic acid **17** with Ac_2O under reflux for 15 minutes gave 1,2-dihydropyrido[1,2-*a*]benzimidazole-4-yl acetate (**18**) in 69% yield (Scheme 3.07). Adduct **18** presumably forms via the enol, and acetate migration from the 3-*N* of imidazole (Scheme 3.08).

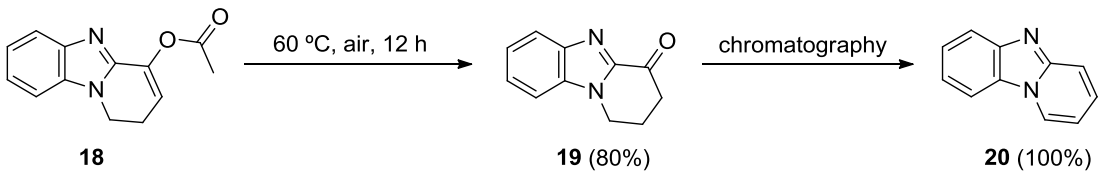


Scheme 3.07: Ac_2O mediated annulation of 4-(1*H*-benzimidazol-1-yl)butanoic acid



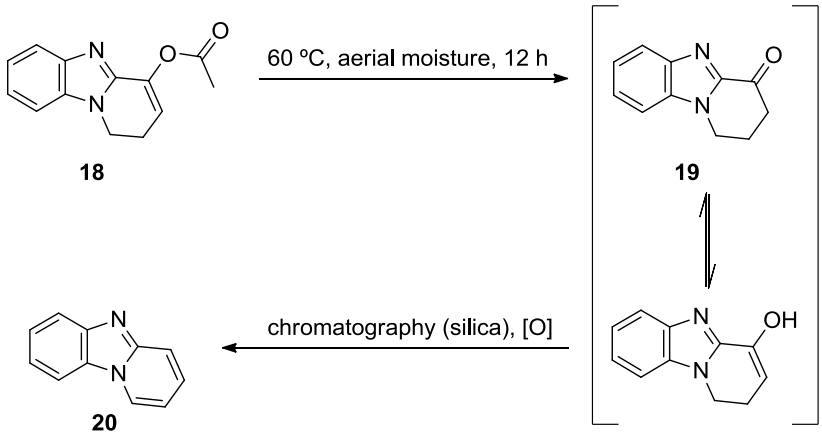
Scheme 3.08: Proposed mechanism for intramolecular condensation of 4-(1*H*-benzimidazol-1-yl)butanoic acid

On further heating of **18** in air at 60 °C for 12 hours, 2,3-dihydropyrido[1,2-*a*]benzimidazol-4(1*H*)-one (**19**) was formed in 80% yield (Scheme 3.09). Ketone **19** was reactive and could only be purified by recrystallization from diethyl ether. All other attempts to purify compound **19** (such as chromatography) led to the quantitative formation of the fully aromatic compound **20** (Scheme 3.09).



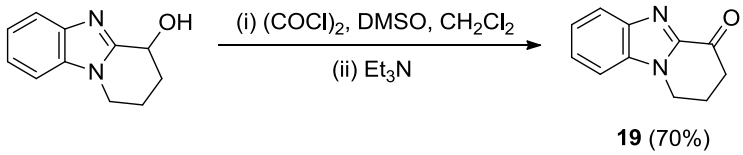
Scheme 3.09: Formation of fully aromatic pyrido[1,2-*a*]benzimidazole

The ketone **19** is formed on hydrolysis of acetate **18**, and enolisation back to the keto-form. The formation of the fully aromatic product **20** on chromatography of ketone **19** presumably occurs via the enol followed by loss of water, and aerial oxidation (Scheme 3.10).



Scheme 3.10: Proposed mechanism for formation of pyrido[1,2-*a*]benzimidazole

Ketone **19** was previously reported by the Swern oxidation shown in Scheme 3.11 and the product was purified by recrystallization from diethyl ether.[120] No degradation study of aromatic ketone **19** was reported.



Scheme 3.11: Reported synthesis of 2,3-dihydropyrido[1,2-*a*]benzimidazol-4(1*H*)-one

3.6 Conclusions

A facile protocol for the formation of benzimidazo[1,2-*b*]isoquinoline-6,11-diones, and benzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-diones from carboxylic acids has been invented using only Ac_2O. The generation of the ylide or NHC is rapid with consumption of carboxylic acid starting material occurring almost instantaneously as observed by TLC. The length of reaction time is dependent on the autoxidation which requires longer periods of time than that of the initial annulation. The role of Ac_2O is as a traceless activator, generating the desired ylide whilst subsequently the counter ion (AcO^-) generated is presumably involved in the removal of the acidic hydrogen at the benzimidazole-2-position. Ac_2O also allows the carboxylic acid OH group to be converted into a good anhydride leaving group. Reaction of 1,4-dimethoxybenzimidazo[1,2-*b*]isoquinoline-6,11-dione with cerium(iv) ammonium nitrate (CAN) produced benzimidazo[1,2-*b*]isoquinoline-1,4,6,11-tetrone, however under the same conditions 7,10-dimethoxybenzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-dione gave no isolable product. This was shown to be due to the instability of the latter which readily ring opened in the presence of methanol with the site of ring opening confirmed using X-ray crystallography. Conversion of the ring opened adduct to the corresponding quinone, occurred readily using CAN.

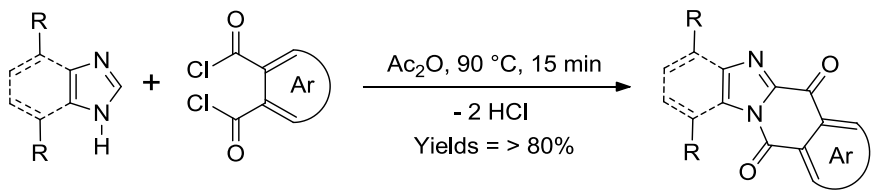
Annulation of the aliphatic carboxylic acid, 4-(1*H*-benzimidazol-1-yl)butanoic acid gave 1,2-dihydropyrido[1,2-*a*]benzimidazol-4-yl acetate formed via acetate migration from the N-3 of imidazole to the enol. Heating the latter acetate generated the ketone which was unstable and readily converted to the fully aromatic pyrido[1,2-*a*]benzimidazole on chromatography.

Chapter 4

Acetic Anhydride Mediated Condensation of Aromatic *o*-Diacid Dichlorides with Benzimidazoles to provide Electro-Reducible *p*-Dione Adducts

4.1 Introduction

In Chapter 3 acetic anhydride (Ac_2O) was shown to behave as a traceless activating agent for the intramolecular condensation of 2-(1*H*-benzimidazol-1-ylmethyl)benzoic and nicotinic acids to give aromatic *p*-dione adducts in 71-91% yield.[115] The *p*-dione adduct, benzimidazo[1,2-*b*]isoquinoline-6,11-dione (**2a**) was earlier reported by condensation of benzimidazole with phthaloyl dichloride in the presence of 1 or 2 molar equivalents of triethylamine in acetonitrile.[57,61] The reported yields for adduct **2a** using this intermolecular method are 33%,[57] and 64%,[61] and there is a requirement for purification of product. Despite these lower yields, the intermolecular reaction is attractive, because the *o*-diacid dichlorides can be readily accessed from commercial dicarboxylic acids. We now describe a convenient method for preparing a range of aromatic *p*-diones in high yields (>80%) using Ac_2O, benzimidazole and *o*-diacid dichlorides in the absence of an external base or additional organic solvent (Scheme 4.01). The procedure involves simply heating the reagents for 15 minutes, and collecting the precipitated aromatic *p*-dione adduct(s).



Scheme 4.01: Ac_2O mediated condensation of aromatic *o*-diacid dichlorides with benzimidazoles (see Table 4.01 for precise structures).

4.2 Results and Discussion

4.2.1 Ac_2O mediated intermolecular condensations

Initial attempts to condense the commercial *o*-dicarboxylic acids with benzimidazoles in the presence of Ac_2O at reflux did not give the desired *p*-dione. Thus, the *o*-diacid dichlorides were prepared by heating the corresponding *o*-dicarboxylic acids in thionyl chloride for 18 hours. After removal of the thionyl chloride, the *o*-diacid dichlorides (2 equiv) with the appropriate benzimidazole were heated in Ac_2O at 90 °C. Upon cooling, the precipitated *p*-dione adducts were collected in 81-88% yield (Table 4.01). The Ac_2O could be evaporated under reduced pressure and recycled for subsequent reactions.

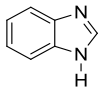
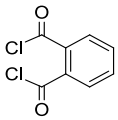
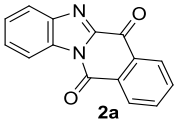
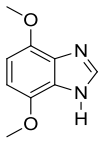
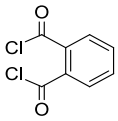
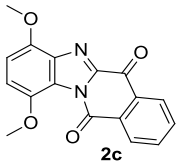
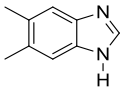
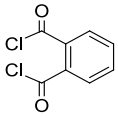
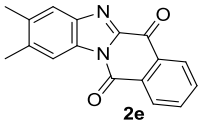
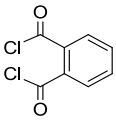
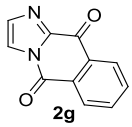
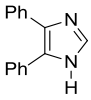
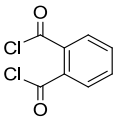
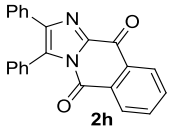
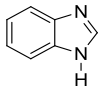
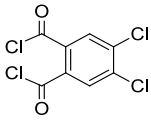
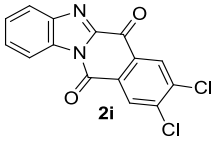
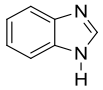
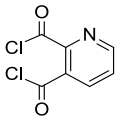
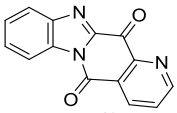
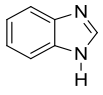
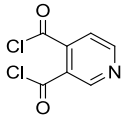
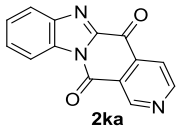
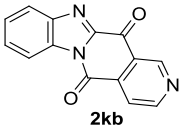
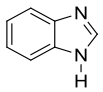
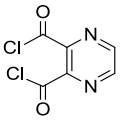
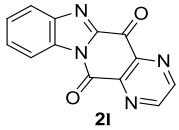
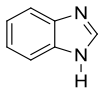
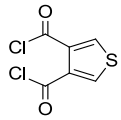
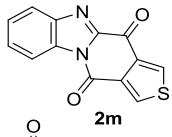
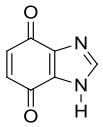
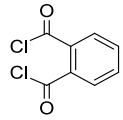
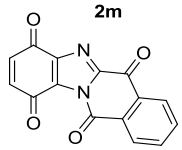
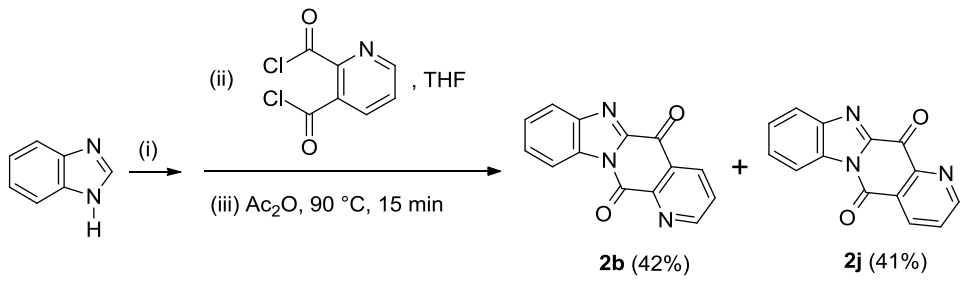
Entry	Imidazole	o-Diacid dichloride	Adducts	Yield %
A			 **2a**	87
B			 **2c**	87
C			 **2e**	88
D			 **2g**	81
E			 **2h**	87
F			 **2i**	81
G			 **2j**	81
H			 **2ka** + (1:1)  **2kb**	82
I			 **2l**	85
J			 **2m**	86
K			 **1**	0

Table 4.01: Substrates and products from the reaction given in Scheme 4.01

No purification of adducts was required when using symmetrical *o*-diacid dichlorides (entries A-F, I and J). The reactions represented by entries G and H condense benzimidazole with unsymmetrical *o*-diacid dichlorides. The condensation in entry G is largely regioselective giving benzimidazo[1,2-*g*]-1,6-naphthyridine-5,12-dione (**2j**) in 81% yield with trace amounts of isomeric adduct **2b** detected in the ^{1}H NMR spectrum, and separated by recrystallization. The structure of novel heterocycle **2j** was confirmed, because isomeric benzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-dione (**2b**) can be selectively accessed using the intramolecular annulation onto the corresponding carboxylic acid discussed in the previous chapter.[115] The formation of 1,6-naphthyridine **2j** from pyridine-2,3-dicarbonyl dichloride indicated that the nucleophilic substitution by the benzimidazolium ylide or NHC (Figure 4.01) was at the more electrophilic 2-carbonyl chloride. Prior treatment of benzimidazole with NaH then reaction with pyridine-2,3-dicarbonyl dichloride in THF under reflux gave no detectable *p*-dione adducts, until the THF was evaporated, and Ac_2O was added with further heating at 90 °C (Scheme 4.02). This gave an approximate 1:1 mixture by ^{1}H NMR spectroscopy, of the two isomeric naphthyridines **2b** and **2j** in 83% combined yield. The loss of regioselectivity by addition of base, indicated that the anionic benzimidazole nitrogens were not as selective nucleophiles as the softer benzimidazolium ylide (or NHC) nucleophile, highlighting the merit of our new simpler base-free protocol.



Scheme 4.02: Treatment of benzimidazole with base prior to condensation with pyridine-2,3-dicarbonyl dichloride: (i) NaH, THF, reflux, 15 min.

For the condensation using pyridine-3,4-dicarbonyl dichloride (entry H), the pyridine-N-atom has negligible influence on the electrophilicity of the acid chloride groups leading to a 1:1 mixture of *p*-dione adducts **2ka** and **2kb** in 82% overall yield. Isomeric adducts **2ka** and **2kb** were separated by chromatography,

and their structures were confirmed by obtaining the X-ray crystal structure of **2kb** using ORTEX to create the drawing[121] (Figure 4.01).

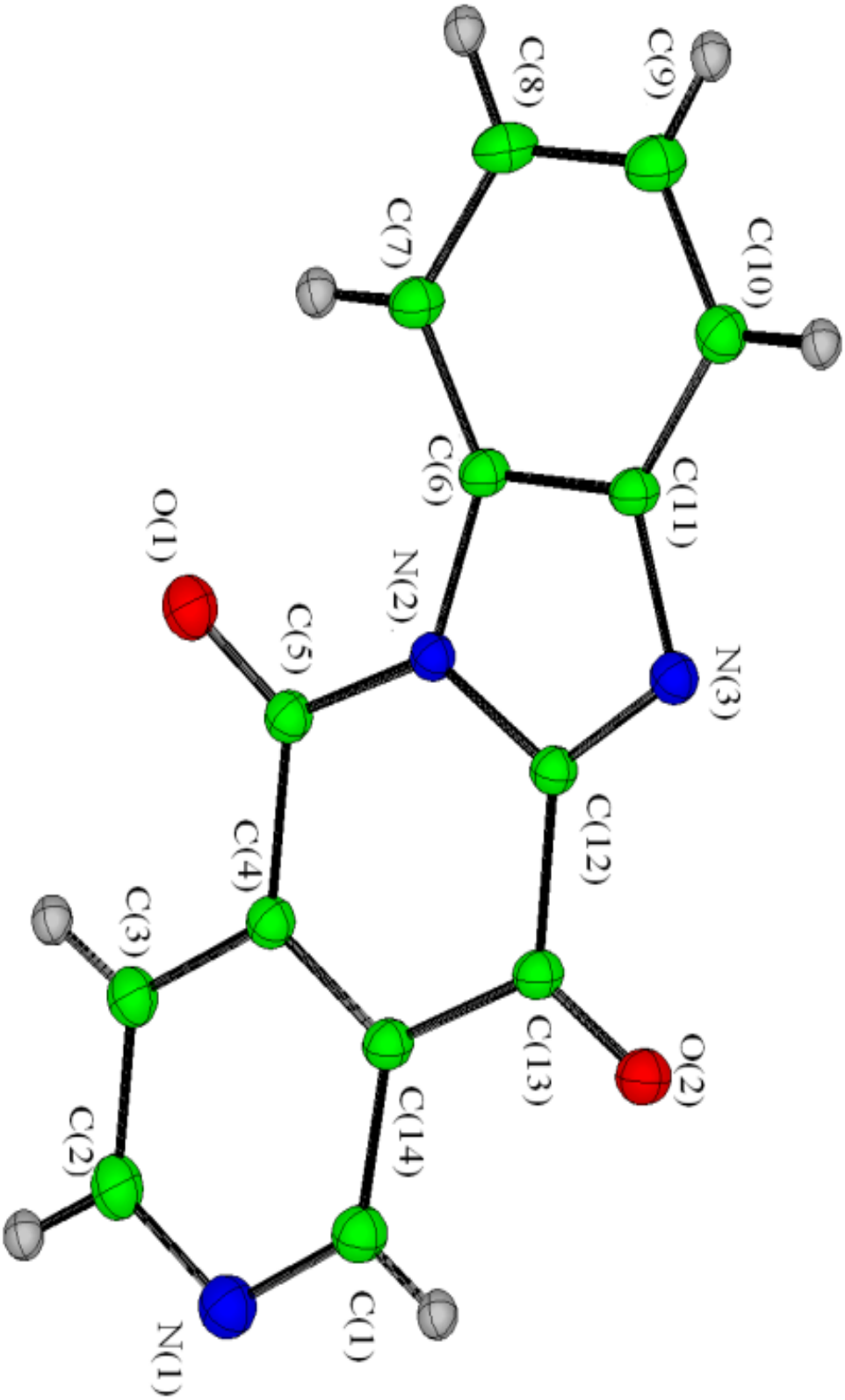
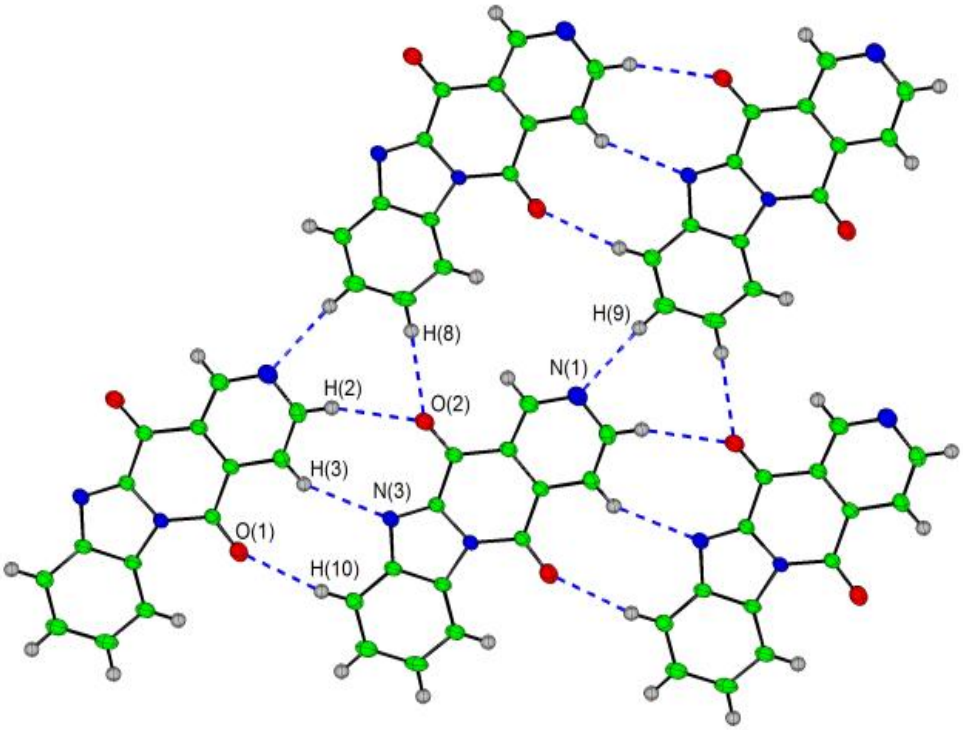


Figure 4.01: X-ray crystal structure of benzimidazo[1,2-*b*]-2,6-naphthyridine-5,12-dione (2kb).

The crystals have a calculated density of 1.54 and the structure contains C-H…O and C-H…N hydrogen bonds, which form sheets parallel to the 101 plane (Figure 4.02 and Table 4.02). The sheets are π-stacked with a mean distance of 3.32 Å between the non-hydrogen atoms (Figure 4.02). This is efficient layer packing and is comparable to the inter-layer separation of graphite, 3.35 Å. The packing coefficient is 0.85, which is at the high end of a range of high density organic compounds.[122]

(a)



(b)

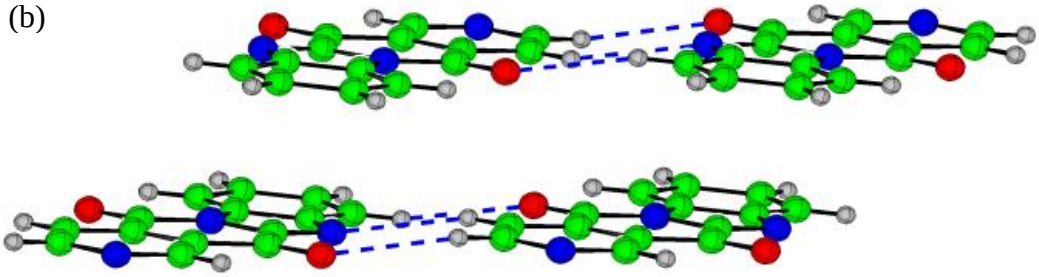


Figure 4.02: (a) Hydrogen bonding and (b) π-stacking for 2kb.

H-bond	H…X/Å	C-H…X/°
C(10)-H(10)…O(1)	2.49	164.52
C(3)-H(3)…N(3)	2.55	146.67
C(2)-H(2)…O(2)	2.58	162.17
C(8)-H(8)…O(2)	2.48	167.45
C(9)-H(9)…N(1)	2.58	173.04

Table 4.02: Hydrogen-bonding distances and bond angles shown in Figure 4.02

Attempts at forming tetrone **1** directly from benzimidazolequinone and phthaloyl dichloride (entry K) were unsuccessful presumably due to the electron withdrawing nature of the quinone moiety impeding the formation of the imidazolium salt, and giving unreacted starting materials.

4.2.2 Cyclic Voltammetry

Cyclic voltammetric experiments were carried out in DMF rather than in aqueous solution to avoid the complexities of protonation.[9,78,88-90] All the compounds analyzed produced a similar type of voltammetric response with slight variations in formal potentials (Figure 4.03, Table 4.03). A formal potential is a measured potential of the half-cell when redox species are present at equal concentrations and in the presence of other specified substances, for example, miscellaneous components of the medium, at designated concentrations.[123] The cathodic sweep gives two peak currents due to the addition of an electron to the *p*-dione to form a radical anion, and a subsequent addition of an electron to give a dianion. Thus, the *p*-dione moiety is shown to be capable of one and two-electron reduction, at potentials indicated by the cathodic peak currents (E_{pc}). The subsequent anodic sweep results in the appearance of peak currents for the re-oxidation of the dianion (E^2_{pa}) and the radical anion (E^1_{pa}), at potentials typically ~60 mV more positive than the corresponding cathodic peak potential, highlighting the stability of the reduced species on the timescale of the voltammetric scan. This behavior is analogous to literature quinones.[90] The imidazole adducts **2g** and **2h** had more negative first formal potentials and similar second formal potentials to analogue **2a**. It is observed that the introduction of electron-donating dimethoxy-

or dimethyl-substituents in benzimidazoles **2c** and **2e**, respectively displaced the formal potentials (E^1_{redox} and E^2_{redox}) towards more negative potentials with respect to **2a**, in contrast to the electron-withdrawing dichloro substituents of compound **2i**. The electronegative N atom of the fused pyridine of compounds **2b**, **2j**, **2ka** and **2kb** shifted the formal potentials towards a more positive region with respect to **2a**, although the effect was surprisingly greater for adduct **2ka** with the N atom further away from the reducible moiety. Moreover **2ka** has similar formal potentials to compound **2l** containing a fused pyrazine. The fused thiophene in adduct **2m** produced formal potentials more negative than any other adduct, due to higher electron density associated with the thiophene ring making oxidation of the reduced species more facile (Figure 4.03). E_{redox} values obtained under identical conditions for reported benzimidazolequinones (E^1_{redox} in a range of −1.05 to −1.17 V, with compounds demonstrating nanoMolar (10^{-9} M) cytotoxicity)[9] are comparable to those observed for the *p*-dione adducts, with compounds **2ka**, and **2l** distinctly more easily reduced.

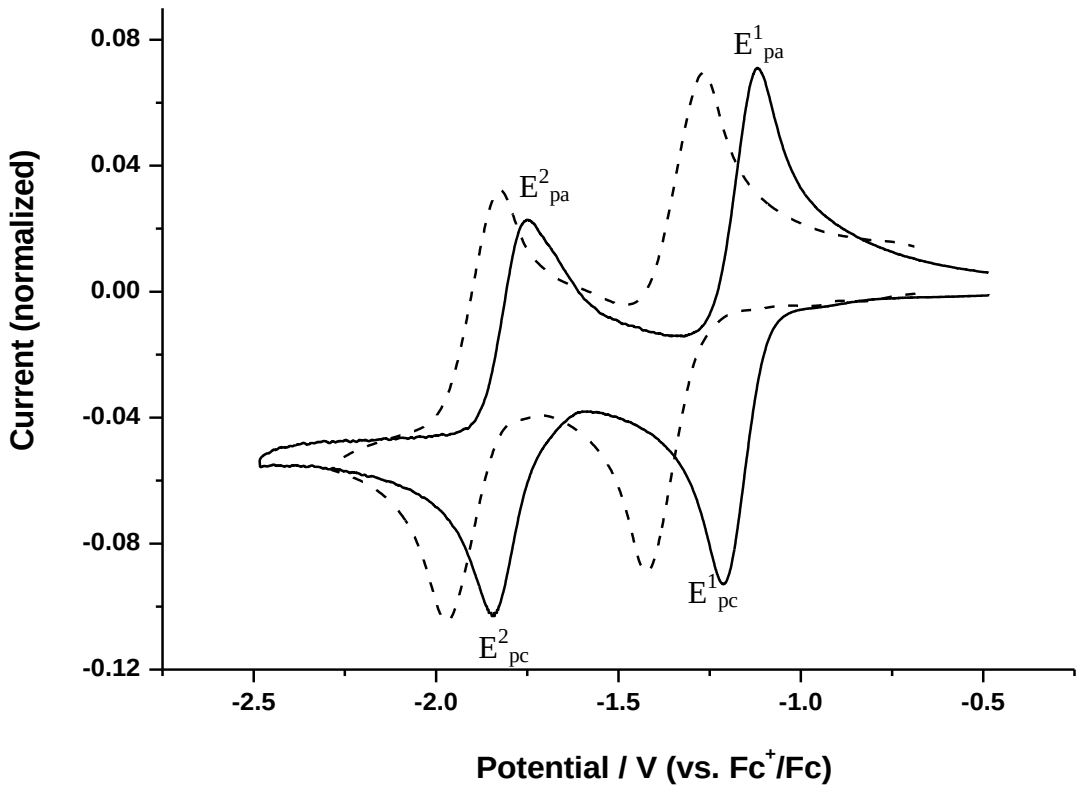


Figure 4.03: Cyclic voltammogram of benzimidazo[1,2-*b*]isoquinoline-6,11-dione (2a) (——) and 4*H*,11*H*-thieno[3',4':4,5]pyrido[1,2-*a*]benzimidazole-4,11-dione (2m) (- - - -) in DMF containing 0.1 M tetrabutylammonium-perchlorate as electrolyte and 1 mM ferrocene (Fc) as reference at a scan rate 100 mVs^{-1}. E_{pc} = cathodic peak potential, E_{pa} = anodic peak potential. E^1_{redox} = (E^1_{pc} + E^1_{pa})/2 (first formal potential), E^2_{redox} = (E^2_{pc} + E^2_{pa})/2 (second formal potential).

Adduct	(E_{redox}) [a] [V] versus Fc	
	E^1_{redox}	E^2_{redox}
2a	-1.17	-1.80
2b	-1.08	-1.72
2c	-1.23	-1.84
2e	-1.19	-1.82
2g	-1.21	-1.84
2h	-1.25	-1.89
2i	-1.00	-1.64
2j	-1.07	-1.71
2ka	-0.95	-1.60
2kb	-1.01	-1.66
2l	-0.97	-1.56
2m	-1.34	-1.90

Table 4.03: Formal potentials (E_{redox})[a]
[a] See Figure 4.03 for experimental detail. E_{redox} (± 0.010 V) calculated as (E_{pc} + E_{pa})/2 from 100 mVs^{-1} cyclic voltammograms.

The cyclic voltamomogram of benzimidazo[1,2-*b*]isoquinoline-1,4,6,11-tetrone (**1**) (Figure 4.04) was more complicated than the *p*-dione adducts due to the four potential sites of reduction. The appearance of peak currents in both the cathodic and anodic sweeps again highlights the stability of the reduced species on the timescale of the voltammetric scan, however further research is required to elucidate which anodic peak corresponds to re-oxidation of the species reduced at each cathodic peak.

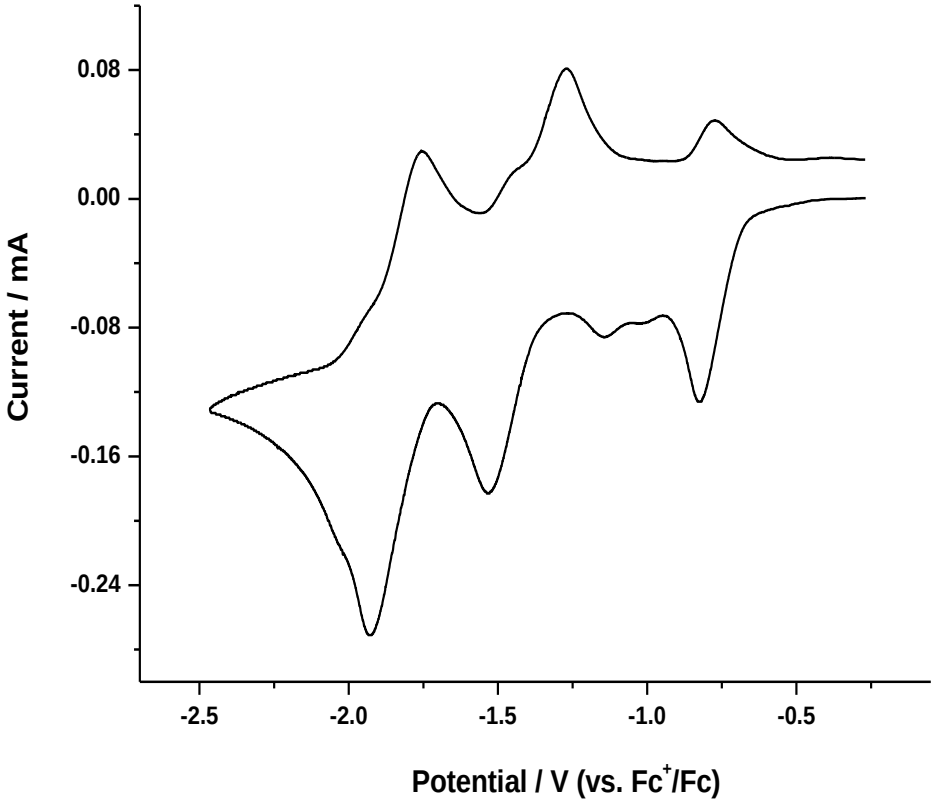
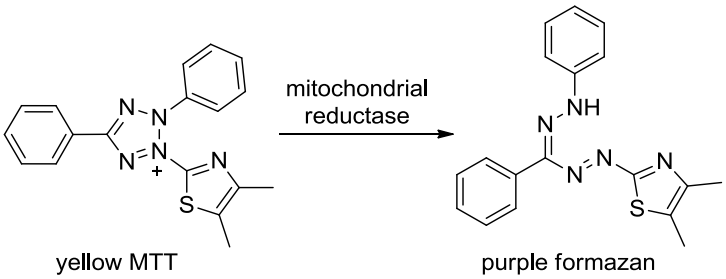


Figure 4.04: Cyclic voltammogram of benzimidazo[1,2-*b*]isoquinoline-1,4,6,11-tetrone (1).

4.2.3 Cytotoxicity evaluation of benzimidazo[1,2-*b*]isoquinoline-6,11-dione and quinone derivative

Cytotoxicity evaluations were carried out using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] colorimetric assay.[124] Cells were incubated in the presence of the test compound for a set period of time (72 h in this case) before addition of a solution of MTT. The yellow MTT is reduced to the purple formazan by mitochondrial reductase enzymes (Scheme 4.03). This reduction can only take place in metabolically active cells. Therefore the amount of formazan produced is directly related to the number of viable (living) cells. The amount of purple formazan can be quantified by measuring the absorbance using a spectrophotometer. The percentage cell viability can be determined by comparing the amount of formazan produced by the cells treated with the test compound, in a particular solvent, to the amount of formazan produced by the control cells treated with the solvent alone. This process is repeated for different concentrations of the test compound so that a dose response curve can be produced. From this dose response curve an IC_{50} (concentration of compound required to inhibit cell viability by 50%) is determined, which is a measure of the cytotoxicity of the compound.



Scheme 4.03: Reduction of MTT to the purple formazan by viable cells.

IC_{50} values were obtained against both prostate (DU145) cancer cells and a human normal skin fibroblast cell line (GM00637). The DU145 cell line is a human cancer cell line reported to contain high levels of the reductase enzyme NQO1.[65] A cell viability plot of *p*-dione adduct **2a** and quinone derivative **1** (Figure 4.05) highlights the selectivity of the former towards the prostate (DU145) cancer cell line. Table 4.04 shows IC_{50} values obtained.

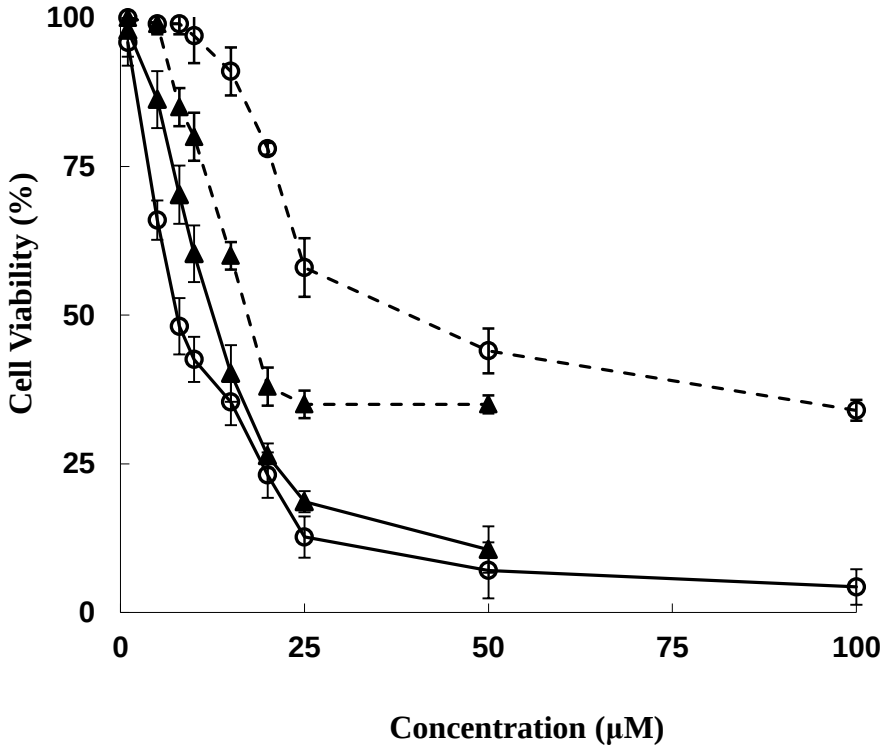


Figure 4.05: Viability of human normal skin fibroblast (GM00637) (- - - -), and prostate cancer (DU145) (——) cell lines determined using the MTT assay following treatment with benzimidazo[1,2-*b*]isoquinoline-6,11-dione (2a) (○) and benzimidazo[1,2-*b*]isoquinoline-1,4,6,11-tetrone (1) (▲) under aerobic conditions for 72 h at 37 °C. Each data point is the mean of at least three independent experiments. The lines shown are trend lines.

Compound	Cell Lines[b]	
	GM00637	DU145
2a	47.00 ± 4.75	8.09 ± 0.40
1	18.80 ± 1.03	12.30 ± 1.04

Table 4.04: Cytotoxicity evaluation: IC_{50} values (µM).[a]
[a] IC_{50} represents the concentration required for the reduction of the mean cell viability to 50% of the control value after incubation for 72 h at 37 °C,
***[b]* Human normal skin fibroblast (GM00637), prostate cancer (DU145).**

Table 4.04 shows that **2a** is more cytotoxic to the DU145 cell line and less cytotoxic to the human normal skin fibroblast cell line than **1.** Future work will involve the addition of reactive functionality (e.g., aziridine) onto *p*-diones, such as **2a** in order to increase cytotoxicity. This work indicates *p*-diones may be promising bioreductive prodrug alternatives to widely used heterocyclic quinones. [9,20,66,73-81,87-90]

4.3 Nomenclature of *p*-dione adducts

All compounds were named according to International Union of Pure and Applied Chemistry (IUPAC) rules.[116] The nomenclature of pyrazino[2',3':4,5]pyrido[1,2-*a*]benzimidazole-5,12-dione (**2l**) is explained in detail to illustrate the procedure for naming such fused ring systems. The parent component (red) was identified as benzimidazole (Figure 4.06). The pyrido ring was identified as the first order component and the pyrazine ring the second order component. The outer bonds of the parent component are labeled with letter locants (a-i), the atoms of the first order component are labeled with numerical locants starting from the N-1 position (1-6) and the atoms of the second order component are labeled with primed numerical locants (1'-6'). Fusion between the pyrido ring and benzimidazole is indicated by the numerical locants of the fusion atoms of the pyrido ring followed by the letter locant of the fusion bond in benzimidazole, separated by a hyphen and cited within square brackets; Pyrido[1,2-*a*]benzimidazole.

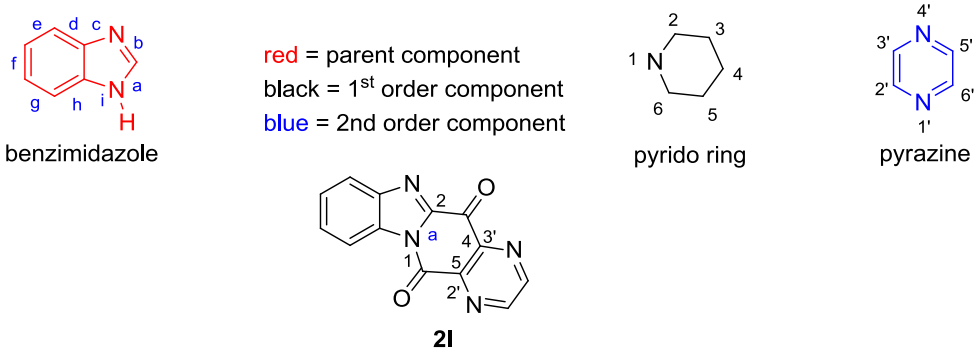


Figure 4.06: Parent, first and second order component assignments

The fusion between the pyrido ring and pyrazine is indicated by the primed numerical locants of the fusion atoms of the pyrazine followed by the numerical locants of the fusion atoms of the pyrido ring, separated by a colon and cited in square brackets; pyrazino[2',3':4,5]pyrido

The combined second and first order components are now viewed as a new first order component generating; pyrazino[2',3':4,5]pyrido[1,2-*a*]benzimidazole

The molecule is drawn with the maximum number of rings in a horizontal line using the available shapes allowed in order to assign peripheral numbers

(Figure 4.07). Numbering begins with the most counter-clockwise non-fusion atom of the ring furthest to the right in the upper right hand quadrant and proceeds clockwise. If more than one orientation is equally allowed then the following rules are applied, in order, until one orientation is preferred;

(1) Give low numbers to heteroatoms as a set.

(2) Give low numbers to heteroatoms when considered in the order: O, S, Se, Te, N, P, As, Sb, Bi, Si, Ge, Sn, Pb, B, Hg

(3) Give low numbers to fusion carbons as a set.

(4) Give low numbers to fusion rather than non-fusion atoms of the same heteroelement

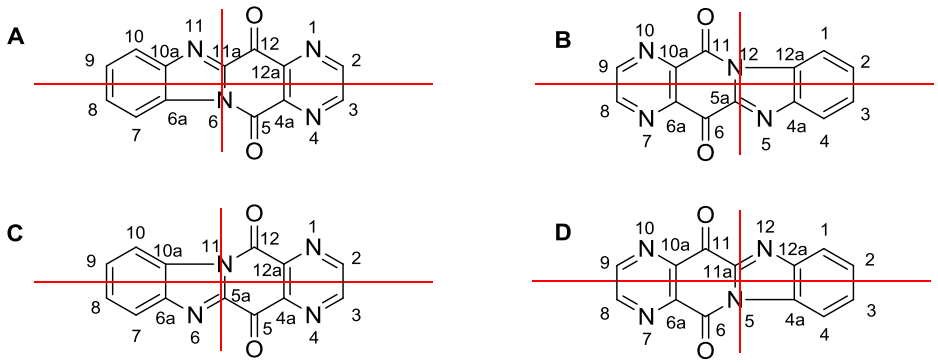


Figure 4.07: Peripheral numbering

Application of rule (1) eliminates (**B**) and (**D**) as the sum of the numbers on the nitrogens is 34 as opposed to 22 for (**A**) and (**C**).

Application of rule (2) still leaves (**A**) and (**C**) as the nitrogens are numbered the same in both.

Application of rule (3) eliminates (**A**) leaving (**C**) [37a is the sum of the fusion carbons for (**C**) as opposed to 43a for (**A**)].

Rule (4) is not required.

The peripheral numbering of (**C**) identifies the location of the two ketone functional groups thus completing the name; pyrazino[2',3':4,5]pyrido[1,2-*a*]benzimidazole-5,12-dione.

4.4 Conclusions

Ac_2O allows the facile and rapid condensation of aromatic *o*-diacid dichlorides with benzimidazoles to give a range of *p*-diones. These products are isolated by precipitation from the reaction mixture, in a procedure devoid of arduous precursor synthesis, and requiring no external base or additional solvent. Condensation of benzimidazole and pyridine-2,3-dicarbonyl dichloride produced one isomer as the major product, this regioselective attack was not observed however when benzimidazole was reacted with base followed by pyridine-2,3-dicarbonyl dichloride prior to condensation with acetic anhydride. The regioselectivity for the original condensation (without base) indicates nucleophilic substitution by the benzimidazolium ylide or NHC was at the more electrophilic 2-carbonyl chloride. The only reaction requiring chromatography was between benzimidazole and pyridine-3,4-dicarbonyl dichloride, which gave a 1:1 mixture of isomeric *p*-dione adducts. One of the latter *p*-diones exhibited an unusual highly ordered crystal packing with density at the high end for organic compounds.

Using cyclic voltammetry, *p*-diones (many new heterocyclic systems) were shown to undergo two consecutive one electron-reductions in DMF, in an analogous manner to previously reported highly active quinone anti-tumour agents. Cytotoxicity results showed benzimidazo[1,2-*b*]isoquinoline-6,11-dione to be more selective and cytotoxic towards the prostate cancer cell line than that of the tetrone derivative benzimidazo[1,2-*b*]isoquinoline-1,4,6,11-tetrone. *p*-Diones may therefore be promising alternatives to widely studied heterocyclic quinones.

Chapter 5

Experimental Section

5.1 General

5.1.1 Materials and methods

All commercially available reagents and solvents were used without purification except for DMF, THF, MeCN, DCM and toluene which were dried prior to use according to conventional methods. Thin layer chromatography (TLC) was carried out on aluminium-backed plates coated with silica gel (Merck Kieselgel 60 F_{254}). Dry column vacuum chromatography was carried out using Merck Kieselgel silica gel 60 (particle size 0.015-0.040 mm), using the specified eluent.[125,126] Automated chromatography to separate compounds **2ka** and **2kb** was carried out on a Grace Reveleris Flash System (Instrument serial no. 2810M00134) with an 80 gram silica (40 µm) column using dichloromethane as eluent.

5.1.2 Instrumental

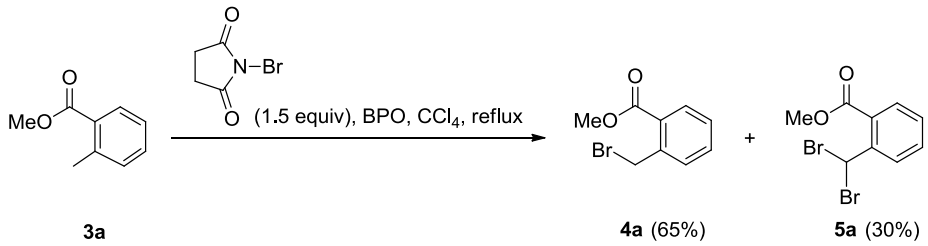
Melting points were measured on a Stuart Scientific melting point apparatus SMP3. Infrared spectra were recorded using a Perkin-Elmer Spec 1 with ATR attached. NMR spectra were recorded using a Joel GXFT 400 MHz instrument equipped with a DEC AXP 300 computer workstation. All chemical shifts are expressed in parts per million (ppm) downfield from trimethylsilane as internal standard. NMR assignments of new compounds were supported by DEPT and ^{1}H-^{13}C NMR 2D spectra. High resolution mass spectra for all other compounds were carried out using ESI on a Waters LCT Premier XE spectrometer by manual peak matching. The precision of all accurate mass measurements were better than 5 ppm. HPLC chromatograms were obtained using an Agilent Technologies 1200 series instrument with the UV detector set at 254 nm. The purity of compounds that underwent cytotoxicity evaluation was validated using HPLC, with purity greater than 97% in all cases. A Phenomenex, sphereclone 5*u* (ODS) 150 x 4.6 mm 5 micron column was used with acetonitrile as eluent. Hydrogenation reactions were carried out using a Parr® 5500 Series Compact reactor. UV absorbance measurements were carried out on a Cary UV-VIS spectrophotometer. The photochemical reactions were carried out at 250 and 350 nm using a RPR-100 Rayonet photochemical reactor, encompassing sixteen mercury lamps. For photochemical reactions carried out at 250 nm a quartz tube was used as the reaction vessel whereas a pyrex tube was used for the 350 nm experiments. Absorbance was measured in the MTT assay using a Wallac Victor 2 1420 multi-label Counter.

NMR spectra for compounds **8a-8d**, **9a-9d**, **2a-2d**, **12**, **13**, **1**, **14** and **15** can be found in the supporting information of
Joyce, E.; McArdle, P.; Aldabbagh, F. *Synlett* **2011**, 1097-1100.[115]

NMR spectra for compounds **2e, 2g, 2i, 2j, 2ka, 2kb, 2l** and **2m** as well as the cyclic voltammograms not shown in Chapter 4 can be found in the supporting information of
Joyce, E.; Kavanagh, P.; Leech, D.; Karpinska, J.; McArdle, P.; Aldabbagh, F. *Tetrahedron Lett.* **2012**, *53*, 3788-3791.[127]

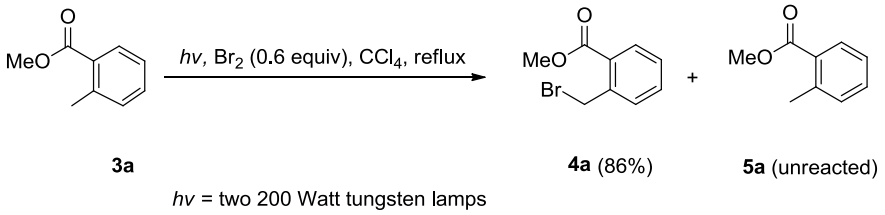
5.1.3 Experimental for chapter 2

Experiment 1; Synthesis of methyl 2-(bromomethyl)benzoate (**4a**) using NBS



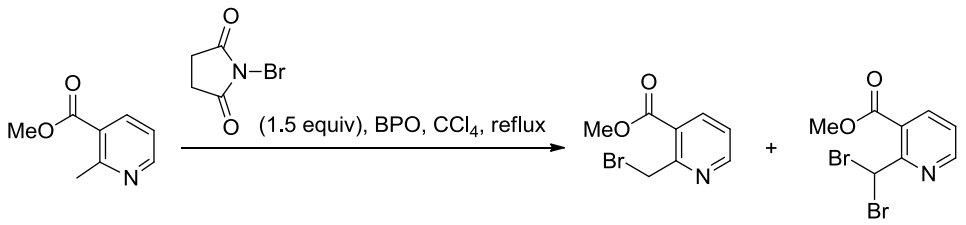
A mixture of methyl 2-methylbenzoate (5.000 g, 33.30 mmol), *N*-bromosuccinimide (NBS) (8.430 g, 47.36 mmol) and benzoyl peroxide (BPO) (0.100 g, 0.41 mmol) in carbon tetrachloride (150 mL) was heated under reflux for 6 h. The precipitated succinimide was filtered and the filtrate evaporated to dryness. The brown residue was purified by reduced pressure distillation to give methyl 2-(bromomethyl)benzoate (4.957 g, 65%); clear solid; mp 31-32 °C (lit.[105] mp 33-34.5 °C); ν_{max} (neat, cm^{-1}): 1717 (C=O), 1434, 1261, 1224, 1113, 1075; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.44-7.37 (m, 2H), 7.32-7.28 (m, 1H), 4.89 (s, 2H, CH_2), 3.87 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0 (C=O), 139.3 (C), 132.7 (CH), 131.8 (CH), 131.4 (CH), 129.1 (C), 128.6 (CH), 52.4 (CH_3), 31.8 (CH_2); and methyl 2-(dibromomethyl)benzoate (3.076 g, 30%) remained in the distillation flask; white solid; mp 49-51 °C (lit.[128] mp 51.5-52.5 °C); ν_{max} (neat, cm^{-1}): 1713 (C=O), 1572, 1432, 1289, 1260, 1189, 1154, 1134, 1078; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (dd, *J* = 8.0, 1.1 Hz, 1H), 8.05 (s, 1H, $CHBr_2$), 7.86 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.62-7.58 (m, 1H), 7.37-7.33 (m, 1H), 3.92 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6 (C=O), 143.3 (C), 133.4, 131.7, 130.1, 129.5 (all CH), 124.8 (C), 52.8 (CH_3), 38.4 ($CHBr_2$).

Experiment 2; Synthesis of methyl 2-(bromomethyl)benzoate (**4a**) using bromine and two 200 Watt tungsten lamps



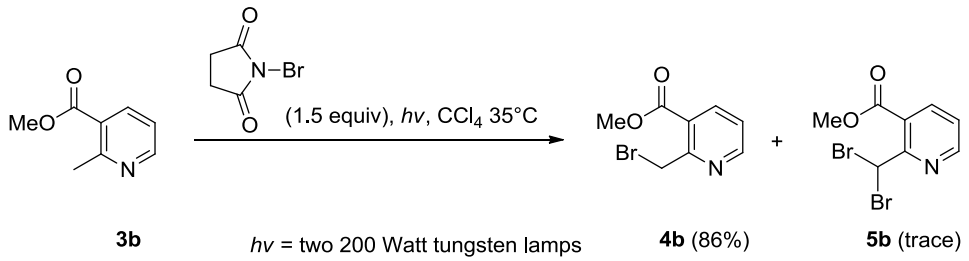
A brown mixture of methyl 2-methylbenzoate (10.000 g, 66.59 mmol), bromine (2.00 mL, 38.83 mmol) and carbon tetrachloride (50 mL) was irradiated using two 200 Watt tungsten lamps for 15 minutes, until the mixture became clear. The solution was evaporated to dryness to give a clear residue which was purified by reduced pressure distillation, separating non-reacted methyl 2-methyl benzoate (4.100 g) leaving methyl 2-(bromomethyl)benzoate (7.650 g, 86%) in the reaction flask as a clear solid. Spectroscopic data was consistent with that of previous experiments.

Experiment 3; Synthesis of methyl 2-(bromomethyl)nicotinate (**4b**) using NBS



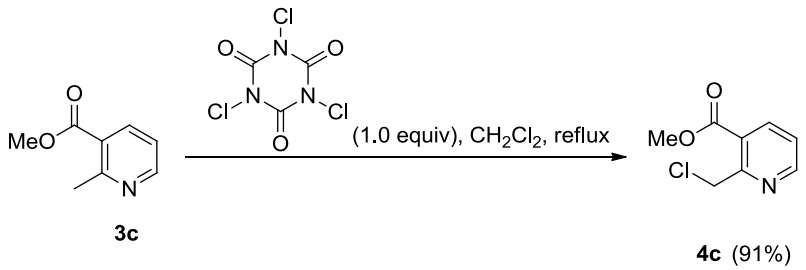
A mixture of methyl 2-methylnicotinate (50.0 mg, 0.33 mmol), N-bromosuccinimide (NBS) (88.3 mg, 0.50 mmol) and benzoyl peroxide (BPO) (5.0 mg, 0.02 mmol) in carbon tetrachloride (50 mL) was heated under reflux for 6 hours. The precipitated succinimide was filtered and the filtrate evaporated to dryness. The brown residue was purified by preparitive TLC using DCM as solvent to give methyl 2-(bromomethyl)nicotinate (41.8 mg, 55%); R_f = 0.69 (CH_2Cl_2); yellow oil; ν_{max} (neat, cm^{-1}): 1722 (C=O), 1570, 1431, 1262, 1113, 1077, 1052, 958; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71 (dd, *J* = 4.8, 1.8 Hz, 1H, 6-H), 8.28 (dd, *J* = 8.0, 1.8 Hz, 1H, 4-H), 7.33 (dd, *J* = 8.0, 4.8 Hz, 1H, 5-H), 5.03 (s, 2H, CH_2), 3.97 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9 (C=O), 158.0 (C), 152.5 (6-CH), 139.4 (4-CH), 125.2 (C), 123.2 (5-CH), 52.8 (CH_3), 32.6 (CH_2); HRMS (ESI): *m/z* calcd for $C_8H_9NO_2{}^{80}Br$: 229.9817, found: 229.9822 $[M+H]^+$; and methyl 2-(dibromomethyl)nicotinate (35.76 mg, 35%); R_f = 0.59 (CH_2Cl_2); buff white solid; mp 68-70 °C; ν_{max} (neat, cm^{-1}): 1706 (C=O), 1578, 1563, 1426, 1272, 1252, 1189, 1133, 1075, 1055; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.84 (dd, *J* = 4.6, 1.7 Hz, 1H, 6-H), 8.22 (dd, *J* = 8.0, 1.7 Hz, 1H, 4-H), 7.97 (s, 1H, $CHBr_2$), 7.34 (dd, *J* = 8.0, 4.6 Hz, 1H, 5-H), 3.93 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3 (C=O), 157.9 (C), 153.5 (6-CH), 138.9 (4-CH), 124.3 (5-CH), 120.9 (C), 53.5 (CH_3), 39.7 ($CHBr_2$); HRMS (ESI): *m/z* calcd for $C_8H_8NO_2{}^{80}Br_2$: 307.8922, found: 307.8921 $[M+H]^+$.

Experiment 4; Synthesis of methyl 2-(bromomethyl)nicotinate (**4b**) using two 200 Watt tungsten lamps and NBS



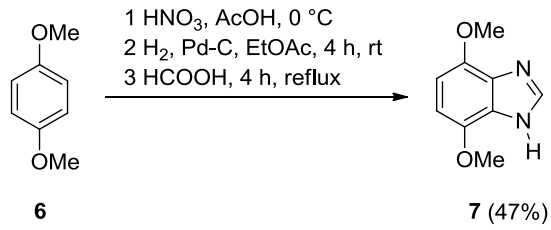
A mixture of methyl 2-methylnicotinate (0.600 g, 3.97 mmol), N-bromosuccinimide (NBS) (1.100 g, 6.18 mmol) and carbon tetrachloride (50.00 mL) was irradiated using two 200 Watt tungsten lamps whilst maintaining the temperature of the solution at 35 °C for 18 hours. The solution was filtered and evaporated to dryness. The mixture was purified by dry column vacuum chromatography using silica gel with gradient elution of hexane and ethyl acetate to give methyl 2-(bromomethyl)nicotinate (0.786 g, 86%) and trace amounts of **5b**; Spectroscopic data was consistent with that of previous experiments.

Experiment 5; Synthesis of methyl 2-(chloromethyl)nicotinate (**4c**)



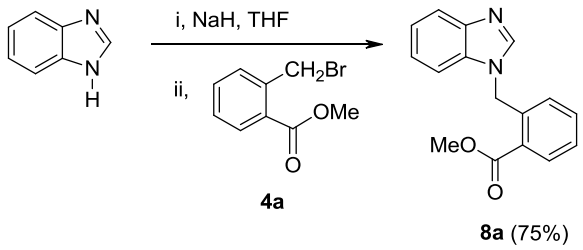
Trichloroisocyanuric acid (12.91 g, 55.55 mmol) was added to methyl 2-methylnicotinate (4.200 g, 27.79 mmol) in dichloromethane (100 mL) and heated under reflux for 18 hours. The solution was cooled and filtered. The filtrate was washed with sodium hydroxide solution and the extracts evaporated to dryness to give methyl 2-(chloromethyl)nicotinate (4.693 g, 91%); yellow oil; ν_{max} (neat, cm^{-1}): 2947, 1717 (C=O), 1580, 1568, 1441, 1429, 1269, 1183, 1168, 1128, 1080, 1055; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (dd, J = 4.8, 1.7 Hz, 1H, 6-H), 7.94 (dd, J = 7.9, 1.7 Hz, 1H, 4-H), 7.05 (dd, J = 7.9, 4.8 Hz, 1H, 5-H), 4.80 (s, 2H, CH_2), 3.62 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5 (C=O), 157.0 (C), 152.1 (6-CH), 138.9 (4-CH), 125.1 (C), 123.2 (5-CH), 52.5 (CH_3), 45.4 (CH_2); HRMS (ESI): *m/z* calcd for $C_8H_9NO_2{}^{35}Cl$: 186.0322, found: 186.0320 $[M+H]^+$

Experiment 6; Synthesis of 4,7-dimethoxy-1*H*-benzimidazole (**7**)



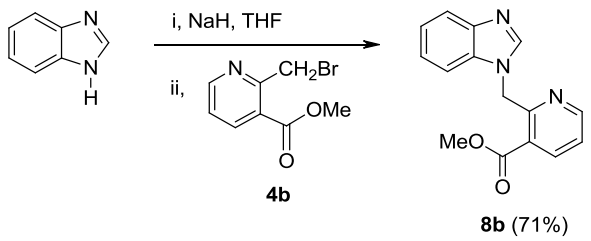
Concentrated nitric acid (18.00 mL, 70-72%) was added drop wise to a stirring solution of 1,4-dimethoxybenzene (13.800 g, 0.100 mol) in glacial acetic acid (35 mL) at 0°C. After the vigorous reaction had subsided a further portion of nitric acid (18.00 mL, 70-72%) was added. The reaction was then heated at 80-90 °C for 30 minutes to release a characteristic red gas. The reaction was cooled and diluted with distilled H_2O (100 mL). The yellow precipitate was filtered under vacuo and washed to remove any acetic acid. The crude yellow solid was left to dry and used without further purification. ^{1}H NMR spectroscopy revealed a 4:1 isomeric mixture of 1,4-dimethoxy-2,3-dinitrobenzene and 1,4-dimethoxy-2,5-dinitrobenzene which were dissolved in ethyl acetate (200 mL) with Pd-C (10%) and agitated under 5 barr H_2 pressure at 20 °C for 18 hours. The catalyst was removed by filtration and the filtrate evaporated to dryness giving 1,4-dimethoxy-2,3-diaminobenzene and 1,4-dimethoxy-2,5-diaminobenzene which were used without further purification. The crude mixture was dissolved in formic acid (50 mL, 95-97%) and heated under reflux for 4 hours. The reaction was cooled and neutralised with sodium carbonate. The percipitate was filtered and dried to give 4,7-dimethoxy-1*H*-benzimidazole (8.365 g, 47% overall yield) as a brown solid; mp 222-223 °C (mp 218-222 °C)[110]; spectroscopic data was consistent with that previously reported in the group.[9]

Experiment 7; Synthesis of methyl 2-(1*H*-benzimidazol-1-ylmethyl)benzoate (**8a**)



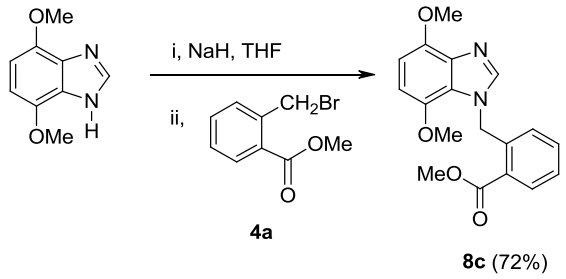
A mixture of benzimidazole (4.000 g, 33.86 mmol), sodium hydride (0.820 g, 34.17 mmol) in THF (100 mL) was heated under reflux for 1 hour. Methyl 2-(bromomethyl)benzoate (7.756 g, 33.86 mmol) was added and the mixture stirred for 18 hours at room temperature. The mixture was filtered through celite, and purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of hexane and ethyl acetate as eluent to give methyl 2-(1*H*-benzimidazol-1-ylmethyl)benzoate (6.762 g, 75%); R_f = 0.50 (9:1 EtOAc:MeOH); pale brown solid; mp 139-142 °C; ν_{max} (neat, cm^{-1}): 2917, 2846, 2061, 1977, 1709 (C=O), 1492, 1431, 1287, 1259, 1206, 1115, 1049; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05-8.02 (m, 1H), 7.95 (s, 1H, BnIm-2-H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.33-7.31 (m, 2H), 7.27-7.19 (m, 3H), 6.73-6.71 (m, 1H), 5.79 (s, 2H, CH_2), 3.89 (s, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2 (C=O), 144.0 (BnIm-2-CH), 143.9, 138.0, 134.2 (all C), 133.1 (CH), 131.5 (CH), 128.1 (C), 128.0, 127.7, 123.2, 122.3 (all CH), 120.5 (BnIm-4-CH), 110.2 (BnIm-7-CH), 52.4 (Me), 47.2 (CH_2); HRMS (ESI): *m/z* calcd for $C_{16}H_{15}N_2O_2$: 267.1134, found: 267.1131 $[M+H]^+$

Experiment 8; Synthesis of methyl 2-(1*H*-benzimidazol-1-ylmethyl)nicotinate (**8b**)



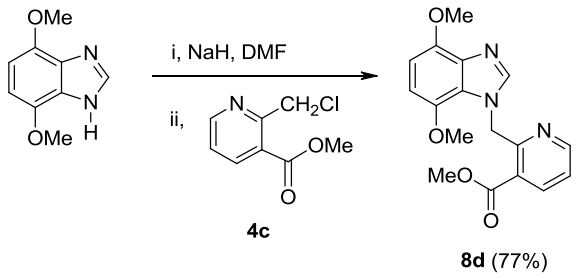
A mixture of benzimidazole (2.000 g, 16.93 mmol), sodium hydride (0.410 g, 17.08 mmol) in THF (100 mL) was heated under reflux for 1 hour. The solution was cooled to 5°C, and methyl 2-(bromomethyl)nicotinate (3.910 g, 17.00 mmol) was added and the mixture was stirred for 18 hours at room temperature. The mixture was filtered through celite, and purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of hexane and ethyl acetate as eluent to give methyl 2-(1*H*-benzimidazol-1-ylmethyl)nicotinate (3.210 g, 71%); R_f = 0.54 (EtOAc); white solid; mp 145-147 °C; ν_{max} (neat, cm^{-1}): 2162, 1709 (C=O), 1568, 1494, 1431, 1353, 1285, 1257, 1206, 1077; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.59 (dd, *J* = 4.9, 1.8 Hz, 1H, Pyr-6-H), 8.22 (dd, *J* = 7.9, 1.8 Hz, 1H, Pyr-4-H), 8.15 (s, 1H, BnIm-2-H), 7.78-7.76 (m, 1H, BnIm-4-H), 7.51-7.49 (m, 1H, BnIm-7-H), 7.25-7.20 (m, 3H), 5.90 (s, 2H, CH_2), 3.92 (s, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.1 (C=O), 156.1 (C), 152.5 (Pyr-6-CH), 144.6 (BnIm-2-CH), 143.6 (C), 139.1 (Pyr-4-CH), 134.5 (C), 124.7 (C), 123.1, 122.8 122.0 (all CH), 120.0 (BnIm-4-CH), 110.7 (BnIm-7-CH), 52.8 (Me), 49.0 (CH_2); HRMS (ESI): *m/z* calcd for $C_{15}H_{14}N_3O_2$: 268.1086, found: 268.1095 $[M+H]^+$

Experiment 9; Synthesis of methyl 2-[(4,7-dimethoxy-1*H*-benzimidazol-1-yl)methyl]benzoate (**8c**)



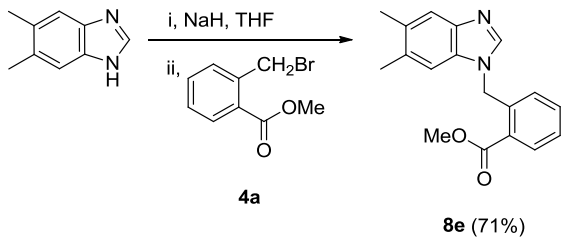
A mixture of 4,7-dimethoxy-1*H*-benzimidazole (1.940 g, 10.89 mmol), sodium hydride (0.320 g, 13.33 mmol) in DMF (50.00 mL) was heated to 80 °C for one hour. Methyl 2-(bromomethyl)benzoate (2.500 g, 10.91 mmol) was added and the mixture stirred for 18 hours at room temperature. The mixture was filtered through celite, and purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of hexane, ethyl acetate and methanol as eluent to give methyl 2-[(4,7-dimethoxy-1*H*-benzimidazol-1-yl)methyl]benzoate (2.565 g, 72%); R_f = 0.33 (EtOAc); pale brown solid; mp 135-137 °C; ν_{max} (neat, cm^{-1}): 1719 (C=O), 1525, 1492, 1439, 1373, 1257, 1237, 1194, 1171, 1090, 1075; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03-8.01 (m, 1H), 7.77 (s, 1H, BnIm-2-H), 7.35-7.30 (m, 2H), 6.67-6.64 (m, 1H), 6.54 (s, 2H, BnIm-5 & 6-H), 6.00 (s, 2H, CH_2), 3.98 (s, 3H, Me), 3.95 (s, 3H, Me), 3.65 (s, 3H, COOMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5 (C=O), 146.3 (C), 143.0 (BnIm-2-CH), 142.0, 140.2, 136.1 (all C), 132.9 (CH), 131.0 (CH), 127.6 (C), 127.4 (CH), 127.2 (CH), 125.4 (C), 103.90 (BnIm-5 or 6-CH), 102.1 (BnIm-5 or 6-CH), 56.1 (Me), 56.0 (COOMe), 52.4 (Me), 48.6 (CH_2); HRMS (ESI): m/z calcd for $C_{18}H_{19}N_2O_4$: 327.1345, found: 327.1360 $[M+H]^+$

Experiment 10; Synthesis of methyl 2-[(4,7-dimethoxy-1*H*-benzimidazol-1-yl)methyl]nicotinate (**8d**)



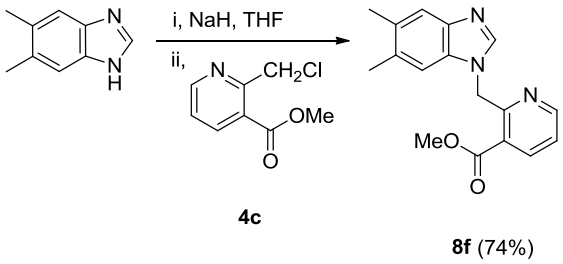
A mixture of 4,7-dimethoxy-1*H*-benzimidazole (1.000 g, 5.61 mmol), sodium hydride (0.160 g, 6.67 mmol) in DMF (50.00 mL) was heated to 80°C for one hour. Methyl 2-(chloromethyl)nicotinate (1.373 g, 7.40 mmol) was added and stirred for 18 hours at 80 °C. The mixture was filtered through celite, and purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of hexane, ethyl acetate and methanol as eluent to give methyl 2-[(4,7-dimethoxy-1*H*-benzimidazol-1-yl)methyl]nicotinate (1.414 g, 77%); R_f = 0.31 (6:3:1 Hexane:EtOAc:MeOH); pale brown solid; mp 150-155 °C; ν_{max} (neat, cm^{-1}): 1719 (C=O), 1570, 1515, 1340, 1259, 1226, 1171, 1140, 1098, 1080; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (dd, *J* = 4.8, 1.6 Hz, 1H, Pyr-6-H), 8.42 (bs, 1H, BnIm-2-H), 8.30 (dd, *J* = 7.9, 1.6 Hz, 1H, Pyr-4-H), 7.28 (dd, *J* = 7.9, 4.8 Hz, 1H, Pyr-5-H), 6.61 (d(AB-q), *J* = 8.6 Hz, 1H, BnIm-5 or 6-H), 6.57 (d(AB-q), *J* = 8.6 Hz, 1H, BnIm-5 or 6-H), 6.18 (s, 2H, CH_2), 4.00 (s, 3H, Me), 3.95 (s, 3H, Me), 3.64 (s, 3H, COOMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3 (C=O), 156.4 (C), 152.5 (Pyr-6-CH), 145.0 (C), 143.2 (BnIm-2-CH), 142.3 (C), 141.8 (C), 138.7 (Pyr-4-CH), 124.7 (C), 124.1 (C), 122.5 (Pyr-5-CH), 104.8 (BnIm-5 or 6-CH), 103.4 (BnIm-5 or 6-CH), 56.2 (Me), 56.0 (COOMe), 52.8 (Me), 50.9 (CH_2); HRMS (ESI): m/z calcd for $C_{17}H_{18}N_3O_4$: 328.1297, found: 328.1295 $[M+H]^+$

Experiment 11; Synthesis of methyl 2-[(5,6-dimethyl-1*H*-benzimidazol-1-yl)methyl]benzoate (**8e**)



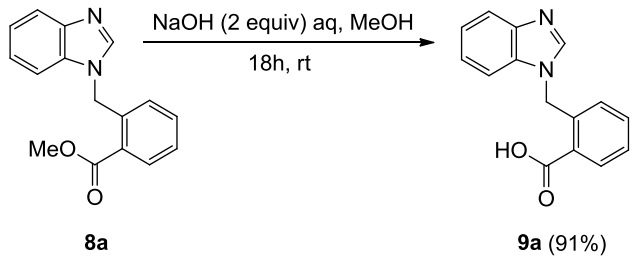
A mixture of 5,6-dimethyl-1*H*-benzimidazol (0.813 g, 5.56 mmol), sodium hydride (0.137 g, 5.70 mmol) in THF (100 mL) was heated under reflux for 1 hour. Methyl 2-(bromomethyl)benzoate (1.401 g, 6.12 mmol) was added and the mixture left to stir at room temperature for 72 hours. The mixture was purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of hexane and ethyl acetate as eluent to give methyl 2-[(5,6-dimethyl-1*H*-benzimidazol-1-yl)methyl]benzoate (1.162 g, 71%); brown solid; R_f = 0.54 (9:1 EtOAc:methanol); mp 128-131 °C; ν_{max} (neat, cm^{-1}): 3095, 3025, 2947, 1709 (C=O), 1601, 1579, 1495, 1471, 1448, 1435, 1385, 1352, 1329, 1275, 1223, 1195, 1140, 1129, 1079, 1048; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08-8.06 (m, 1H, CH), 7.88 (s, 1H, BnIm-2-H), 7.60 (s, 1H, BnIm-4-H), 7.38-7.34 (m, 2H, CH), 7.00 (s, 1H, BnIm-7-H), 6.72-6.70 (m, 1H, CH), 5.78 (s, 2H, CH_2), 3.94 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.31 (s, 3H, CH_3); ^{13}CNMR (100 MHz, $CDCl_3$): δ = 167.3 (C=O), 143.0 (BnIm-2-CH), 142.1 (C), 138.3 (C), 133.2 (CH), 132.7 (C), 132.6 (C), 131.5 (C), 131.4 (CH), 128.0 (C), 127.9 (CH), 127.5 (CH), 120.3 (BnIm-4-CH), 110.3 (BnIm-7-CH), 52.4 (CH_3), 47.2 (CH_2), 20.6 (CH_3), 20.4 (CH_3); HRMS (ESI): *m/z* calcd for $C_{18}H_{19}N_2O_2$: 295.1447, found: 295.1448 $[M+H]^+$

Experiment 12; Synthesis of methyl 2-[(5,6-dimethyl-1*H*-benzimidazol-1-yl)methyl]nicotinate (**8f**)



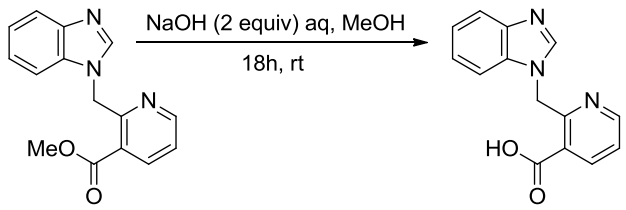
A mixture of 5,6-dimethyl-1*H*-benzimidazol (1.418 g, 9.70 mmol), sodium hydride (0.242 g, 10.08 mmol) in THF (100 mL) was heated under reflux for one hour. Methyl 2-(chloromethyl)nicotinate (2.700 g, 14.55 mmol) was added and the mixture left to stir at room temperature for 72 hours. The mixture was purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of hexane and ethyl acetate as eluent to give methyl 2-[(5,6-dimethyl-1*H*-benzimidazol-1-yl)methyl]nicotinate (2.120 g, 74%); R_f = 0.58 (9:1 EtOAc:MeOH); brown solid; mp 157-160 °C; ν_{max} (neat, cm^{-1}): 2922, 1711 (C=O), 1630, 1583, 1570, 1498, 1472, 1444, 1429, 1375, 1359, 1329, 1285, 1263, 1221, 1192, 1142, 1079, 1058, 1023; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.65 (dd, J = 4.8, 1.8 Hz, 1H, Pyr-6-H), 8.26 (dd, J = 7.9, 1.8 Hz, 1H, Pyr-4-H), 8.00 (s, 1H, BnIm-2-H), 7.51 (s, 1H, BnIm-4-H), 7.30 (dd, J = 7.9, 4.8 Hz, 1H, Pyr-5-H), 7.22 (s, 1H, BnIm-7-H), 5.86 (s, 2H, CH_2), 3.94 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.32 (s, 3H, CH_3); ^{13}CNMR (100 MHz, $CDCl_3$): δ = 166.2 (C=O), 156.4 (C), 152.5 (Pyr-6-CH), 143.8 (BnIm-2-CH), 142.1 (C), 139.1 (Pyr-4-CH), 133.0 (C), 132.0 (C), 130.9 (C), 124.8 (C), 123.1 (Pyr-5-CH), 120.1 (BnIm-4-CH), 110.7 (BnIm-7-CH), 52.8 (CH_3), 49.1 (CH_2), 20.7 (CH_3), 20.3 (CH_3); HRMS (ESI): *m/z* calcd. for $C_{17}H_{18}N_3O_2$: 296.1399, found: 296.1409 $[M+H]^+$

Experiment 13; Synthesis of 2-(1*H*-benzimidazol-1-ylmethyl)benzoic acid (**9a**)



Sodium hydroxide (1.000 g, 25.00 mmol) in distilled water (30 mL) was added to methyl 2-(1*H*-benzimidazol-1-ylmethyl)benzoate (3.000 g, 11.27 mmol) in methanol (30 mL) and stirred for 18 hours at room temperature. The methanol was evaporated under reduced pressure and the remaining aqueous solution was neutralized with dilute hydrochloric acid. The precipitate was filtered and dried to give 2-(1*H*-benzimidazol-1-ylmethyl)benzoic acid (2.586 g, 91%) as a white solid; mp 206-208 ºC; v_{max} (neat, cm^{-1}): 2400, 1686 (C=O), 1606, 1575, 1499, 1459, 1305, 1232, 1199, 1178, 1140; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.31 (s, 1H, BnIm-2-H), 7.95 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.69-7.67 (m, 1H, BnIm-4-H), 7.39-7.36 (m, 3H), 7.19-7.14 (m, 2H), 6.71 (d, *J* = 7.2 Hz, 1H), 5.87 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.8 (C=O), 145.3 (BnIm-2-CH), 143.9, 138.6, 134.5 (all C), 133.0 (CH), 131.4 (CH), 130.0 (C), 128.3, 128.0, 123.1, 122.3 (all CH), 120.1 (BnIm-4-CH), 111.2 (BnIm-7-CH), 46.8 (CH_2); HRMS (ESI): *m/z* calcd for $C_{15}H_{13}N_2O_2$: 253.0977, found: 253.0989 $[M+H]^+$; λ max = 227 nm, (ε = 10,741 L/mol·cm)

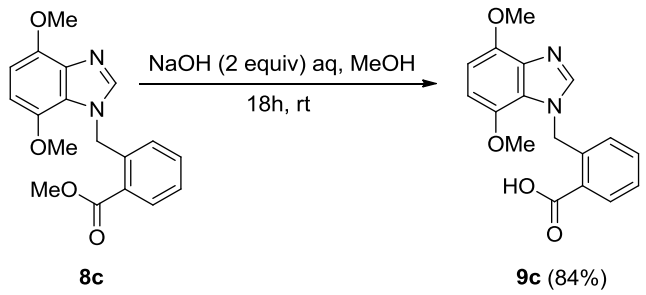
Experiment 14; Synthesis of 2-(1*H*-benzimidazol-1-ylmethyl)nicotinic acid (**9b**)



8b **9b** (87%)

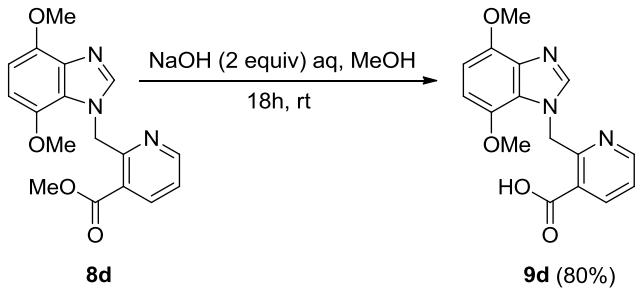
Sodium hydroxide (0.100 g, 2.50 mmol) in distilled water (25 mL) and methyl 2-(1*H*-benzimidazole-1-ylmethyl)nicotinate (0.320 g, 1.20 mmol) in methanol (25 mL) were stirred for 18 hours at room temperature. The methanol was evaporated under reduced pressure and the remaining aqueous solution was neutralized with dilute hydrochloric acid. The precipitate was filtered and dried to give 2-(1*H*-benzimidazol-1-ylmethyl)nicotinic acid (0.264 g, 87%); white solid; mp 216-219 ºC; ν_{max} (neat, cm^{-1}): 2486, 1914, 1699 (C=O), 1578, 1497, 1454, 1429, 1368, 1247, 1194, 1143, 1080; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.51 (dd, *J* = 4.8, 1.7 Hz, 1H, Pyr-6-H) 8.27 (dd, *J* = 7.8, 1.7 Hz, 1H, Pyr-4-H), 8.23 (s, 1H, BnIm-2-H), 7.61-7.59 (m, 1H, BnIm-4-CH), 7.43-7.37 (m, 2H), 7.15-7.11 (m, 2H, BnIm-5 & 6-H), 5.94 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.1 (C=O). 156.2 (C), 152.0 (Pyr-6-CH), 145.8 (BnIm-2-CH), 143.6 (C), 139.3 (Pyr-4-CH), 135.0 (C), 126.9 (C), 123.5, 122.8, 121.9 (all CH), 119.7 (BnIm-4-CH), 111.2 (BnIm-7-CH), 48.6 (CH_2); HRMS (ESI): *m/z* calcd for $C_{14}H_{12}N_3O_2$: 254.0930, found: 254.0935 $[M+H]^+$; λ max = 251 nm, (ε = 4,895 L/mol·cm)

Experiment 15; Synthesis of 2-[(4,7-dimethoxy-1*H*-benzimidazol-1-yl)methyl]benzoic acid (**9c**)



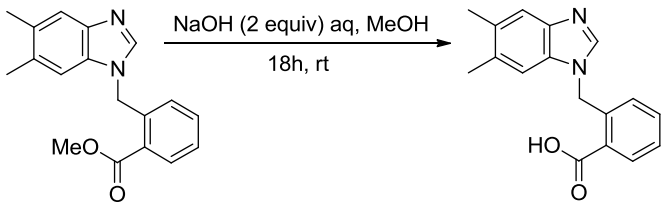
Sodium hydroxide (0.245 g, 6.13 mmol) in distilled water (20 mL) was added to methyl 2-[(4,7-dimethoxy-1*H*-benzimidazol-1-yl)methyl]benzoate (1.000 g, 3.06 mmol) in methanol (25.00 mL) were stirred for 18 hours at room temperature. The methanol was evaporated under reduced pressure and the remaining aqueous solution was neutralized with dilute hydrochloric acid. The precipitate was filtered and dried to give 2-[(4,7-dimethoxy-1*H*-benzimidazol-1-yl)methyl]benzoic acid (0.803 g, 84%); white solid; mp 158-162 ºC; ν_{max} (neat, cm^{-1}): 1692 (C=O), 1525, 1459, 1373, 1264, 1229, 1171, 1138, 1095, 1060; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.13 (s, 1H, BnIm-2-H), 7.91 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.38-7.31 (m, 2H), 6.56 (d(AB-q), *J* = 8.6 Hz, 1H, BnIm-5 or 6-H), 6.53 (d(AB-q), *J* = 8.6 Hz, 1H, BnIm-5 or 6-H), 6.41 (d, *J* = 7.4 Hz, 1H), 5.93 (s, 2H, CH_2), 3.84 (s, 3H, Me), 3.53 (s, 3H, Me); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.8 (C=O), 146.2 (C), 144.3 (BnIm-2-CH), 141.9, 140.6, 136.0 (all C), 132.9 (CH), 131.0 (CH), 129.3 (C), 127.6 (CH), 126.6 (CH), 125.3 (C), 104.6 (BnIm-5 or 6-CH), 103.3 (BnIm-5 or 6-CH), 56.5 (Me), 56.3 (Me), 48.4 (CH_2); HRMS (ESI): m/z calcd for $C_{17}H_{17}N_2O_4$: 313.1188, found: 313.1196 $[M+H]^+$; λ max = 214 nm, (ε = 24,910 L/mol·cm)

Experiment 16; Synthesis of 2-[(4,7-dimethoxy-1*H*-benzimidazol-1-yl)methyl]nicotinic acid (**9d**)



Sodium hydroxide (0.308 g, 7.70 mmol) in distilled water (25 mL) and methyl 2-[(4,7-dimethoxy-1*H*-benzimidazol-1-yl)methyl]nicotinate (1.260 g, 3.85 mmol) in methanol (30 mL) were stirred for 18 hours at room temperature. The methanol was evaporated under reduced pressure and the remaining aqueous solution was neutralized with dilute hydrochloric acid. The precipitate was filtered and dried to give 2-[(4,7-dimethoxy-1*H*-benzimidazol-1-yl)methyl]nicotinic acid (0.965 g, 80%); white solid; mp 258-262 ºC; ν_{max} (neat, cm^{-1}): 2506, 1914, 1704 (C=O), 1585, 1515, 1467, 1451, 1406, 1378, 1230, 1272, 1224, 1171, 1140, 1100; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.42 (dd, *J* = 4.8, 1.7 Hz, 1H, Pyr-6-H), 8.26 (s, 1H, BnIm-2-H), 8.23 (dd, *J* = 7.8, 1.7 Hz, 1H, Pyr-4-H), 7.35 (dd, *J* = 7.8, 4.8 Hz, 1H, Pyr-5-H), 6.54 (d(AB-q), *J* = 8.8 Hz, 1H, BnIm-5 or 6-H), 6.52 (d(AB-q), *J* = 8.8 Hz, 1H, BnIm-5 or 6-H), 6.03 (s, 2H, CH_2), 3.84 (s, 3H, Me), 3.48 (s, 3H, Me); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.9 (C=O), 157.5 (C), 152.2 (Pyr-6-CH), 145.6 (C), 144.8 (BnIm-2-CH), 142.0 (C), 139.0 (Pyr-4-CH), 134.4, 125.4, 125.3 (all C), 123.0 (Pyr-5-CH), 104.6 (BnIm-5 or 6-CH), 103.5 (BnIm-5 or 6-CH), 56.4 (Me), 56.3 (Me), 50.2 (CH_2); HRMS (ESI): m/z calcd for $C_{16}H_{16}N_3O_4$: 314.1141, found: 314.1141 $[M+H]^+$; λ max = 215 nm, (ε = 25,682 L/mol·cm)

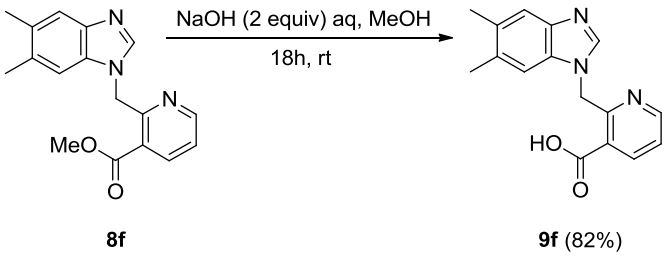
Experiment 17; Synthesis of 2-[(5,6-dimethyl-1*H*-benzimidazol-1-yl)methyl]benzoic acid (**9e**)



8e **9e** (70%)

Sodium hydroxide (1.000 g, 25.00 mmol) in distilled water (30 mL) was added to methyl 2-[(5,6-dimethyl-1*H*-benzimidazol-1-yl)methyl]benzoate (0.900 g, 3.06 mmol) in methanol (30 mL) and left to stir at room temperature for 18 hours. The methanol was evaporated under reduced pressure and the remaining aqueous solution was neutralized with dilute hydrochloric acid. The precipitate was filtered and dried to give 2-[(5,6-dimethyl-1*H*-benzimidazol-1-yl)methyl]benzoic acid (0.602 g, 70%); cream solid; mp 149-152 ºC; ν_{max} (neat, cm^{-1}): 2923, 2422, 1693 (C=O), 1601, 1579, 1496, 1473, 1449, 1375, 1212, 1173, 1145, 1077; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.13 (s, 1H, BnIm-2-H), 7.93 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.42 (s, 1H, BnIm-4-H), 7.40-7.33 (m, 2H), 7.14 (s, 1H, BnIm-7-H), 6.58 (d, *J* = 7.5 Hz, 1H), 5.78 (s, 2H, CH_2), 2.25 (s, 3H, CH_3), 2.21 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.8 (C=O), 144.4 (BnIm-2-CH), 142.6, 138.9, 133.0 (all C), 132.9 (CH), 131.8 (C), 131.4 (CH), 130.6 (C), 130.0 (C), 128.1 (CH), 127.6 (CH), 120.1 (BnIm-4-CH), 111.0 (BnIm-7-CH), 46.7 (CH_2), 20.6 (CH_3), 20.4 (CH_3); HRMS (ESI): *m/z* calcd. for $C_{17}H_{17}N_2O_2$: 281.1290, found: 281.1292 $[M+H]^+$; λ max = 251 nm, (ε = 7,113 L/mol·cm)

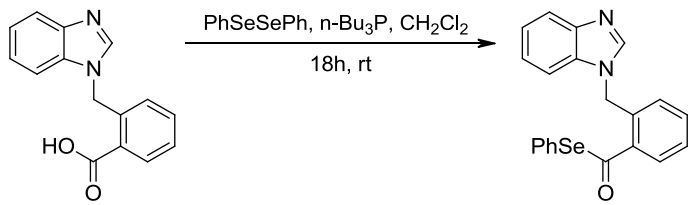
Experiment 18; Synthesis of 2-[(5,6-dimethyl-1*H*-benzimidazol-1-yl)methyl]nicotinic acid (**9f**)



Sodium hydroxide (1.000 g, 25.00 mmol) in distilled water (30 mL) was added to methyl 2-[(5,6-dimethyl-1*H*-benzimidazol-1-yl)methyl]nicotinate (1.603 g, 5.43 mmol) in methanol (30 mL) and left to stir at room temperature for 18 hours. The methanol was evaporated under reduced pressure and the remaining aqueous solution was neutralized with dilute hydrochloric acid. The precipitate was filtered and dried to give 2-[(5,6-dimethyl-1*H*-benzimidazol-1-yl)methyl]nicotinic acid (1.253 g, 82%); cream solid; mp 133-136 ºC; ν_{max} (neat, cm^{-1}): 2922, 2853, 1598 (C=O), 1499, 1451, 1377, 1263, 1177, 1086, 1022; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.50-8.48 (m, 1H, Pyr-6-H), 8.25 (dd, *J* = 7.8, 1.7, 1H, Pyr-4-H), 8.09 (s, 1H, BnIm-2-CH), 7.41-7.38 (m, 1H, Pyr-5-H), 7.37 (s, 1H, BnIm-4-H), 7.14 (s, 1H, BnIm-7-CH), 5.87 (s, 2H, CH_2), 2.24 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.8 (C=O), 156.6 (C), 152.3 (Pyr-6-CH), 144.8 (BnIm-2-CH), 142.1 (C), 139.3 (Pyr-4-CH), 133.5 (C), 131.3 (C), 130.2 (C), 126.1 (C), 123.5 (Pyr-5-CH), 119.7 (BnIm-4-CH), 111.1 (BnIm-7-CH), 48.6 (CH_2), 20.6 (CH_3), 20.4 (CH_3); HRMS (ESI): m/z calcd. for $C_{16}H_{16}N_3O_2$: 282.1243, found: 282.1234 $[M+H]^+$; λ max = 256 nm, (ε = 5,516 L/mol·cm)

Experiment 19; Synthesis of

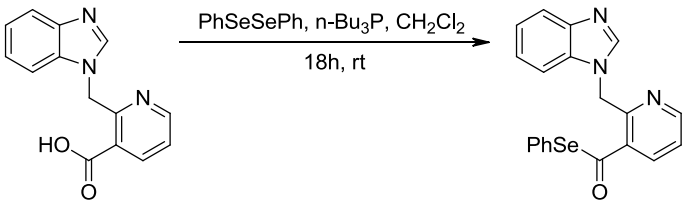
2-(1*H*-benzimidazol-1-ylmethyl)benzenecarbophenylselenoate (**10a**)



9a **10a** (72%)

2-(1*H*-benzimidazol-1-ylmethyl)benzoic acid (0.500 g, 1.98 mmol) was added to a solution of diphenyl diselenide (1.000 g, 3.20 mmol) and tributyl phosphine (1.00 mL, 4.05 mmol) in dichloromethane (50 mL) and stirred for 18 hours. The solution was evaporated to dryness and petroleum ether was added. The flask was shaken vigorously causing the product to precipitate out. The hexane was decanted and the precipitate was dissolved in dichloromethane (1 mL). Petroleum ether (50 mL) was added and the precipitate was filtered and dried to give 2-(1*H*-benzimidazol-1-ylmethyl)benzenecarbophenylselenoate (0.558 g, 72%); white solid; mp 101-103 ºC; ν_{max} (neat, cm^{-1}): 1676 (C=O), 1573, 1487, 1454, 1348, 1282, 1262, 1194; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06-8.04 (m, 1H), 7.91 (s, 1H, BnIm-2-H), 7.85-7.83 (m, 1H), 7.55-7.53 (m, 2H), 7.46-7.42 (m, 5H), 7.29-7.22 (m, 3H), 6.88-6.86 (m, 1H), 5.59 (s, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.3 (C=O), 143.9 (BnIm-2-CH), 143.7 (C), 137.2 (C), 136.4 (2 x CH), 134.2 (C), 134.0 (C), 133.3 (CH), 129.9 (CH), 129.7 (2 x CH), 129.5, 128.6, 128.4 (all CH), 126.2 (C), 123.4 (CH), 122.5 (CH), 120.5 (BnIm-4-CH), 110.2 (BnIm-7-CH), 46.7 (CH_2); HRMS (ESI): *m/z* calcd for $C_{21}H_{17}N_2O^{80}Se$: 393.0506, found: 393.0504 $[M+H]^+$; λ max = 244 nm, (ε = 20,984 L/mol·cm)

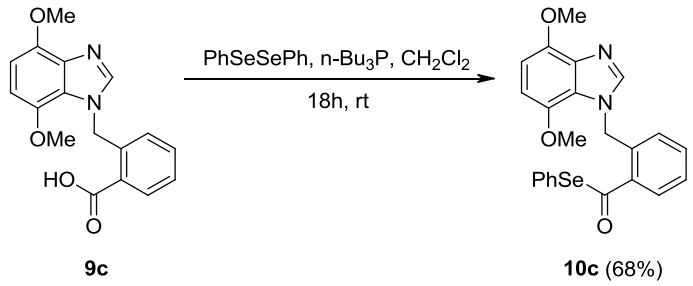
Experiment 20; Synthesis of 2-(1*H*-benzimidazol-1-ylmethyl)pyridine-3-carbophenylselenoate (**10b**)



9b **10b** (73%)

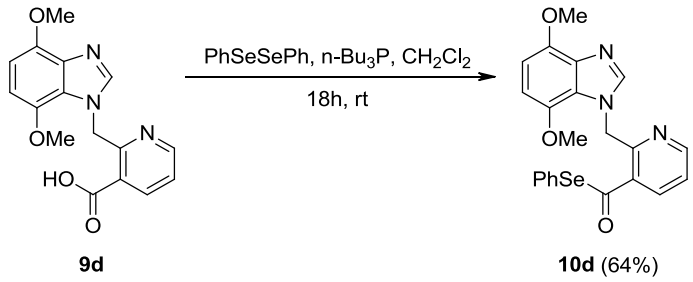
2-(1*H*-benzimidazol-1-ylmethyl)nicotinic acid (0.500 g, 1.97 mmol) was added to a solution of diphenyl diselenide (1.000 g, 3.20 mmol) and tributyl phosphine (1.00 mL, 4.05 mmol) in dichloromethane (50 mL) and stirred for 18 hours. The solution was evaporated to dryness and petroleum ether was added. The flask was shaken vigorously causing the product to precipitate out. The hexane was decanted and the precipitate was dissolved in dichloromethane (1 mL). Petroleum ether (50 mL) was added and the precipitate was filtered and dried to give 2-(1*H*-benzimidazol-1-ylmethyl)pyridine-3-carbophenylselenoate (0.565 g, 73%); white solid; m.p. 115-118 ºC; ν_{max} (neat, cm^{-1}): 1674 (C=O), 1616, 1560, 1492, 1457, 1436, 1414, 1383, 1355, 1287, 1269, 1201, 1189, 1060; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.65 (dd, *J* = 4.8, 1.5 Hz, 1H, Pyr-6-H), 8.18 (dd, *J* = 7.9, 1.5 Hz, 1H, Pyr-4-H), 8.00 (s, 1H, BnIm-2-H), 7.79 (dd, *J* = 6.8, 1.8 Hz, 1H, BnIm-4-H), 7.52-7.50 (m, 2H), 7.48-7.45 (m, 3H), 7.39-7.35 (m, 2H), 7.24-7.21 (m, 2H), 5.67 (s, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.1 (C=O), 152.4 (Pyr-6-CH), 152.2 (C), 144.5 (BnIm-2-CH), 143.6 (C), 136.9 (Pyr-4-CH), 136.3 (2 x CH), 134.3 (C), 133.8 (C), 129.8 (3 x CH), 125.6 (C), 123.5, 123.0, 122.2 (all CH), 120.3 (BnIm-4-CH), 110.6 (BnIm-7-CH), 48.6 (CH_2); HRMS (ESI): *m/z* calcd for $C_{20}H_{16}N_3O^{80}Se$: 394.0459, found: 394.0468 $[M+H]^+$; λ max = 247 nm, (ε = 13,175 L/mol·cm)

Experiment 21; Synthesis of 2-[(4,7-dimethoxy-1*H*-benzimidazol-1-yl)methyl]benzenecarbophenylselenoate (**10c**)



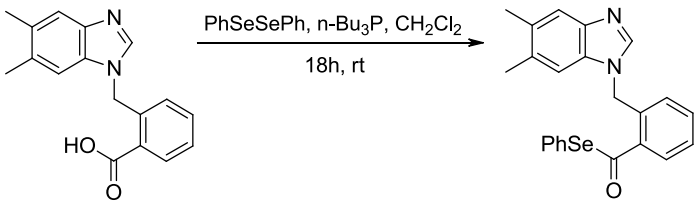
2-[(4,7-dimethoxy-1*H*-benzimidazol-1-ylmethyl)]benzoic acid (1.000 g, 3.20 mmol) was added to a solution of diphenyl diselenide (2.000 g, 6.41 mmol) and tributyl phosphine (2.00 mL, 8.11 mmol) in dichloromethane (100 mL) and stirred for 18 hours. The solution was evaporated to dryness and petroleum ether was added. The flask was shaken vigorously causing the product to precipitate out. The hexane was decanted and the precipitate was dissolved in dichloromethane (2 mL). Petroleum ether (100 mL) was added and the precipitate was filtered and dried to give 2-[(4,7-dimethoxy-1*H*-benzimidazol-1-yl)methyl]benzenecarbophenylselenoate (0.982 g, 68%); white solid; mp 133-137 ºC; ν_{max} (neat, cm^{-1}): 1692 (C=O), 1522, 1462, 1371, 1272, 1229, 1196, 1130, 1092; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05-8.03 (m, 1H), 7.75 (s, 1H, BnIm-2-H), 7.62-7.60 (m, 2H), 7.46-7.45 (m, 3H), 7.40-7.37 (m, 2H), 6.71-6.69 (m, 1H), 6.53 (s, 2H, BnIm-5 & 6-H), 5.78 (s, 2H, CH_2), 3.97 (s, 3H, OMe), 3.67 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.9 (C=O), 146.1 (C), 142.9 (C), 141.8 (C), 136.7 (C), 136.3 (2 x CH), 136.2 (C), 133.4 (CH), 129.7 (3 x CH & BnIm-2-CH), 129.5 (CH), 129.4 (CH), 128.1 (CH), 127.9 (CH), 126.5 (C), 125.0 (C), 104.2 (BnIm-5 or 6-CH), 102.6 (BnIm-5 or 6-CH), 56.3 (OMe), 56.1 (OMe), 48.3 (CH_2); HRMS (ESI): *m/z* calcd for $C_{23}H_{21}N_2O_3{}^{80}Se$: 453.0717, found: 453.0718 $[M+H]^+$; λ max = 205 nm, (ε = 41,424 L/mol·cm)

Experiment 22; Synthesis of 2-[(4,7-dimethoxy-1*H*-benzimidazol-1-yl)methyl]pyridine-3-carbophenylselenoate (**10d**)



2-[(4,7-dimethoxy-1*H*-benzimidazol-1-ylmethyl)]nicotinic acid (0.800 g, 2.55 mmol) was added to a solution of diphenyl diselenide (2.000 g, 6.41 mmol) and tributyl phosphine (2.00 ml, 8.11 mmol) in dichloromethane (100 mL) and stirred for 18 hours. The solution was evaporated to dryness and petroleum ether was added. The flask was shaken vigorously causing the product to precipitate out. The hexane was decanted and the precipitate was dissolved in dichloromethane (2 mL). Petroleum ether (100 mL) was added and the precipitate was filtered and dried to give 2-[(4,7-dimethoxy-1*H*-benzimidazol-1-yl)methyl]pyridine-3-carbophenylselenoate (0.738 g, 64%); pale white solid; m.p. 189-193 ºC; ν_{max} (neat, cm^{-1}): 2928, 2831, 1690 (C=O), 1559, 1519, 1487, 1436, 1367, 1276, 1263, 1236, 1196, 1169, 1140, 1092, 1060; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (dd, *J* = 4.8, 1.6 Hz, 1H, Pyr-6-H), 8.25 (dd, *J* = 7.9, 1.7 Hz, 1H, Pyr-4-H), 7.81 (s, 1H, BnIm-2-H), 7.58-7.56 (m, 2H), 7.48-7.44 (m, 3H), 7.31 (dd, *J* = 7.9, 4.9 Hz, 1H), 6.48 (d (AB-q), *J* = 8.5 Hz, 1H, BnIm-5 or 6-H), 6.45 (d (AB-q), *J* = 8.5 Hz, 1H, BnIm-5 or 6-H), 5.83 (s, 2H, CH_2), 3.95 (s, 3H, OMe), 3.63 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.7 (C=O), 154.0 (C), 152.6 (Pyr-6-CH), 146.3 (C), 143.9 (BnIm-2-CH), 141.8 (C), 136.6 (Pyr-4-CH), 136.1 (2 x CH), 135.9 (C), 132.5 (C), 129.8 (2 x CH), 129.6 (CH), 125.9 (C), 125.4 (C), 122.5 (CH), 103.5 (BnIm-5 or 6-CH), 102.0 (BnIm-5 or 6-CH), 56.1 (OMe), 55.9 (OMe), 49.7 (CH_2); HRMS (ESI): *m/z* calcd for $C_{22}H_{20}N_3O_3{}^{80}Se$: 454.0670, found: 454.0650 $[M+H]^+$; λ max = 254 nm, (ε = 12,138 L/mol·cm)

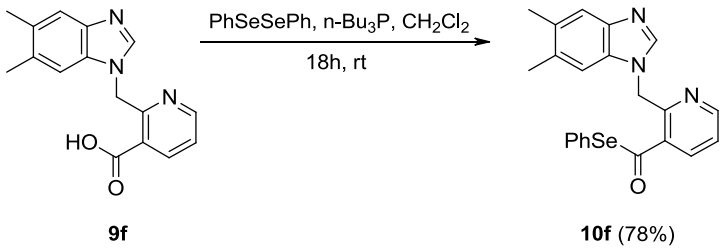
Experiment 23; Synthesis of 2-[(5,6-dimethyl-1*H*-benzimidazol-1-yl)methyl]benzenecarbophenylselenoate (**10e**)



9e **10e** (76%)

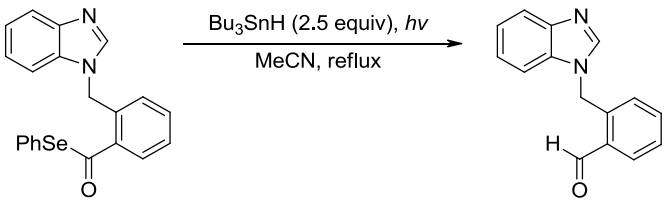
2-[(5,6-dimethyl-1*H*-benzimidazol-1-yl)methyl]benzoic acid (0.500 g, 1.78 mmol) was added to a solution of diphenyl diselenide (1.000 g, 3.20 mmol) and tributyl phosphine (1.00 mL, 4.05 mmol) in dichloromethane (50 mL) and stirred for 18 hours. The solution was evaporated to dryness and petroleum ether was added. The flask was shaken vigorously causing the product to precipitate out. The hexane was decanted and the precipitate was dissolved in dichloromethane (1 mL). Petroleum ether (50 mL) was added and the precipitate was filtered and dried to give 2-[(5,6-dimethyl-1*H*-benzimidazol-1-yl)methyl]benzenecarbophenylselenoate (0.569 g, 76%); white solid; mp 189-192 ºC; ν_{max} (neat, cm^{-1}): 2957, 2567, 1687 (C=O), 1671, 1570, 1537, 1477, 1439, 1345, 1323, 1292, 1242, 1206, 1173; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.42 (s, 1H, BnIm-2-H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.68 (s, 1H, BnIm-4-H), 7.56-7.49 (m, 2H), 7.46-7.44 (m, 2H), 7.39-7.34 (m, 4H), 7.22 (s, 1H, BnIm-7-H), 5.80 (s, 2H, CH_2), 2.29 (s, 3H, CH_3), 2.28 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.7 (C=O), 139.2 (BnIm-2-CH), 137.9 (C), 137.0 (C), 136.8 (C), 136.2 (2 x CH), 133.8 (CH), 130.6 (CH), 130.5 (C), 130.0 (CH), 129.9 (CH), 129.7 (2 x CH), 129.6 (2 x C), 129.6 (CH), 125.9 (C), 115.6 (BnIm-4-CH), 112.1 (BnIm-7-CH), 48.0 (CH_2), 20.8 (CH_3), 20.4 (CH_3); HRMS (ESI): *m/z* calcd for $C_{23}H_{21}N_2O^{80}Se$: 421.0819, found: 421.0825 $[M+H]^+$; λ max = 242 nm, (ε = 16,311 L/mol·cm)

Experiment 24; Synthesis of 2-[(5,6-dimethyl-1*H*-benzimidazol-1-yl)methyl]pyridine-3-carbophenylselenoate (**10f**)



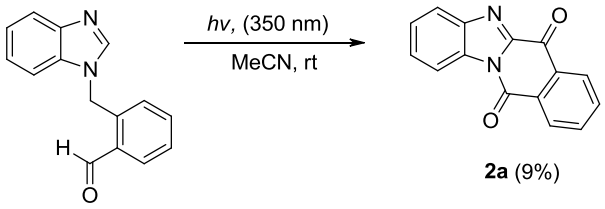
2-[(5,6-dimethyl-1*H*-benzimidazol-1-yl)methyl]nicotinic acid (0.500 g, 1.78 mmol) was added to a solution of diphenyl diselenide (1.000 g, 3.20 mmol) and tributyl phosphine (1.00 mL, 4.05 mmol) in dichloromethane (50 mL) and stirred for 18 hours. The solution was evaporated to dryness and petroleum ether was added. The flask was shaken vigorously causing the product to precipitate out. The hexane was decanted and the precipitate was dissolved in dichloromethane (1 mL). Petroleum ether (50 mL) was added and the precipitate was filtered and dried to give 2-[(5,6-dimethyl-1*H*-benzimidazol-1-yl)methyl]pyridine-3-carbophenylselenoate (0.583 g, 78%); white solid; mp 223-225 ºC (dec. 201-205ºC); ν_{max} (neat, cm^{-1}): 2972, 2537, 2491, 1697, 1669 (C=O), 1558, 1550, 1446, 1436, 1406, 1343, 1199; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.32 (1H, s, BnIm-2-H), 8.58 (d, *J* = 4.8, 1.4 Hz, 1H, Pyr-6-H), 8.36 (d, *J* = 7.9, 1.4 Hz, 1H, Pyr-4-H), 7.73 (s, 1H, BnIm-4-H), 7.60-7.57 (m, 2H), 7.48-7.44 (m, 4H), 7.29 (s, 1H, BnIm-7-H), 5.91 (s, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.31 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.0 (C=O), 153.0 (Pyr-6-CH), 149.3 (C), 139.9 (BnIm-2-CH), 137.8 (Pyr-4-CH), 136.8 (C), 136.6 (C), 136.3 (2 x CH), 132.9 (C), 130.0 (CH), 130.0 (2 x CH & 1 x C), 129.5 (C), 125.2 (C), 124.3 (CH), 115.8 (BnIm-4-CH), 111.9 (BnIm-7-CH), 49.4 (CH_2), 20.8 (CH_3), 20.4 (CH_3); HRMS (ESI): *m/z* calcd for $C_{22}H_{20}N_3O^{80}Se$: 422.0772, found: 422.0772 $[M+H]^+$; λ max = 230 nm, (ε = 14,007 L/mol·cm)

Experiment 25; Synthesis of 2-(1*H*-benzimidazol-1-ylmethyl)benzaldehyde (**11**)



2-(1*H*-benzimidazol-1-ylmethyl)benzenecarbophenylselenoate (0.200 g, 0.51 mmol) and tributyltin hydride (0.34 mL, 1.26 mmol) were heated under reflux in acetonitrile (50 mL) and irradiated with two 200 Watt tungsten lamps for 18 hours. The mixture was purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of hexane, ethyl acetate and methanol to give 2-(1*H*-benzimidazol-1-ylmethyl)benzaldehyde (70 mg, 58%); R_f = 0.24 (6:3:1 Hexane: EtOAc:MeOH); pale white solid; mp 150-154 ºC (lit.[111] mp 152-153 °C); v_{max} (neat, cm^{-1}): 2922, 2851, 1717 (C=O), 1613, 1492, 1446, 1378, 1239, 1060; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.17 (s, 1H, CHO), 7.99 (s, 1H, BnIm-2-H), 7.90 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.85 (d, *J* = 7.7 Hz, 1H), 7.55-7.51 (m, 1H), 7.48-7.43 (m, 1H), 7.32-7.23 (m, 3H), 6.75 (d, *J* = 7.7 Hz, 1H), 5.88 (s, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.9 (CHO), 143.8 (BnIm-2-CH), 143.8 (C), 137.7 (C), 136.2 (CH), 134.5 (CH), 134.5 (C), 133.1 (C), 128.6, 127.7, 123.4, 122.5 (all CH), 120.6 (BnIm-4-CH), 110.1 (BnIm-7-CH), 46.6 (CH_2); HRMS (ESI): *m/z* calcd for $C_{15}H_{13}N_2O$: 237.1028, found: 237.1028 $[M+H]^+$; λ max = 250 nm (ε = 4,342 L/mol·cm)

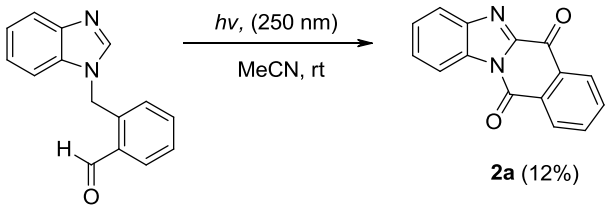
Experiment 26; Synthesis of benzimidazo[1,2-*b*]isoquinoline-6,11-dione (**2a**) from 2-(1*H*-benzimidazol-1-ylmethyl)benzaldehyde (**11**) using a Rayonet photochemical reactor (350 nm)



11 **2a** (9%)

2-(1*H*-benzimidazol-1-ylmethyl)benzaldehyde (0.250 g, 1.06 mmol) and acetonitrile (50 mL) was irradiated with light of wavelength 350 nm in a pyrex tube in a rayonet photochemical reactor for 18 hours. The solution was evaporated to dryness and purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of hexane and ethyl acetate to give benzimidazo[1,2-*b*]isoquinoline-6,11-dione (24 mg, 9%); R_f = 0.31 (CH_2Cl_2); yellow solid; mp 266-268 ºC (lit.[61] mp 268-271 °C); ν_{max} (neat, cm^{-1}): 2917, 1712 (C=O), 1684 (C=O), 1590, 1520, 1482, 1331, 1343, 1237, 1143, 1049, 1012; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45-8.38 (m, 3H), 8.00 (d, *J* = 8.1 Hz, 1H), 7.93-7.88 (m, 2H), 7.65-7.61 (m, 1H), 7.54-7.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1 (C=O), 158.9 (C=O), 144.3 (C), 143.4 (C), 135.4 (CH), 135.2 (CH), 132.9, 131.5, 129.9 (all C), 129.8, 129.7, 128.0, 127.0, 123.2, 116.2 (all CH); HRMS (ESI): *m/z* calcd for $C_{15}H_9N_2O_2$: 249.0664, found: 249.0664 $[M+H]^+$; λ max = 247 nm (ε = 13,724 L/mol·cm); and a mixture of other unidentifiable products.

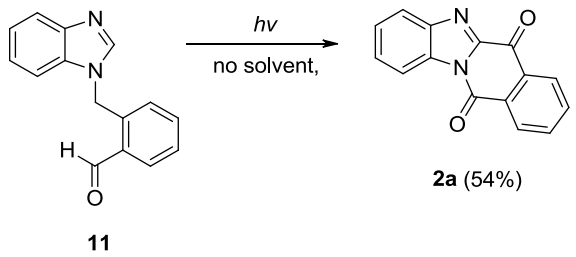
Experiment 27; Synthesis of benzimidazo[1,2-*b*]isoquinoline-6,11-dione (**2a**) from 2-(1*H*-benzimidazol-1-ylmethyl)benzaldehyde (**11**) using a Rayonet photochemical reactor (250 nm)



11

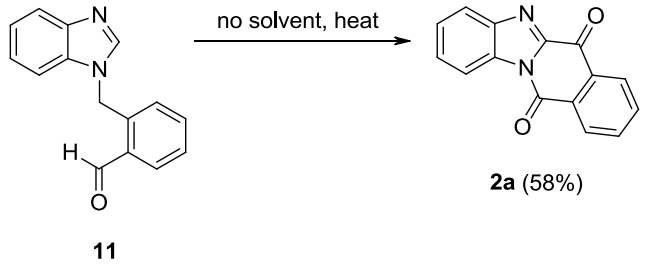
2-(1*H*-benzimidazol-1-ylmethyl)benzaldehyde (0.250 g, 1.06 mmol) and acetonitrile (50.00 mL) was irradiated with light of wavelength 250 nm in a quartz tube in a photochemical reactor for 8 hours. The solution was evaporated to dryness and purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of ethyl acetate and hexane to give benzimidazo[1,2-*b*]isoquinoline-6,11-dione (32 mg, 12%) and a mixture of other unidentifiable products. Spectroscopic data was consistent with that of previous experiments.

Experiment 28; Synthesis of benzimidazo[1,2-*b*]isoquinoline-6,11-dione (**2a**) from 2-(1*H*-benzimidazol-1-ylmethyl)benzaldehyde (**11**) in absence of solvent



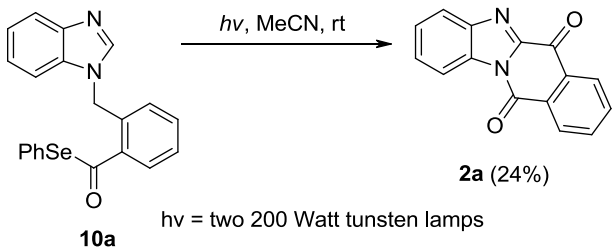
2-(1*H*-benzimidazol-1-ylmethyl)benzaldehyde (0.160 g, 0.68 mmol) was irradiated with light from two 200 watt tungsten lamps for 18 hours without solvent. The mixture was purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of ethyl acetate and hexane to give benzimidazo[1,2-*b*]isoquinoline-6,11-dione (91 mg, 54%) and a mixture of other unidentifiable products. Spectroscopic data was consistent with that of previous experiments.

Experiment 29; Synthesis of benzimidazo[1,2-*b*]isoquinoline-6,11-dione (**2a**) from 2-(1*H*-benzimidazol-1-ylmethyl)benzaldehyde (**11**) using only heat



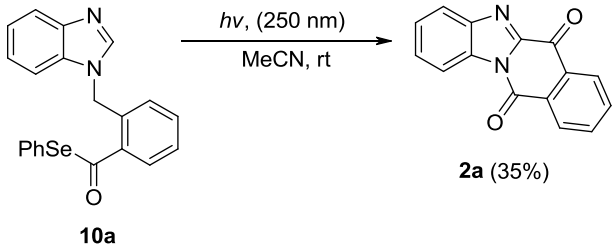
2-(1*H*-benzimidazol-1-ylmethyl)benzaldehyde (0.160 g, 0.68 mmol) was heated to 100 °C for 18 hours. The mixture was purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of hexane and ethyl acetate to give benzimidazo[1,2-*b*]isoquinoline-6,11-dione (97 mg, 58%) and a mixture of other unidentifiable products. Spectroscopic data was consistent with that of previous experiments.

Experiment 30; Synthesis of benzimidazo[1,2-*b*]isoquinoline-6,11-dione (**2a**) from phenyl selenoester (**10a**) using two 200 Watt lamps (*hv*)



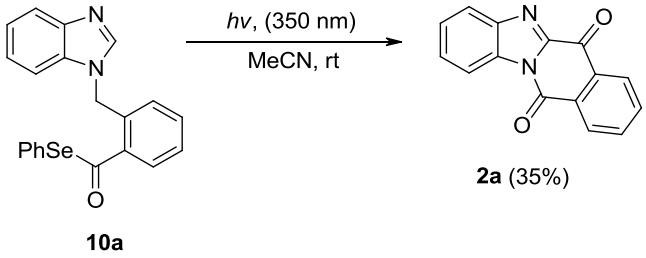
2-(1*H*-benzimidazol-1-ylmethyl)benzenecarbophenylselenoate (0.137 g, 0.35 mmol) in acetonitrile (20 mL) was irradiated with two 200 Watt tungsten lamps for 18 hours. The solution was heated under reflux due to the heat from the bulbs. The solution was evaporated to dryness and purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of hexane and ethyl acetate to give benzimidazo[1,2-*b*]isoquinoline-6,11-dione (21 mg, 24%) as well as an intractable mixture of other unidentifiable products (68%) and trace amounts of acid **9a**. Spectroscopic data was consistent with that of previous experiments.

Experiment 31; Synthesis of benzimidazo[1,2-*b*]isoquinoline-6,11-dione (**2a**) from phenyl selenoester (**10a**) using a Rayonet photochemical reactor (250 nm)



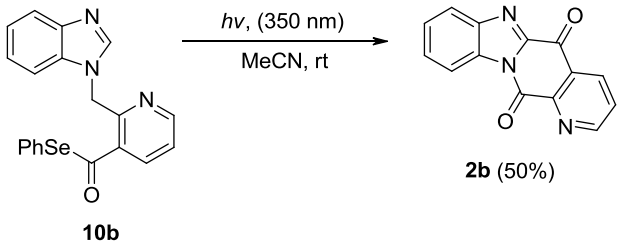
2-(1*H*-benzimidazol-1-ylmethyl)benzenecarbophenylselenoate (0.137 g, 0.35 mmol) and acetonitrile (20 mL) in a quartz tube were irradiated with light of wavelength 250 nm in a Rayonet photochemical reactor for 8 hours. The solution was evaporated to dryness and purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of hexane and ethyl acetate to give benzimidazo[1,2-*b*]isoquinoline-6,11-dione (30 mg, 35%) as well as an intractable mixture of other unidentifiable products (42%) and trace amounts of acid **9a**. Spectroscopic data was consistent with that of previous experiments.

Experiment 32; Synthesis of benzimidazo[1,2-*b*]isoquinoline-6,11-dione (**2a**) from phenyl selenoester (**10a**) using a Rayonet photochemical reactor (350 nm)



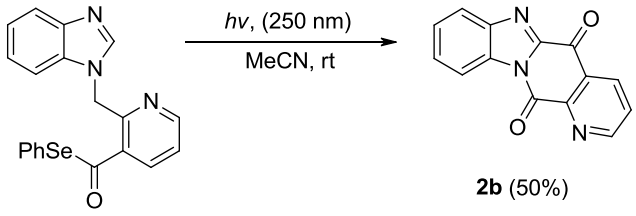
2-(1*H*-benzimidazol-1-ylmethyl)benzenecarbophenylselenoate (0.137 g, 0.35 mmol) and acetonitrile (20 mL) in a pyrex tube were irradiated with light of wavelength 350 nm in a Rayonet photochemical reactor for 18 hours. The solution was evaporated to dryness and purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of hexane and ethyl acetate to give benzimidazo[1,2-*b*]isoquinoline-6,11-dione (30 mg, 35%) as well as an intractable mixture of other unidentifiable products (42%) and trace amounts of acid **9a**. Spectroscopic data was consistent with that of previous experiments.

Experiment 33; Synthesis of benzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-dione (**2b**) from phenyl selenoester (**10b**) using a Rayonet photochemical reactor (350 nm)



2-(1*H*-benzimidazol-1-ylmethyl)pyridine-3-carbophenylselenoate (0.137 g, 0.35 mmol) and acetonitrile (20 mL) in a pyrex tube were irradiated with light of wavelength 350 nm in a Rayonet photochemical reactor for 18 hours. The solution was evaporated to dryness and purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of hexane and ethyl acetate to give benzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-dione (43 mg, 50%); R_f = 0.52 (EtOAc); yellow solid; mp 291-294 °C; ν_{max} (neat, cm^{-1}): 1727 (C=O), 1682 (C=O), 1580, 1517, 1335, 1244, 1173, 1143, 1100, 1065, 1022; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.20 (dd, *J* = 4.6, 1.8 Hz, 1H, 2-H), 8.72 (dd, *J* = 7.9, 1.8 Hz, 1H, 4-H), 8.53 (d, *J* = 8.2 Hz, 1H, 7-H), 8.04 (d, *J* = 8.1 Hz, 1H, 10-H), 7.86 (dd, *J* = 7.9, 4.6 Hz, 1H, 3-H), 7.72-7.67 (m, 1H), 7.59-7.57 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4 (C=O), 156.6 (C=O), 156.0 (2-CH), 146.6 (C), 143.4 (C), 135.9 (4-CH), 131.6 (C), 130.4 (CH), 130.2 (C), 128.8 (3-CH), 127.5 (CH), 123.4 (10-CH), 116.5 (7-CH); HRMS (ESI): *m/z* calcd for $C_{14}H_8N_3O_2$: 250.0617, found: 250.0624 $[M+H]^+$; λ max = 226 nm (ε = 24,926 L/mol·cm); as well as an intractable mixture of other unidentifiable products (31%) and trace amounts of acid **9b**.

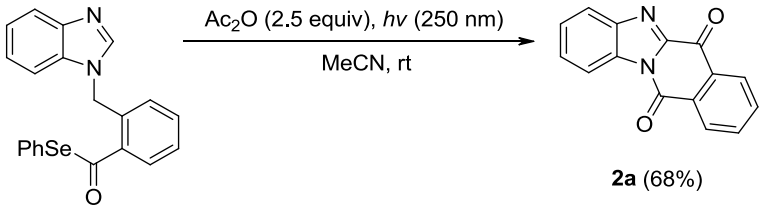
Experiment 34; Synthesis of benzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-dione (**2b**) from phenyl selenoester (**10b**) using a Rayonet photochemical reactor (250 nm)



10b **2b** (50%)

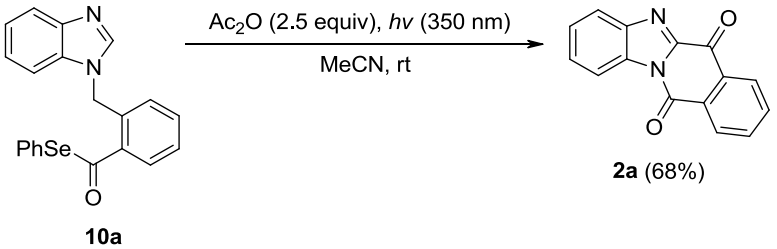
2-(1*H*-benzimidazol-1-ylmethyl)pyridine-3-carbophenylselenoate (0.137 g, 0.35 mmol) and acetonitrile (20 mL) in a quartz tube were irradiated with light of wavelength 250 nm in a Rayonet photochemical reactor for 8 hours. The solution was evaporated to dryness and purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of hexane and ethyl acetate to give benzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-dione as a yellow solid (43 mg, 50%) as well as an intractable mixture of other unidentifiable products (31%) and trace amounts of acid **9b**. Spectroscopic data was consistent with that of previous experiments.

Experiment 35; Synthesis of benzimidazo[1,2-*b*]isoquinoline-6,11-dione (**2a**) from phenyl selenoester (**10a**) using acetic anhydride to quaternize the 3-*N* in a Rayonet photochemical reactor (250 nm)



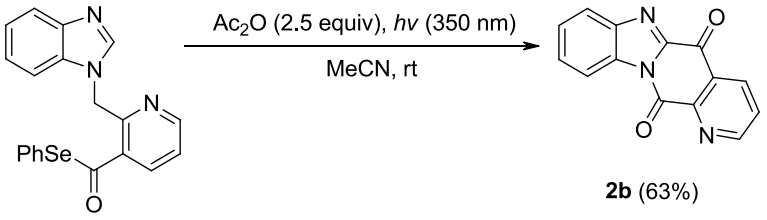
2-(1*H*-benzimidazol-1-ylmethyl)benzenecarbophenylselenoate (0.137 g, 0.35 mmol), acetic anyhydride (83 µL, 0.88 mmol) and acetonitrile (20 mL) in a quartz tube were irradiated with light of wavelength 250 nm in a Rayonet photochemical reactor for 8 hours. The solution was evaporated to dryness and purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of ethyl acetate and hexane to give benzimidazo[1,2-*b*]isoquinoline-6,11-dione (59 mg, 68%) as well as an intractable mixture of other unidentifiable products (12%) and trace amounts of acid **9a**. Spectroscopic data was consistent with that of previous experiments.

Experiment 36; Synthesis of benzimidazo[1,2-*b*]isoquinoline-6,11-dione (**2a**) from phenyl selenoester (**10a**) using acetic anhydride to quaternize the 3-*N* in a Rayonet photochemical reactor (350 nm)



2-(1*H*-benzimidazol-1-ylmethyl)benzenecarbophenylselenoate (0.137 g, 0.35 mmol), acetic anyhydride (83 µL, 0.88 mmol) and acetonitrile (20 mL) in a pyrex tube were irradiated with light of wavelength 350 nm in a Rayonet photochemical reactor for 18 hours. The solution was evaporated to dryness and purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of hexane and ethyl acetate to give benzimidazo[1,2-*b*]isoquinoline-6,11-dione (59 mg, 68%) as well as an intractable mixture of other unidentifiable products (12%) and trace amounts of acid **9a**. Spectroscopic data was consistent with that of previous experiments.

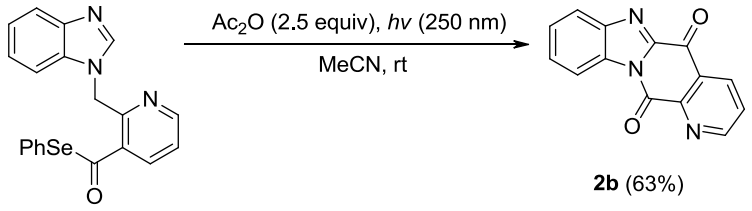
Experiment 37; Synthesis of benzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-dione (**2b**) from phenyl selenoester (**10b**) using acetic anhydride to quaternize the 3-*N* in a Rayonet photochemical reactor (350 nm)



10b

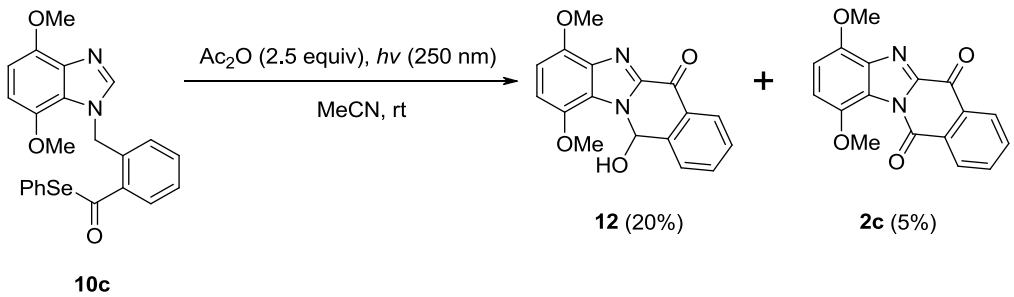
2-(1*H*-benzimidazol-1-ylmethyl)pyridine-3-carbophenylselenoate (0.137 g, 0.35 mmol), acetic anhydride (83 µL, 0.88 mmol) and acetonitrile (20 mL) in a pyrex tube were irradiated with light of wavelength 350 nm in a Rayonet photochemical reactor for 18 hours. The solution was evaporated to dryness and purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of hexane and ethyl acetate to give benzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-dione as a yellow solid (55 mg, 63%) as well as an intractable mixture of other unidentifiable products (15%) and trace amounts of acid **9b**. Spectroscopic data was consistent with that of previous experiments.

Experiment 38; Synthesis of benzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-dione (**2b**) from phenyl selenoester (**10b**) using acetic anhydride to quaternize the 3-*N* in a Rayonet photochemical reactor (250 nm)



2-(1*H*-benzimidazol-1-ylmethyl)pyridine-3-carbophenylselenoate (0.137 g, 0.35 mmol), acetic anhydride (83 µL, 0.88 mmol) and acetonitrile (20 mL) in a quartz tube were irradiated with light of wavelength 250 nm in a Rayonet photochemical reactor for 8 hours. The solution was evaporated to dryness and purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of hexane and ethyl acetate to give benzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-dione as a yellow solid (55 mg, 63%) as well as an intractable mixture of other unidentifiable products (15%) and trace amounts of acid **9b**. Spectroscopic data was consistent with that of previous experiments.

Experiment 39; Synthesis of 1,4-dimethoxybenzimidazo[1,2-*b*]isoquinolin-6,11-dione (**2c**) and 11-hydroxy-1,4-dimethoxybenzimidazo[1,2-*b*]isoquinolin-6,(11*H*)-one (**12**) from phenyl selenoester (**10c**) using acetic anhydride to quaternize the 3-*N* in a Rayonet photochemical reactor (250 nm)

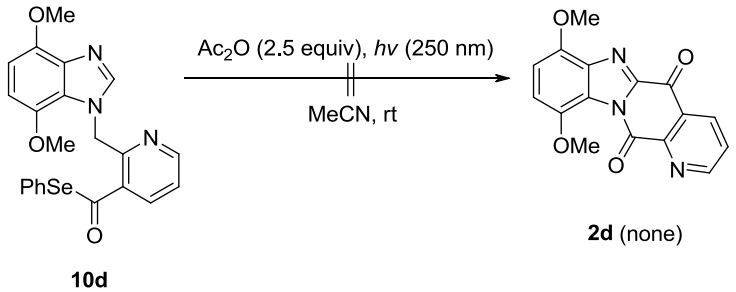


2-[(4,7-dimethoxy-1*H*-benzimidazol-1-yl)methyl]benzenecarbophenylselenoate (0.158 g, 0.35 mmol), acetic anhydride (83 µL, 0.88 mmol) and acetonitrile (20 mL) in a quartz tube were irradiated with light of wavelength 250 nm in a Rayonet photochemical reactor for 8 hours. The solution was evaporated to dryness and purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of hexane and ethyl acetate to give 11-hydroxy-1,4-dimethoxybenzimidazo[1,2-*b*]isoquinolin-6,(11*H*)-one (**12**) (22 mg, 20%); R_f = 0.63 (9:1 EtOAc:MeOH); yellow solid; mp 197-200 ºC (dec.); ν_{max} (neat, cm^{-1}): 2927, 1676 (C=O), 1601, 1525, 1502, 1431, 1340, 1282, 1257, 1226, 1178, 1158, 1108, 1037; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 8.0 Hz, 1H), 7.82-7.75 (m, 2H, 8 & 9-H), 7.63-7.60 (m, 1H), 7.09 (s, 1H, 11-H), 6.81 (d, *J* = 8.6 Hz, 1H, 2 or 3-H), 6.62 (d, *J* = 8.6 Hz, 1H, 2 or 3-H), 5.44 (bs, 1H, OH, disappears with D_2O), 4.11 (s, 3H, Me), 3.98 (s, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1 (C=O), 148.3, 141.8, 140.0, 138.0, 136.3 (all C), 134.4 (8 or 9-CH), 130.3 (C) 130.0 (CH), 128.7 (8 or 9-CH), 127.5 (CH), 125.1 (C), 106.6 (2 or 3-CH), 103.8 (2 or 3-CH), 76.8 (11-CH), 56.7 (Me), 56.3 (Me); HRMS (ESI): *m/z* calcd for $C_{17}H_{15}N_2O_4$: 311.1032, found: 311.1018 $[M+H]^+$; λ max = 269 nm (ε = 1,372 L/mol·cm); and 1,4-dimethoxybenzimidazo[1,2-*b*]isoquinolin-6,11-dione (**2c**) (5 mg, 5%); R_f = 0.58 (EtOAc); red solid; mp 209-212 °C; ν_{max} (neat, cm^{-1}): 2917, 1722 (C=O), 1679 (C=O), 1590, 1515, 1457, 1436, 1358, 1325, 1307, 1249, 1211, 1173, 1156, 1108; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43-8.41 (m, 1H), 8.35-8.33 (m, 1H), 7.90-7.83 (m, 2H, 8,9-H), 7.05 (d, *J* = 8.8 Hz, 1H, 2

or 3-H), 6.83 (d, *J* = 8.8 Hz, 1H, 2 or 3-H), 4.01 (s, 3H, Me), 3.99 (s, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6 (C=O), 157.2 (C=O), 148.2, 144.3, 142.3, 136.0 (all C), 135.3 (8 or 9-CH), 134.8 (8 or 9-CH), 132.4 (C), 130.8 (C), 130.2 (CH), 127.5 (CH), 123.0 (C), 114.0 (2 or 3-CH), 107.6 (2 or 3-CH), 58.2 (Me), 56.4 (Me); HRMS (ESI): *m/z* calcd for $C_{17}H_{13}N_2O_4$: 309.0875, found: 309.0870 $[M+H]^+$; λ max = 246 nm (ε = 37,428 L/mol·cm); as well as an intractable mixture of other unidentifiable products (70%) and trace amounts of acid **9c**.

Repeating the experiment at 350 nm for 18 hours in a pyrex tube produced identical results.

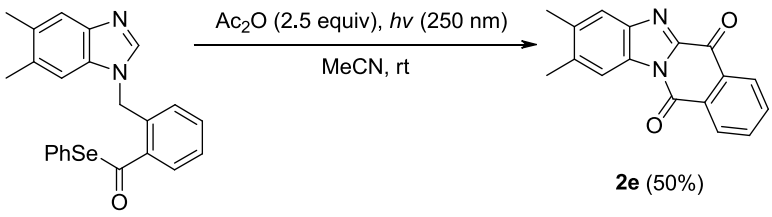
Experiment 40; Attempted synthesis of 7,10-dimethoxybenzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-dione (**2d**) from phenyl selenoester (**10d**) using acetic anhydride to quaternize the 3-*N* in a Rayonet photochemical reactor (250 nm)



2-[(4,7-dimethoxy-1*H*-benzimidazol-1-ylmethyl)pyridine-3-carbophenylselenoate (0.158 g, 0.35 mmol), acetic anhydride (83 µL, 0.88 mmol) and acetonitrile (20 mL) in a quartz tube were irradiated with light of wavelength 250 nm in a Rayonet photochemical reactor for 8 hours. The solution was evaporated to dryness to give an intractable mixture of unidentifiable products (95%) and trace amounts of acid **9d**.

Repeating the experiment at 350 nm for 18 hours in a pyrex tube produced identical results.

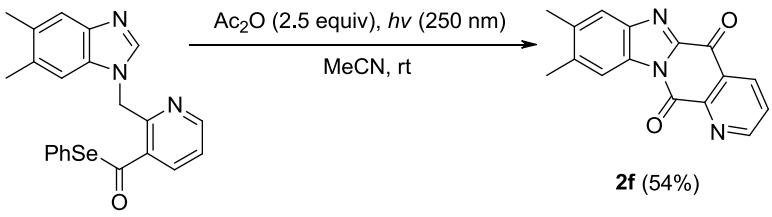
Experiment 41; Synthesis of 2,3-dimethylbenzimidazo[1,2-*b*]isoquinoline-6,11-dione (**2e**) from phenyl selenoester (**10e**) using acetic anhydride to quaternize the 3-*N* in a Rayonet photochemical reactor (250 nm)



2-[(5,6-dimethyl-1*H*-benzimidazol-1-yl)methyl]benzenecarbophenylselenoate (0.147 g, 0.35 mmol), acetic anyhydride (83 µL, 0.88 mmol) and acetonitrile (20 mL) in a quartz tube were irradiated with light of wavelength 250 nm in a Rayonet photochemical reactor for 8 hours. The solution was evaporated to dryness and purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of hexane and ethyl acetate to give 2,3-dimethylbenzimidazo[1,2-*b*]isoquinoline-6,11-dione (48 mg, 50%); R_f = 0.53 (4:1 hexane:EtOAc); yellow powder; mp 300-302 ºC; ν_{max} (neat, cm^{-1}): 3071, 2911, 1703 (C=O), 1671 (C=O), 1595, 1520, 1474, 1445, 1359, 1347, 1311, 1260, 1236, 1162, 1046, 1013; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43-8.41 (m, 1H), 8.38-8.36 (m, 1H), 8.17 (s, 1H, 1-H), 7.91-7.85 (m, 2H), 7.71 (s, 1H, 4-H), 2.46 (s, 3H, Me), 2.41 (s, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.0 (C=O), 158.9 (C=O), 143.8, 142.2, 140.3, 136.6 (all C), 135.2 (CH), 135.0 (CH), 133.0, 130.0 X 2 (all C), 129.7 (CH), 127.9 (CH), 122.9 (4-CH), 116.1 (1-CH), 21.1 (Me), 20.6 (Me); HRMS (ESI): *m/z* calcd for $C_{17}H_{13}N_2O_2$: 277.0977, found: 277.0985 $[M+H]^+$; λ max = 231 nm, (ε = 20,779 L/mol·cm); as well as an intractable mixture of other unidentifiable products (45%) and trace amounts of acid **9e**.

Repeating the experiment at 350 nm for 18 hours in a pyrex tube produced identical results.

Experiment 42; Synthesis of 8,9-dimethylbenzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-dione (**2f**) from phenyl selenoester (**10f**) using acetic anhydride to quaternize the 3-*N* in a Rayonet photochemical reactor (250 nm)

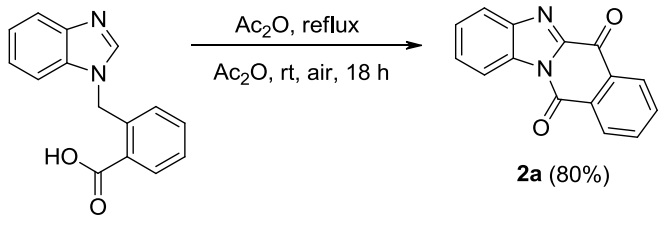


2-[(5,6-dimethyl-1*H*-benzimidazol-1-yl)methyl]pyridine-3-carbophenylselenoate (0.147 g, 0.35 mmol), acetic anyhydride (83 µL, 0.88 mmol) and acetonitrile (20 mL) in a quartz tube were irradiated with light of wavelength 250 nm in a Rayonet photochemical reactor for 8 hours. The solution was evaporated to dryness and purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of hexane and ethyl acetate to give 8,9-dimethylbenzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-dione (52 mg, 54%); R_f = 0.49 (EtOAc); yellow powder; m.p. 284-287 ºC (dec.); ν_{max} (neat, cm^{-1}): 3063, 3018, 1717 (C=O), 1671 (C=O), 1580, 1525, 1474, 1454, 1360, 1340, 1315, 1254, 1173, 1098, 1067, 1019; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.17 (dd, *J* = 4.6, 1.8 Hz, 1H, 2-H), 8.69 (dd, *J* = 7.9, 1.8 Hz, 1H, 4-H), 8.26 (s, 1H, 10-H), 7.82 (dd, *J* = 7.9, 4.6 Hz, 1H, 3-H), 7.74 (s, 1H, 7-H), 2.49 (s, 3H, CH_3), 2.43 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 173.2 (C=O), 156.6 (C=O), 155.8 (2-CH), 146.7 (C), 143.1 (C), 142.2 (C), 141.2 (C), 137.3 (C), 135.8 (4-CH), 130.3 (C), 130.1 (C), 128.6 (3-CH), 123.1 (7-CH), 116.3 (10-CH), 21.2 (CH_3), 20.7 (CH_3); HRMS (ESI): *m/z* calcd for $C_{16}H_{12}N_3O_2$: 278.0930, found: 278.0930 $[M+H]^+$; λ max = 230 nm, (ε = 28,619 L/mol·cm) as well as an intractable mixture of other unidentifiable products (41%) and trace amounts of acid **9f**.

Repeating the experiment at 350 nm for 18 hours in a pyrex tube produced identical results.

5.1.4 Experimental for chapter 3

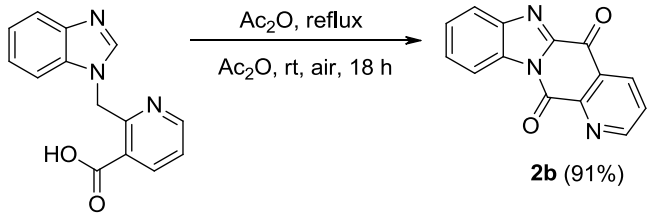
Experiment 43; Synthesis of benzimidazo[1,2-*b*]isoquinoline-6,11-dione (**2a**) from carboxylic acid (**9a**)



9a

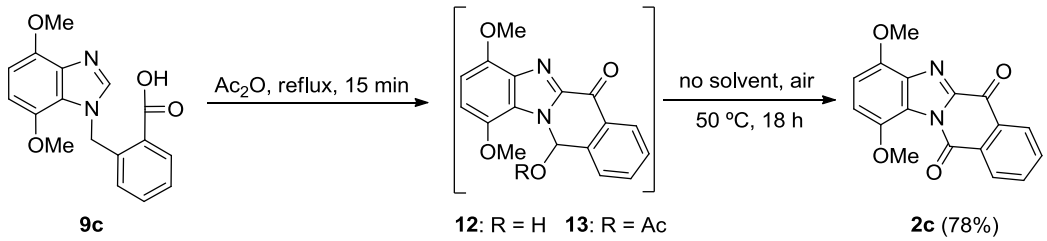
2-(1*H*-Benzimidazol-1-ylmethyl)benzoic acid (0.200 g, 0.79 mmol) in acetic anhydride (50 mL) was heated under reflux for 15 minutes. The solution was stirred at room temperature for 18 hours. The solution was evaporated to dryness and purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of hexane, ethyl acetate and methanol to give benzimidazo[1,2-*b*]isoquinoline-6,11-dione (0.157 g, 80%). Spectroscopic data was consistent with previous experiments.

Experiment 44; Synthesis of benzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-dione (**2b**) from carboxylic acid (**9b**)



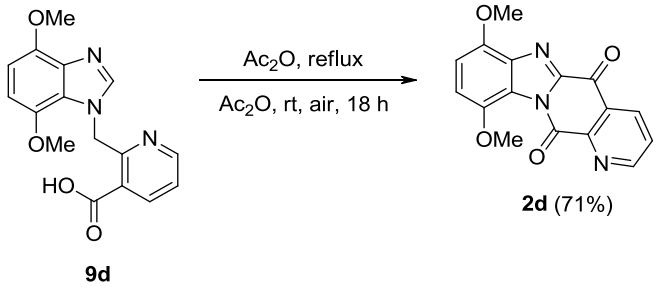
2-(1*H*-benzimidazol-1-ylmethyl)nicotinic acid (0.200 g, 0.79 mmol) in acetic anhydride (50 mL) was heated under reflux for 15 minutes. The solution was stirred at room temperature for 18 hours. The solution was evaporated to dryness and purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of hexane, ethyl acetate and methanol to give benzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-dione (0.179 g, 91%). Spectroscopic data was consistent with previous experiments.

Experiment 45; Synthesis of 1,4-dimethoxybenzimidazo[1,2-*b*]isoquinoline-6,11-dione (**2c**) from carboxylic acid (**9c**)



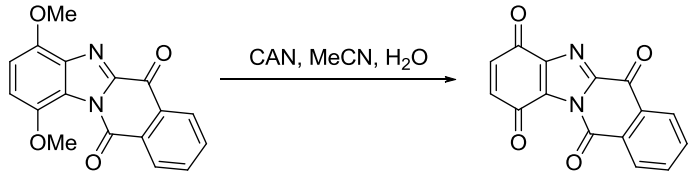
2-[(4,7-Dimethoxy-1*H*-benzimidazol-1-yl)methyl]benzoic acid (0.247 g, 0.79 mmol) in acetic anhydride (50 mL) was heated under reflux for 15 minutes. The solution was evaporated to dryness and part of the resuidue purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of hexane, ethyl acetate and methanol to give 11-hydroxy-1,4-dimethoxybenzimidazo[1,2-*b*]isoquinolin-6(11*H*)-one (**12**) (~ 60% of the residue) (slowly changing to **2c**) and 1,4-dimethoxy-6-oxo-6,11-dihydrobenzimidazo[1,2-*b*]isoquinolin-11-yl acetate (**13**) (~ 40% of the residue) yellow solid; R_f = 0.56 (EtOAc); mp 171-174 ºC (dec.); ν_{max} (neat, cm^{-1}): 2922, 2847, 1746 (C=O), 1679 (C=O), 1599, 1527, 1506, 1455, 1418, 1367, 1354, 1290, 1263, 1204, 1180, 1108, 1079, 1009; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (s, 1H, 11-H), 8.36 (dd, *J* = 7.8, 1.4 Hz, 1H); 7.93 (d, *J* = 7.7 Hz, 1H), 7.74-7.71 (m, 1H, 8 or 9-H), 7.66-7.63 (m, 1H, 8 or 9-H), 6.76 (d, *J* = 8.6 Hz, 1H, 2 or 3-H), 6.65 (d, *J* = 8.6 Hz, 1H, 2 or 3-H), 4.01 (s, 3H, Me), 3.91 (s, 3H, Me), 2.01 (s, 3H, COOMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1 (C=O), 169.9 (C=O), 147.8, 143.2, 141.6, 136.6, 136.1 (all C), 134.7 (8 or 9-CH), 130.8 (C), 130.6 (8 or 9-CH), 128.9 (CH), 127.8 (CH), 124.9 (C), 106.9 (2 or 3-CH), 104.4 (2 or 3-CH), 76.0 (11-CH), 56.4 (Me), 55.9 (Me), 21.2 (COOMe); HRMS (ESI): *m/z* calcd for $C_{19}H_{17}N_2O_5$: 353.1137, found: 353.1124 $[M+H]^+$; The intermediates **12** and **13** were combined with the derived residue and heated at 50 ºC for 18 hours. The mixture was purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of hexane, ethyl acetate and methanol to give 1,4-dimethoxybenzimidazo[1,2-*b*]isoquinolin-6,11-dione (0.190 g, 78%). Spectroscopic data was consistent with previous experiments.

Experiment 46; Synthesis of 7,10-dimethoxybenzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-dione (**2d**) from carboxylic acid (**9d**)



2-[(4,7-dimethoxy-1*H*-benzimidazol-1-yl)methyl]nicotinic acid (0.248 g, 0.79 mmol) in acetic anhydride (50 mL) was heated under reflux for 15 minutes. The solution was stirred at room temperature for 18 hours.The solution was evaporated to dryness and purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of hexane, ethyl acetate and methanol as eluent to give 7,10-dimethoxybenzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-dione (0.174 g, 71%); R_f = 0.27 (100% EtOAc); red solid; mp 195-198 ºC; ν_{max} (neat, cm^{-1}): 1750 (C=O), 1689 (C=O), 1585, 1520, 1441, 1355, 1310, 1278, 1257, 1189, 1115, 1065; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.15 (dd, *J* = 4.6, 1.6 Hz, 1H, 2-H), 8.65 (dd, *J* = 8.0, 1.6 Hz, 1H, 4-H), 7.81 (dd, *J* = 8.0, 4.6 Hz, 1H, 3-H), 7.09 (d, *J* = 8.8 Hz, 1H, 8 or 9-H), 6.85 (d, *J* = 8.8 Hz, 1H, 8 or 9-H), 4.02 (s, 3H, Me), 3.99 (s, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9 (C=O), 155.9 (2-CH), 154.8 (C=O), 148.3, 147.3, 143.6, 142.5, 135.9 (all C), 135.6 (4-CH), 129.5 (C), 128.4 (3-CH), 123.4 (C), 115.2 (8 or 9-CH), 108.0 (8 or 9-CH), 58.6 (Me), 56.5 (Me); HRMS (ESI): *m/z* calcd for $C_{16}H_{12}N_3O_4$: 310.0828, found: 310.0836 $[M+H]^+$; λ max = 244 nm, (ε = 24,371 L/mol·cm)

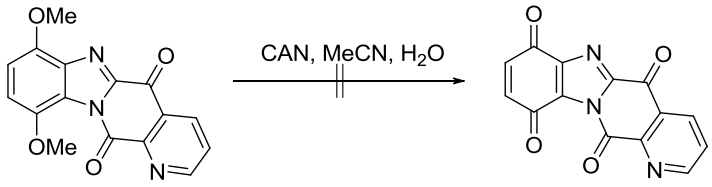
Experiment 47; Synthesis of benzimidazo[1,2-*b*]isoquinoline-1,4,6,11-tetrone (**1**)



2c **1** (79%)

A solution of 1,4-dimethoxybenzimidazo[1,2-*b*]isoquinoline-6,11-dione (83 mg, 0.27 mmol) and acetonitrile (20 mL) was cooled to -5 °C. Cerrium ammonium nitrate (CAN) (0.296 g, 0.54 mmol) in water (5 mL) was added dropwise to the cooled solution. After 5 minutes water (20 mL) was added and the product extracted into dichloromethane (30 mL). The solution was evaporated to dryness and recrystalized using chloroform to give benzimidazo[1,2-*b*]isoquinoline-1,4,6,11-tetrone as a brown solid (60 mg, 79%); brown solid; mp 203-205 °C (dec.); ν_{max} (neat, cm^{-1}): 1752 (C=O), 1684 (C=O), 1671 (C=O), 1583, 1515, 1494, 1396, 1358, 1287, 1259, 1239, 1189, 1062; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.32-8.30 (m, 1H), 8.22-8.20 (m, 1H), 8.01-7.99 (m, 2H, 8 & 9-H), 6.98 (d (AB-q), *J* = 10.3 Hz, 1H, 2 or 3-H), 6.93 (d (AB-q), *J* = 10.3 Hz, 1H, 2 or 3-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 181.3, 175.6, 173.7, 157.2 (all C=O), 146.6 (C), 143.4 (C), 139.1 (2 or 3-CH), 136.0 (8 or 9-CH), 135.9 (8 or 9-CH), 135.8 (2 or 3-CH), 132.8, 131.0, 130.3 (all C), 130.1 (CH), 127.4 (CH); HRMS (ESI): *m/z* calcd for $C_{15}H_7N_2O_4$: 279.0406, found: 279.0400 $[M+H]^+$

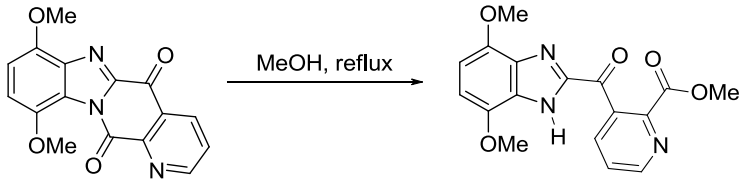
Experiment 48; Attempted synthesis of benzimidazo[2,1-*g*]-1,7-naphthyridine-5,7,10,12-tetrone



2d

A solution of 7,10-dimethoxybenzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-dione (83 mg, 0.27 mmol) and acetonitrile (20 mL) was cooled to -5 °C. Cerrium ammonium nitrate (CAN) (0.329 g, 0.60 mmol) in water (5 mL) was added dropwise to the cooled solution. After 5 minutes water (20 mL) was added and the solution was washed with dichloromethane (30 mL). The extract contained no aromatic product and the starting material was lost to the water layer.

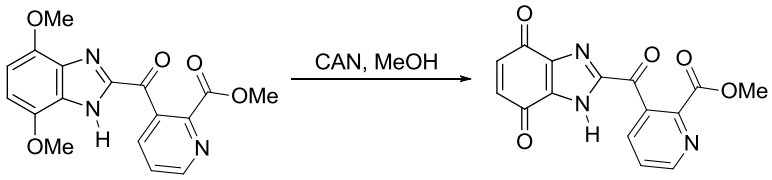
Experiment 49; Synthesis of methyl 3-[(4,7-dimethoxy-1*H*-benzimidazol-2-yl)carbonyl]pyridine-2-carboxylate (**14**)



2d **14** (92%)

7,10-Dimethoxybenzimidazo[2,1-*g*]-1,7-naphthyridine-5,12-dione (0.500 g, 1.62 mmol) was stirred in methanol (50 mL) for 18 hours. The solution was evaporated to dryness and recrystalised using dichloromethane and hexane to give methyl 3-[(4,7-dimethoxy-1*H*-benzimidazol-2-yl)carbonyl]pyridine-2-carboxylate (0.508 g, 92%); yellow solid; mp 96-99 ºC; ν_{max} (neat, cm^{-1}): 2947, 1719 (C=O), 1674 (C=O), 1580, 1527, 1446, 1431, 1378, 1340, 1305, 1257, 1216, 1138, 1095, 1017; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.80 (dd, *J* = 4.7, 1.1 Hz, 1H, Pyr-6-H), 8.14 (dd, *J* = 7.8, 1.1 Hz, 1H, Pyr-4-H), 7.54 (dd, *J* = 7.8, 4.7 Hz, 1H, Pyr-5-H), 6.65 (d, *J* = 8.4 Hz, 1H, BnIm-5 or 6-H), 6.52 (d, *J* = 8.4 Hz, 1H, BnIm-5 or 6-H), 3.89 (s, 3H, Me), 3.86 (s, 3H, Me), 3.77 (s, 3H, COOMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.6 (C=O), 166.0 (C=O), 150.9 (Pyr-6-CH), 148.2, 147.2, 146.6, 140.8, (all C), 137.6 (Pyr-4-CH), 135.7, 135.1, 126.3 (all C), 126.0 (Pyr-5-CH), 106.0 (BnIm-5 or 6-CH), 102.8 (BnIm-5 or 6-CH), 56.1 (Me), 56.0 (Me), 53.2 (COOMe); HRMS (ESI): *m/z* calcd for $C_{17}H_{16}N_3O_5$: 342.1090, found: 342.1085 $[M+H]^+$

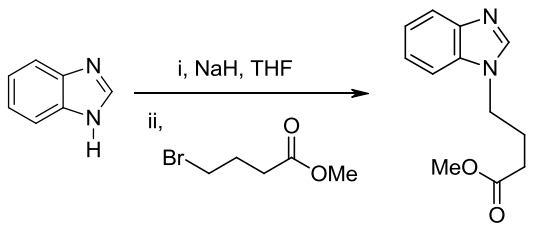
Experiment 50; Synthesis of methyl 3-[(4,7-dioxo-4,7-dihydro-1*H*-benzimidazol-2-yl)carbonyl]pyridine-2-carboxylate (**15**)



14 **15** (86%)

A solution of methyl 3-[(4,7-dimethoxy-1*H*-benzimidazol-2-yl)carbonyl]pyridine-2-carboxylate (92 mg, 0.27 mmol) and acetonitrile (20 mL) was cooled to -5 °C. Cerrium ammonium nitrate (CAN) (0.296 g, 0.54 mmol) in water (5 mL) was added dropwise. After 5 minutes water (20 mL) was added and the product was extracted with dichloromethane (30 mL). The solution was evaporated to dryness and recrystalized using ethyl acetate and hexane to give methyl 3-[(4,7-dioxo-4,7,-dihydro-1*H*-benzimidazol-2-yl)carbonyl]pyridine-2-carboxylate (72 mg, 86%); brown solid; mp 109-111 ºC; ν_{max} (neat, cm^{-1}): 3408, 1671 (C=O), 1623 (C=O), 1436, 1290, 1062, 1037; ^{1}H NMR (400 MHz, CD_3OD): δ = 8.83 (d, *J* = 3.6 Hz, 1H, Pyr-6-H), 8.22 (d, *J* = 7.5 Hz, 1H, Pyr-4-H), 7.86-7.83 (m, 1H, Pyr-5-H), 6.78 (s, 2H, BnIm-5,6-H), 3.75 (s, 3H, Me); ^{13}C NMR (100 MHz, CD_3OD): δ = 184.1, 179.5 (x 2), 165.3 (all C=O), 150.6 (Pyr-6-CH), 148.2 (C), 146.4 (C), 138.3 (Pyr-4-CH), 137.3 (2 x C), 137.0 (BnIm-5,6-CH), 135.4 (C), 127.2 (Pyr-5-CH), 52.5 (Me); HRMS (ESI): *m/z* calcd for $C_{15}H_{10}N_3O_5$: 312.0620, found: 312.0630 $[M+H]^+$

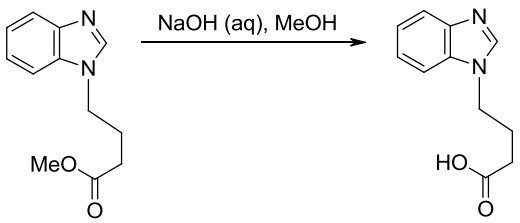
Experiment 51; Synthesis of methyl 4-(1*H*-benzimidazol-1-yl)butanoate (**16**)



16 (75%)

A mixture of benzimidazole (1.090 g, 9.23 mmol), sodium hydride (0.240 g, 10.00 mmol) in THF (50 mL) was heated under reflux for one hour. Methyl 4-bromobutyrate (2.500 g, 13.81 mmol) was added and heated under reflux for 18 hours. The mixture was filtered through celite, and purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of dichloromethane and ethyl acetate as eluent to give methyl 4-(1*H*-benzimidazol-1-yl)butanoate (1.511 g, 75%); R_f = 0.29 (6:3:1, hexane:EtOAc:MeOH); yellow oil; ν_{max} (neat, cm^{-1}): 2947, 1727 (C=O), 1611, 1492, 1457, 1436, 1363, 1285, 1252, 1196, 1158; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (s, 1H, BnIm-2-H), 7.74-7.72 (m, 1H, BnIm-4-H), 7.35-7.33 (m, 1H, BnIm-7-H), 7.23-7.20 (m, 2H, BnIm-5 & 6-H), 4.14 (t, *J* = 7.0 Hz, 2H, NCH_2), 3.58 (s, 3H, OMe), 2.24 (t, *J* = 7.1 Hz, 2H, $COCH_2$), 2.13-2.06 (m, 2H, $CH_2\mathit{CH_2}CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9 (C=O), 143.8 (C), 143.0 (BnIm-2-CH), 133.7 (C), 123.1 (BnIm-5 or 6-CH), 122.3 (BnIm-5 or 6-CH), 120.4 (BnIm-4-CH), 109.8 (BnIm-7-CH), 51.9 (CH_3), 44.0 (NCH_2), 30.5 ($COCH_2$), 25.0 ($CH_2\mathit{CH_2}CH_2$); HRMS (ESI): *m/z* calcd for $C_{12}H_{15}N_2O_2$: 219.1134, found: 219.1126 $[M+H]^+$

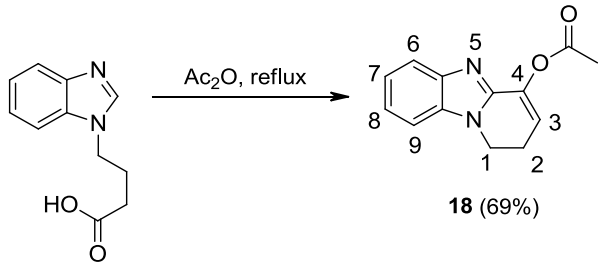
Experiment 52; Synthesis of 4-(1*H*-benzimidazol-1-yl)butanoic acid (**17**)



16 **17** (96%)

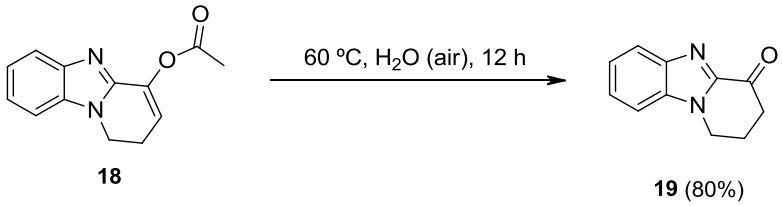
Sodium hydroxide (0.909 g, 22.73 mmol) in distilled water (30 mL) was added to methyl 4-(1*H*-benzimidazol-1-yl)butanoate (2.48 g, 11.36 mmol) in methanol (40 mL) and left to stir at room temperature for 18 hours. The methanol was evaporated under reduced pressure and the remaining aqueous solution was neutralized with dilute hydrochloric acid. The precipitate was filtered and dried to give 4-(1*H*-benzimidazol-1-yl)butanoic acid (2.228 g, 96%); white solid; mp 137-141 ºC; ν_{max} (neat, cm^{-1}): 2917, 2441, 1907, 1704 (C=O), 1613, 1507, 1459, 1371, 1323, 1272, 1234, 1186, 1092, 1042, 1004; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.21 (s, 1H, BnIm-2-H), 7.64 (d, *J* = 7.8 Hz, 1H, BnIm-4-H), 7.57 (d, *J* = 7.9 Hz, 1H, BnIm-7-CH), 7.24-7.15 (m, 2H, BnIm-5 & 6-H), 4.24 (t, *J* = 7.1 Hz, 2H, NCH_2), 2.21 (t, *J* = 7.3 Hz, 2H, $COCH_2$), 2.03-1.95 (m, 2H, $CH_2CH_2CH_2$); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.3 (C=O), 144.5 (BnIm-2-CH), 143.9 (C), 134.3 (C), 122.9 (BnIm-5 or 6-CH), 122.0 (BnIm-5 or 6-CH), 120.0 (BnIm-4-CH), 110.9 (BnIm-7-CH), 44.0 (NCH_2), 31.2 ($COCH_2$), 25.5 ($CH_2CH_2CH_2$); HRMS (ESI): m/z calcd for $C_{11}H_{13}N_2O_2$: 205.0977, found: 205.0970 $[M+H]^+$

Experiment 53; Synthesis of 1,2-dihydropyrido[1,2-*a*]benzimidazol-4-yl acetate (**18**)



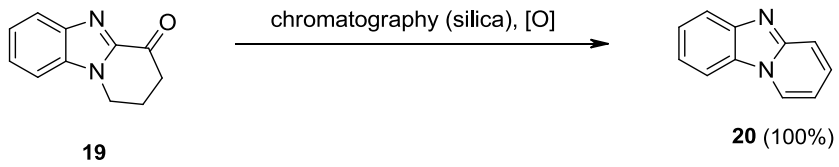
4-(1*H*-benzimidazol-1-yl)butanoic acid (62 mg, 0.30 mmol) and acetic anhydride (20 mL) was heated under reflux for 30 minutes. The solution was evaporated to dryness and purified by dry column vacuum chromatography using silica gel as absorbent with gradient elution of dichloromethane and ethyl acetate as eluent to give 1,2-dihydropyrido[1,2-*a*]benzimidazol-4-yl acetate (48 mg, 69%); R_f = 0.58 (EtOAc); clear gel; ν_{max} (neat, cm^{-1}): 1757 (C=O), 1659, 1611, 1520, 1474, 1444, 1424, 1368, 1328, 1295, 1285, 1186, 1125, 1103, 1037, 1004; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 7.8 Hz, 1H, 6-H), 7.27-7.21 (m, 3H), 6.05 (t, *J* = 4.7 Hz, 1H, CH_2CH), 4.21 (t, *J* = 7.5 Hz, 2H, NCH_2), 2.85 (dt, *J* = 7.5, 4.7 Hz, 2H, $CHCH_2$), 2.37 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2 (C=O), 145.0, 143.3, 139.3, 134.6 (all C), 123.6 (7 or 8-CH), 122.5 (7 or 8-CH), 120.5 (6-CH), 118.3 (CH_2CH), 109.1 (9-CH), 39.8 (NCH_2), 23.0 ($CHCH_2$), 21.0 (CH_3); HRMS (ESI): *m/z* calcd for $C_{13}H_{13}N_2O_2$: 229.0977, found: 229.0968 $[M+H]^+$

Experiment 54; Synthesis of 2,3-dihydropyrido[1,2-*a*]benzimidazol-4(1*H*)-one (**19**)



1,2-Dihydropyrido[1,2-*a*]benzimidazol-4-yl acetate (0.167 g, 0.73 mmol) was heated without a solvent at 60 ºC for 12 hours. The mixture was recrystalized from diethyl ether to give 2,3-dihydropyrido[1,2-*a*]benzimidazol-4(1*H*)-one (0.109 g, 80%); yellow solid; mp 176-178 ºC (lit.[120] 178-179 ºC); ν_{max} (neat, cm^{-1}): 2947, 1687 (C=O), 1575, 1482, 1472, 1401, 1330, 1247, 1199, 1178, 1151, 1105, 1017; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.0 Hz, 1H, 6-H), 7.45-7.41 (m, 2H), 7.40-7.35 (m, 1H), 4.37 (t, *J* = 5.9 Hz, 2H, NCH_2), 2.91 (t, *J* = 6.5 Hz, 2H, $COCH_2$), 2.54-2.48 (m, 2H, $CH_2\mathit{CH_2}CH_2$); ^{13}C NMR (100 MHz,$CDCl_3$): δ = 188.1 (C=O), 144.6, 143.1, 134.0 (all C), 126.2 (7or 8-CH), 124.6 (7 or 8-CH), 122.7 (6-CH), 110.7 (9-CH), 42.5 (NCH_2), 38.0 ($COCH_2$), 23.1 ($CH_2\mathit{CH_2}CH_2$); HRMS (ESI): *m/z* calcd for $C_{11}H_{11}N_2O$: 187.0871, found: 187.0866 $[M+H]^+$

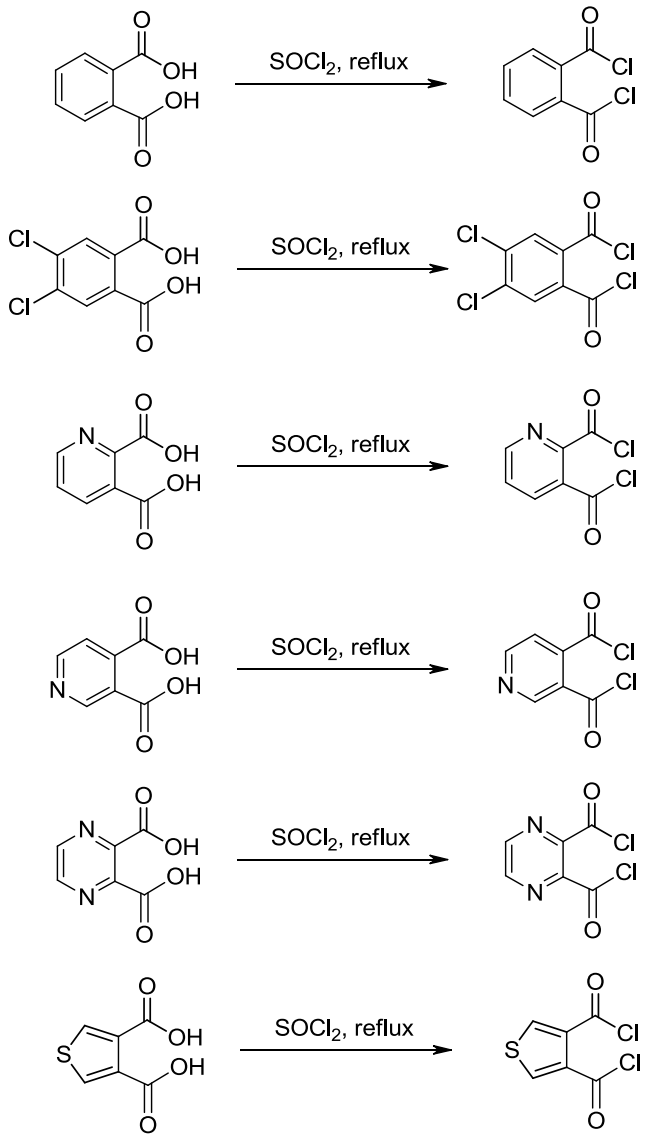
Experiment 55; Synthesis of pyrido[1,2-*a*]benzimidazole (**20**)



2,3-dihydropyrido[1,2-*a*]benzimidazol-4(1*H*)-one (0.107 g, 58 mmol) on purification by dry column vacuum chromatography was quantitatively converted to pyrido[1,2-*a*]benzimidazole (97 mg, 100%); pale white solid; mp 176-178 °C (lit.[129] mp 178-179); ν_{max} (neat, cm^{-1}): 3008, 1641, 1606, 1499,1462, 1444, 1353, 1307, 1252, 1226, 1140; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38 (td, *J* = 6.9, 1.1 Hz, 1H), 7.91 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.65 (td, *J* = 9.3, 1.0 Hz, 1H), 7.51-7.47 (m, 1H), 7.39-7.30 (m, 2H), 6.78 (td, *J* = 6.7, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.5 (C), 144.6 (C), 129.4 (CH), 128.7 (C), 125.7, 125.3, 121.1, 120.0, 118.0, 110.5, 110.4 (all CH); HRMS (ESI): *m/z* calcd for $C_{11}H_9N_2$: 169.0766, found: 169.0760 $[M+H]^+$

5.1.5 Experimental for chapter 4

General procedure for conversion of *o*-dicarboxylic acids to *o*-diacid chlorides

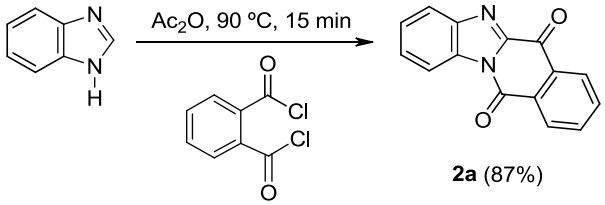


o-Dicarboxylic acids (2 eq in relation to the imidazoles) were heated under reflux in excess thionyl chloride for 18 hours. The solution was evaporated to dryness to give the crude *o*-diacid dichlorides as yellow oils which were used without further purification.

General procedure for synthesis of *p*-dione adducts

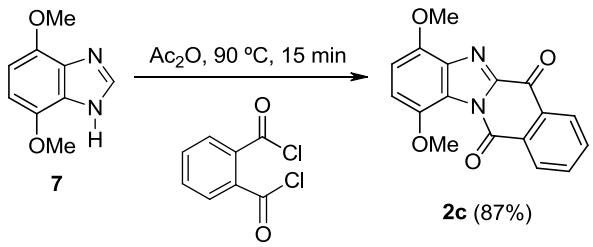
The *o*-diacid dichlorides (2 equiv) with the appropriate benzimidazole (2.12 mmol) were heated in Ac_2O (30 mL) at 90 °C for 15 minutes. Upon cooling, the precipitated *p*-dione adducts were filtered and dried.

Experiment 56; Synthesis of benzimidazo[1,2-*b*]isoquinoline-6,11-dione (**2a**) from the *o*-diacid dichloride



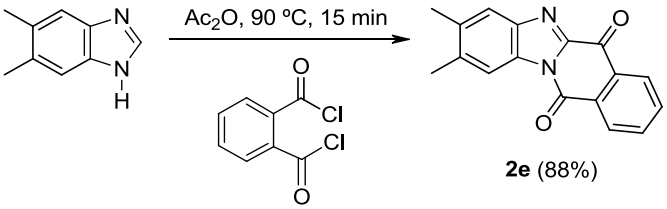
(0.457 g, 87%); Spectroscopic data was consistent with that of previous experiments.

Experiment 57; Synthesis of 1,4-dimethoxybenzimidazo[1,2-*b*]isoquinoline-6,11-dione (**2c**) from the *o*-diacid dichloride



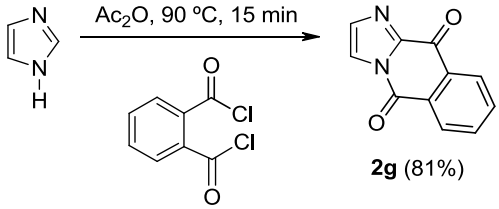
(0.567 g, 87%); Spectroscopic data was consistent with that of previous experiments.

Experiment 58; Synthesis of 2,3-dimethylbenzimidazo[1,2-*b*]isoquinoline-6-11-dione (**2e**) from the *o*-diacid dichloride



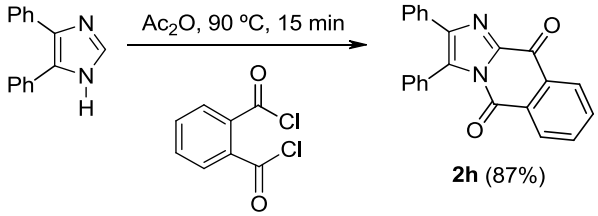
(0.513 g, 88%); Spectroscopic data was consistent with that of previous experiments.

Experiment 59; Synthesis of imidazo[1,2-*b*]isoquinoline-5,10-dione (**2g**) from the *o*-diacid dichloride



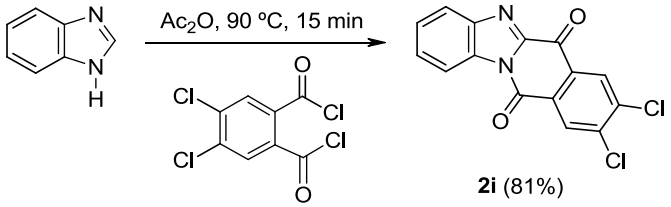
(0.338 g, 81%); yellow crystals; mp 239-241 ºC (lit.[61] 238-239 ºC) (lit.[57] 238 ºC); ν_{max} (neat, cm^{-1}): = 3139, 1719 (C=O), 1671 (C=O), 1593, 1575, 1522, 1439, 1396, 1325, 1297, 1274, 1232, 1194, 1151, 1120, 1075; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37-8.36 (m, 1H), 8.35-8.34 (m, 1H), 7.91-7.85 (m, 2H), 7.82 (d, *J* = 1.4 Hz, 1H), 7.47 (d, *J* = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1 (C=O), 157.9 (C=O), 142.4 (C), 135.7, 134.8, 134.1 (all CH), 133.1 (C), 130.0 (CH), 128.7 (C), 128.1 (CH), 117.5 (CH); HRMS (ESI): *m/z* calcd for $C_{11}H_7N_2O_2$: 199.0508; found: 199.0503 $[M+H]^+$;

Experiment 60; Synthesis of 2,3-diphenylimidazo[1,2-*b*]isoquinoline-5,10-dione (**2h**) from the *o*-diacid dichloride



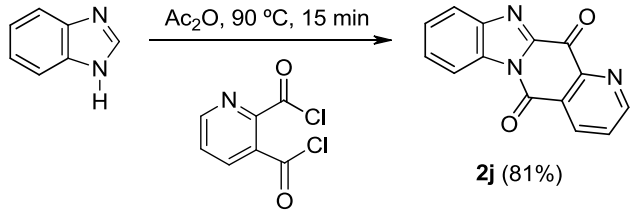
(0.646 g, 87%); bright orange powder; mp 297-299 ºC (lit.[57] mp 290 ºC); ν_{max} (neat, cm^{-1}): 3058, 1735 (C=O), 1666 (C=O), 1588, 1507, 1464, 1439, 1368, 1307, 1272, 1244, 1206, 1128, 1103, 1032; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38-8.36 (m, 1H), 8.23-8.20 (m, 1H), 7.88-7.78 (m, 2H), 7.57-7.47 (m, 7H), 7.25-7.22 (m, 3H); ^{13}C NMR ($CDCl_3$): δ = 172.3 (C=O); 158.6 (C=O), 143.7 (C), 142.0 (C), 135.4 (CH), 134.8 (CH), 132.8 (2 x C), 131.8 (2 x C), 130.3 (2 x CH), 129.9 (CH), 129.7 (CH), 129.6 (C), 129.0 (2 x CH), 128.4 (CH), 128.3 (2 x CH), 128.0 (2 x CH), 127.7 (CH); HRMS (ESI): *m/z* calcd for $C_{23}H_{15}N_2O_2$: 351.1134, found: 351.1123 $[M+H]^+$;

Experiment 61; Synthesis of 8,9-dichlorobenzimidazo[1,2-*b*]isoquinoline-6-11-dione (**2i**) from the *o*-diacid dichloride



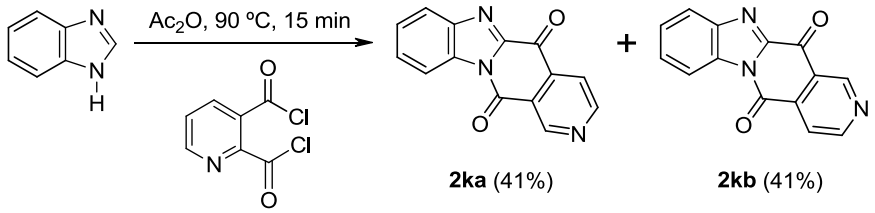
(0.542 g, 81%); yellow powder; mp 302-304 ºC; ν_{max} (neat, cm^{-1}): 3094, 1707 (C=O), 1674 (C=O), 1575, 1510, 1484, 1429, 1338, 1274, 1237, 1173, 1146, 1044; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.44 (s, 1H, 7 or 10-H), 8.33 (s, 1H, 7 or 10-H), 8.33-8.30 (m, 1H, 1-H), 8.00-7.98 (m, 1H, 4-H), 7.70-7.65 (m, 1H, 2 or 3-H), 7.57-7.53 (m, 1H, 2 or 3-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.0 (C=O), 158.2 (C=O), 145.5, 143.2, 138.6, 138.5, 133.4, 131.5 (all C), 130.9 (7 or 10-CH), 130.7 (C), 129.8 (2 or 3-CH), 129.0 (7 or 10-CH), 127.2 (2 or 3-CH), 123.0 (4-CH), 116.1 (1-CH); HRMS (ESI): *m/z* calcd for $C_{15}H_7N_2O_2{}^{35}Cl_2$: 316.9885, found: 316.9892 $[M+H]^+$

Experiment 62; Synthesis of benzimidazo[1,2-*g*]-1,6-naphthyridine-5,12-dione (**2j**) from the *o*-diacid dichloride



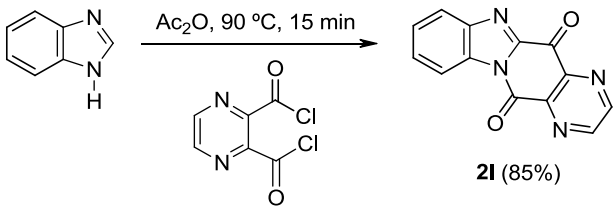
Recrystallized from CH_3OH; (0.427 g, 81%); yellow powder; mp 320-322 ºC; ν_{max} (neat, cm^{-1}): 3048, 1714 (C=O), 1699 (C=O), 1601, 1560, 1573, 1517, 1482, 1441, 1365, 1335, 1277, 1247, 1234, 1158, 1138, 1100, 1077, 1017; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.09 (dd, *J* = 4.6, 1.7 Hz, 1H, 2-H), 8.66 (dd, *J* = 7.9, 1.7 Hz, 1H, 4-H), 8.32-8.29 (m, 1H, 7-H), 8.00-7.98 (m, 1H, 10-H), 7.94 (dd, *J* = 7.9, 4.6 Hz, 1H, 3-H), 7.68-7.64 (m, 1H, 8 or 9-H), 7.57-7.52 (m, 1H, 8 or 9-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.3 (C=O), 159.4 (C=O), 155.2 (2-CH), 149.4, 146.0, 143.2 (all C), 137.2 (4-CH), 131.3 (C), 129.6 (8 or 9-CH), 128.9 (3-CH), 128.5 (C), 127.1 (8 or 9-CH), 122.9 (10-CH), 116.0 (7-CH); HRMS (ESI): *m/z* calcd for $C_{14}H_8N_3O_2$: 250.0617, found: 250.0605 $[M+H]^+$

Experiment 63; Synthesis of benzimidazo[1,2-*b*]-2,7-naphthyridine-5-12-dione (**2ka**) and benzimidazo[1,2-*b*]-2,6-naphthyridine-5-12-dione (**2kb**) from the *o*-diacid dichloride



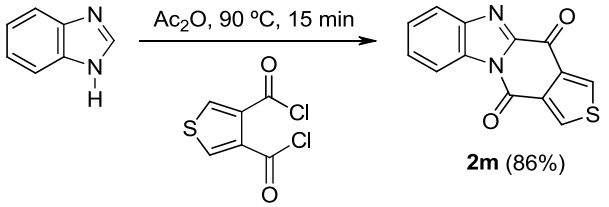
Automated column chromatography to separate isomers **2ka** and **2kb** was carried out using a Grace Reveleris Flash System (Instrument serial no. 2810M00134) with an 80 gram silica (40 µm) column using dichloromethane as eluent to give benzimidazo[1,2-*b*]-2,7-naphthyridine-5-12-dione (0.216 g, 41%); R_f = 0.60 (1:1 CH_2Cl_2:EtOAc); yellow powder; mp 279-281 ºC; ν_{max} (neat, cm^{-1}): 3063, 1717 (C=O), 1689 (C=O), 1585, 1510, 1343, 1254, 1229, 1156, 1138, 1108, 1057, 1022, 1001; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.70 (s, 1H, 1-H), 9.21 (d, *J* = 5.0 Hz, 1H, 3-H), 8.44 (d, *J* = 8.2 Hz, 1H, 10-H), 8.15 (d, *J* = 5.0 Hz, 1H, 4-H), 8.03 (d, *J* = 8.2 Hz, 1H, 7-H), 7.71-7.67 (m, 1H, 8 or 9-H), 7.58-7.54 (m, 1H, 8 or 9-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4 (C=O), 157.9 (C=O), 156.7 (3-CH), 151.6 (1-CH), 143.7, 143.5, 138.1, 131.3 (all C), 130.6 (8 or 9-CH), 127.5 (8 or 9-CH), 123.5 (7-CH), 123.1 (C), 119.4 (4-CH), 116.3 (10-CH); HRMS (ESI): *m/z* calcd for $C_{14}H_8N_3O_2$: 250.0617, found: 250.0624 $[M+H]^+$ and benzimidazo[1,2-*b*]-2,6-naphthyridine-5-12-dione (0.216 g, 41%); R_f = 0.57 (1:1 CH_2Cl_2:EtOAc); yellow powder; mp 275-277 ºC; ν_{max} (neat, cm^{-1}): 3063, 1714 (C=O), 1676 (C=O), 1585, 1515, 1489, 1439, 1365, 1335, 1249, 1229, 1153, 1105, 1057, 1019; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.63 (s, 1H, 1-H), 9.22 (d, *J* = 5.0 Hz, 1H, 3-H), 8.41 (d, *J* = 8.2 Hz, 1H, 7-H), 8.25 (d, *J* = 5.0 Hz, 1H, 4-H), 8.03 (d, *J* = 8.2 Hz, 1H, 10-H), 7.70-7.66 (m, 1H, 8 or 9-H), 7.58-7.54 (m, 1H, 8 or 9-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3 (C=O), 157.7 (C=O), 156.7 (3-CH), 150.0 (1-CH), 143.5, 143.4, 136.2, 131.2 (all-C), 130.4 (8 or 9-CH), 127.6 (8 or 9-CH), 125.7 (C), 123.6 (10-CH), 121.6 (4-CH), 116.2 (7-CH); HRMS (ESI): *m/z* calcd for $C_{14}H_8N_3O_2$: 250.0617, found: 250.0614 $[M+H]^+$

Experiment 64; Synthesis of pyrazino[2',3':4,5]pyrido[1,2-*a*]benzimidazole-5-12-dione (**2l**) from the *o*-diacid dichloride



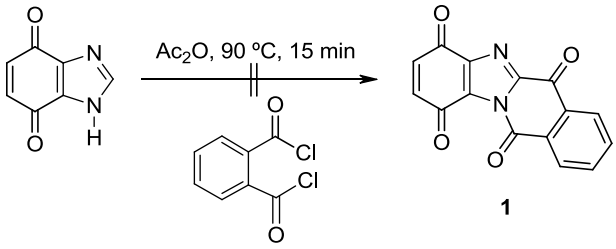
(0.450 g, 85%); yellow powder; mp 276-282 ºC (dec.); ν_{max} (neat, cm^{-1}): 3063, 1727 (C=O), 1692 (C=O), 1580, 1515, 1487, 1451, 1424, 1365, 1333, 1269, 1254, 1232, 1196, 1153, 1118, 1080, 1017; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.17 (AB-q, *J* = 2.2 Hz, 2H, 2 & 3-H), 8.35 (d, *J* = 8.1 Hz, 1H, 10-H), 8.02 (d, *J* = 8.2 Hz, 1H, 7-H), 7.69 (ddd, *J* = 8.2, 1.0, 1.0 Hz, 1H, 8 or 9-H), 7.57 (ddd, *J* = 8.1, 1.0, 1.0 Hz, 1H, 8 or 9-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.1 (C=O), 157.4 (C=O), 149.4 (2 or 3-CH), 149.1 (2 or 3-CH), 145.9, 145.8, 144.2, 143.1, 131.4 (all-C), 129.9 (8 or 9-CH), 127.4 (8 or 9-CH), 123.1 (7-CH), 116.1 (10-CH); HRMS (ESI): *m/z* calcd for $C_{13}H_7N_4O_2$: 251.0569, found: 251.0568 $[M+H]^+$

Experiment 65; Synthesis of 4*H*,11*H*-thieno[3',4':4,5]pyrido[1,2-*a*]benzimidazole-4-11-dione (**2m**) from the *o*-diacid dichloride



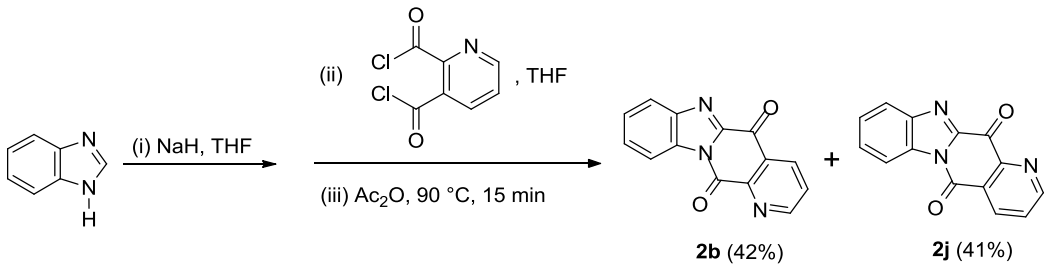
(0.464 g, 86%); pale yellow powder; mp 305-307 ºC; ν_{max} (neat, cm^{-1}): 3044, 1721 (C=O), 1669 (C=O), 1600, 1587, 1512, 1447, 1434, 1406, 1352, 1316, 1202, 1150, 1137, 1088, 1034, 1003; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.79 (d, *J* = 2.9 Hz, 1H, 1 or 3-H), 8.73 (d, *J* = 2.9 Hz, 1H, 1 or 3-H), 8.30-8.28 (m, 1H, 9-H), 7.93-7.91 (m, 1H, 6-H), 7.63-7.59 (m, 1H, 7 or 8-H), 7.52-7.48 (m, 1H, 7 or 8-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.5 (C=O), 156.4 (C=O), 147.4 (C), 143.5 (C), 137.2 (1 or 3-CH), 136.7 (C), 135.9 (1 or 3-CH), 132.9 (C), 131.8 (C), 129.2 (7 or 8-CH), 126.7 (7 or 8-CH), 122.8 (6-CH), 116.1 (9-CH); HRMS (ESI): *m/z* calcd for $C_{13}H_7N_2O_2S$: 255.0228, found: 255.0235 $[M+H]^+$

Experiment 66; Attempted synthesis of benzimidazo[1,2-*b*]isoquinoline-1,4,6,11-tetrone (**1**) from the *o*-diacid dichloride



Benzimidazolequinone (0.314 g, 2.12 mmol) and phthaloyl dichloride (2 eq) were heated in acetic anhydride (30 mL) at 90 °C for 15 minutes to give unreacted starting materials.

Experiment 67; Synthesis of benzimidazo[2,1-*g*]-1,7-naphthyridine-5-12-dione (**2b**) and benzimidazo[1,2-*g*]-1,6-naphthyridine-5-12-dione (**2j**) via reaction of benzimidazole with sodium hydride prior to addition of the *o*-diacid dichloride



Benzimidazole (0.250 g, 2.12 mmol) and sodium hydride (0.051 g, 2.12 mmol) were heated under reflux in THF (50 mL) prior to addition of pyridine-2,3-dicarbonyl dichloride. The THF was removed under reduced presure, acetic anhydride (30 mL) was added and heated to 90 ºC for 15 minutes. The precipitate was filtered and dried to give an equal mixture (by ^{1}H NMR) of adducts **2b** and **2j.** Spectroscopic data was consistent with that of previous experiments.

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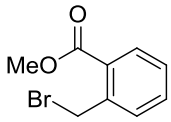
Appendix

NMR Spectra



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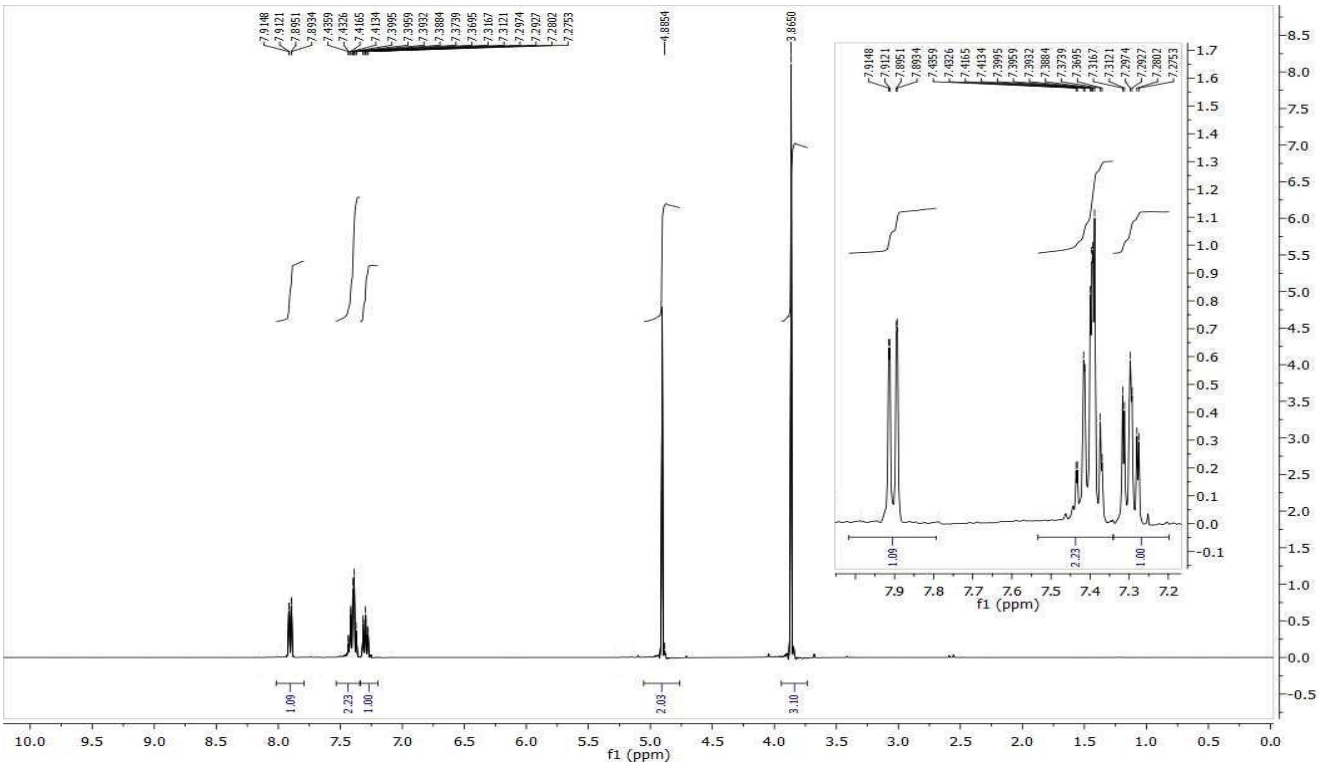

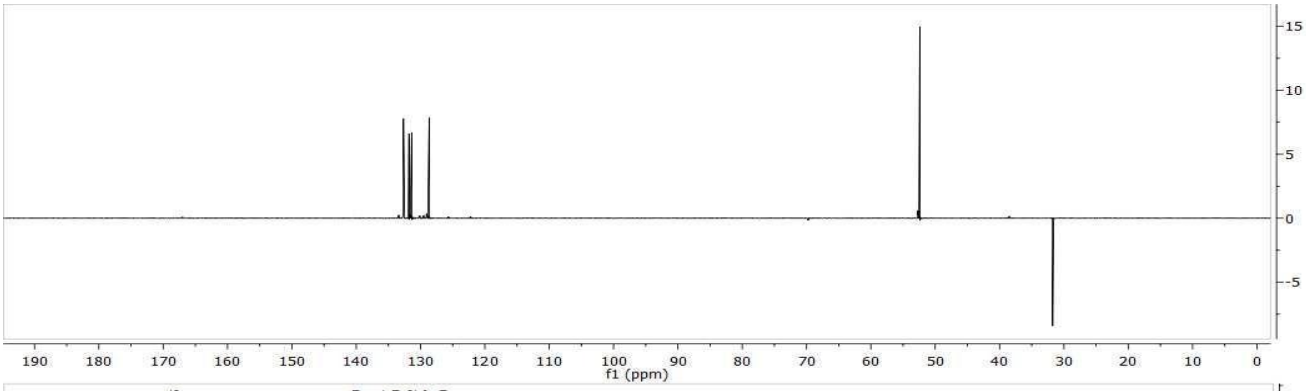

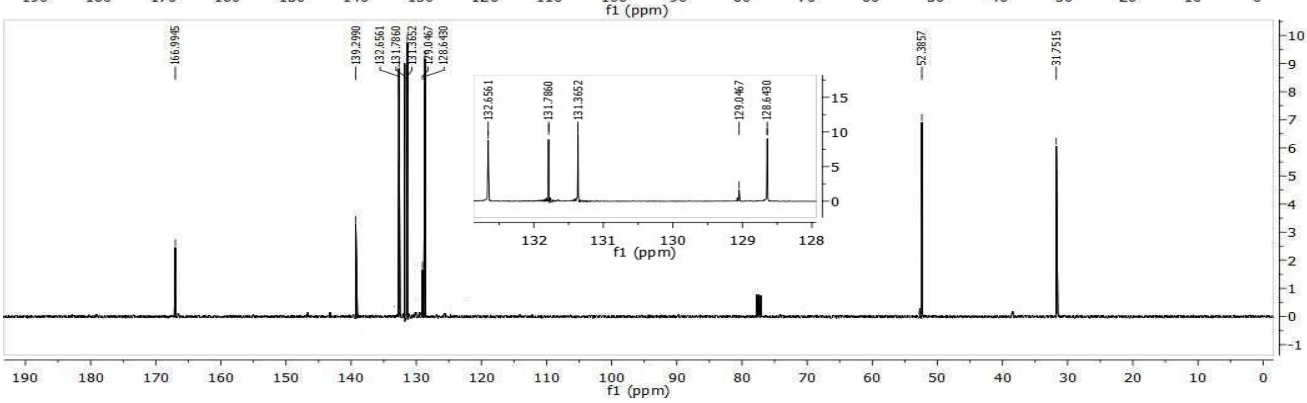

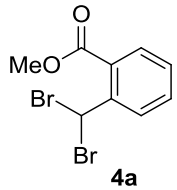

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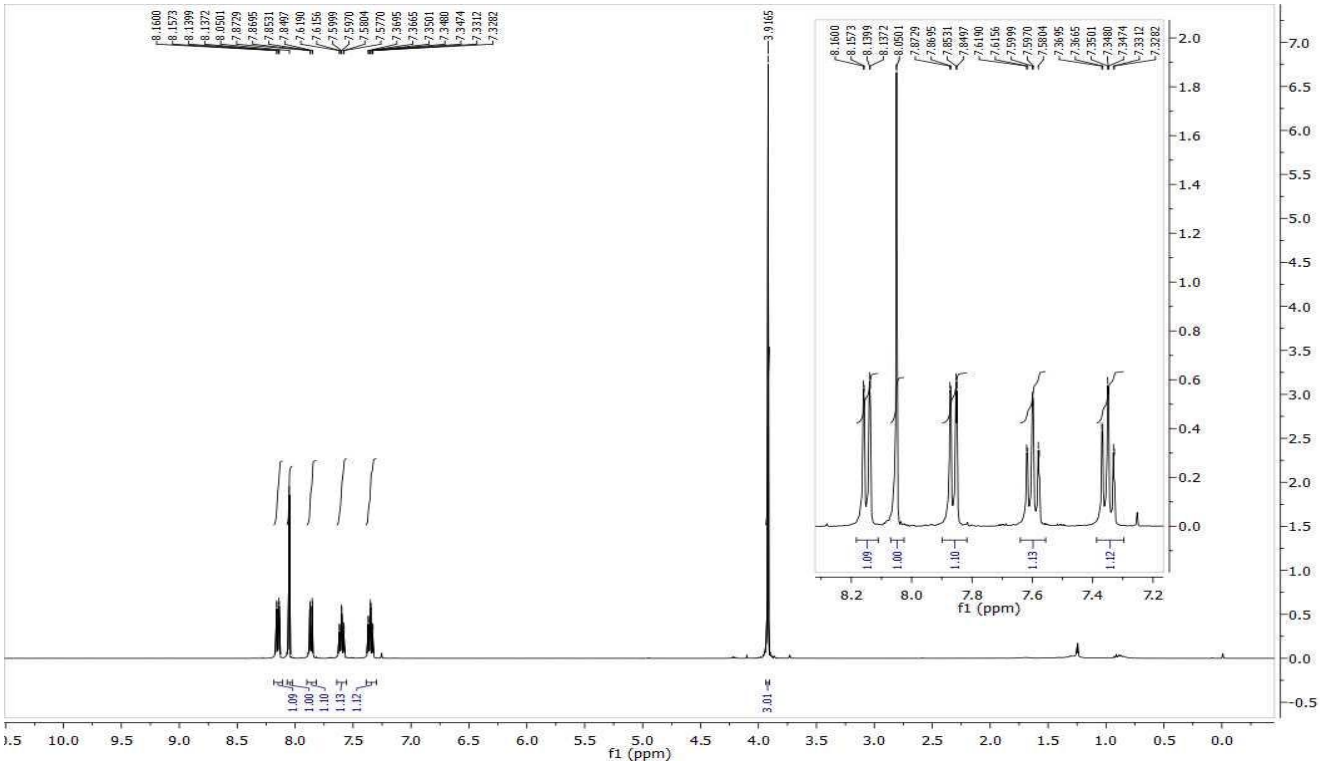

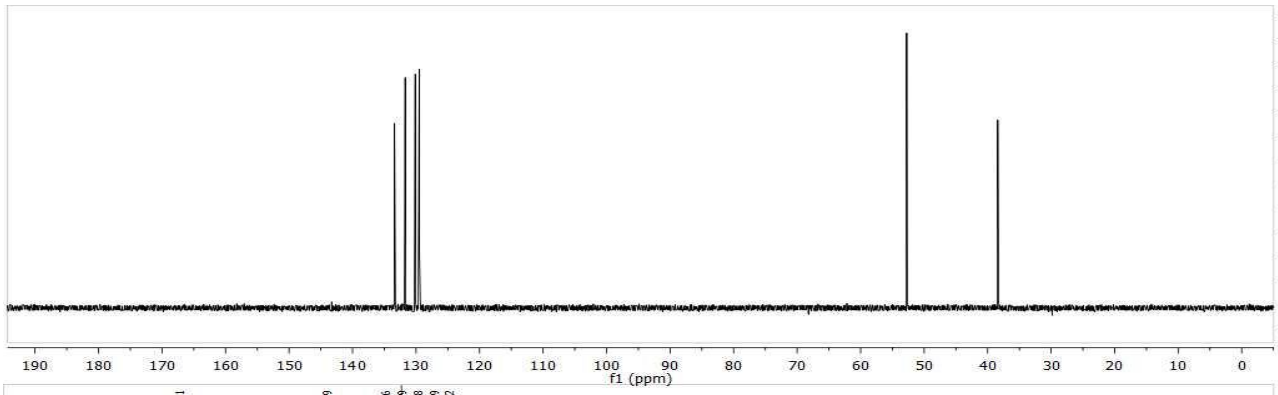

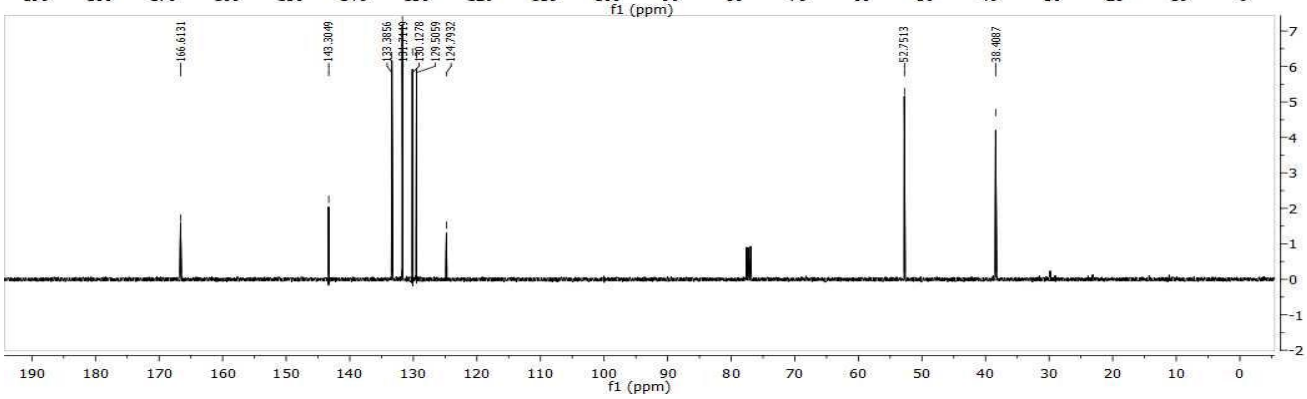

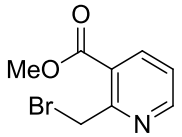

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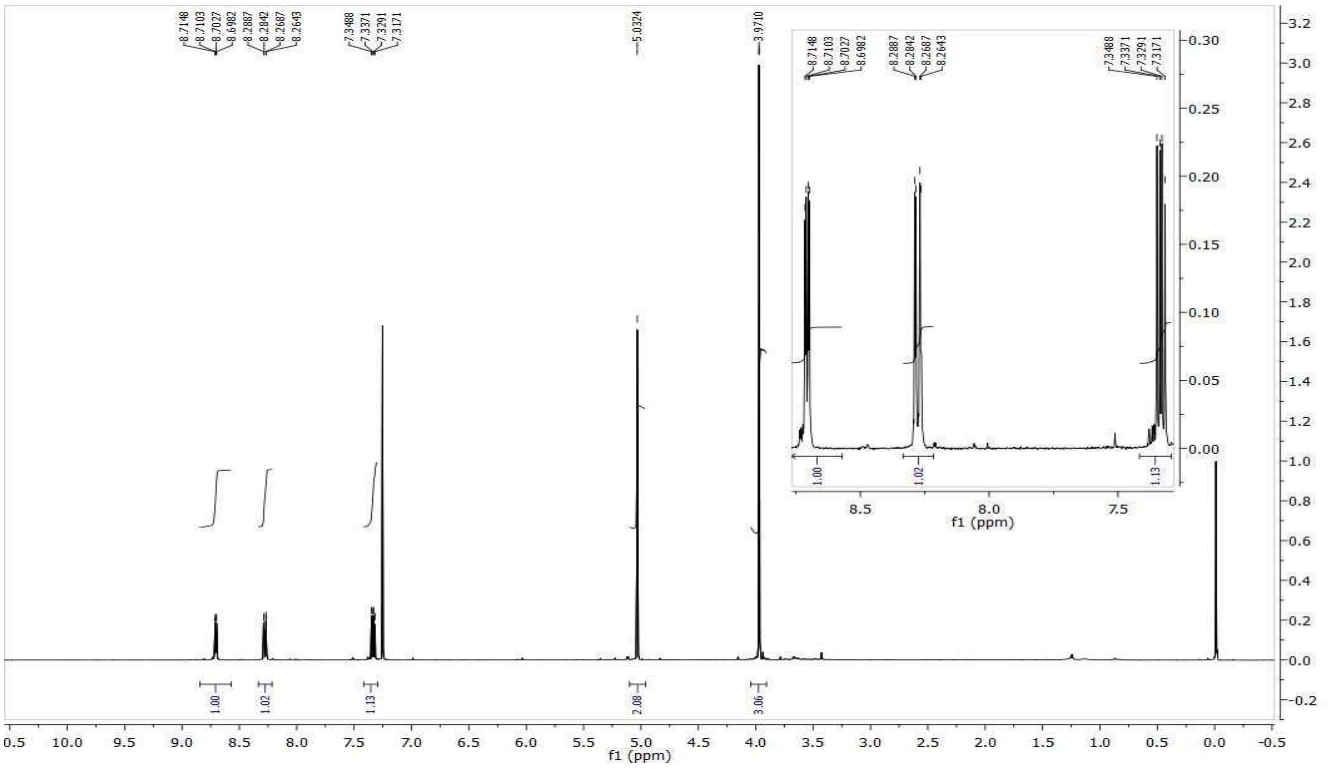
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8.7027
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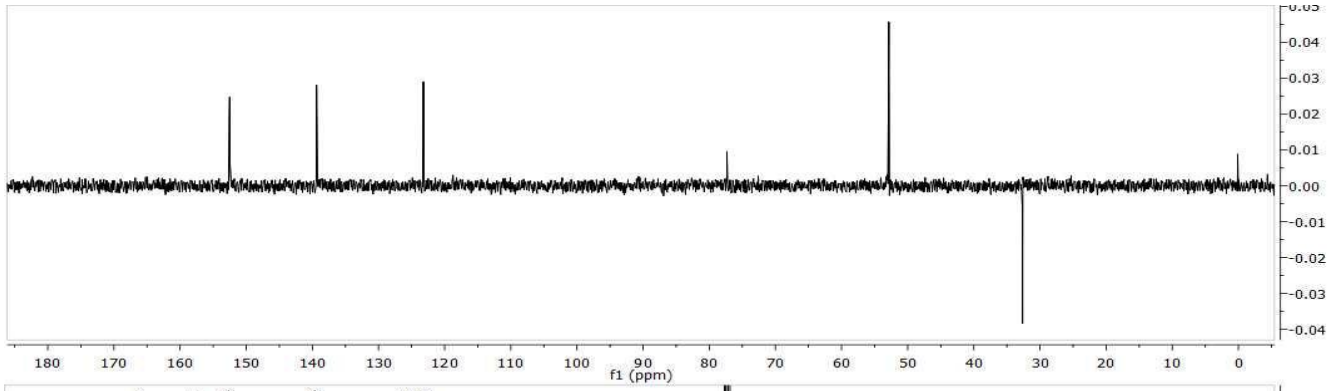
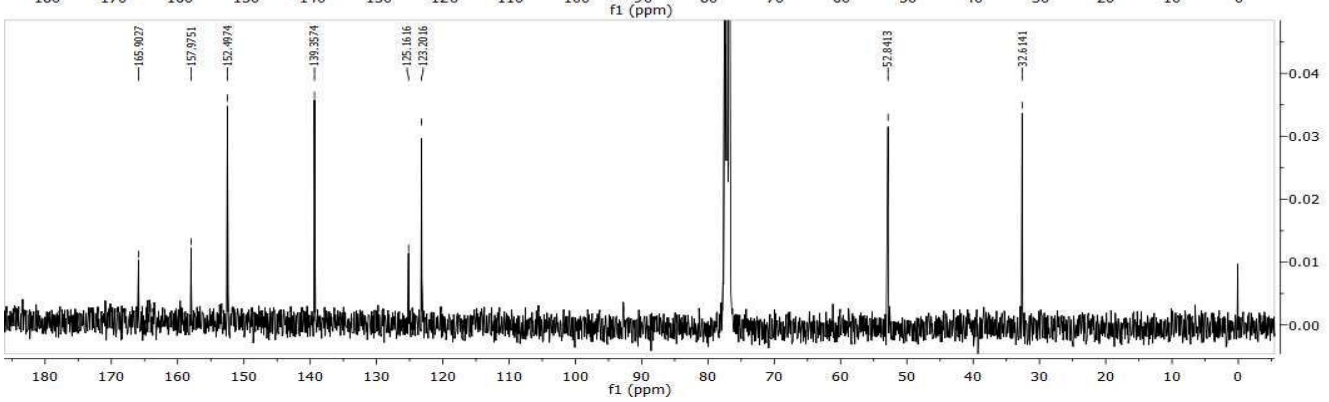
8.2887
8.2842
8.2687
8.2643
7.3488
7.3371
7.3291
7.3171
5.0324
3.9710
1.00
1.02
1.13
2.08
3.06
f1 (ppm)


f1 (ppm)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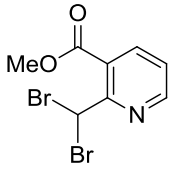
152.4974
139.3574
125.1616
123.2016
52.8413
32.6141
f1 (ppm)



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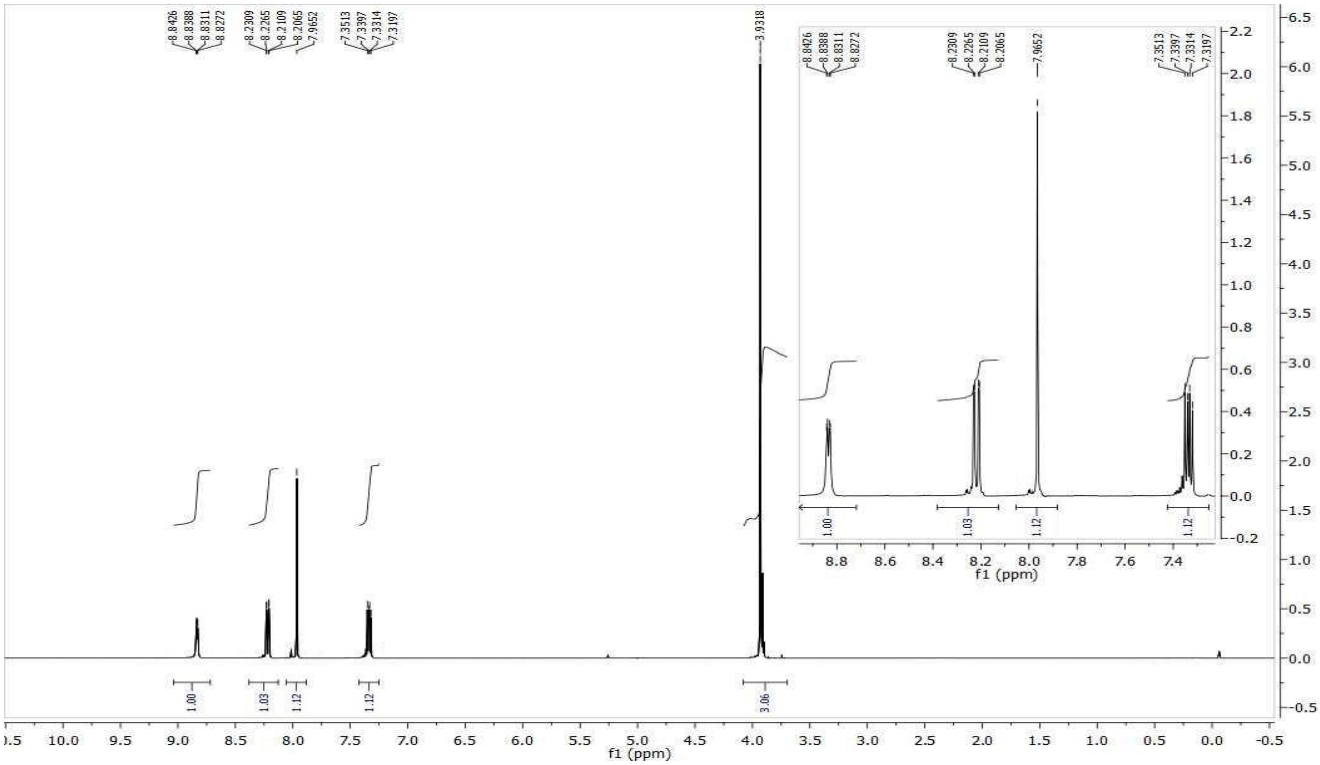
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8.2309
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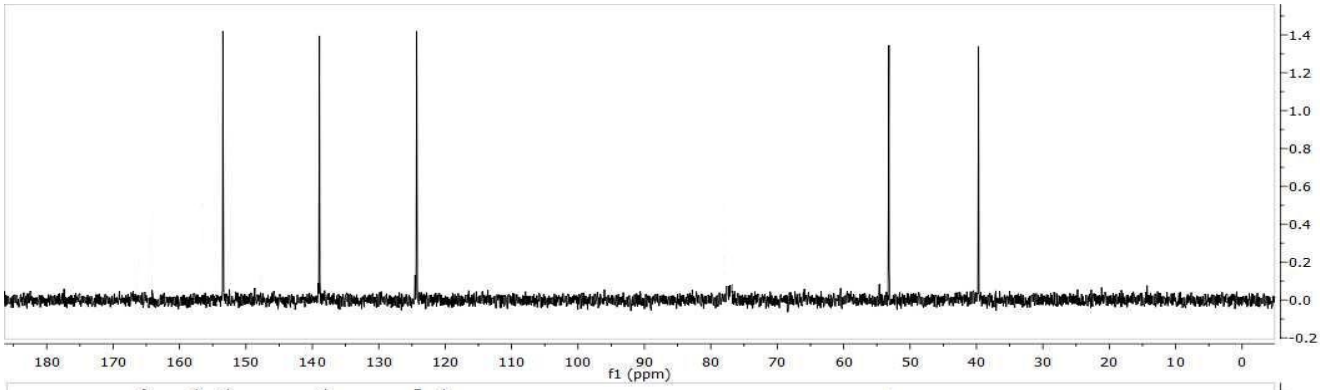
7.3314
7.3197
3.9318
1.00
1.03
1.12
1.12
3.06
f1 (ppm)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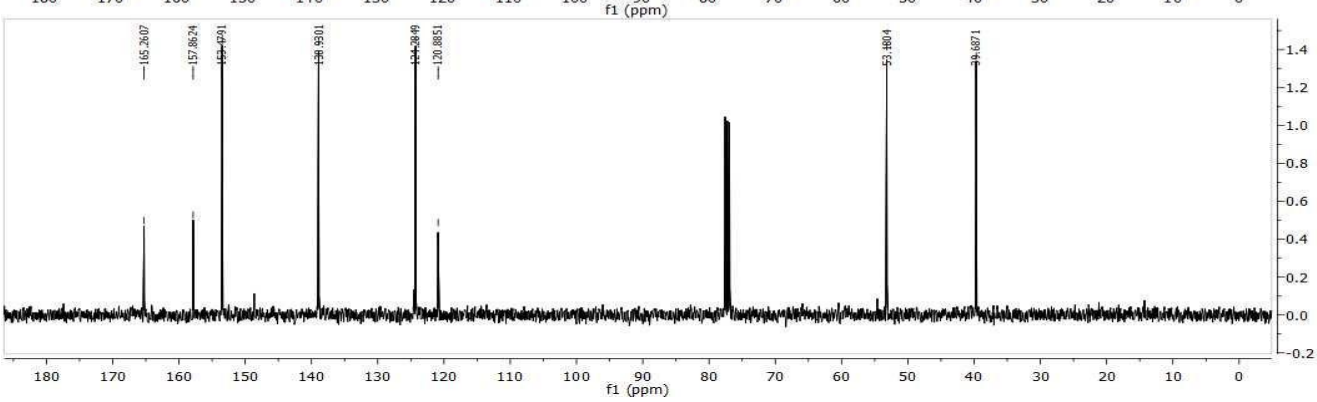
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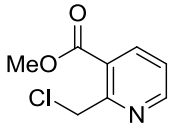
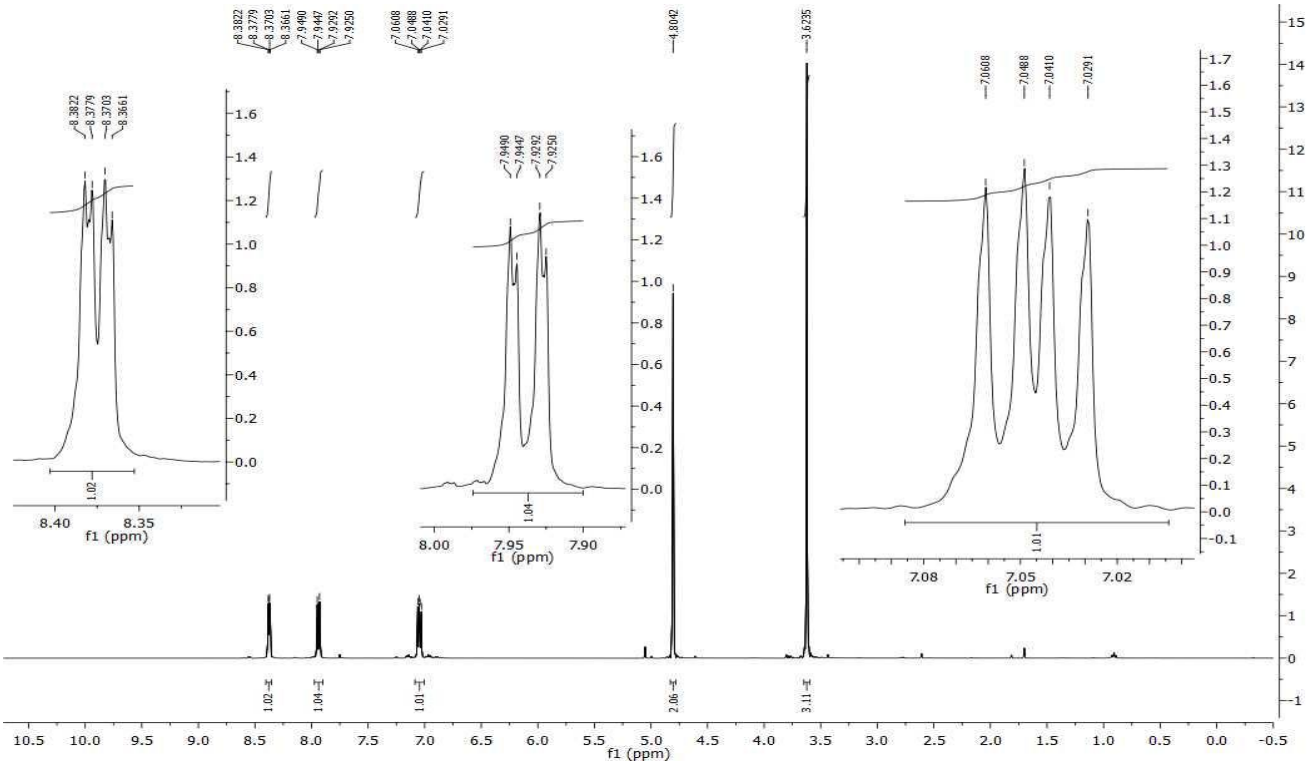

O
MeO
Cl
N

3c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7.0608
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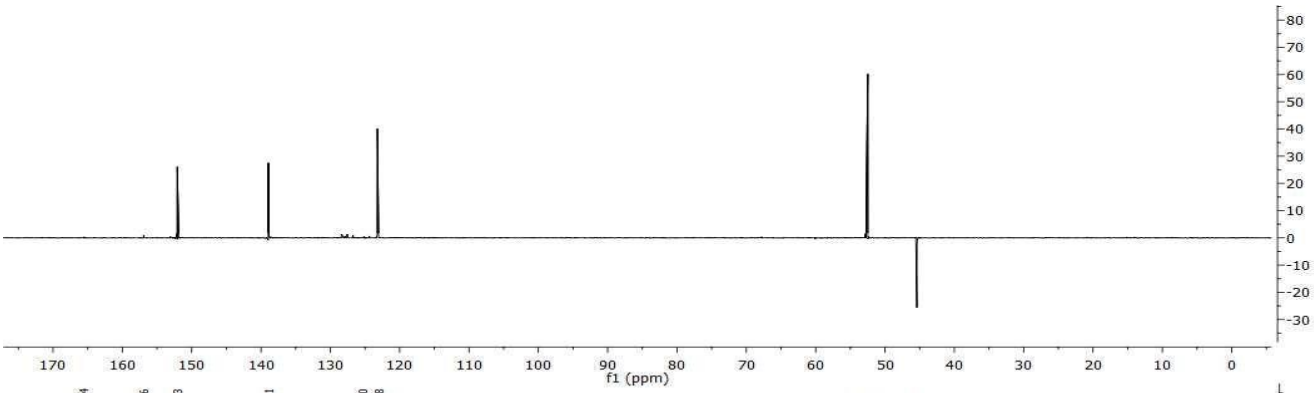
1.04
1.01
2.06
3.11
f1 (ppm)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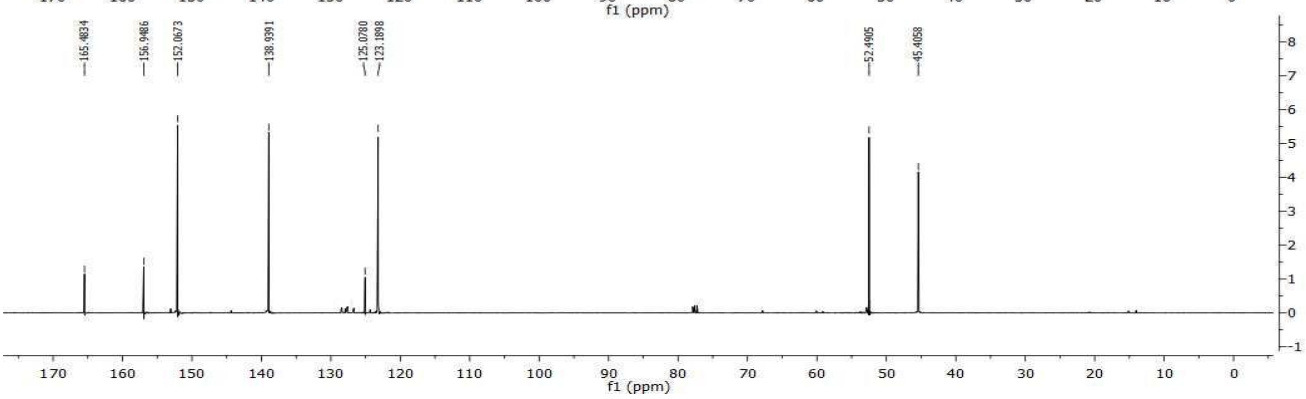
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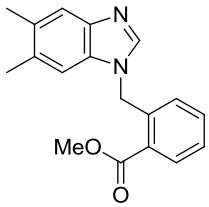
f1 (ppm)



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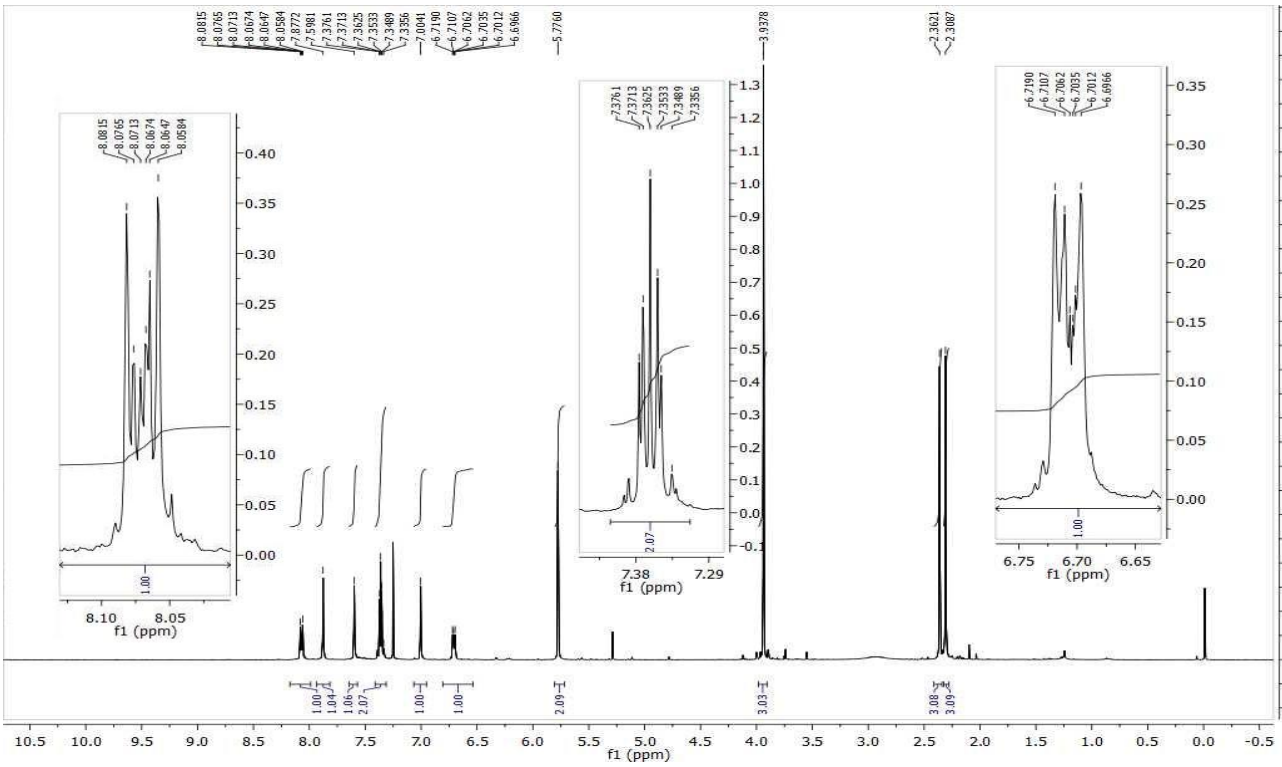

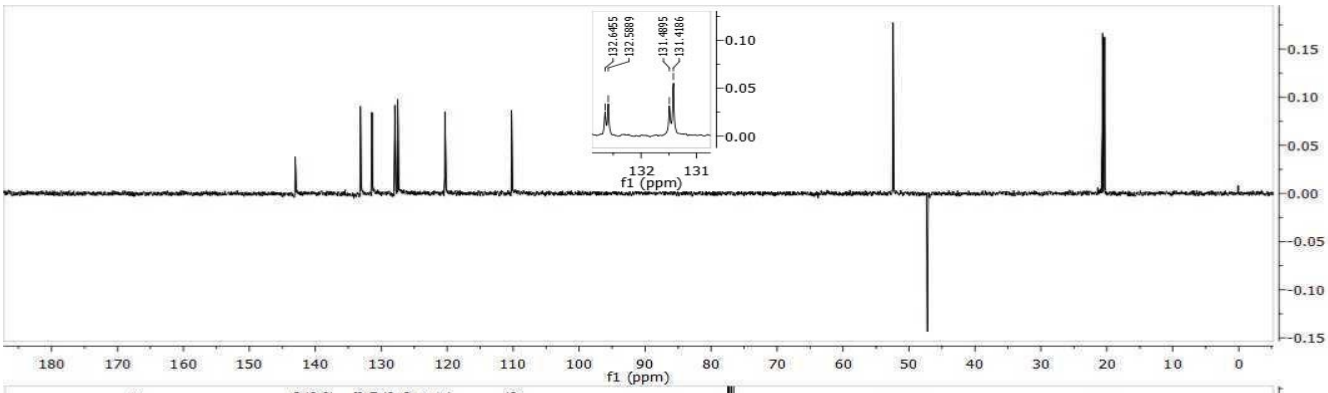

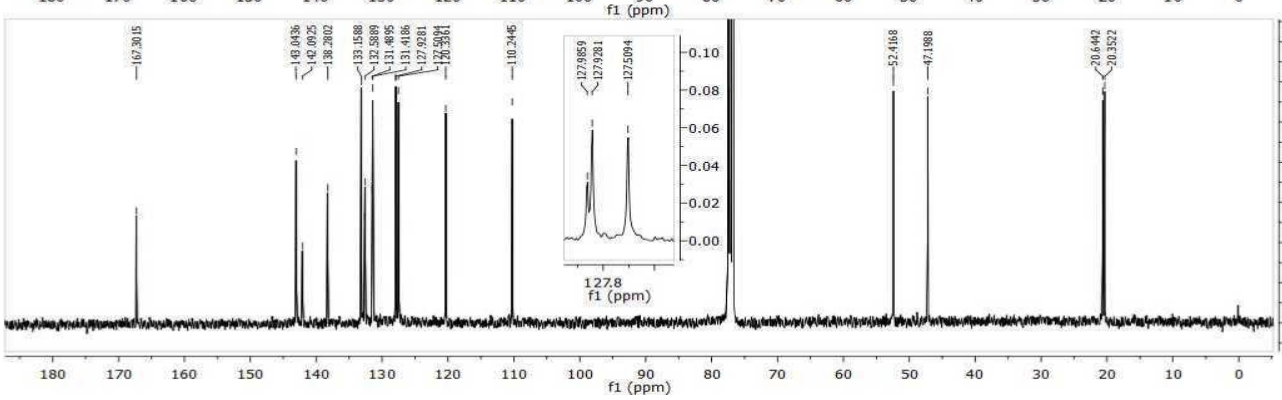

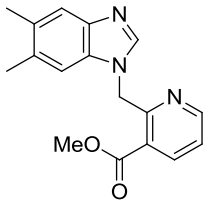

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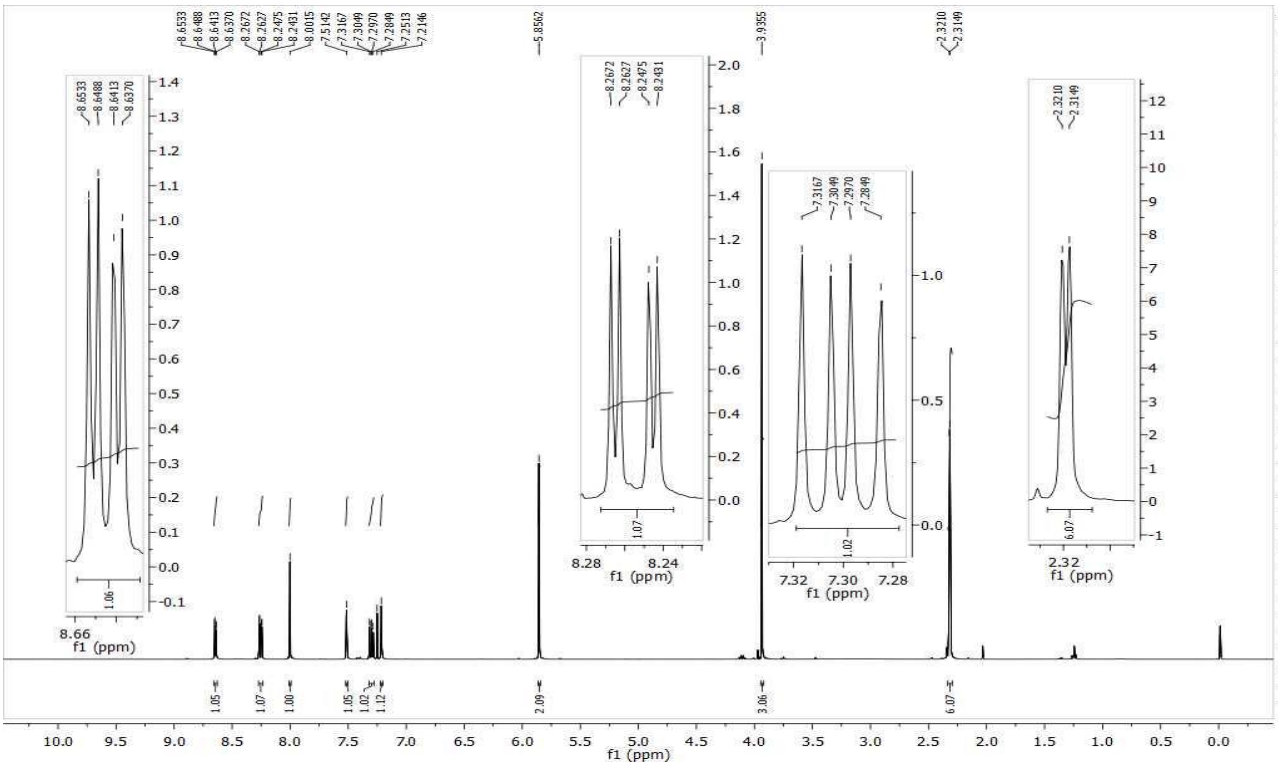

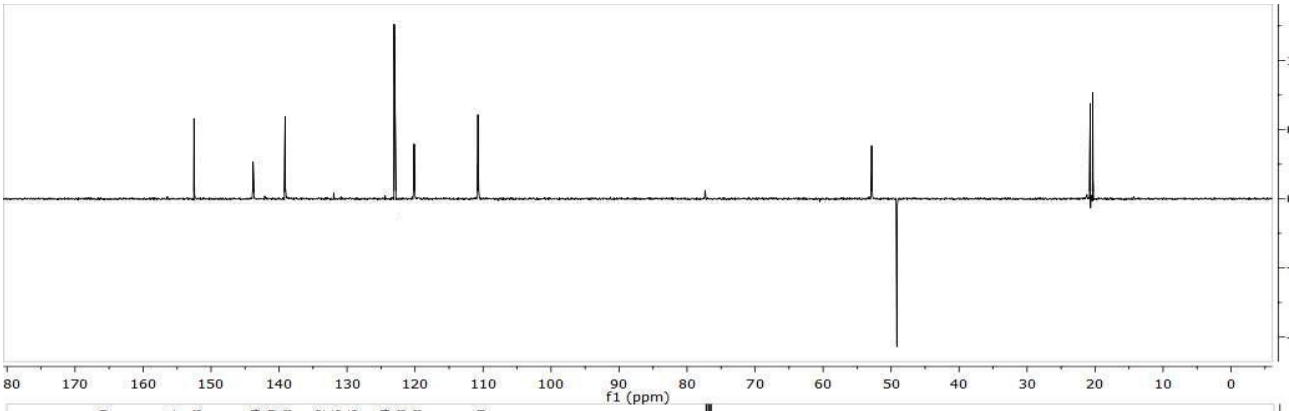

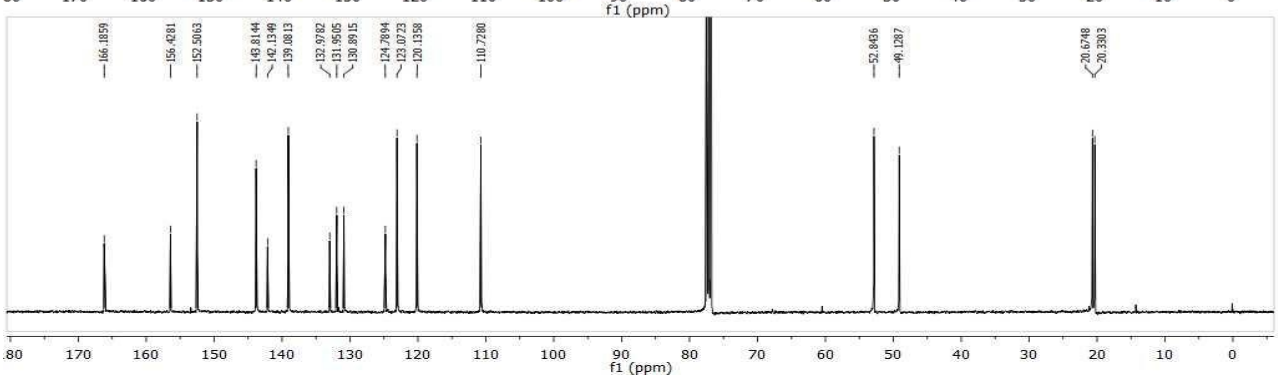

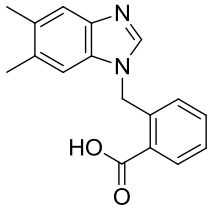

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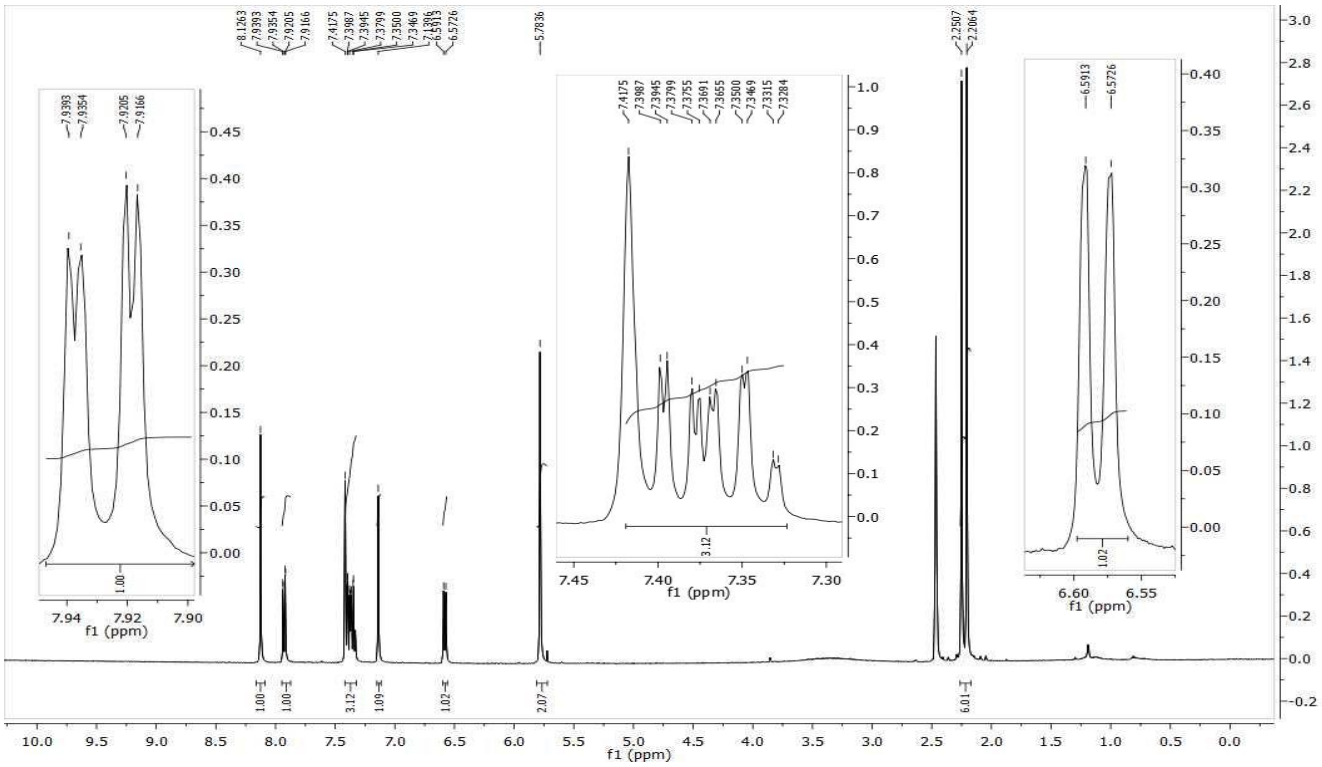

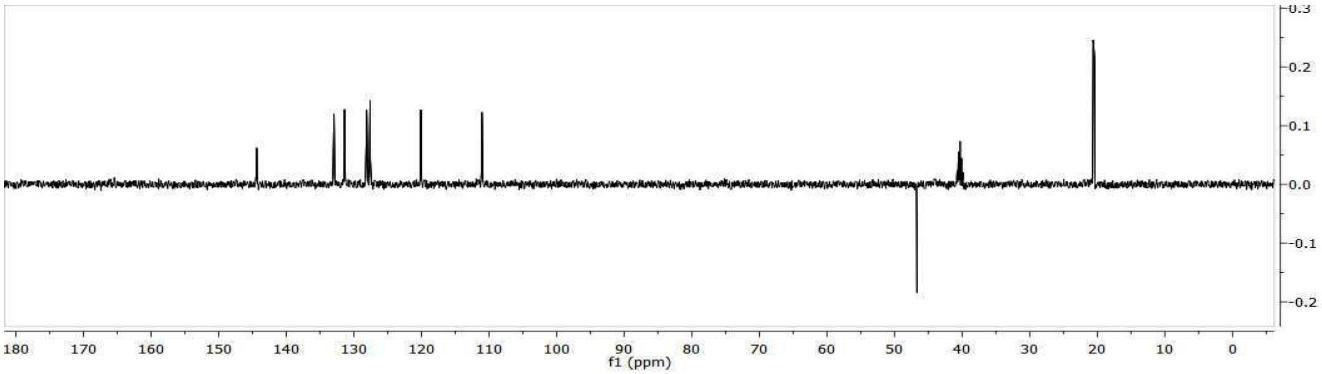

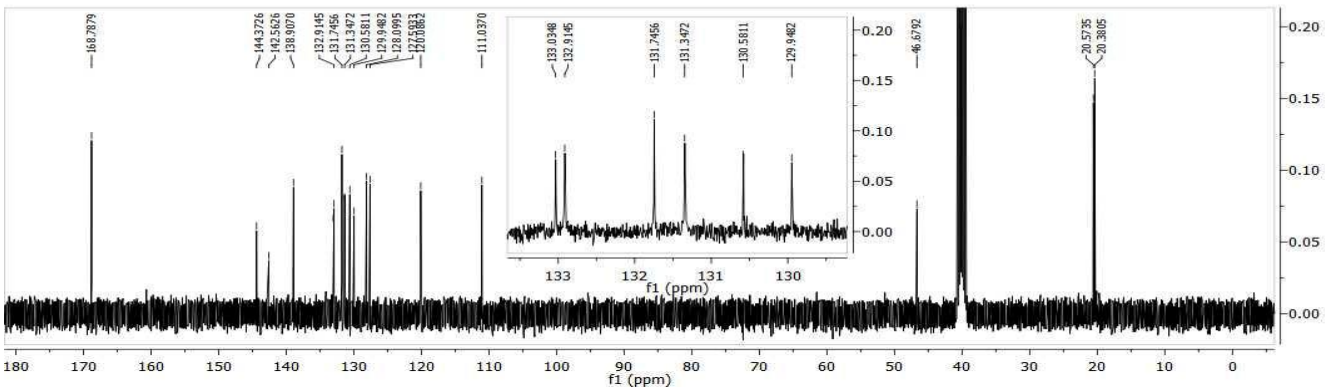

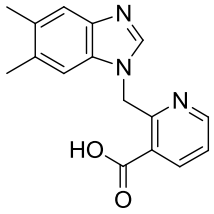

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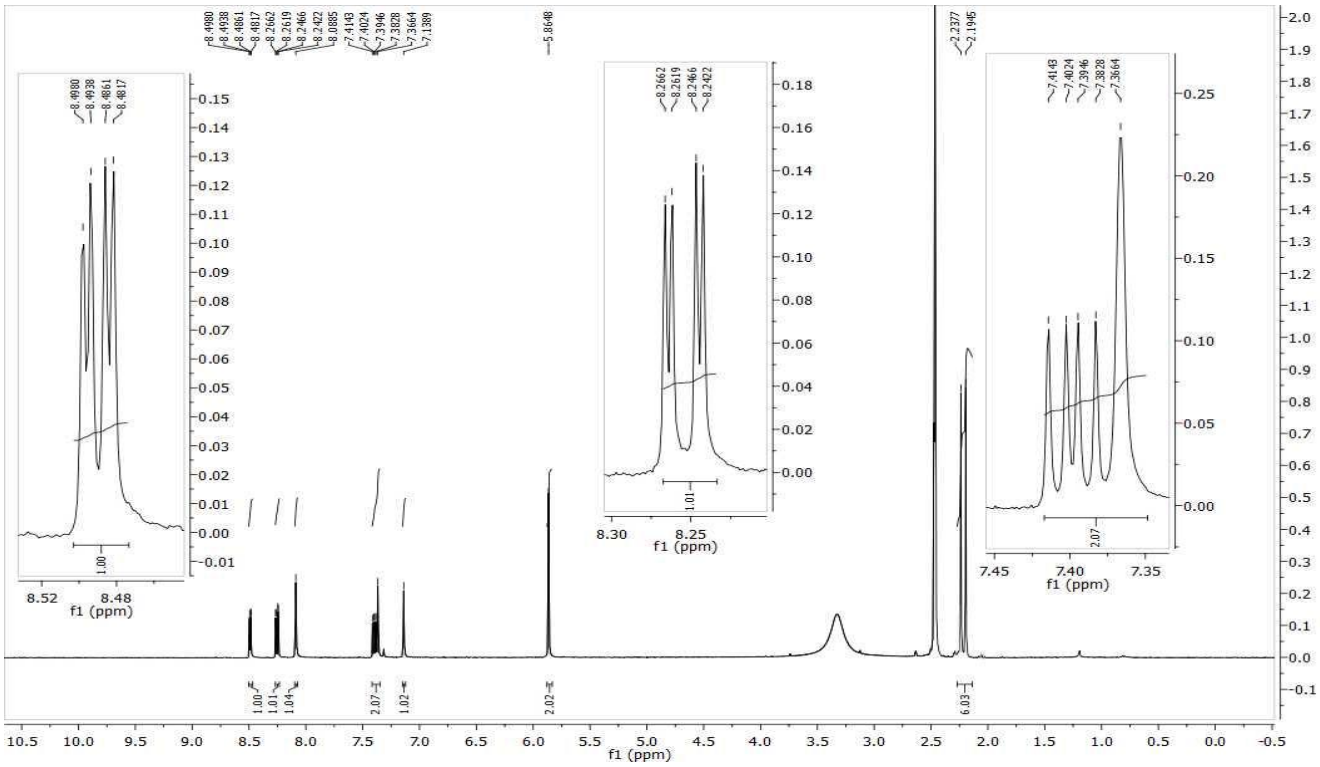

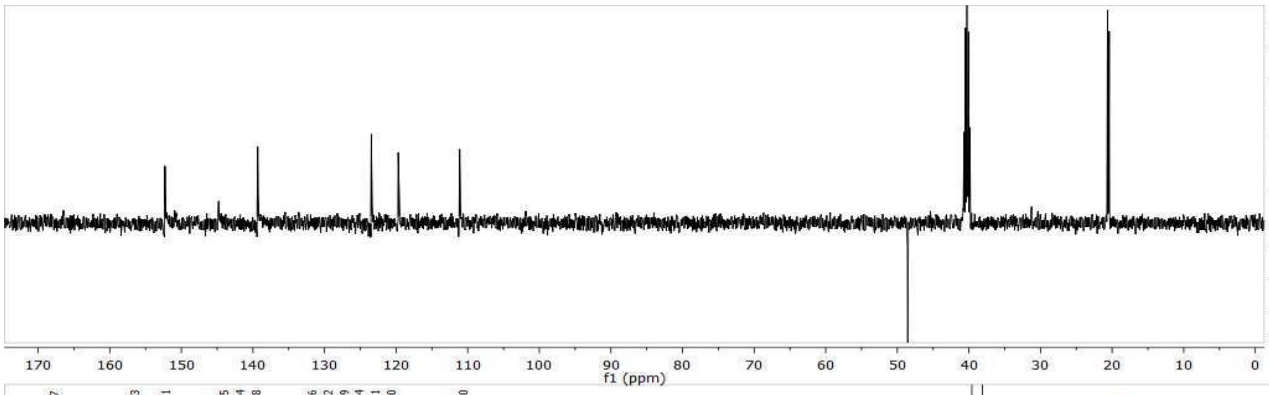

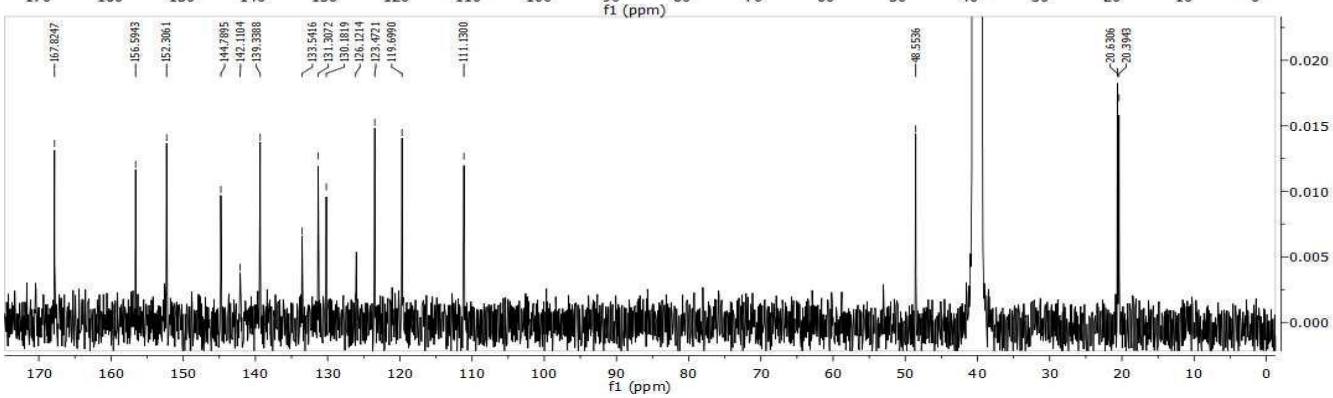

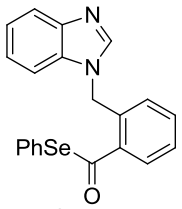

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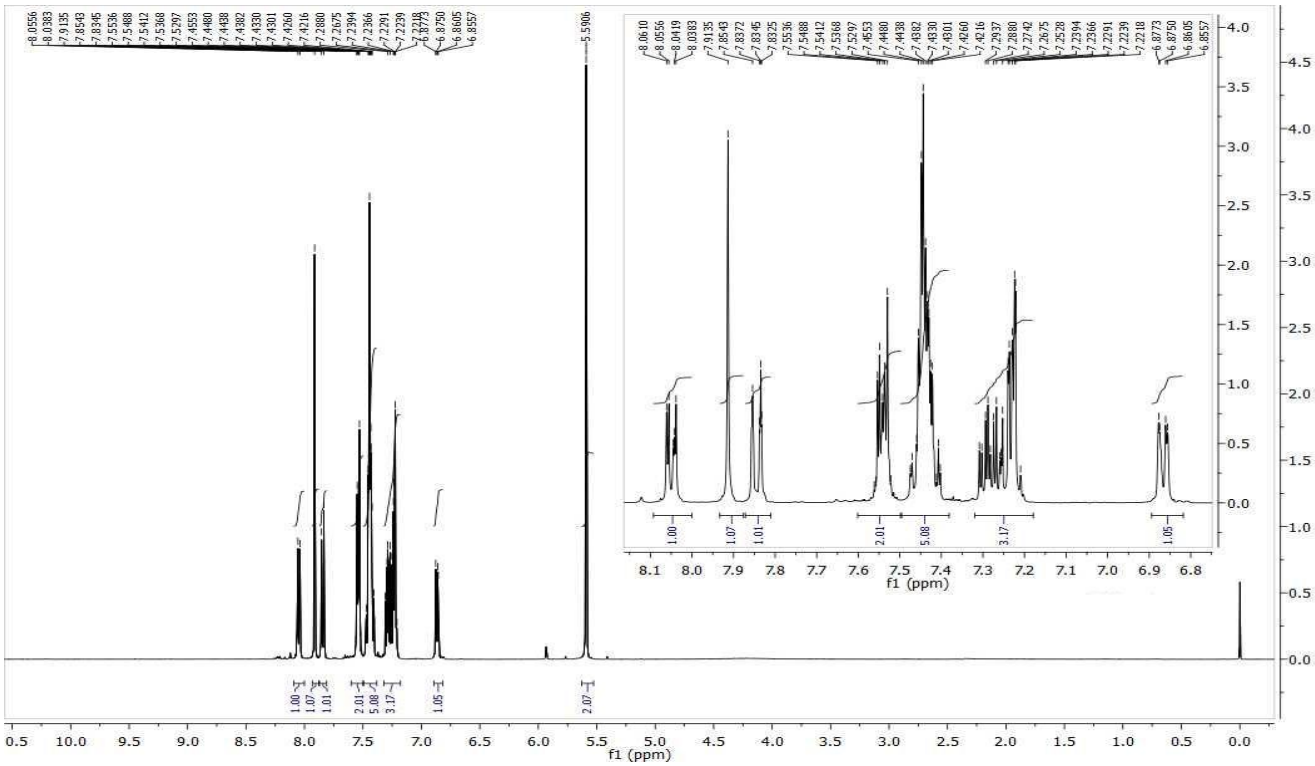

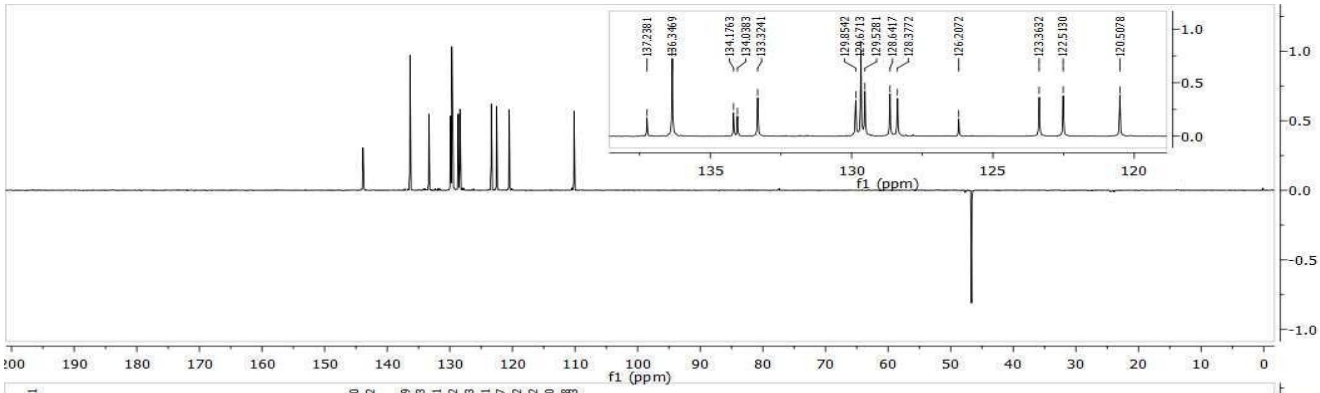

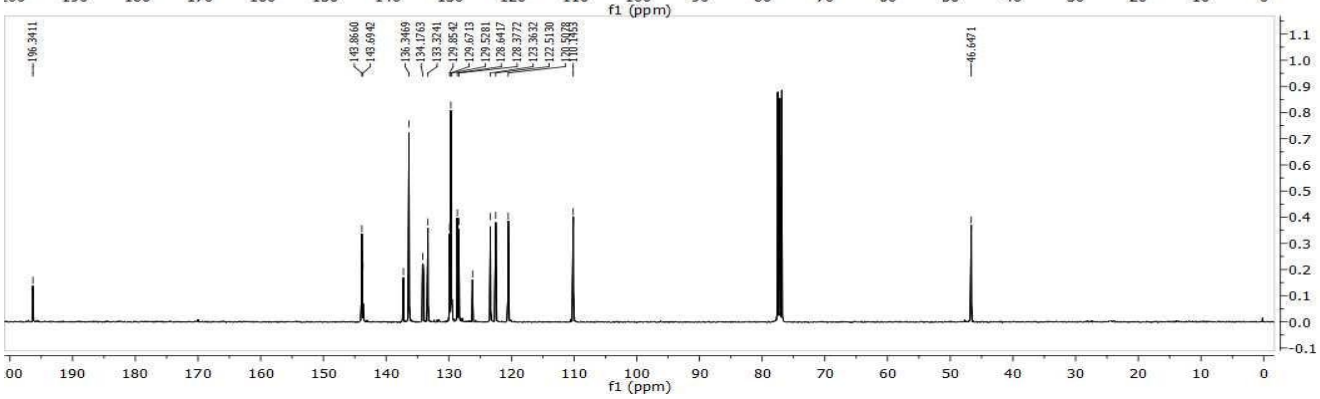

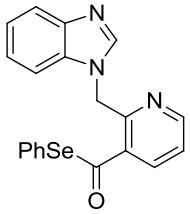

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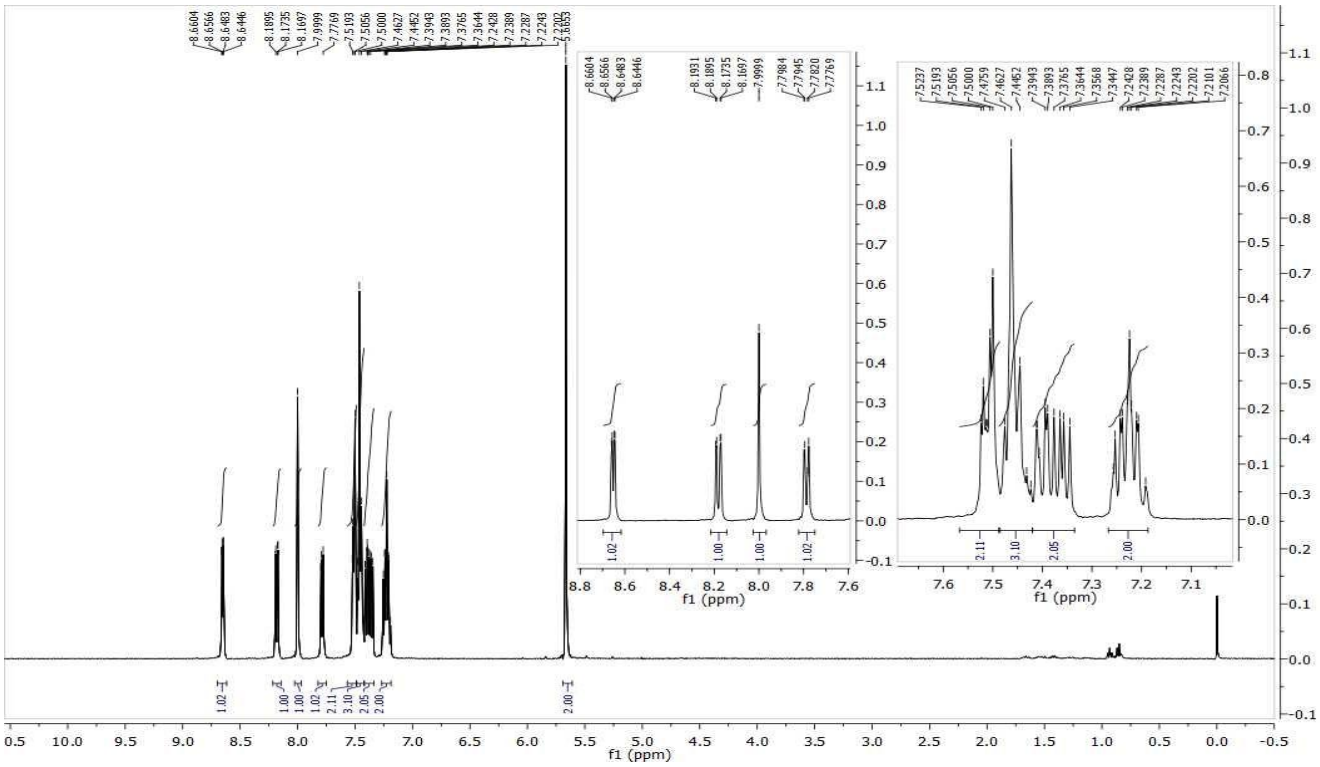

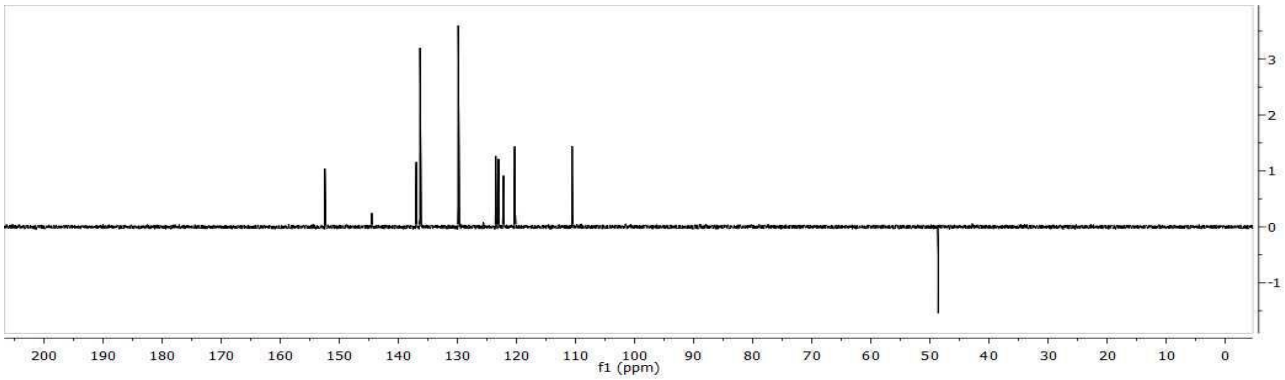

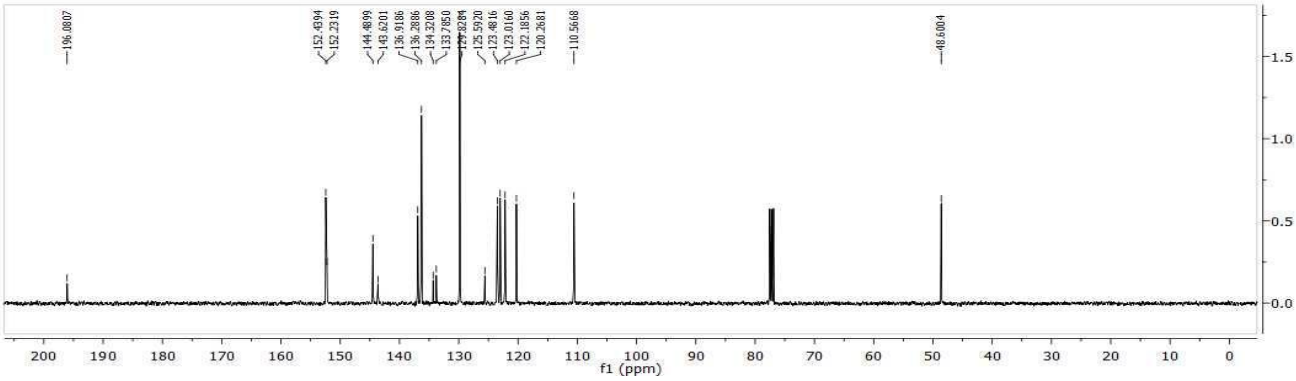

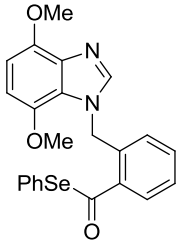

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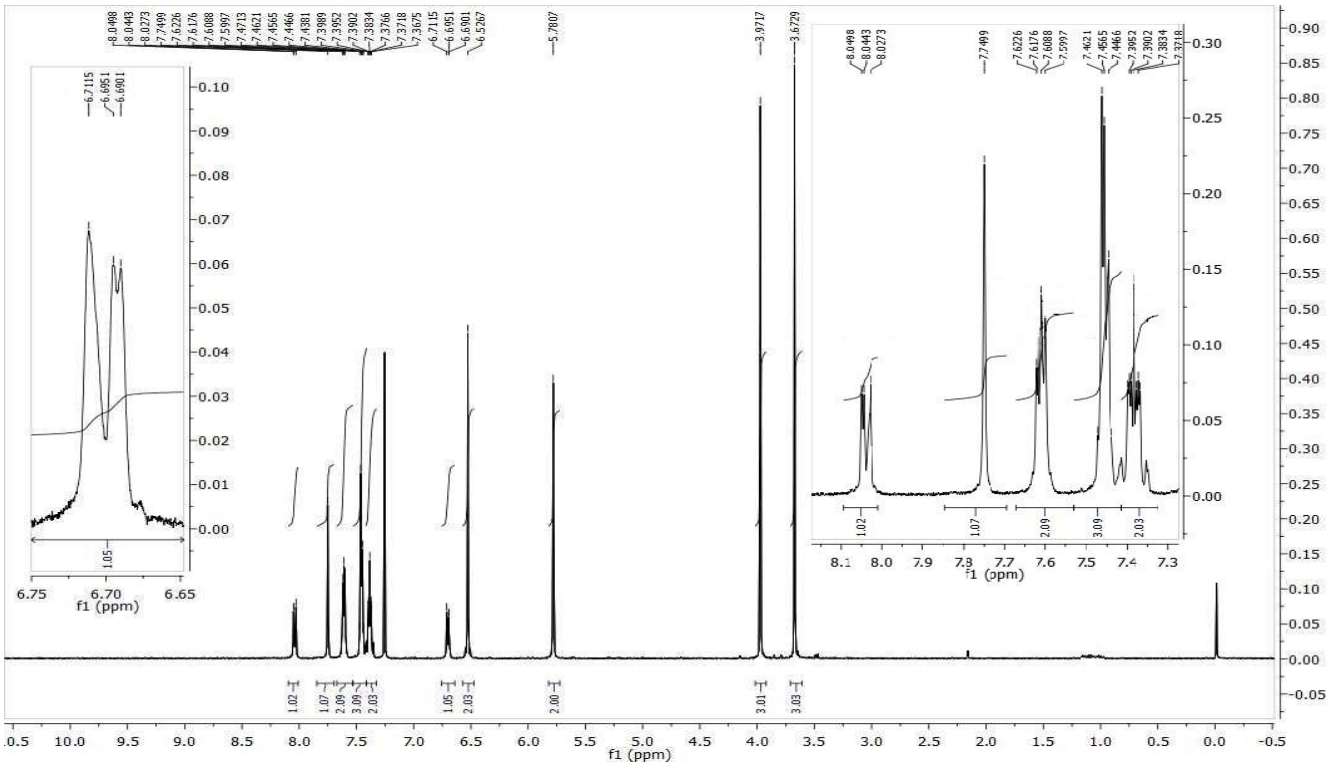

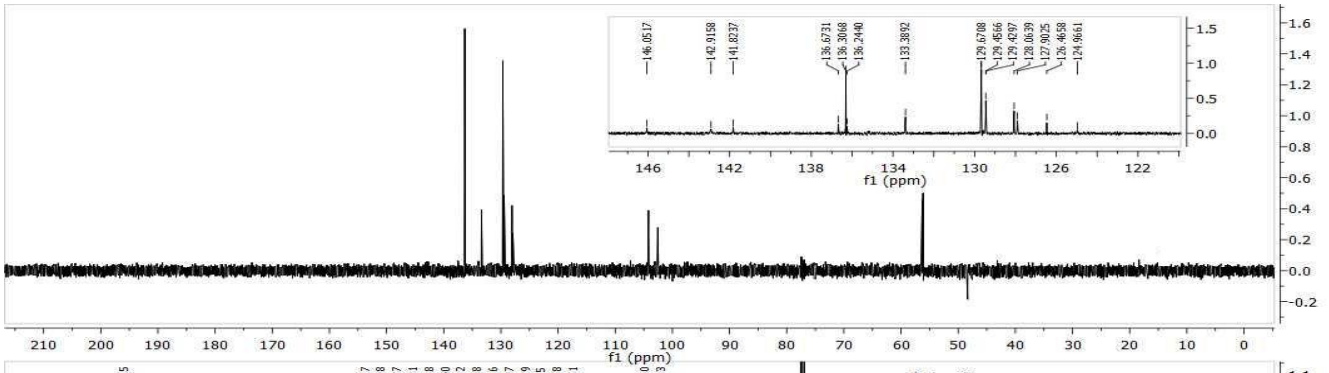

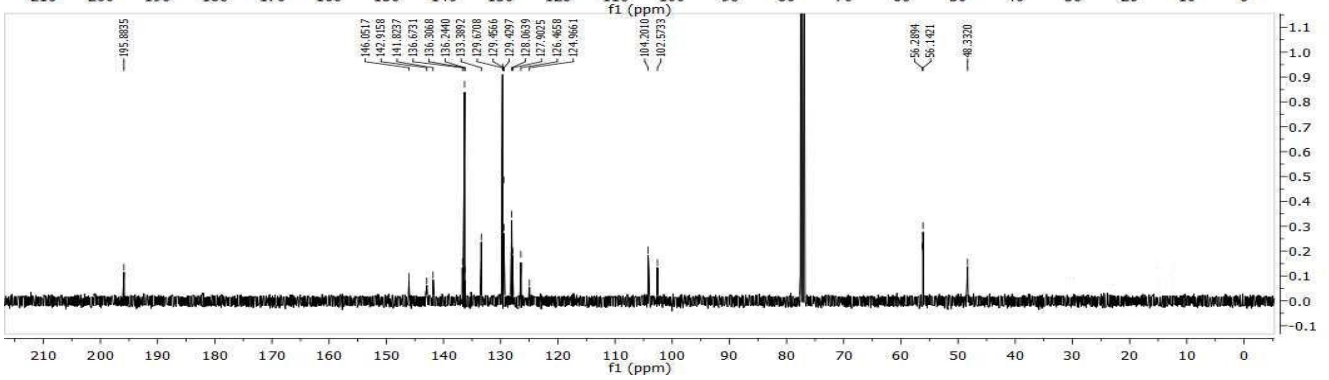

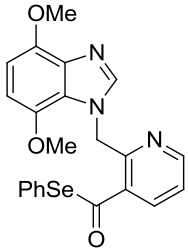

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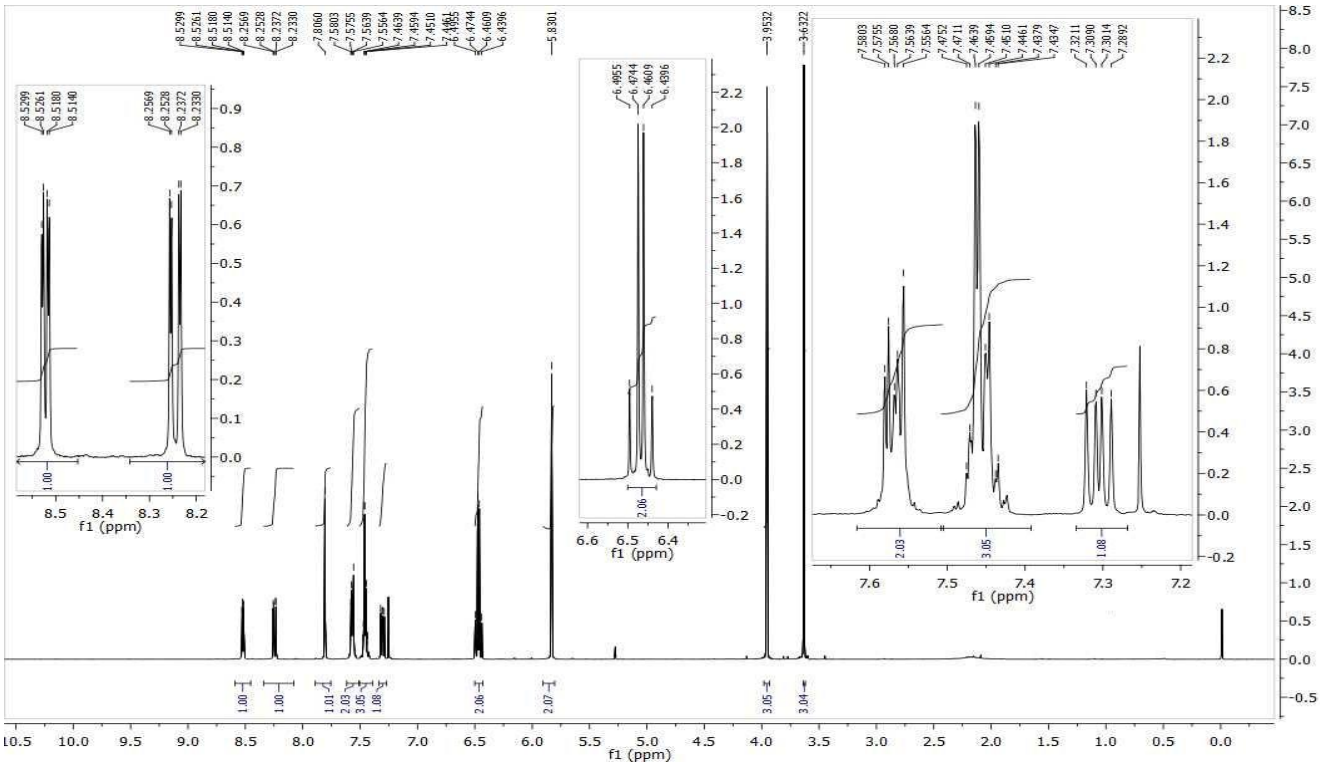

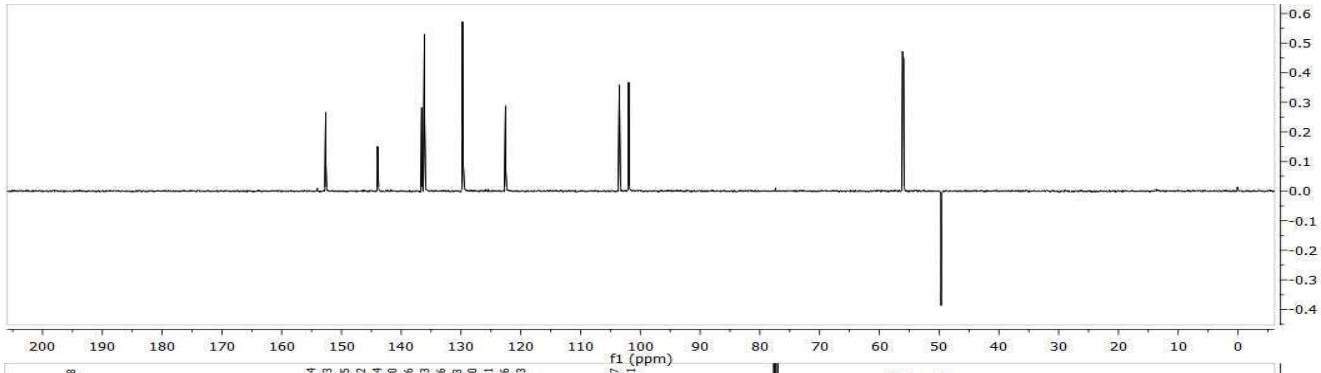

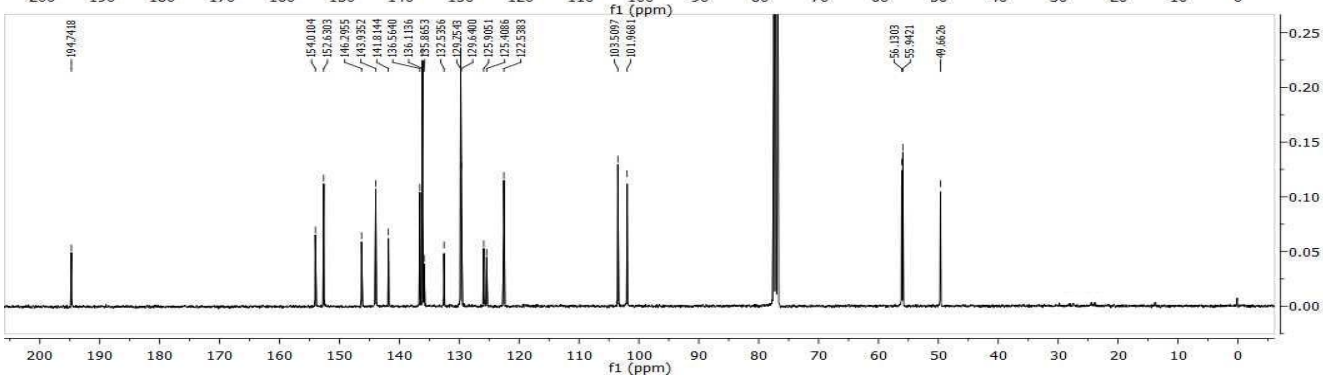

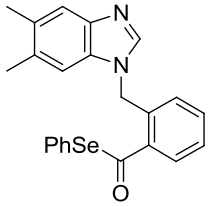

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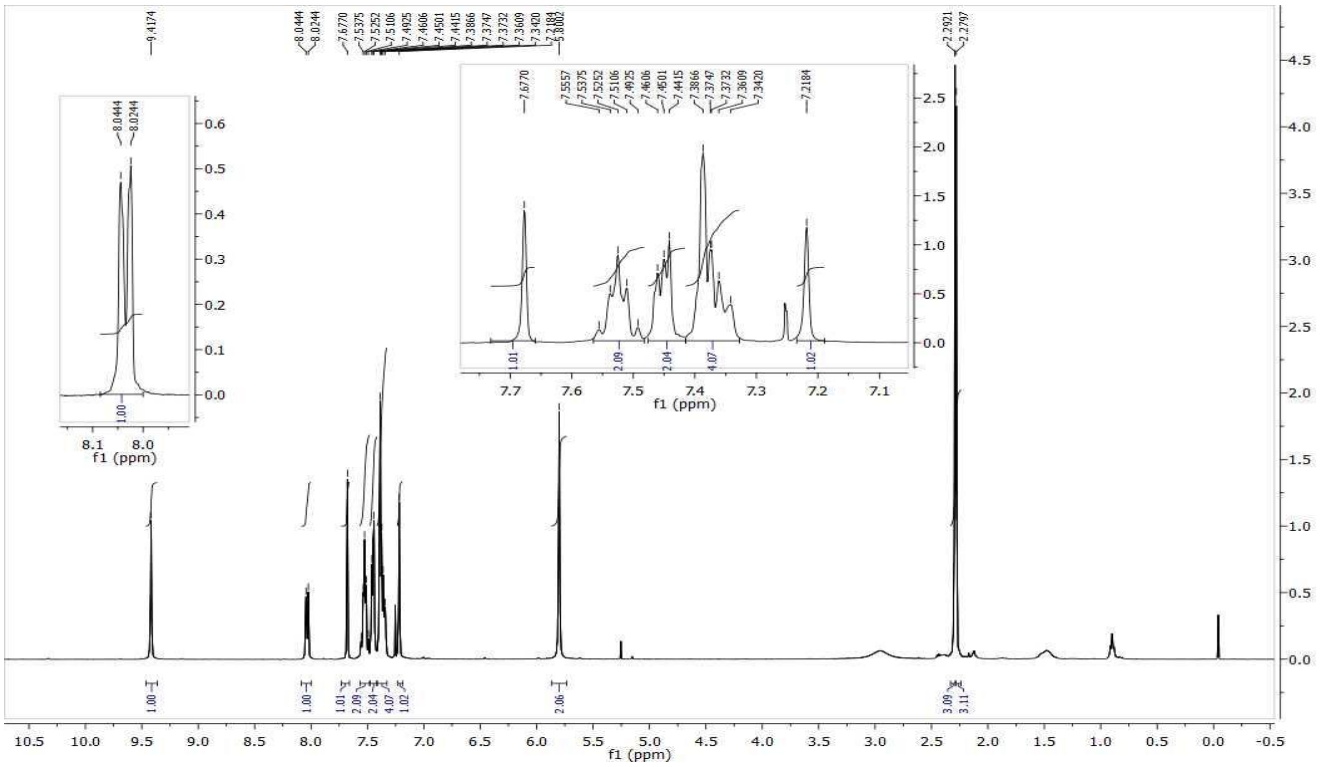

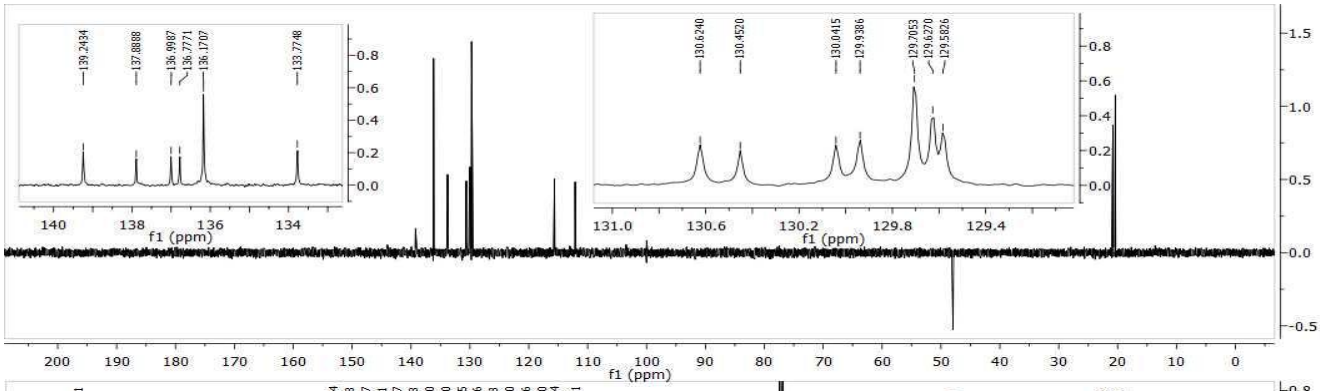

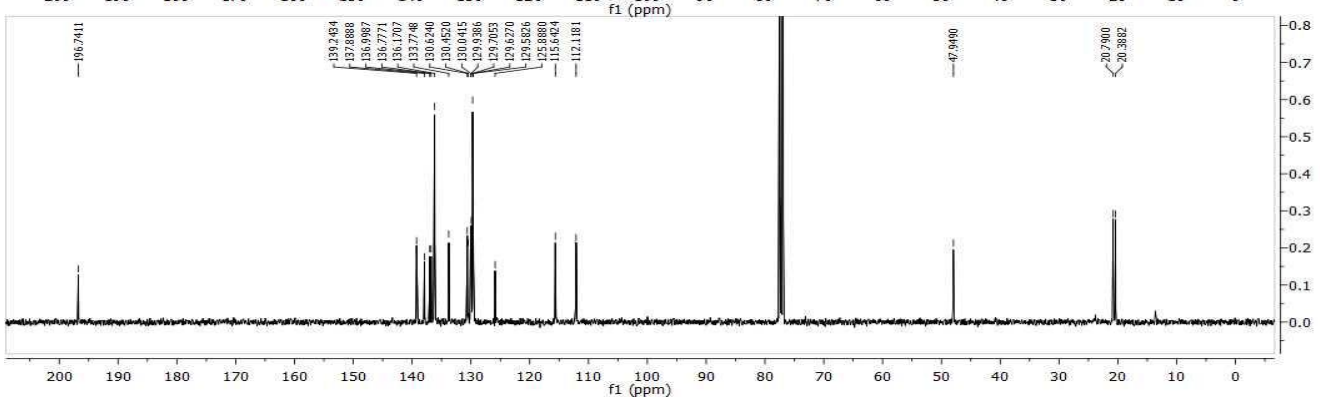

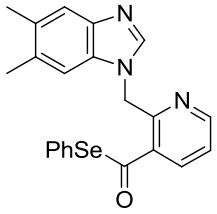

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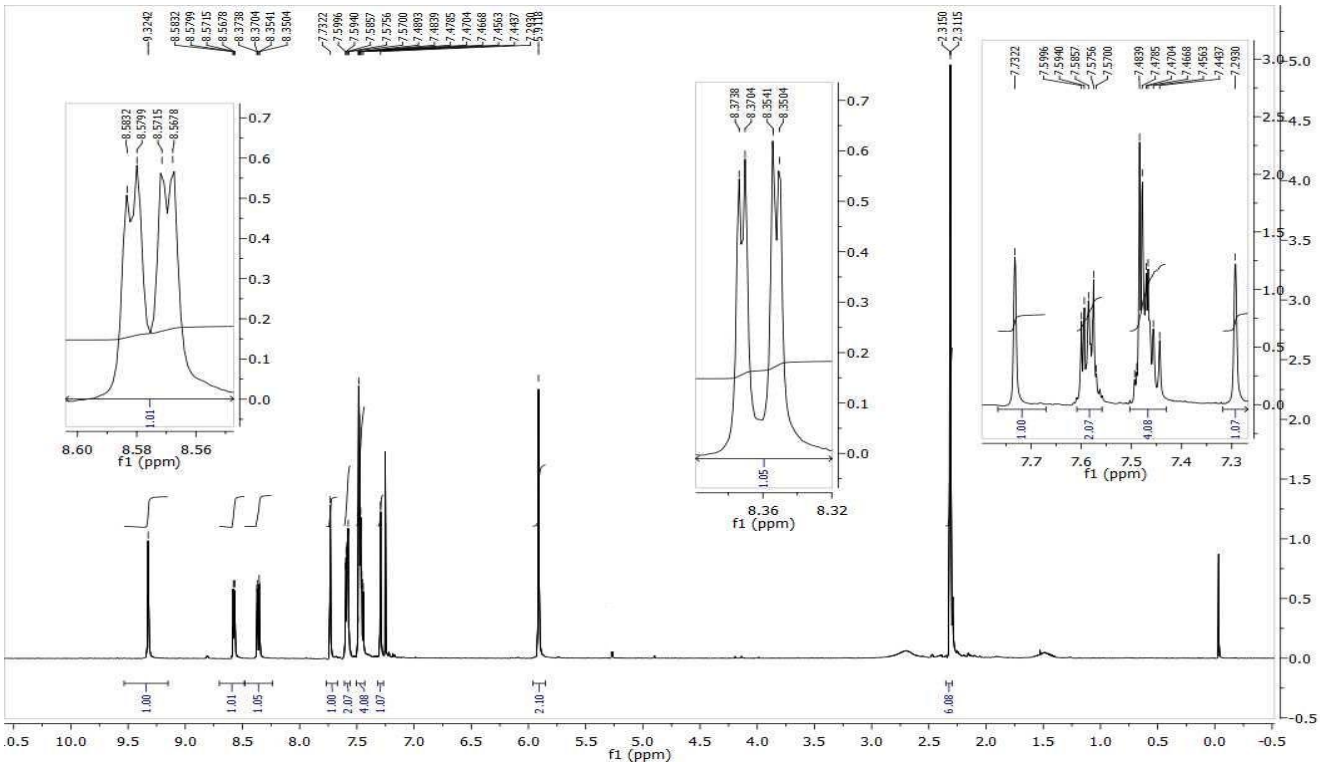

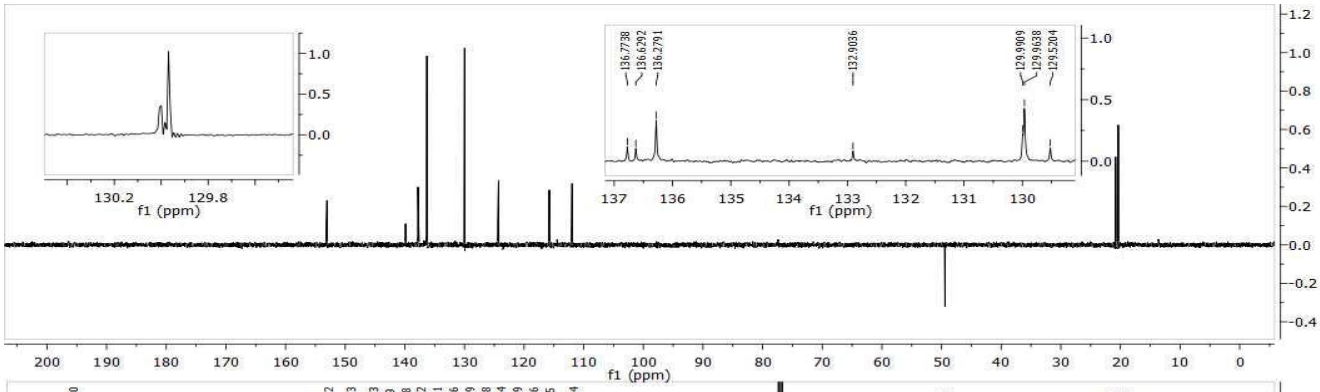

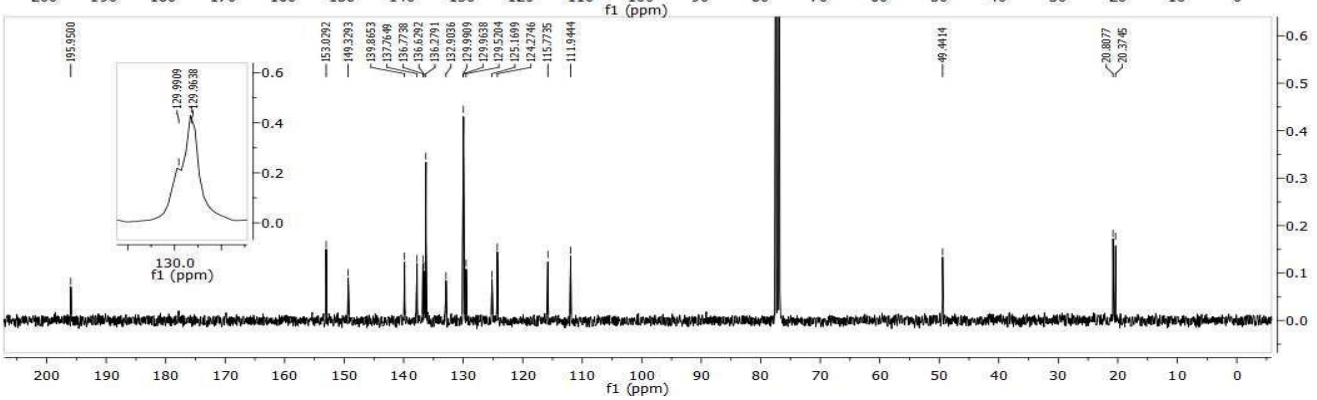

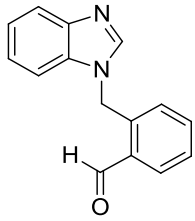

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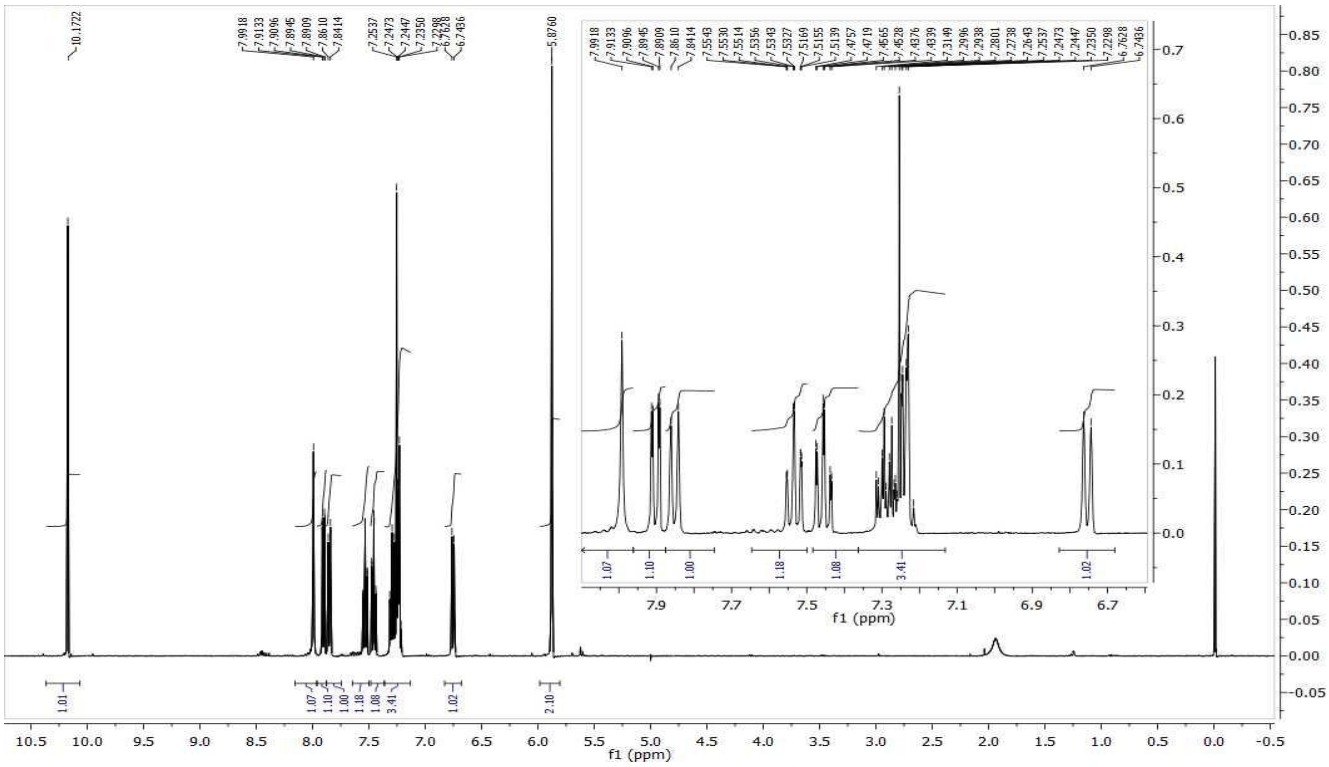

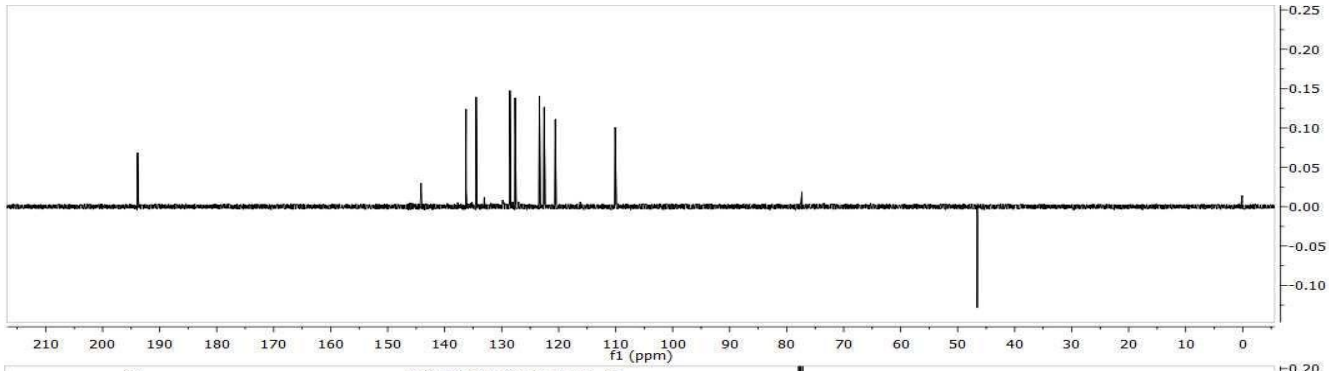

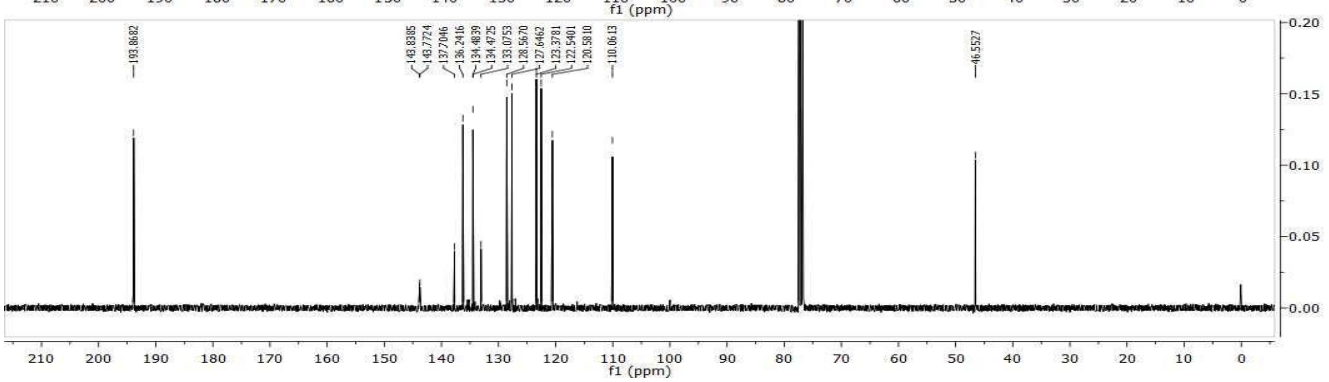

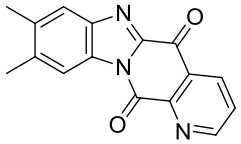

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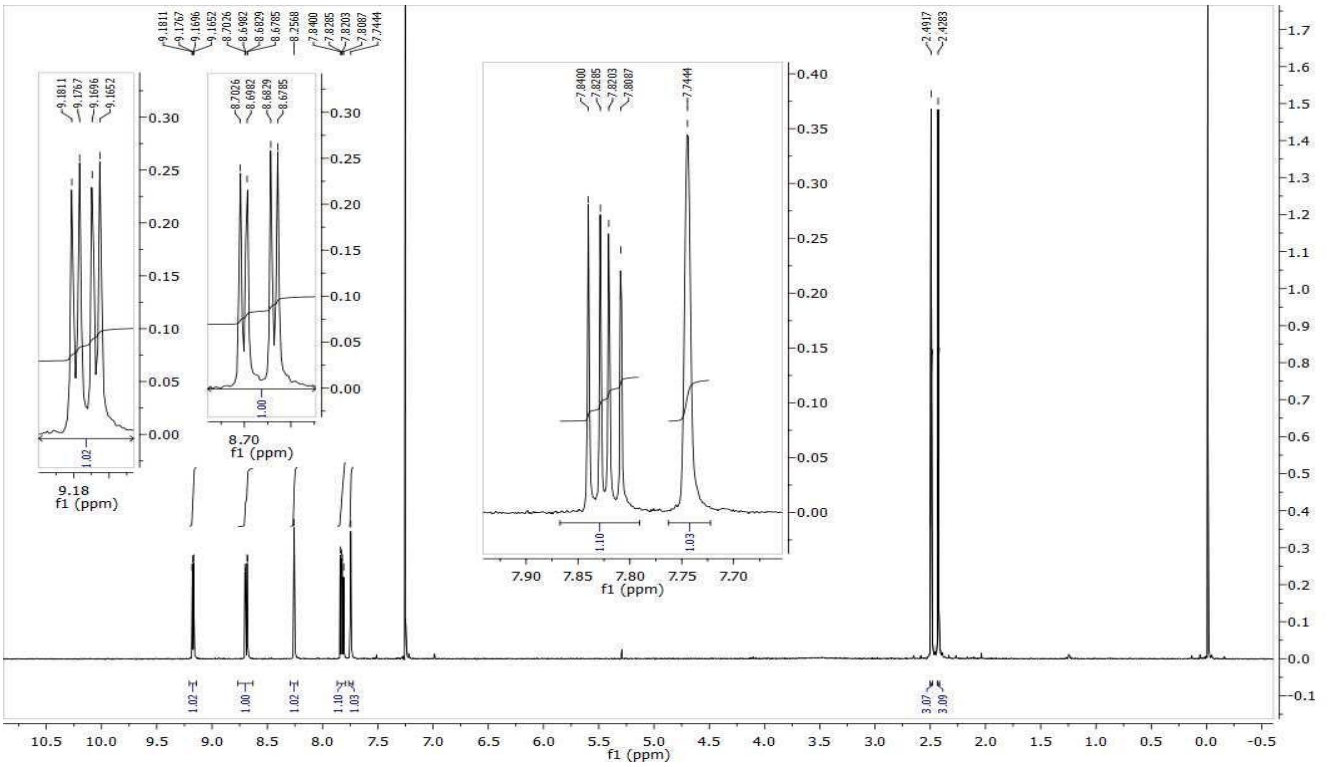
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9.1696
9.1652
8.7026
8.6982
8.6829
8.6785
8.2568
7.8400
7.8285
7.8203
7.8087
7.7444
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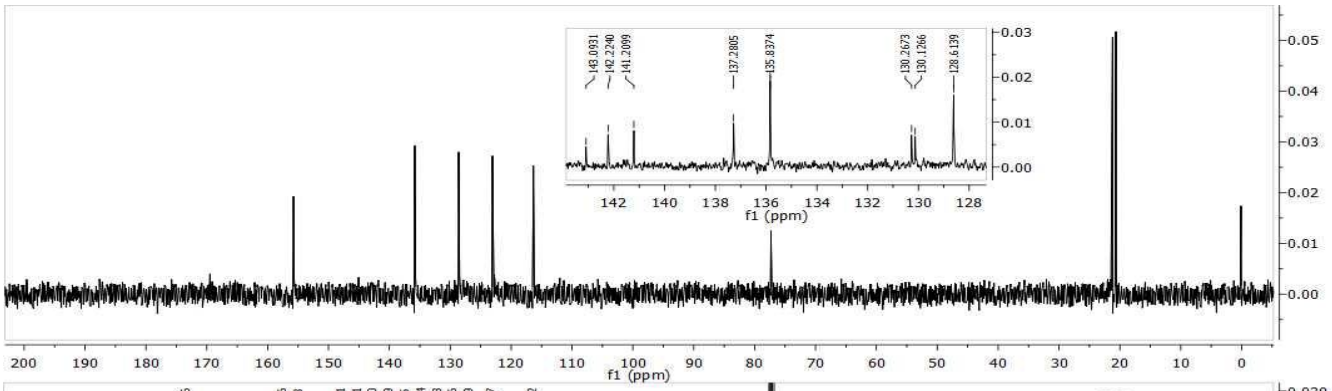
9.18
8.70
f1 (ppm)
1.02
1.00
1.10
1.03
3.07
3.09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141.2099
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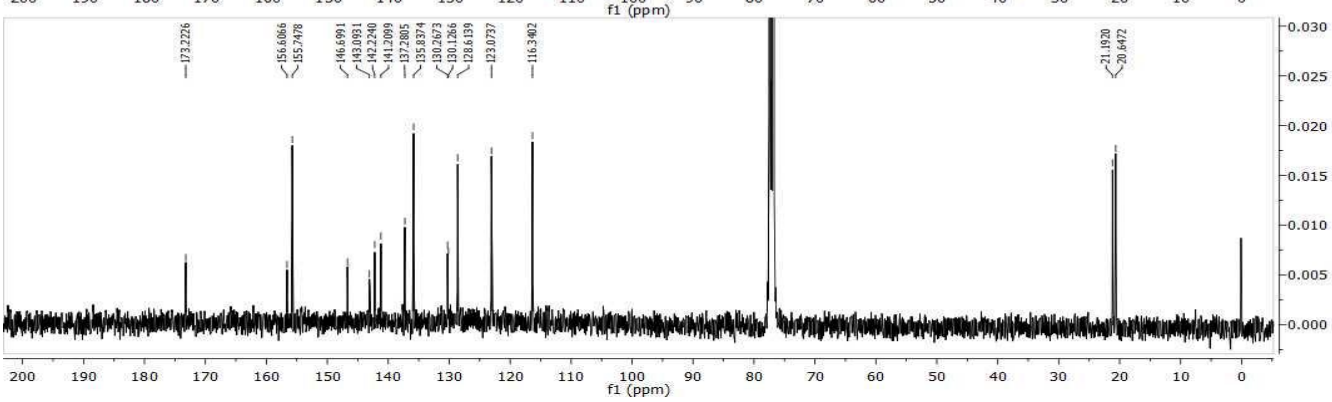
130.1266
128.6139
f1 (ppm)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155.7478
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141.2099
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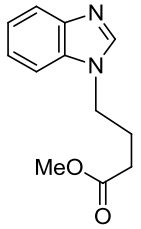
20.6472
f1 (ppm)



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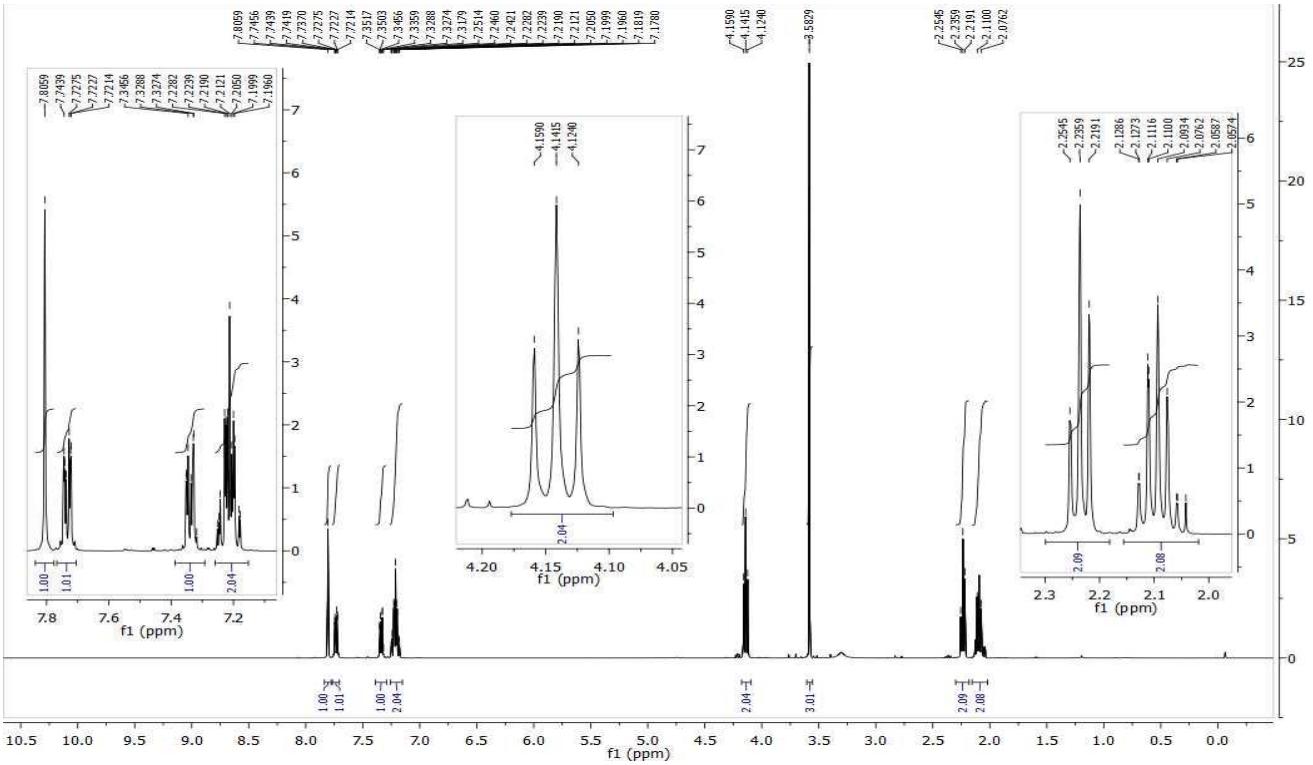

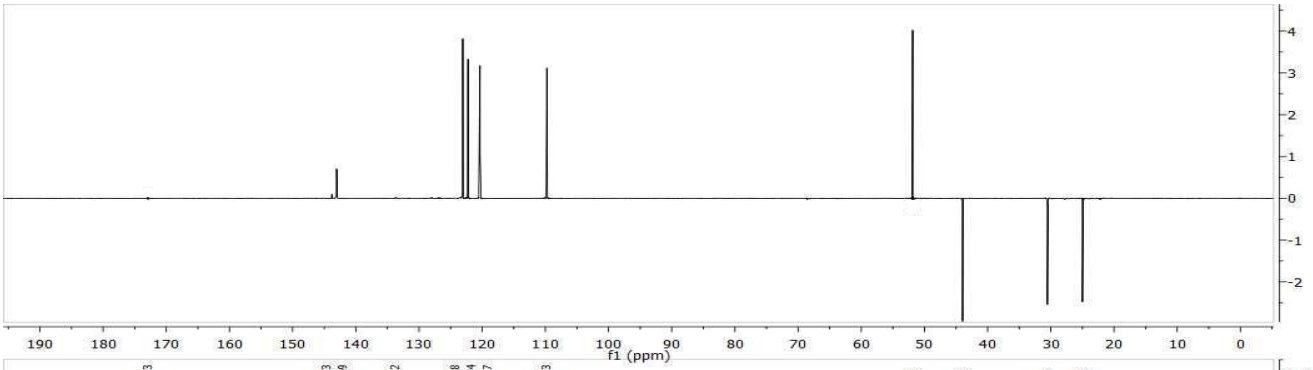

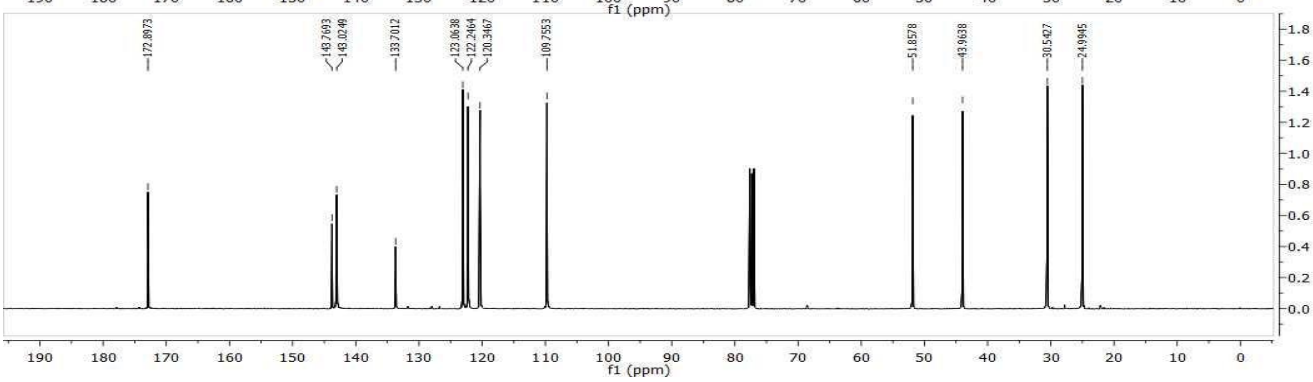

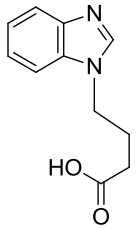

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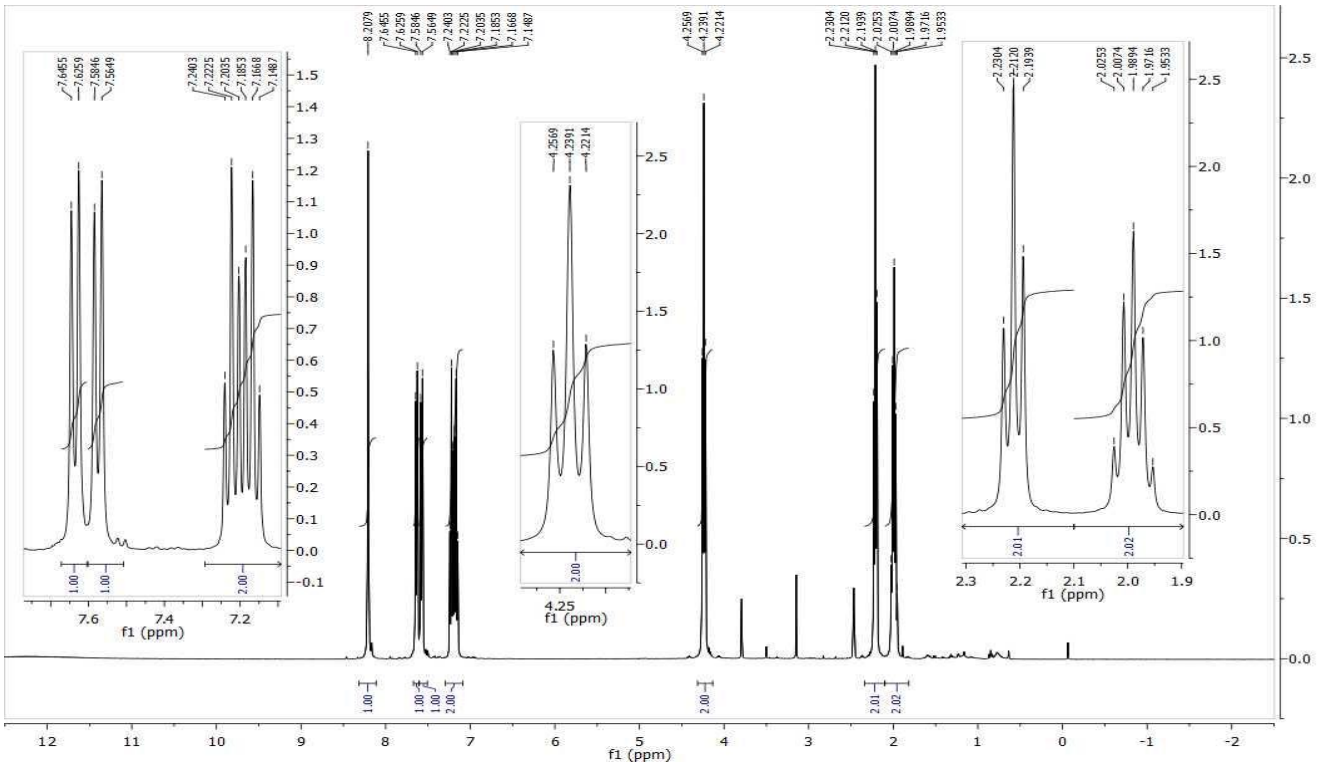

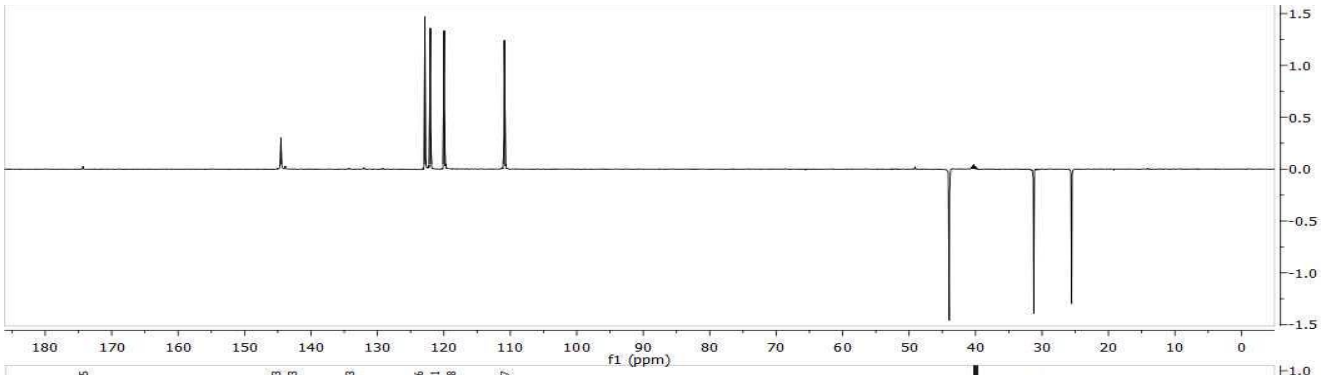

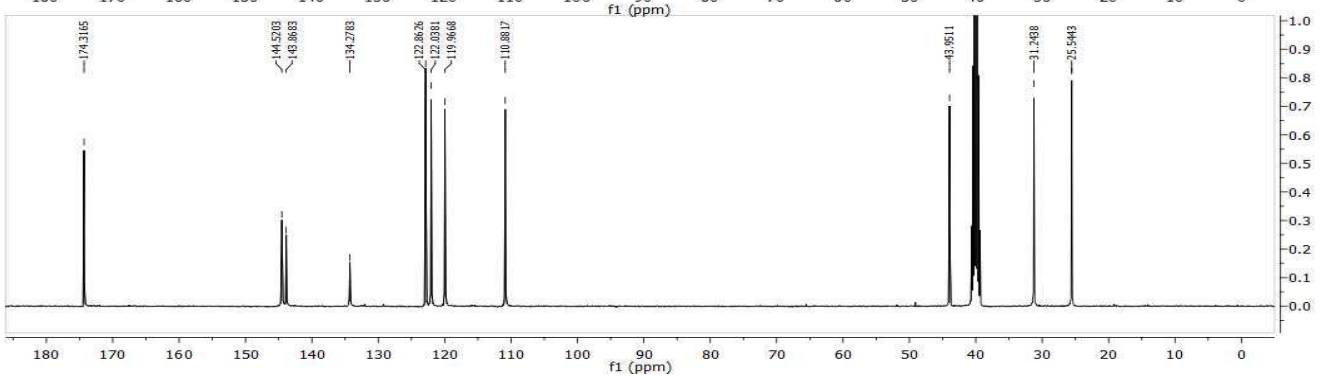

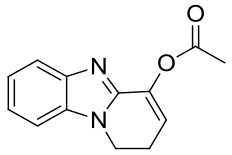

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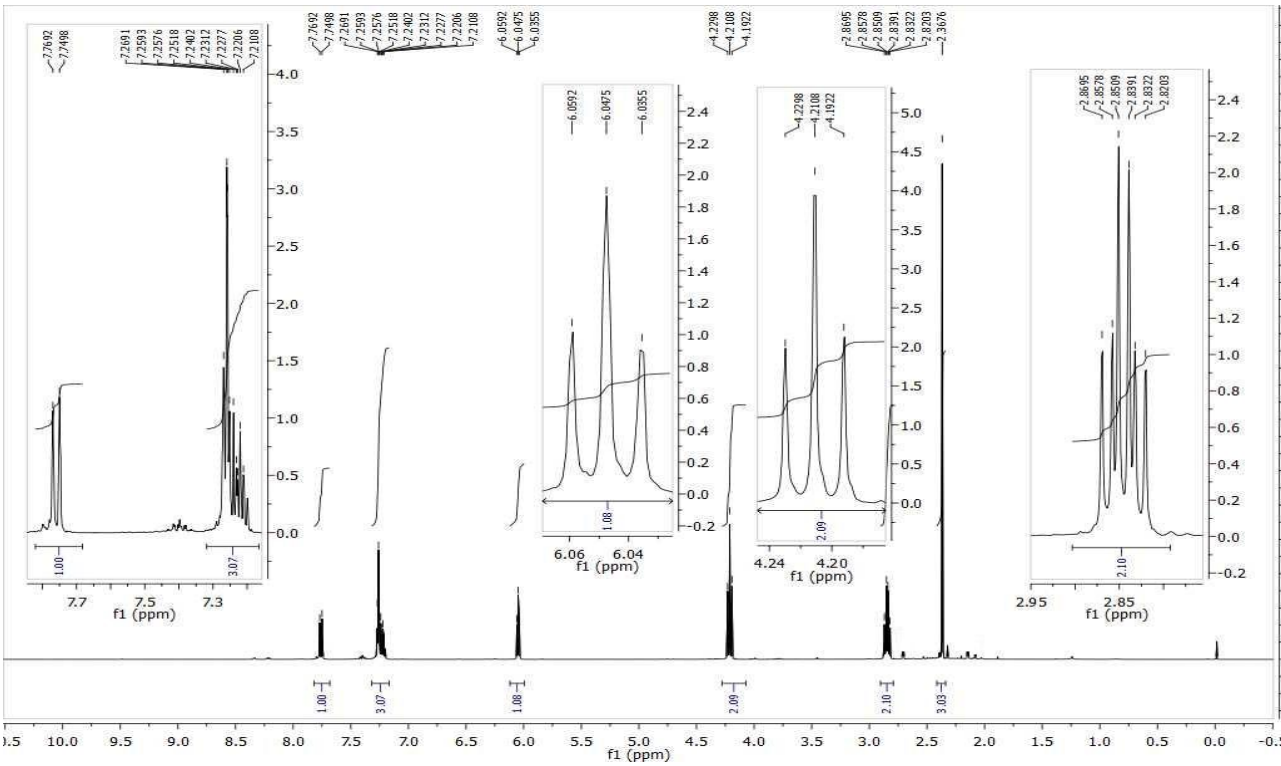

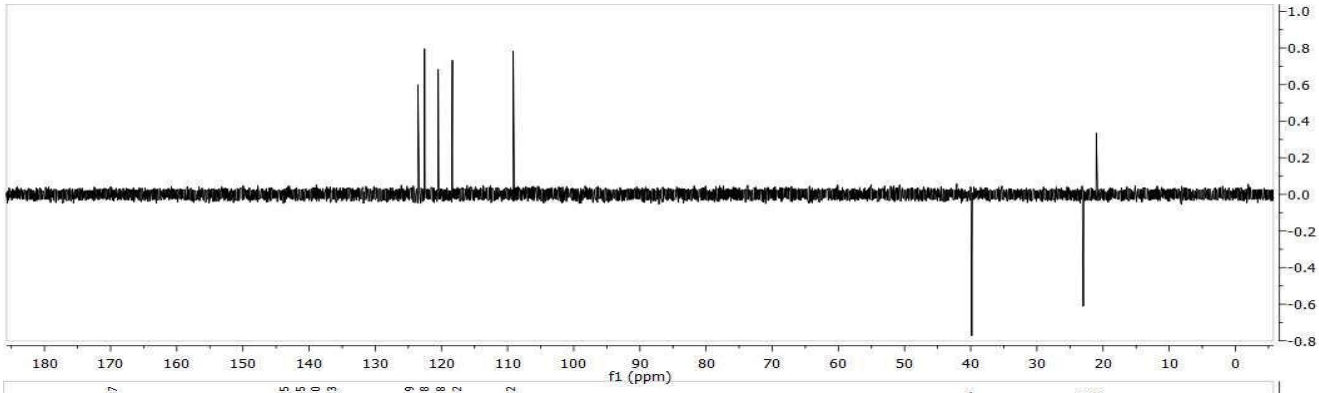

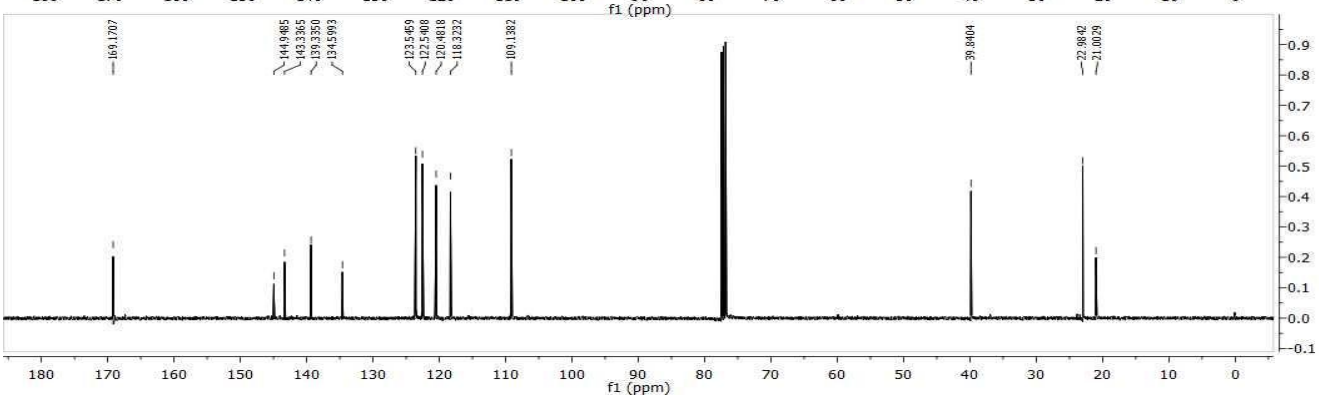

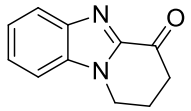

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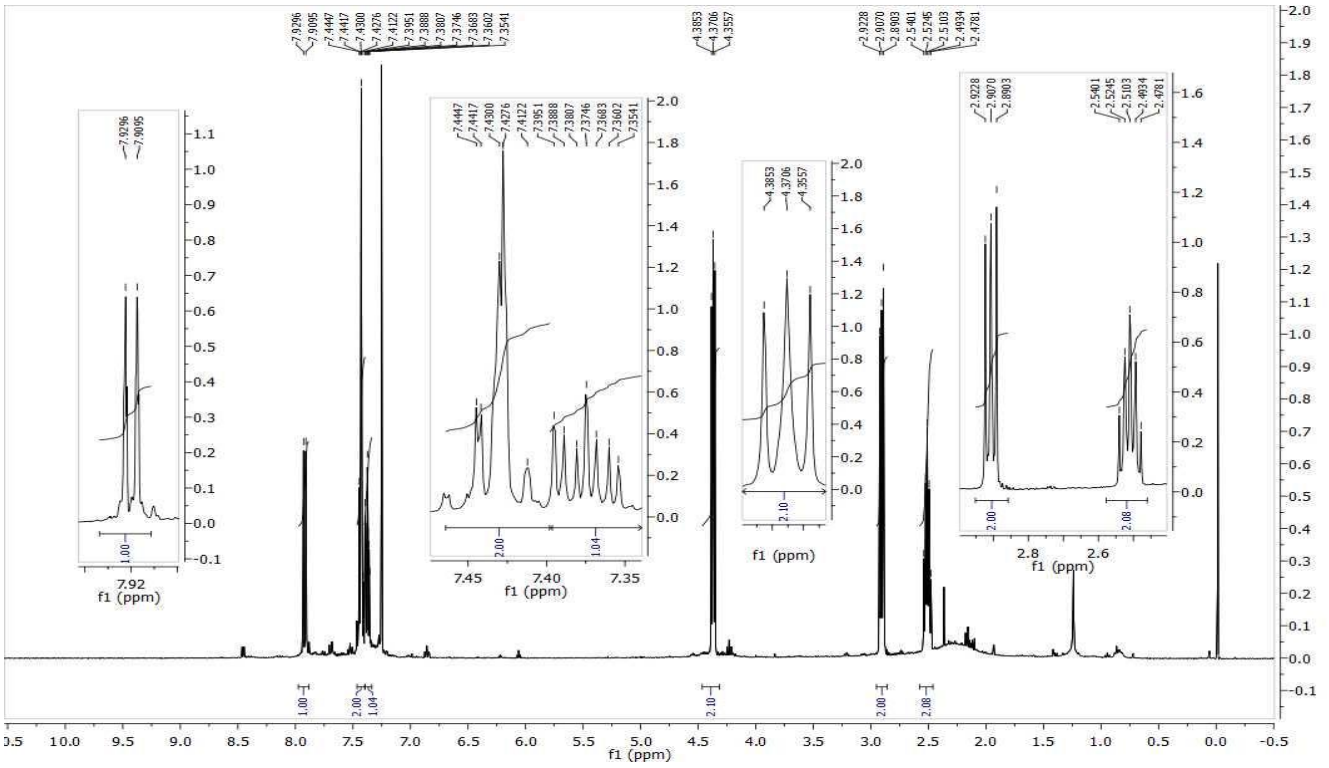
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7.3683
7.3602
7.3541
4.3853
4.3706
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2.9070
2.8903
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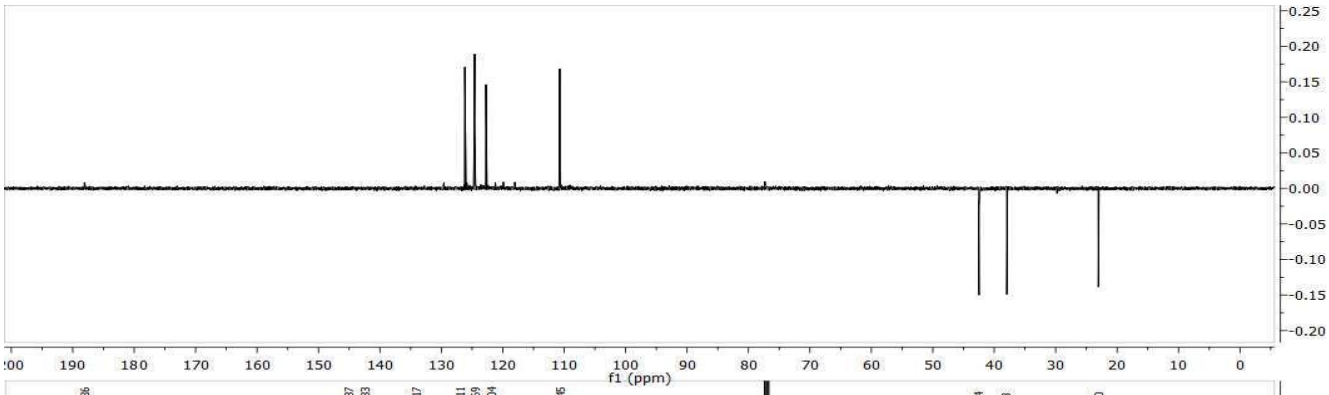
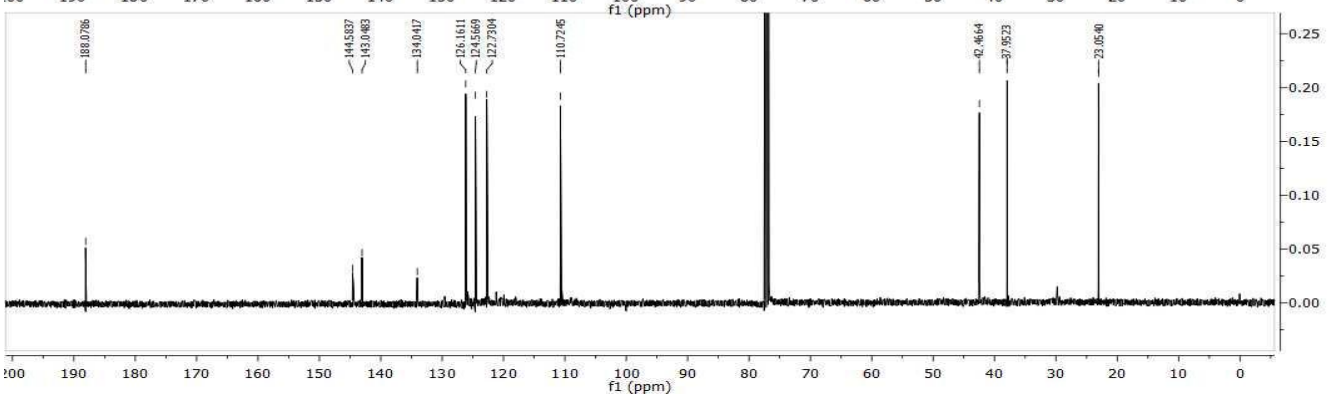
2.5245
2.5103
2.4934
2.4781
f1 (ppm)


f1 (ppm)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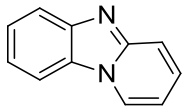
f1 (ppm)



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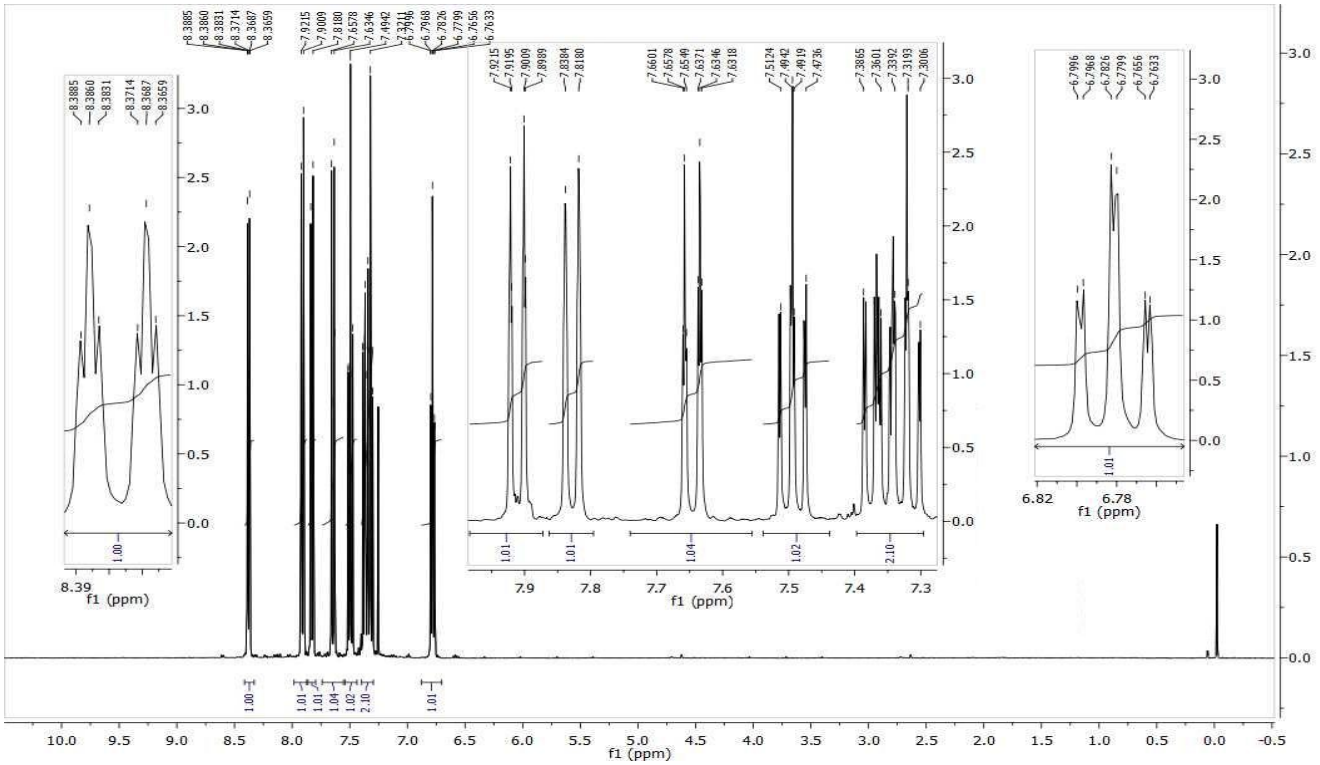

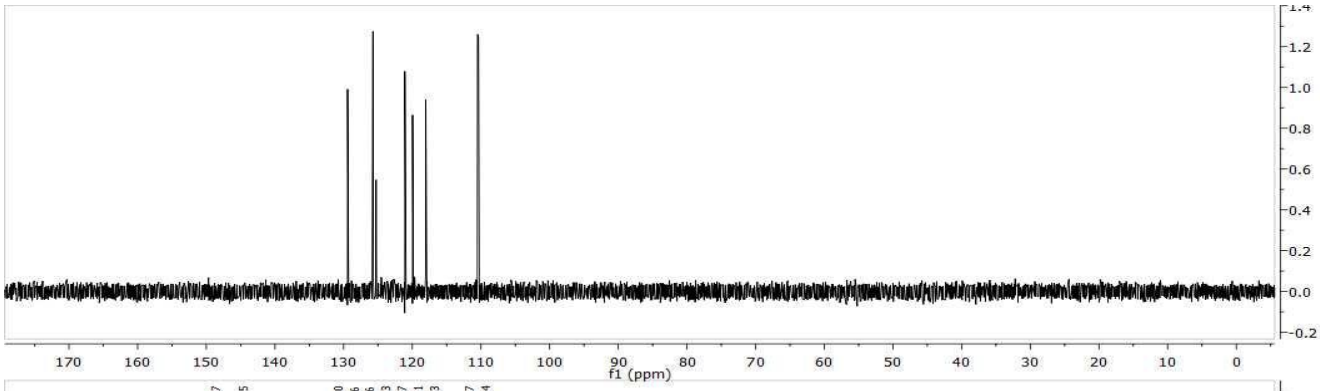

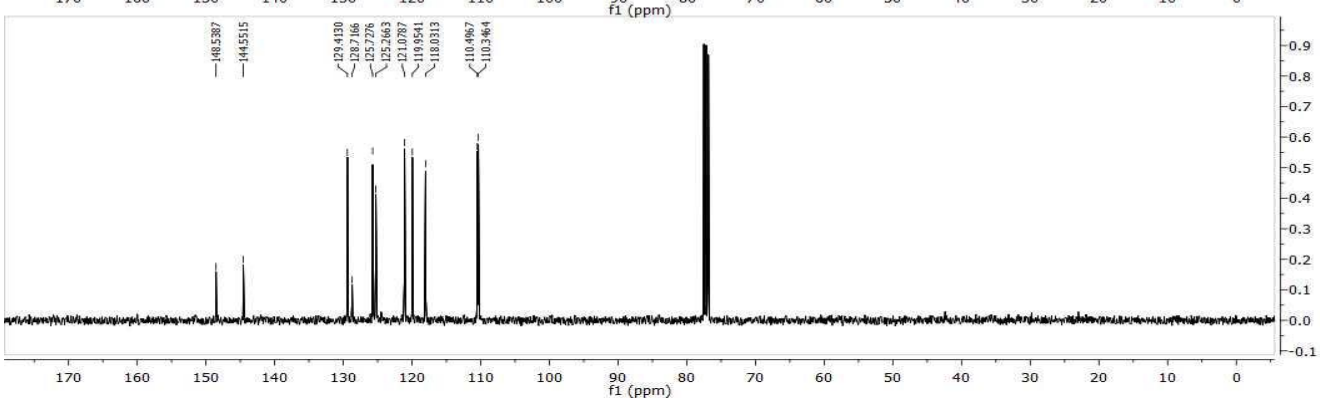

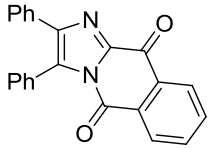

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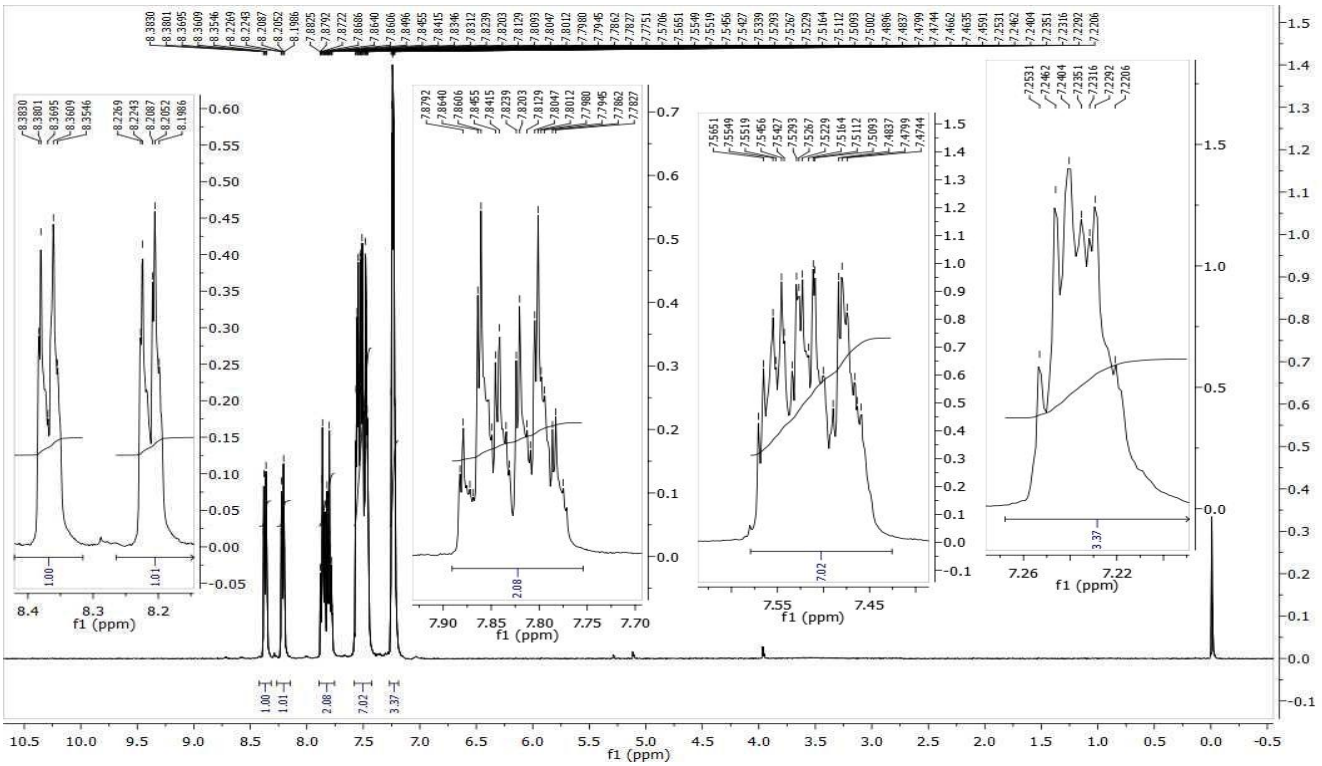
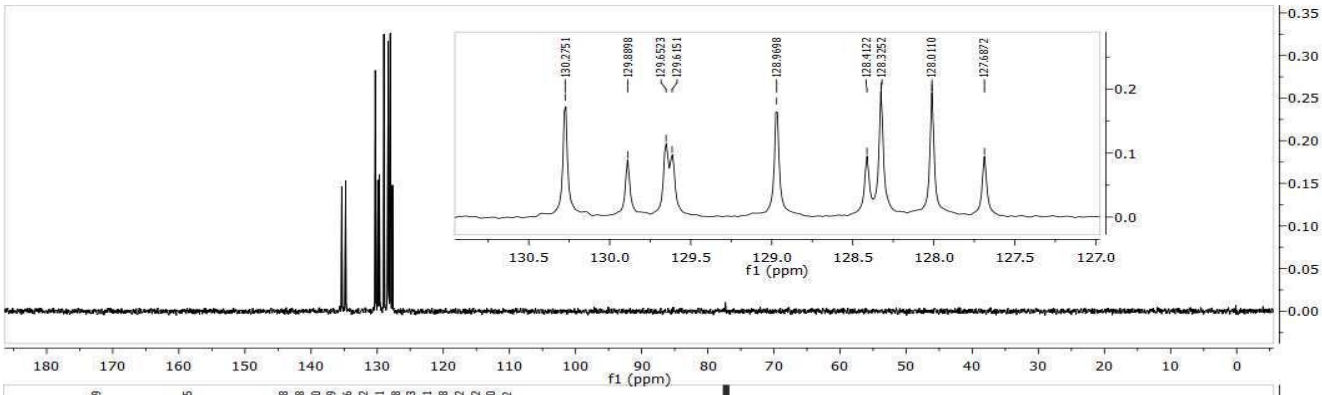
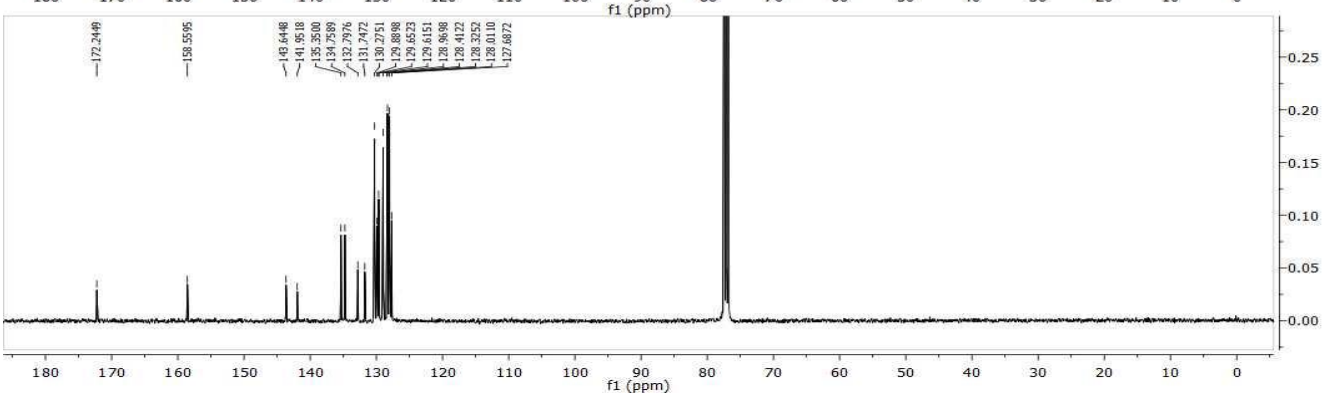






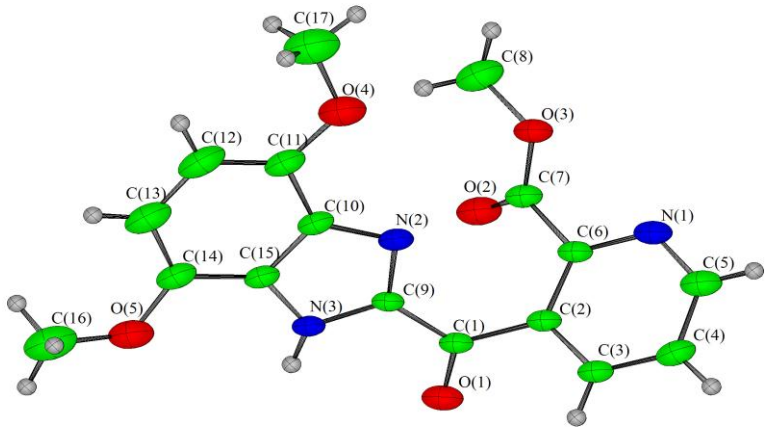
X-Ray crystallographic data

The structures were solved by direct methods, SHELXS-97, and refined by full matrix least squares using SHELXL-971.[1] SHELX operations were automated using Oscail which was also used to obtain the drawings.[2] Hydrogen atoms were included in calculated positions with thermal parameters 30% larger than the atom to which they were attached. The non-hydrogen atoms were refined anisotropically. All calculations were performed on a Pentium PC.

1 G.M. Sheldrick, Acta Cryst. A, 2008, 64, 112-122.

2 P. McArdle J. Appl.Cryst. (1995) 28, 65.

Table A.1: X-ray crystallographic data and structure refinement for methyl 3-[(4,7-dimethoxy-1*H*-benzimidazol-2-yl)carbonyl]pyridine-2-carboxylate (**14**).



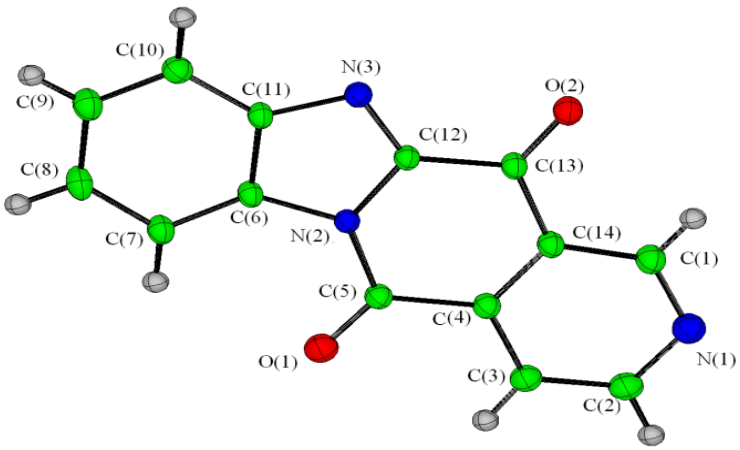
Oscail ORTEX ejoy1_m

Identification code	ejoy1
Empirical formula	$C_{17}H_{15}N_3O_5.5CH_2Cl_2$
Formula weight	383.78
Temperature	291.6 K
Wavelength	0.7107 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 12.6579(17)Å
	b = 34.653(3)Å □ = 110.790(14)°
	c = 9.4483(10)Å
Volume	3874.5(7) $Å^3$
Z	8
Density (calculated)	1.316 Mg/m^3
Absorption coefficient	0.229 mm^{-1}
F(000)	1592
Crystal size	0.45 x 0.32 x 0.25 mm
Theta range for data collection	2.8972 to 27.9872 °.
Index ranges	-15<=h<=7; -21<=k<=45; -10<=l<=11
Reflections collected	9924
Independent reflections	6298 [R_{int} = 0.0587]
Reflections observed (>2□)	4230
Data Completeness	0.886
Absorption correction	Semi-empirical from equivalents

Max. and min. transmission	1.00000 and 0.64130
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6298 / 0 / 484
Goodness-of-fit on F^2	1.063
Final R indices [I>2□(I)]	R_1 = 0.0784 wR_2 = 0.2039
R indices (all data)	R_1 = 0.1095 wR_2 = 0.2412
Largest diff. peak and hole	0.802 and -0.469 e.Å^{-3}

$^{a}R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. $^{b}wR_2 = |\Sigma w(|Fo|^2 - |Fc|^2)|/\Sigma|w(F_o)^2|^{1/2}$, $w = 1/[\sigma^2(Fo^2) + (0.1185P)^2 + 1.4088P]$. $P = (F_o^2 + 2Fc^2)/3$.

Table A.2: X-ray crystallographic data and structure refinement for benzimidazo[1,2-*b*]-2,6-naphthyridine-5-12-dione (**2kb**)



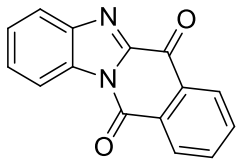
Identification code	E_Joyce3
Empirical formula	C14 H7 N3 O2
Formula weight	249.23
Temperature	150.0 K
Wavelength	0.7107 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 7.8277(5)Å α = 82.660(4)°
	b = 8.4011(4)Å β = 74.940(6)°
	c = 8.7841(5)Å γ = 75.710(5)°
Volume	539.30(5) $Å^3$
Z	2
Density (calculated)	1.535 Mg/m^3
Absorption coefficient	0.107 mm^{-1}
F(000)	256
Crystal size	0.50 x 0.50 x 0.50 mm
Theta range for data collection	3.1992 to 29.0701 °.
Index ranges	-9<=h<=10; -8<=k<=10; -12<=l<=10
Reflections collected	3768
Independent reflections	1975 [R_{int} = 0.0150]
Reflections observed (>2σ)	1559
Data Completeness	0.998
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.99564
Refinement method	Full-matrix least-squares on F^2

Data / restraints / parameters	1975 / 0 / 172
Goodness-of-fit on F^2	1.040
Final R indices [I>2σ(I)]	R_1 = 0.0353 wR_2 = 0.0816
R indices (all data)	R_1 = 0.0506 wR_2 = 0.0874
Largest diff. peak and hole	0.209 and -0.185 e.Å^{-3}

$^{a}R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. $^{b}wR_2 = |\Sigma w(|Fo|^2 - |Fc|^2)|/\Sigma|w(F_o)^2|^{1/2}$, $w = 1/[\sigma^2(Fo^2) + (0.0407P)^2 + 0.0263P]$. $P = (F_o^2 + 2Fc^2)/3$.

Cell viability graphs

Benzimidazo[1,2-*b*]isoquinoline-6,11-dione (2a)



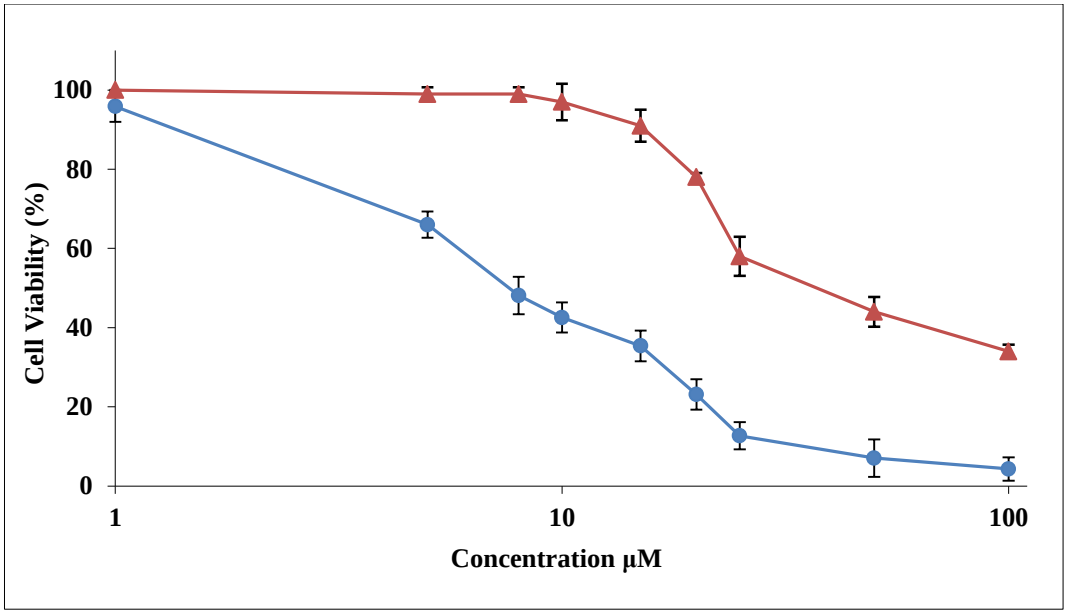
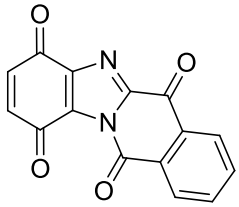


Figure A.1: Viability of human skin fibroblasts (GM00637) (▲), DU145 (HTB-81) (●) cell lines determined using the MTT assay following treatment with benzimidazo[1,2-*b*]isoquinoline-6,11-dione (**2a**) under aerobic conditions for 72 hours at 37°C using DMSO as solvent. Each data point is the mean of at least three independent experiments. The lines shown are trend lines.

Benzimidazo[1,2-*b*]isoquinoline-1,4,6,11-tetrone (1)



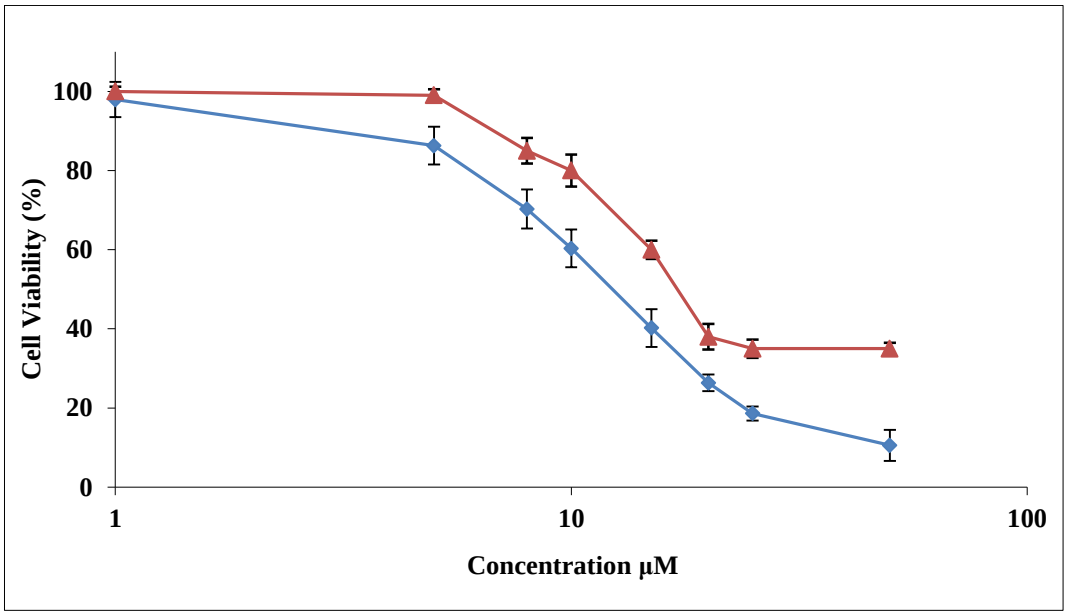


Figure A.2: Viability of human skin fibroblasts (GM00637) (▲), DU145 (HTB-81) (●) cell lines determined using the MTT assay following treatment with benzimidazo[1,2-*b*]isoquinoline-1,4,6,11-tetrone (**1**) under aerobic conditions for 72 hours at 37°C using DMSO as solvent. Each data point is the mean of at least three independent experiments. The lines shown are trend lines.

Conference proceedings

"Benzoyl and Nicotinyl Acyl Radical Cyclizations onto Benzimidazoles: Access to a New Family of Bioreductive Anti-Cancer Agents"
Eamonn Joyce and Fawaz Aldabbagh; The 12th RSC-SCI Joint Meeting on Heterocyclic Chemistry, Brighton, UK, June 2010. Book of Abstracts; P9.
Poster Communication

"Acetic Anhydride Generated Imidazolium Ylide in Ring Closures onto Carboxylic Acids"
Eamonn Joyce, Patrick McArdle and Fawaz Aldabbagh; The 20th Lakeland Symposium on Heterocyclic Chemistry, Grasmere, UK, May 2011. Book of Abstracts; P15.
Poster Communication

"Acetic Anhydride Generated Imidazolium Ylide in Ring Closures onto Carboxylic Acids: Synthesis of New Potential Benzimidazolequinone Anti-Tumour Agents"
Eamonn Joyce, Patrick McArdle and Fawaz Aldabbagh; Eli Lilly Symposium, NUIG, November 2010. **First prize awarded**.
Oral Communication

Peer-reviewed publications

Acetic Anhydride Generated Imidazolium Ylide in Ring Closures onto Carboxylic Acids; Part of the Synthesis of New Potential Bioreductive Antitumor Agents

Eamonn Joyce, Patrick McArdle and Fawaz Aldabbagh*, *Synlett*, **2011**, 1097-1100

Acetic anhydride mediated condensation of aromatic *o*-diacid dichlorides with benzimidazoles to provide electro-reducible *p*-dione adducts

Eamonn Joyce, Paul Kavanagh, Dónal Leech, Jolanta Karpinska, Patrick McArdle, Fawaz Aldabbagh*, *Tetrahedron Lett*, **2012**, *53*, 3788-3791