Barton Esters for Initiator-Free Radical Cyclisation with Heteroaromatic Substitution and Anti-Cancer Evaluation of Benzo[*e*][1,2,4]triazin-7-ones

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Abstract

Chapter 1 provides a general introduction to Chapters 2-5. Homolytic aromatic substitution routes to alicyclic ring-fused azoles and diazoles is reviewed. A review of recent literature using the COMPARE program of the National Cancer Institute (NCI, USA) to elucidate anti-cancer activity of small heterocyclic molecules is presented.

Chapter 2 describes *S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium hexafluorophosphate (HOTT) facilitating the first examples of efficient radical cyclisation with (hetero)aromatic substitution via Barton ester intermediates. Cyclopropyl and alkyl radicals allow access to five, six and seven-membered alicyclic-ring fused heterocycles with and without an additional fused cyclopropane, including the skeleton of the anti-cancer agent, cyclopropamitosene, expanded, and diazole analogues. Radical initiators are *not* required for cyclisation from carboxylic acid precursors. For constrained cyclisations such as the seven-membered cyclopropyl radical aromatic substitution onto indole, the Bu_3SnH-mediated reaction was found to give higher yields, and X-ray crystal structure of the adduct, 1,1*a*,2,3,4,10*b*-hexahydrocyclopropa[3,4]azepino[1,2-*a*]indole-10-carbaldehyde was obtained.

Chapter 3 describes a new synthetic use of Barton esters, as precursors for one-pot initiator-free cascade/tandem reactions. The tandem reaction involves intermolecular addition of alkyl radicals onto activated terminal (monosubstituted) alkynes followed by intramolecular substitution of vinyl radicals onto indoles. Investigations into the use of disubstituted alkynes (with two different substituents) are also presented with X-ray crystal structures of substitution products demonstrating the selectivity of the radical addition onto the alkyne.

Chapter 4 describes preliminary investigations into elucidating the anti-cancer activity of diphenylbenzo-[*e*][1,2,4]triazin-7-one (compounds) supplied by the group of Prof. Panayiotis A. Koutentis (University of Cyprus) using cytotoxicity evaluation of the parent compound (1,3-diphenylbenzo-[*e*][1,2,4]triazin-7-one) at the NCI, and MTT assays of analogues. The COMPARE program established a very strong correlation with the naturally occurring antibiotic, pleurotin.

Chapter 5 is a comprehensive description of synthetic and tissue culture procedures carried out.

Acknowledgements

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Lastly to my family and friends for their eternal support and encouragement.

Abbreviations

ACCN	1,1′-azobis(cyclohexanecarbonitrile)
AChE	acetylcholinesterase
AD	Alzheimer's disease
AIBN	2,2′-azobis(isobutyronitrile)
BChE	butyrylcholinesterase
Boc	*tert*-butoxycarbonyl
Bu	butyl
°C	degrees celsius
CCDC	Cambridge Crystallographic Data Centre
Calcd	calculated
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DEPT	distortionless enhancement by polarization transfer
DLP	dilauroyl peroxide
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethyl formamide
DMSO	dimethyl sulfoxide
DTP	development therapeutics program
ESI	electrospray ionization
Et	ethyl
Equiv.	equivalents
EWG	electron withdrawing group
FAD	flavin adenine dinucleotide
FBS	fetal bovine serum
FT-IR	fourier transform infrared
GI_{50}	growth inhibition: concentration required to inhibit cell growth by 50%
h	hours
HMGA2	high-mobility group AT-hook 2
HMQC	heteronuclear multiple quantum coherence
HOTT	*S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium hexafluorophosphate
HRMS	high resolution mass spectra

Hz	hertz
K	kelvin
IC_{50}	inhibition concentration: concentration that inhibits cell population by 50%
LC_{50}	lethal concentration: concentration required to kill 50% of cells
M	molar
MAPK14	Mitogen-activated protein kinase 14
Me	methyl
MEM	minimum essential media
MHz	megahertz
min	minutes
MMC	mitomycin C
µM	micromolar
mM	millimolar
mp	melting point
Ms	mesyl (methane sulfonyl)
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NADH	nicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate
NCI	National Cancer Institute
NMR	nuclear magnetic resonance
NQO1	NAD(P)H:quinone oxidoreductase 1
Ph	phenyl
ppm	parts per million
PTEN	protein tyrosine phosphatase and tensin homolog
PTOC	pyridine-2-thione-N-oxycarbonyl
rt	room temperature
SAS	Statistical Analysis System
SPy	thiopyridine
t	*tertiary*-
TCFH	tetramethylchloroformamidinium hexafluorophosphate
tert-	*tertiary*-
TGI	total growth inhibition
THF	tetrahydrofuran

TLC	thin layer chromatography
TMU	1,1,3,3-tetramethylurea
Tol	toluene
Trx	thioredoxin protein
TrxR	thioredoxin reductase
Ts	tosyl (toluenesulfonyl)

Chapter 1

General Introduction

1.1 Introduction

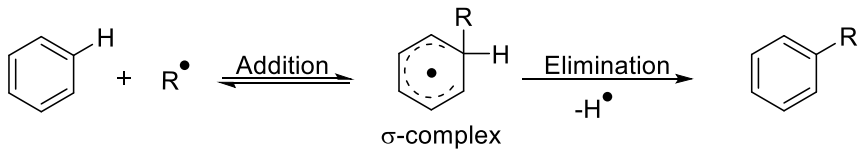
The Introduction is divided into two main parts:

(i) A brief review of the literature related to Chapters 2 and 3;

(ii) A brief review of the literature related to Chapter 4.

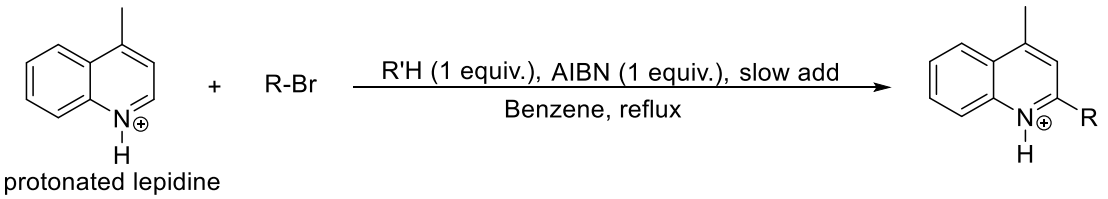
1.1.1 Intramolecular homolytic aromatic substitutions onto heterocycles

Proceeds through an addition-elimination process with radical addition onto an aromatic ring and elimination of a leaving group from the σ-complex (Scheme 1.1).



Scheme 1.1: Oxidative homolytic aromatic substitution

In cases where the leaving group is H•, then the reaction proceeds with oxidative rearomatisation. Many reported intramolecular homolytic aromatic substitutions are mediated by Bu_3SnH/AIBN (2,2′-azobis(2-methylpropionitrile)), and it is now accepted that AIBN or an AIBN-derived radical is involved in the oxidative rearomatisation.[1-4] A brief review of literature homolytic aromatic substitutions that result in similar annulated products to those reported in this thesis follows.



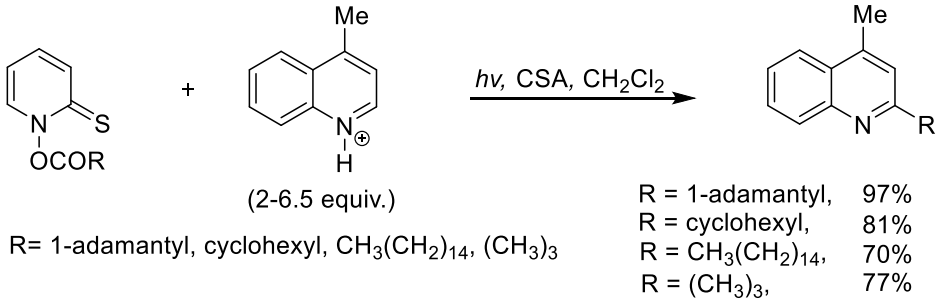
R = *n*-hexyl, cyclohexyl, *tert*-butyl
R' = Bu_3Sn, $(Me_3Si)_3Si$

R = *n*-hexyl, R' = Bu_3Sn: 14%
R = cyclohexyl, R' = Bu_3Sn: 39%
R = *tert*-butyl, R' = Bu_3Sn: 44%

R = *n*-hexyl, R' = $(Me_3Si)_3Si$: 31%
R = cyclohexyl, R' = $(Me_3Si)_3Si$: 51%
R = *tert*-butyl, R' = $(Me_3Si)_3Si$: 87%

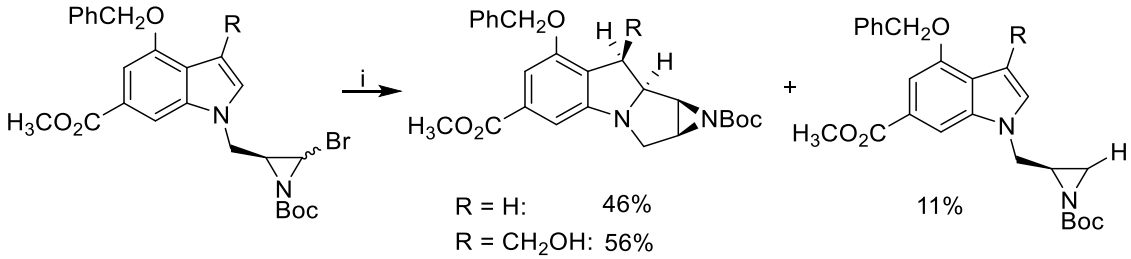
Scheme 1.2. Intermolecular alkyl radical substitution of protonated lepidine

Minisci *et al* demonstrated the first reported "oxidative" aromatic substitution carried out in the presence of the "reductant" Bu_3SnH. Successful Bu_3SnH/AIBN-mediated intermolecular aromatic substitution was possible with protonation of the basic nitrogen of heteroarenes (Scheme 1.2).[1] The incoming nucleophilic (cyclo)alkyl radical substituted selectively onto the electron deficient 2-position of lepidine with highest yields noted for the most nucleophilic tertiary radicals. The use of a $(Me_3Si)_3SiH$/AIBN mediated system improved yields which can be ascribed to the weaker reductant nature of $(Me_3Si)_3SiH$ relative to Bu_3SnH.



Scheme 1.3. Barton decarboxylation/addition onto protonated lepidine

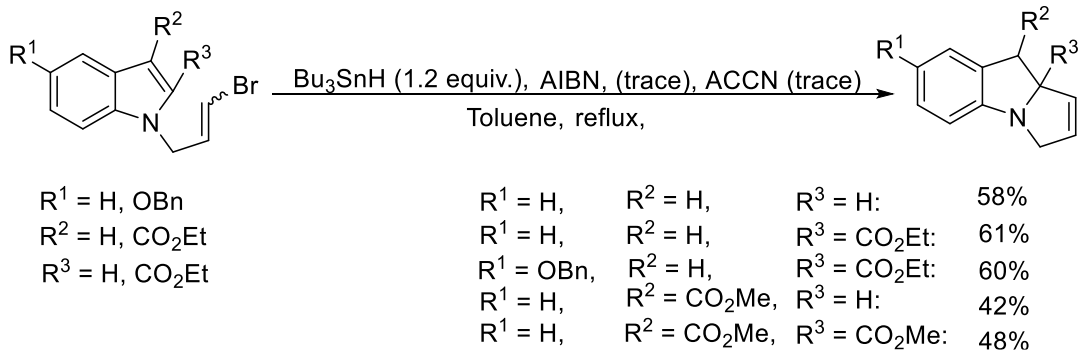
Barton circumvented the use of toxic and hazardous initiators by reporting radical decarboxylations of esters of *N*-hydroxy-2-thiopyridone (Barton ester), which after irradiation undergo efficient radical intermolecular substitution onto heteroarenes containing a protonated basic nitrogen site (Scheme 1.3).[5] The activated form of the heteroarene was obtained through CSA protonation, which was found crucial to obtaining high yields of substitution product.



i. Bu_3SnH (1 equiv.), ACCN (0.2 equiv.), Tol, reflux

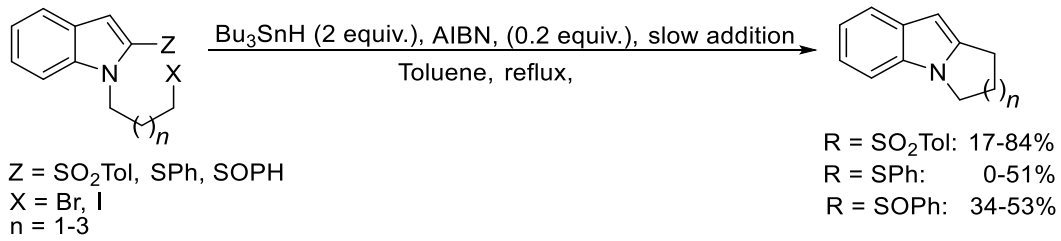
Scheme 1.4. Aziridinyl radical cyclisations onto indoles without activating groups at the 3-position of indole

Bu_3SnH/ACCN mediated reductive cyclisation of aziridinyl and vinyl radicals from bromine precursors with and without substitution at the *3-C* position of indole have been reported (Schemes 1.4, 1.5).[6,7]



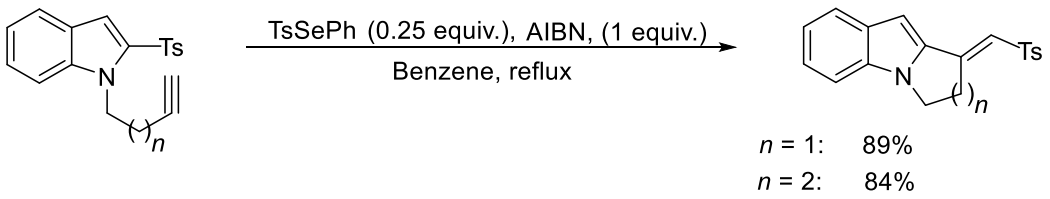
Scheme 1.5. Reductive radical cyclisations of vinyl radicals onto indoles

Hydrogen abstraction from Bu_3SnH is thought to be responsible for the formation of the dihydroindoles in moderate yields (42-61%) while the use of less than full equivalents of azo-initiator may explain the lack of aromatic substitution product.



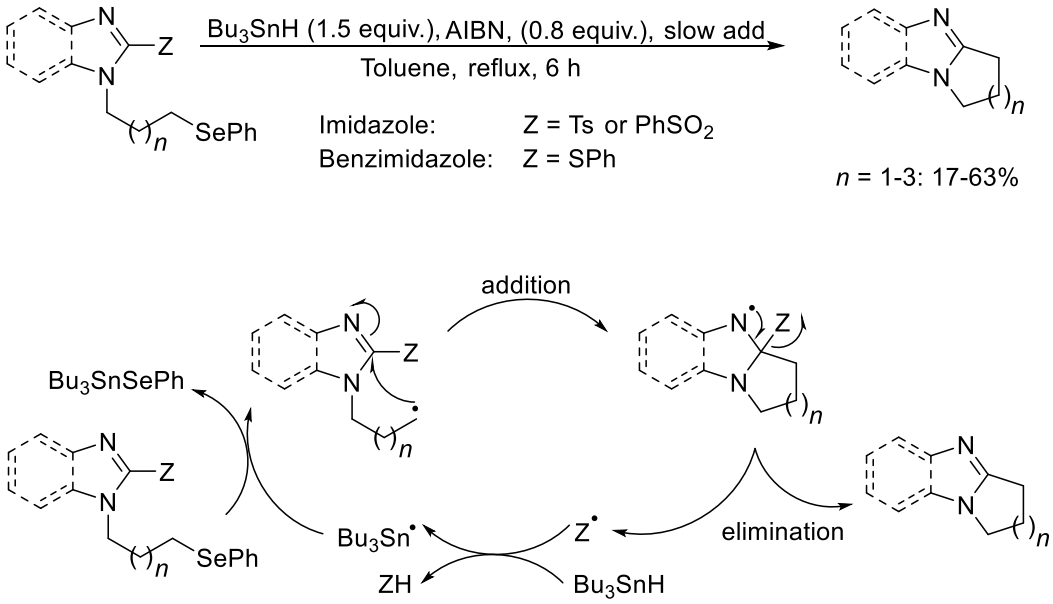
Scheme 1.6. Intramolecular aromatic substitution *via ipso*-substitution onto indole substituted sulfones, sulfides and sulfoxides

Radical *ipso*-substitution can lead to high yielding and regioselective reactions. Caddick et al synthesized pyrrolo-, pyrido- and azepino-fused [1,2-*a*]indoles involving radical *ipso*-substitution of sulfone, sulfide and sulfoxide substituted at the 2-position of indoles. (Scheme 1.6).[8]



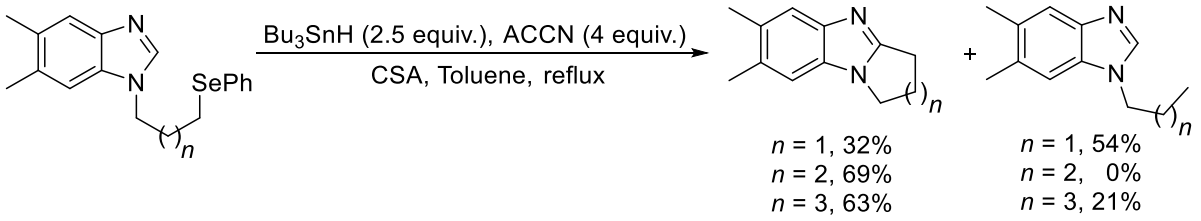
Scheme 1.7. Intramolecular aromatic substitution of vinyl radicals *via ipso*-substitution onto indole substituted sulfones

Moreover, vinyl radical cyclisations can be achieved in high yields onto sulfone substituted indoles using sub-stoichiometric Se-phenyl-p-tolueneseleno-sulfonate (TsSePh)/AIBN-radical chain conditions (Scheme 1.7).[9]



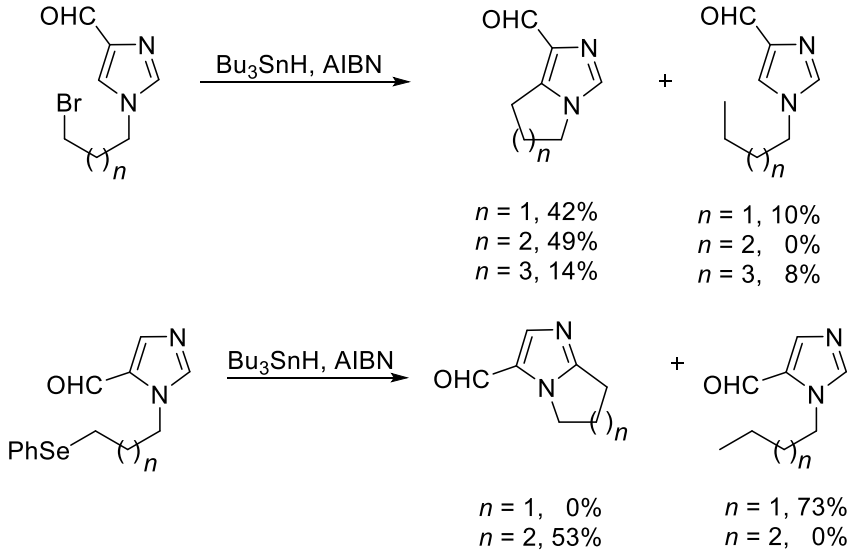
Scheme 1.8 Bu_3SnH/AIBN-mediated intramolecular aromatic substitution of imidazole and benzimidazole

Aldabbagh and Bowman reported radical *ipso*-substitution at the *C-2* position of benzimidazoles and imidazoles when using phenylselenides precursors for radical cyclisations (Scheme 1.8).[10] When using good sulfur-leaving groups, the sulfur radical generated is thought to be reduced by Bu_3SnH to regenerate the $Bu_3Sn^{\bullet}$ chain carrier.



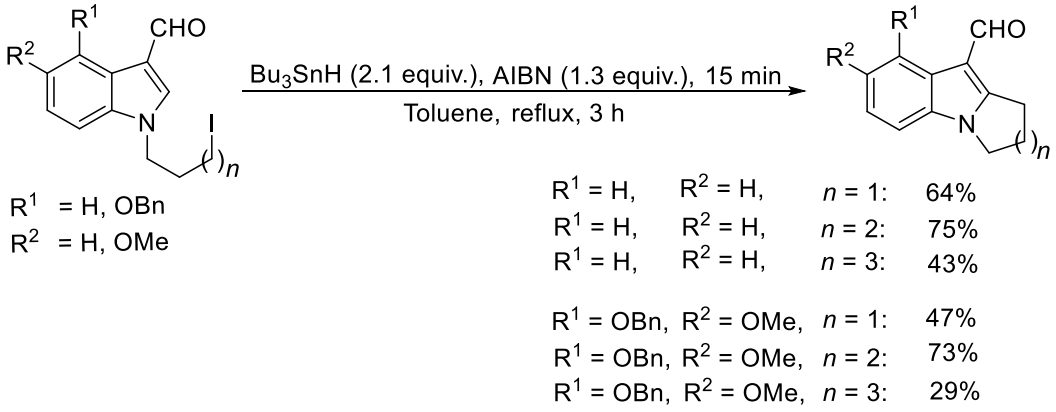
Scheme 1.9. Bu_3SnH/ACCN-mediated intramolecular aromatic substitution

Lynch *et al* utilized a Bu_3SnH/ACCN-mediated homolytic aromatic substitution protocol towards the synthesis of tricyclic bioreductive benzimidazolequinones, without the requirement for radical leaving groups (Scheme 1.9).[3] CSA activation of the heteroarene and large excesses of initiators allowed for good yields of pyrido- and azepino[1,2-*a*]-fused benzimidazoles with more moderate yields obtained for the strained five-membered cyclisation. The use of non-functionalised heterocycles is advantageous, since radical precursors used in *ipso*-substitutions[8-10] require prior synthesis using time-consuming and moderate yielding organometallic heterocycle protection-deprotection procedures.



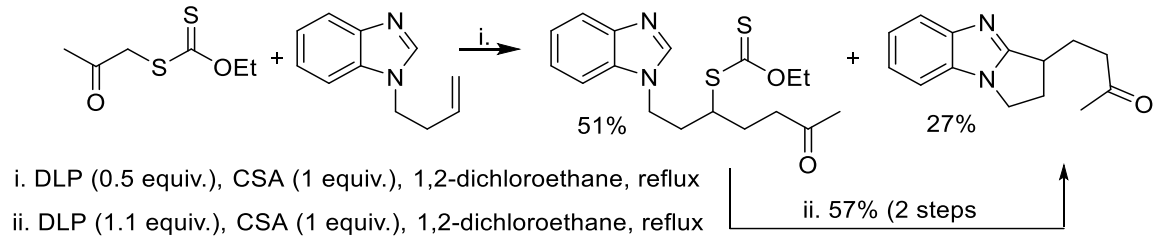
Scheme 1.10. Alkyl radical cyclisations onto imidazole-4-carbaldehydes and imidazole-5-carbaldehydes

Aldabbagh *et al* demonstrated Bu_3SnH/AIBN mediated primary alkyl radical cyclisations onto imidazole-4 and 5-carbaldehydes (Scheme 1.10) occurred selectively at the *C-5* and *C-2* sites of imidazole respectively.[11]



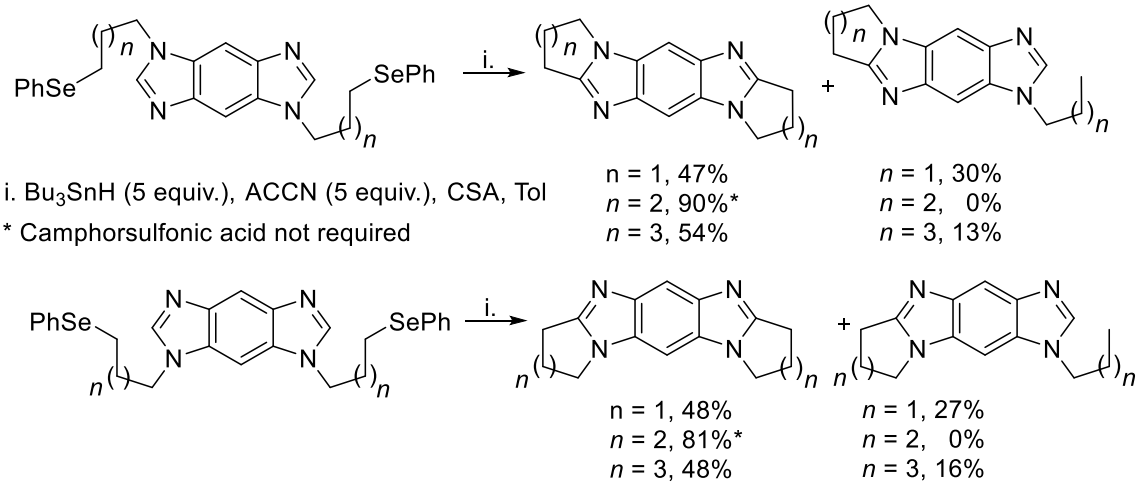
Scheme 1.11. Bu_3SnH/AIBN-mediated intramolecular aromatic substitution of indole-3-carbaldehyde

Moody and Norton used homolytic aromatic substitution of primary alkyl radicals to give [1,2-*a*]indoles fused with five-, six- and seven-membered rings in 29-75% yield (Scheme 1.11).[12] Stoichiometric amounts of AIBN were used as the source of initiating radical and presumably to facilitate the re-aromatisation step.



Scheme 1.12. Formation of pyrrolo[1,2-*a*]benzimidazole *via* oxidative radical cyclisation

Gagosz and Zard have reported fused azoles *via* intramolecular aromatic substitution using xanthate and dilauroyl peroxide (DLP)-mediated procedure (Scheme 1.12), where the peroxide is probably involved in the oxidative rearomatisation.[13] CSA is critical to the reaction, through basic nitrogen quaternization, thus activating the benzimidazole-2-position towards nucleophilic radical attack. Moreover CSA serves to prevent inadvertent nucleophilic attack from the basic benzimidazole 3-*N* onto the xanthate moiety.



Scheme 1.13. One-pot double Bu_3SnH/ACCN-mediated intramolecular aromatic substitution

One-pot double intramolecular radical cyclisations of primary alkyl radicals onto imidazobenzimidazoles from phenylselenide precursors were recently reported by Fagan *et al* (Scheme 1.13).[14] Quaternization of the basic nitrogen allows for pyrrolo- and azepiono fused heteroarenes to be formed in reasonable yields, with large excesses of Bu_3SnH and ACCN required to drive the non-chain reaction process.

1.1.2 COMPARE: Anti-cancer activity analysis of small heterocyclic compounds

1.1.2.1 DTP NCI-60 human tumour cell line screen

Fully operational since 1990, the cytotoxicity screen ran by the National Cancer Institute (NCI) under the Developmental Therapeutics Program (DTP) allows free evaluation of compounds with potential anti-cancer activity. The screen consists of two stages with the first involving a single 10μM dose to generate a mean growth % graph for the 60 human tumour cell lines derived from nine major histological tissue types; breast, colon, central nervous system, leukemia, melanoma, non-small cell lung, prostate, ovarian and renal.

Compounds are then selected by the NCI for stage 2 evaluation which is five dose screening, allowing GI_{50} LC_{50} and TGI to be established. [15-17]

- GI_{50} represents the concentration of a compound required to inhibit cell growth by 50%
- LC_{50} represents the concentration of a compound required to reduce cell population by 50%.
- TGI represents the concentration of a compound required to mediate a cytostatic effect

The stated parameters provide the seed vector through which the NCI COMPARE algorithm determines closely matching cytotoxicity profiles. COMPARE allows comparisons to be carried out against a standard agents' database. The standard agents' database includes ~200 well documented compounds with anti-tumour activity and presumed mechanisms of action. COMPARE also allows comparisons to be carried out towards the ~70000 synthetic compounds in the NCI database.

Comparisons are made using a commercially available SAS statistical package to calculate a Pearson product moment correlation coefficient (0- ± 1) to establish the degree of similarity or lack thereof between two cytotoxicity profiles.[16,17] Pearsons in the range (±0.3- ±0.5) are considered medium strength, while those above (±0.5) are considered strong.[18] Negative correlation coefficients represent a general inverse relationship for the seed parameter across the 60 human tumour cell lines, between the test and correlated compound.

The COMPARE program allows a possible mode of action of a test compound to be determined, should its cytotoxicity response share strong similarities to a compound whose mode of action is known.

Alternatively the mode of action can be determined should a biological response correlate to the activity of a known molecular target. Some examples where the COMPARE program has been applied now follow.

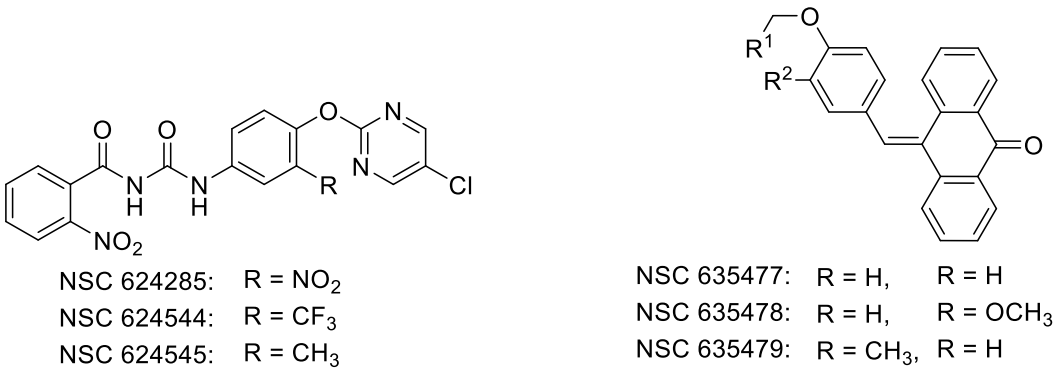


Figure 1.1. Novel antimitotic agents discovered through COMPARE analysis of known antimitotic agents

Through COMPARE Paull *et al.* discovered a number of novel antimitotic agents acting through inhibition of tubulin polymerisation and causing the mitotic arrest of cells grown in culture (Figure 1.1).[19]

Using the cytotoxicity response profiles of ten known antimitotic agents including taxol, vincristine and vinblastine as COMPARE seeds, 82 compounds were identified by COMPARE correlation. Fifty compounds identified were the seeds or seed analogues, 32 were novel compounds broken down into 19 distinct chemical species with a correlation coefficient of 0.6 or greater to the seed compounds, and a GI_{50} of 1μM or less towards HL-60 human leukemia cell-line. Of the 32 compounds, 23 inhibited *in vitro* tubulin polymerisation with the majority (21) identified by six or more seeds.

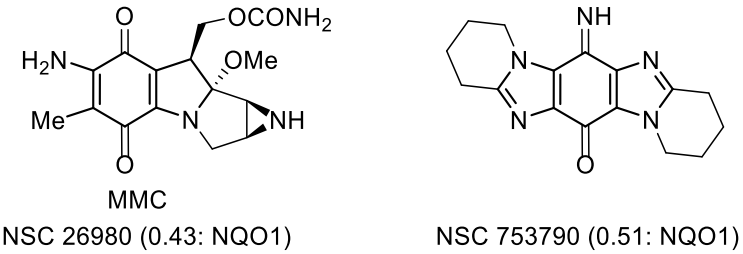


Figure 1.2. Correlations of the clinically used bioreductive anti-cancer agent MMC and iminoquinone NSC753790 to the two-electron reductase NQO1

Recently iminoquinone (NSC 753790) synthesized by Fagan *et al.* showed a superior correlation of 0.51 than mitomycin C (MMC) with a correlation of 0.43 towards NAD(P)H:quinone oxidoreductase 1 (NQO1). MMC is a known substrate for this enzyme, which is overexpressed in many human tumour cell lines. NQO1 reductive activation of prodrugs induces a cytotoxic effect (Figure 1.2). Computational docking further established the iminoquinone and MMC as substrates for the NQO1 active site.[20]

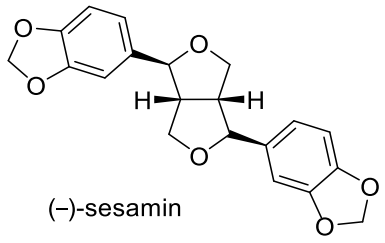


Figure 1.3 (⁻)-Sesamin a lignin present in sesame oil and a number of medicinal plants

COMPARE analysis recently determined an alternative mode of action for a series of iridium complexes in comparison to cisplatin and related transition metal complexes,[21] while (⁻)-sesamin, a compound with known anticancer activity, was subjected to standard and reverse COMPARE analysis to determine genes responsible for resistance and sensitivity towards (⁻)-sesamin .[22]

Standard COMPARE correlates a compound with high levels of molecular target, while reverse COMPARE correlates a compound with low levels of molecular target, or where a molecular target confers resistance.

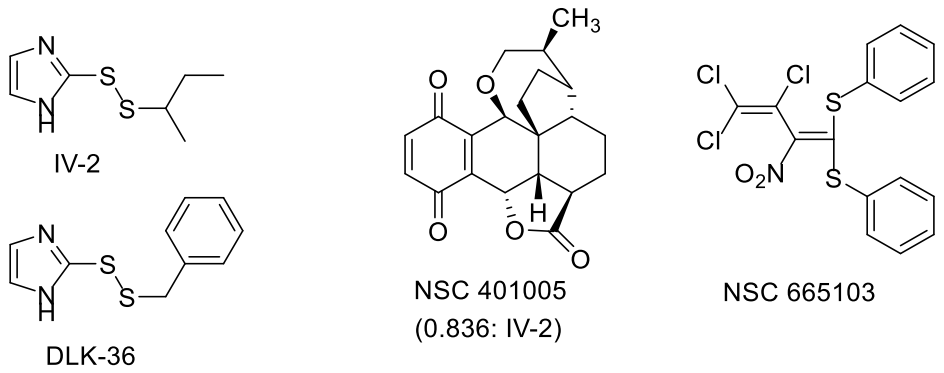
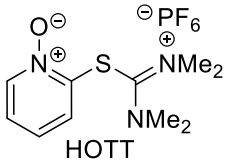


Figure 1.4. Novel thioredoxin reductase inhibitors discovered through COMPARE analysis of known imidazole disulfide inhibitors

Kunkel *et al.* utilized the cytotoxicity profile of known thioredoxin reductase inhibitors, 1-methylpropyl 2-imizolyl-disulfide (IV-2) and benzyl-2-mercaptoimidazolyl disulphide (DLK-36) as COMPARE seeds to determine novel inhibitors of thioredoxin reductase. Pleurotin NSC 401005 had the largest correlation from the synthetic compound database (0.836) to IV-2, while pleurotin and NSC 665103 were the most potent inhibitors in a thioredoxin reductase/thioredoxin-dependent insulin reductase assay. Moreover of the compounds identified from the NCI database, 77% had IC_{50} values of 10 µg/ml or less while 32% had IC_{50} values of 1 µg/ml when subjected to a thioredoxin reductase/thioredoxin assay (Figure 1.4).[23]

1.2 Thesis Aims and Objectives

- To carry out HOTT-mediated initiator free intramolecular aromatic substitution via Barton esters leading to heterocycles with and without fused cyclopropane rings.



HOTT

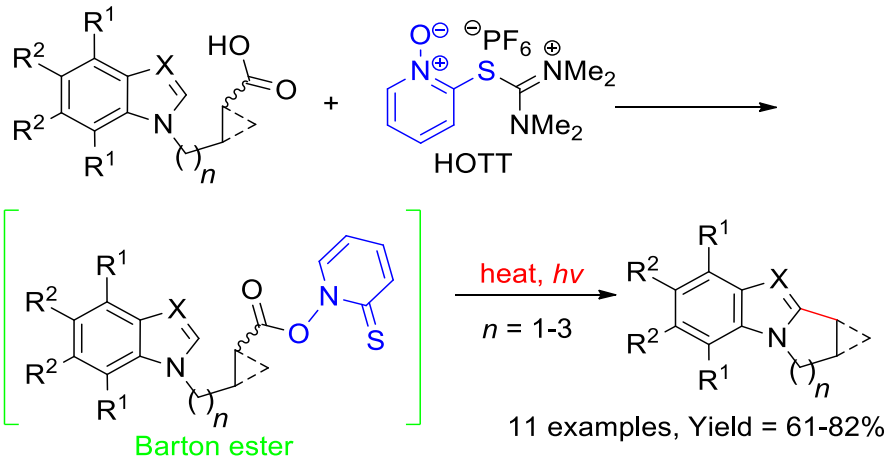
- To carry out HOTT mediated formation of Barton esters for use in tandem intermolecular addition and vinyl radical cyclisations leading to novel alicyclic [1,2-*a*] ring fused indoles.

- To carry out cytotoxicity evaluations using the MTT assay and NCI 60 human tumour cell line screen on benzo-[*e*][1,2,4]-triazine-7-(1H)ones, and to carry out COMPARE analysis of the parent compound against the compounds and molecular targets in the NCI database in order to determine possible biochemical pathways for anti-cancer activity.

Chapter 2

Barton esters for initiator-free radical cyclisation with heteroaromatic substitution

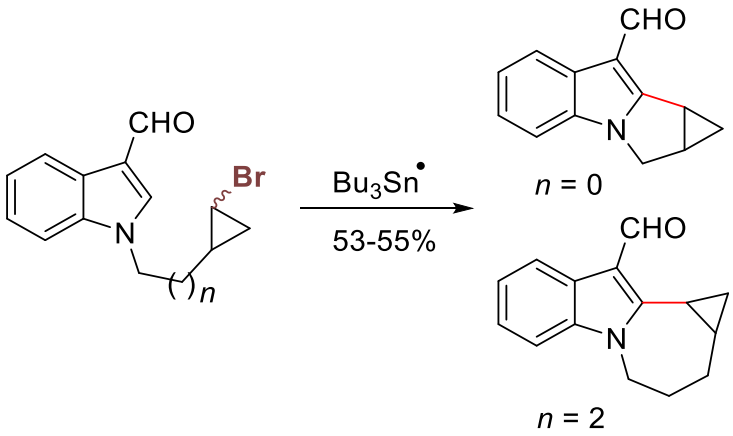
Most of this Chapter is published in two publications:



Barton esters for initiator-free radical cyclisation with heteroaromatic substitution,

Robert Coyle, Karen Fahey and Fawaz Aldabbagh,

Org. Biomol. Chem. **2013**, *11*, 1672-1682



Bu_3SnH-mediated cyclopropyl radical cyclisations onto indole-3-carbaldehyde,

Karen Fahey, Robert Coyle, Patrick McArdle and Fawaz Aldabbagh,

ARKIVOC **2013**, *(iii)*, 401-412

2.1 Introduction

Trialkylmetal hydrides (usually Bu_3SnH) with an azo-initiator are now used commonly in organic synthesis to perform intramolecular homolytic aromatic substitutions.[4] Since effectively a hydrogen atom ($H^{\bullet}$) is lost, it is well-documented that difficulties exist in forming "oxidized" aromatic substitution product in the presence of the "reductant" Bu_3SnH. Moreover, the substitution is thought to proceed via a non-chain reaction, which requires greater than full equivalents of often toxic and hazardous radical initiators.[1-4,14,24-30] The initiators should be added slowly via a syringe pump to minimise reduction of the cyclising radical by Bu_3SnH, in a protocol that can lead to substantial organotin waste with associated disposal issues.

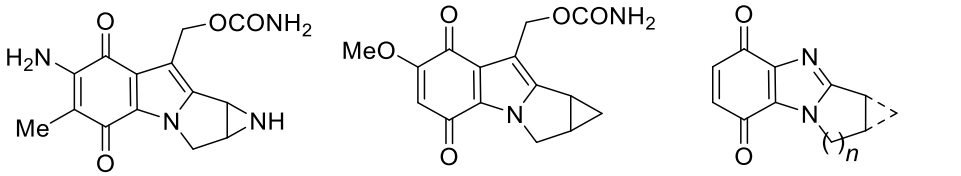
Nevertheless, many alkyl, cycloalkyl, acyl, vinyl, (hetero)aryl and iminyl radical cyclisations have been reported to give aromatic substitution, albeit in often moderate to good yields.[4] There are however scant reports of three-membered ring radicals giving substitution product upon cyclisation with only reports of Bu_3SnH/AIBN (2,2′-azobis(2-methylpropionitrile)) used to cyclise a tertiary cyclopropyl radical to give spiro-adduct.[29-30] The quest for more efficient, and benign cyclisation alternatives led us to Barton ester {pyridine-2-thione-*N*-oxycarbonyl (PTOC) or *O*-acyl thiohydroxamate ester} intermediates.[31-32] Barton esters have been utilised in intermolecular radical addition chain reactions onto alkenes,[33-35] quinones[35-36] and 5-*exo*-*trig* radical cyclisations.[35] Moreover, Barton et al. have proposed a chain reaction mechanism for the use of the esters in intermolecular substitutions onto (hetero)aromatics.[5]

Despite this, Barton esters have thus far not been reported after radical cyclisation onto (hetero)aromatics to give acceptable yields of substitution product. Ziegler *et al.* reported cyclisations onto the indole-2-position by aziridinyl and oxiranyl radicals via Barton esters (formed by treatment of carboxylic acids with 2,2′-dithiobis-(pyridine-*N*-oxide) and *n*-Bu_3P).[6,37-39]

However, in the latter seminal work, the reported yields of aromatic substitution

products formed upon photochemical breakdown of the Barton esters were very low (<10%), and hydride reduction or dimerisation of the cyclised indolyl radical was the major outcome.

Cyclopropane-fused onto pyrrolo[1,2-*a*]indole forms the skeleton of the highly potent anti-tumour agent cyclopropamitosene, an analogue of aziridinomitosene, the bioactivated form of mitomycin C (Fig. 2.1).[40-44] Alicyclic ring-fused benzimidazolequinones with and without the fused cyclopropane possess cytotoxicity in the nanomolar range (10^{-9} M).[3]



Aziridinomitosene | Cyclopropamitosene | Benzimidazolequinones *n* = 1, 2

Figure 2.1: Bioreductive anti-tumour agents

The cyclopropane-fused tetracycles were accessed using traditional intramolecular 1,3-dipolar [3+2] cycloaddition of diazomethine intermediates onto alkenes with subsequent breakdown of the pyrazoline cycloadduct.[40-47]

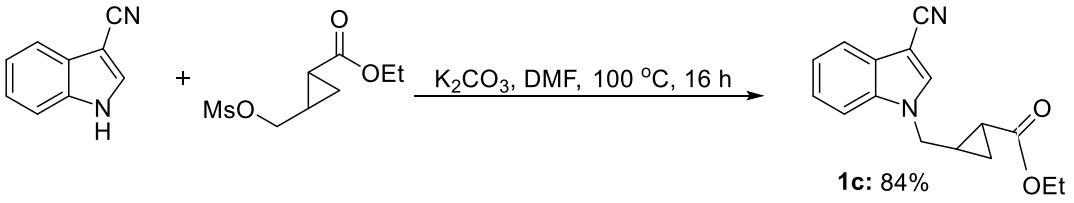
We now report a new means to access cyclopropane-fused tetracycles, involving initiator-free intramolecular aromatic substitutions of cyclopropyl radicals onto the 2-position of indoles and benzimidazoles, formed via the decomposition of Barton esters. The first alkyl radical cyclisations using Barton esters are also performed, allowing comparisons with the cyclopropyl radical.

2.2 Results and discussion

2.2.1 Cyclopropyl radical cyclisations

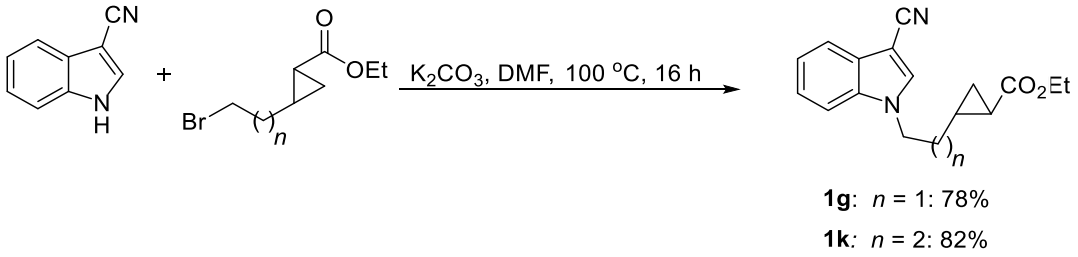
2.2.1.1 Synthesis of cyclopropyl radical precursors

Cyclopropyl radical precursors were readily obtained by *N*-alkylation of the heterocycle with the mesylate[48] or ethyl 2-(ω-bromoalkyl)cyclopropane carboxylate.[49]

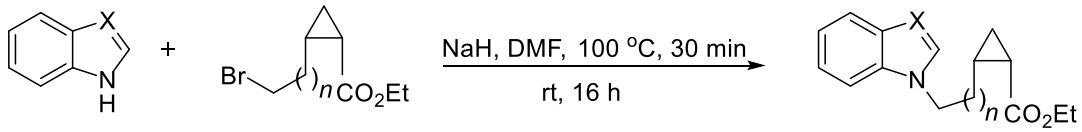


Scheme 2.1. *N*-Alkylation of indole-3-carbonitrile with *trans*-cyclopropane mesylate

Indole-3-carbonitrile underwent *N*-alkylation following treatment with K_2CO_3 in DMF, while benzimidazoles and indole-3-carbaldehyde underwent *N*-alkylation following treatment with sodium hydride in DMF.



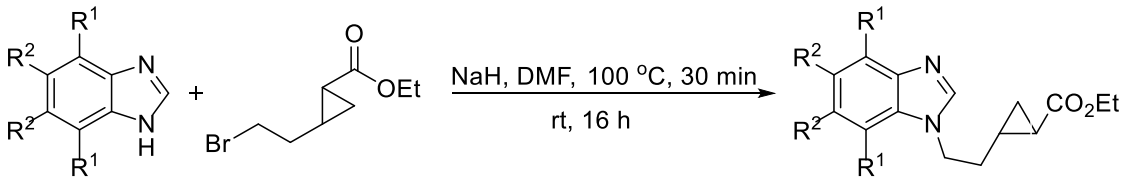
Scheme 2.2. *N*-Alkylation of indole-3-carbaldehyde with *trans*-cyclopropane bromides



X = C(CHO), N

1e*:* X = C(CHO), *n* = 1: 83%
1f*:* X = N, *n* = 2: 77%
1j: X = N, *n* = 2: 81%
1l: X = C(CHO), *n* = 2: 72%

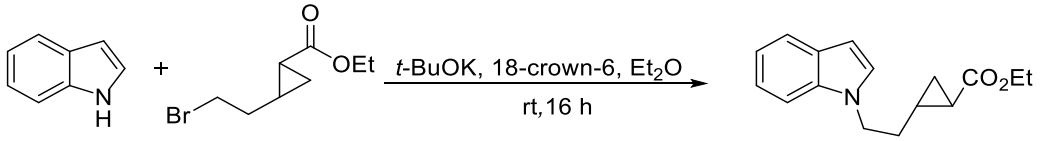
Scheme 2.3. *N*-Alkylation of indole-3-carbaldehyde and benzimidazole with *cis*-cyclopropane bromides



1h*:* R^1 = H, R^2 = Me: 81%
1i*:* R^1 = OMe, R^2 = H: 73%

Scheme 2.4. *N*-Alkylation of 4,7-dimethoxybenzimidazole and 5,6-dimethyl-benzimidazole with *trans*-cyclopropane bromide

N-Alkylation of indole was achieved through treatment with potassium *tert*-butoxide and 18-crown-6 in dry Et_2O at room temperature with rapid stirring prior to addition of the bromide.[50]

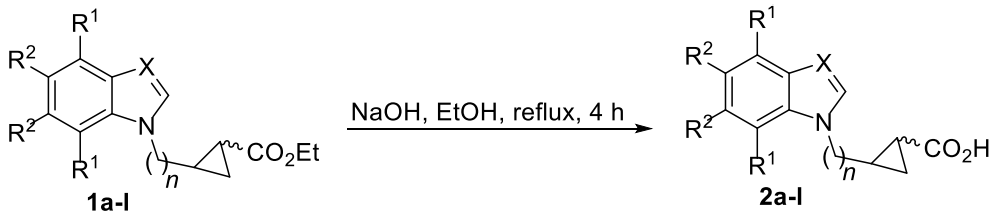


1d*:* 49%

Scheme 2.5. *N*-Alkylation of indole- with *trans*-cyclopropane bromide

Saponification of the ethyl esters **1a**–**l** gave the carboxylic acids **2a**–**l**, which were isolated in high purity, and required no further purification (Scheme 2.6). The use

of carboxylic acids is advantageous because of their robustness, unlike many conventional more labile radical cyclisation precursors.



2c:	*n* = 1,	X = (C(CN),	R^1 = H,	R^2 = H,	74%
2d:	*n* = 2,	X = CH,	R^1 = H,	R^2 = H,	82%
2e:	*n* = 2,	X = C(CHO),	R^1 = H,	R^2 = H,	77%
2f:	*n* = 2,	X = N,	R^1 = H,	R^2 = H,	64%
2g:	*n* = 2,	X = C(CN),	R^1 = H,	R^2 = H,	79%
2h:	*n* = 2,	X = N,	R^1 = H,	R^2 = Me,	64%
2i:	*n* = 2,	X = N,	R^1 = OMe,	R^2 = H,	59%
2j:	*n* = 3,	X = N,	R^1 = H,	R^2 = H,	71%
2k:	*n* = 3,	X = C(CN),	R^1 = H,	R^2 = H,	81%
2l:	*n* = 3,	X = C(CHO),	R^1 = H,	R^2 = H,	78%

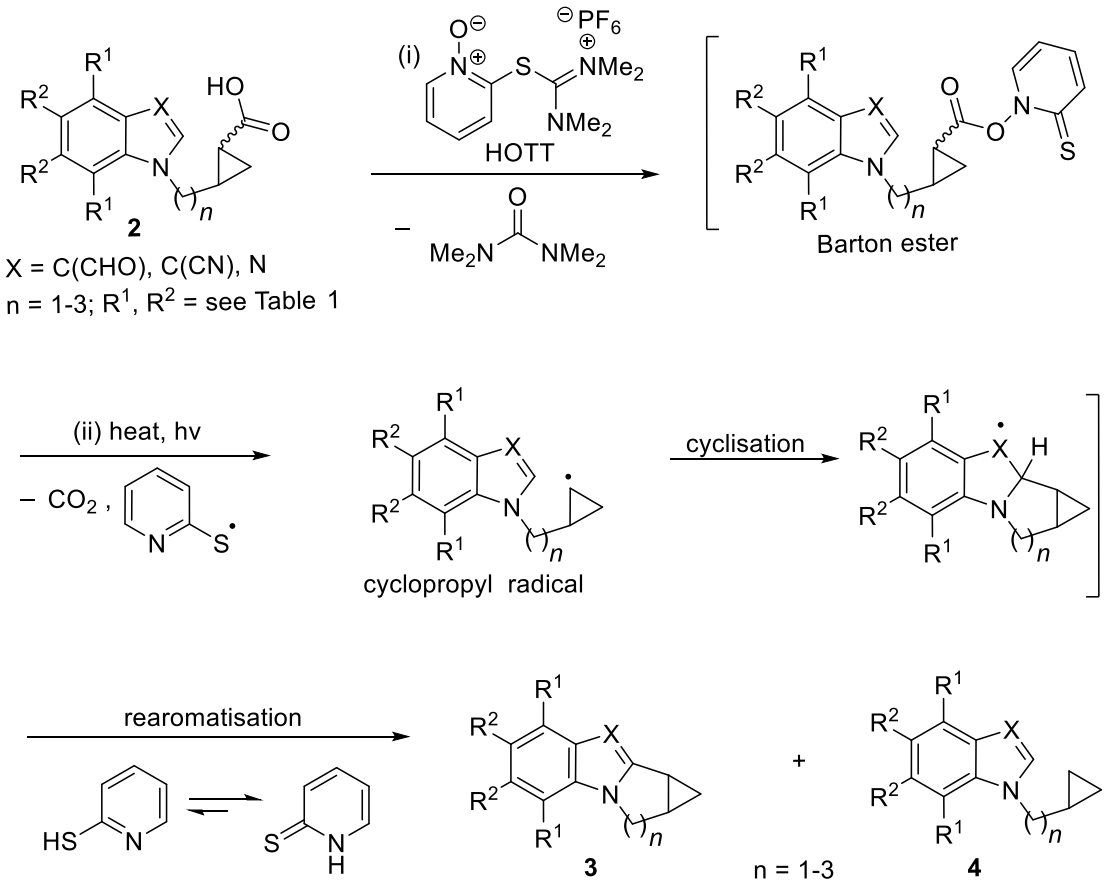
Scheme 2.6. Saponification of cyclopropane carboxylic acids

2.2.1.2 Initiator-free cyclopropyl radical cyclisation

Garner introduced HOTT (S-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium hexafluorophosphate) for the synthesis of "hindered" or "difficult" Barton esters,[51] which upon radical decarboxylation can be used to give reduced, oxygenated, halogenated and intermolecular addition products.[51-57] After surveying available literature methods for forming Barton esters,[58-59] we found HOTT, which has never been utilized in homolytic aromatic substitutions to be the most efficient (Scheme 2.7).

The main difference in optimising the formation of the Barton ester was benzimidazoles, unlike indoles required a catalytic amount of DMAP (Table 2.1). Although it is possible to isolate Barton ester intermediates,[35,60,61] it is more

convenient to perform the intramolecular substitution in the same one-pot reaction.



Scheme 2.7. One pot Barton ester formation and initiator-free cyclopropyl radical cyclisation. Conditions: (i) HOTT (1.5 equiv.), ET_3N (3 equiv.), THF–MeCN 3 : 1 (0.1 M), rt, 40 min[a]; (ii) MeCN (0.01 M), reflux, 2 × 100 W, 6 h[b] (see Table 2.1 for modifications[a,b] and yields).

Traditionally the cyclopropyl radical is thought of as being difficult to generate with predicted increased s-character.[62-63] This would make cyclopropyl radical cyclisations onto indoles containing electron-withdrawing groups and benzimidazoles more difficult in comparison to the analogous alkyl examples.

The breakdown of the Barton esters was carried out in refluxing acetonitrile in the presence of 2 × 100 W light bulbs. From the yields in Table 2.1, it is clear

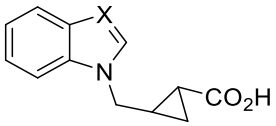
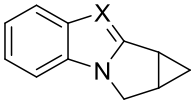
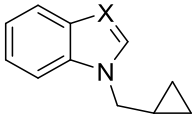
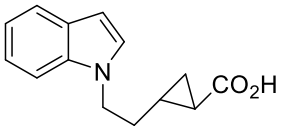
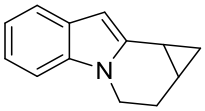
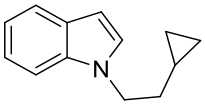
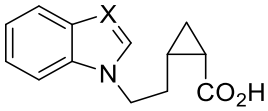
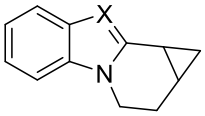
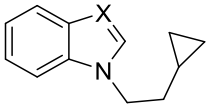
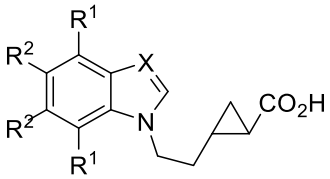
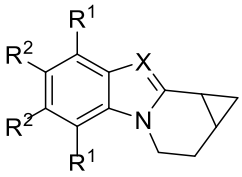
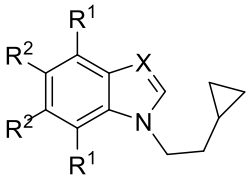
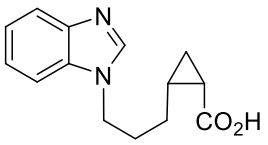
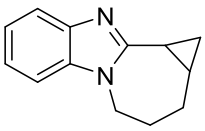
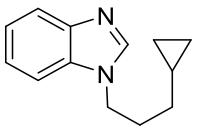
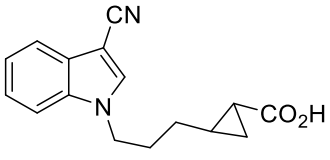
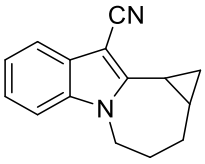
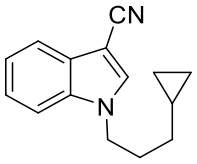
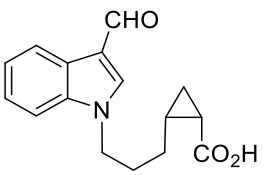
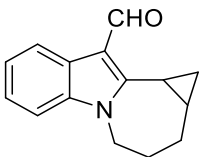
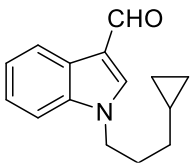
that six-membered cyclisations onto the 2-position of various indoles and benzimidazoles are more favoured than most five and seven-membered analogues, and found to give only the substitution product in excellent yields of 76–81%.

An electron withdrawing group at the 3-position of indole is required, as indicated from the lack of six-membered cyclisation onto unactivated indole **2d**. The formation of radical reduction products **4** is probably due to hydrogen abstraction from the solvent as previously observed in tin-free photochemical reactions of aromatic σ-radicals carried out in acetonitrile,[64-66] however abstraction from other reagents cannot be ruled out. THF was also present from the initial 3 : 1 solvent mixture with acetonitrile,[51] this mix is required to solubilise starting materials (including HOTT).

For more difficult cyclisations onto benzimidazoles, 4 equivalents of camphorsulfonic acid (CSA) was present to quaternise the pyridine-like 3-*N* of imidazole,[1,3,5,13,14,] including for six-membered cyclisation onto 4,7-dimethoxy-benzimidazole **2i**. In the latter case, the dimethoxy substituents make the benzimidazole-2-position less electrophilic, and CSA activation is required to obtain the high yield of 80% of adduct **3i**. The quaternisation was in agreement with reports of nucleophilic character for the cyclopropyl radical obtained from intermolecular reactions.[67-68]

For most five and seven-membered attempted cyclisations approximately equal yields of substitution and reduction products were given, except for the cyclisation onto indole-3-carbonitrile **2c**, which gave only the substitution product **3c** in high yield of 75%. This relatively constrained cyclisation is favourable in comparison to its aldehyde analogue possibly due to polar effects, given that the addition of the nucleophilic *t*-Bu$^{\bullet}$ radical is reported to occur approximately twice as fast onto acrylonitrile in comparison with onto acrolein.[69] The success of this five-membered cyclisation is important, as it allows efficient access to the cyclopropamitosene skeleton.

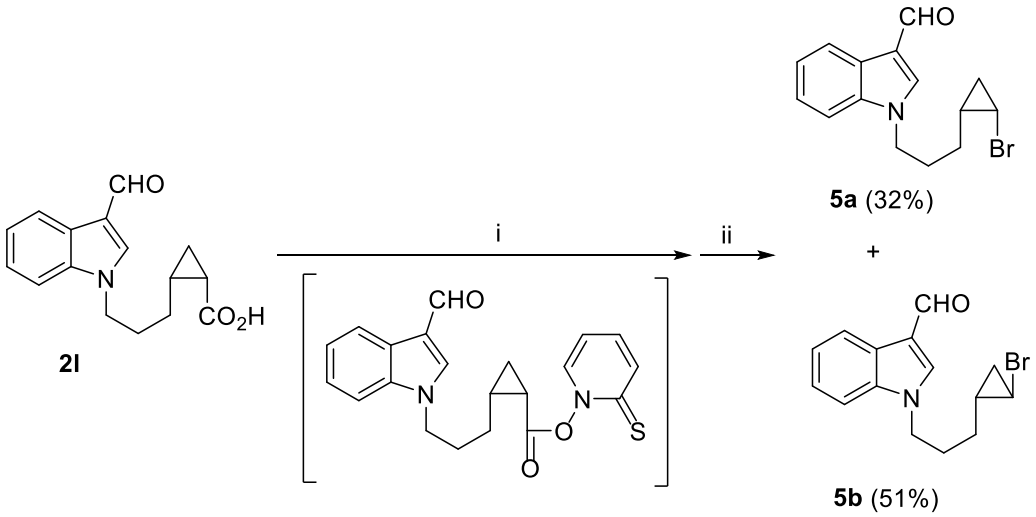
Table 2.1 Optimized HOTT-Mediated Barton Ester Formation & Radical Cyclisations

Entry	Acid	Products[c] (%)	
			
1[d]	**2a** X = C(CHO)	**3a** (38)	**4a** (43)
2[a,b,d]	**2b** X = N	**3b** (44)	**4b** (40)
3	**2c** X = C(CN)	**3c** (75)	**4c** (0)
2			
4	**2d**	**3d** (0)	**4d** (76)
			
5	**2e** X = C(CHO)	**3e** (78)	**4e** (0)
6[a]	**2f** X = N	**3f** (81)	**4f** (0)
			
7	**2g** X = C(CN), $R^1 = R^2 = H$	**3g** (77)	**4g** (0)
8[a]	**2h** X = N, $R^1 = H$, $R^2 = CH_3$	**3h** (76)	**4h** (0)
9[a,b]	**2i** X = N, R^1 = OMe, $R^2 = H$	**3i** (80)	**4i** (0)
			
10[a,b]	**2j**	**3j** (40)	**4j** (42)
			
11	**2k**	**3k** (37)	**4k** (41)
			
12	**2l**	**3l** (39)	**4l** (38)

[a]DMAP (0.1 equiv.). [b]CSA (4 equiv.) added. [c]Isolated yields. [d]K. Fahey, PhD Thesis 2010. NUI Galway.

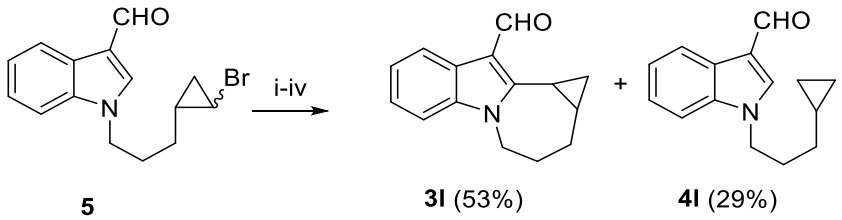
2.2.1.3 Bu_3SnH/AIBN-mediated seven membered cyclopropyl radical cyclisation

The success of previously reported five-membered cyclopropyl radical cyclisation onto indole-3-carbaldehyde[48] led us to investigate the seven-membered analogue. Separable bromides **5** (**5a** + **5b**) were obtained in 83% combined yield from carboxylic acid **2l** via efficient HOTT-mediated Barton ester formation (Scheme 2.8).



Scheme 2.8. HOTT mediated Barton decarboxylation and bromination of indole-3-carbaldehyde. Conditions: i, HOTT, Et_3N, THF-MeCN (3:1), rt, dark, 40 min; ii, $BrCCl_3$ (50 equiv.), $CHCl_3$, reflux, 4h.

Using the cyclisation conditions in Scheme 2.9, bromides **5** were converted into novel cyclopropane-fused adduct 1,1*a*,2,3,4,10*b*-hexahydrocyclopropa[3,4]azepino [1,2-*a*]indole-10-carbaldehyde **(3l)** in 53% yield with 29% reduced cyclopropane **4l** obtained. This compares favourably with yields of 39% and 38% of **3l** and **4l** obtained from carboxylic acid **2l** using the one-pot Barton ester, and radical cyclisation protocol (Table 2.1). X-ray crystal structure of cyclopropane-fused azepino[1,2-*a*]indole **3l** is provided in Figure 2.1 showing the (1a*R*,10b*S*) enantiomer, which is part of a racemic mixture.



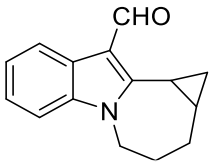
Scheme 2.9. Bu_3SnH/AIBN-mediated cyclopropyl radical cyclisation. Conditions: i. Bu_3SnH (1.2 equiv.), AIBN (1 equiv.) added over 15 min, toluene, reflux; ii. reflux, 3 h; iii, Bu_3SnH (0.4 equiv.), AIBN (0.3 equiv.) added over 5 min, toluene, reflux; iv, reflux, 15 min.

The reasons for improved yields using the Bu_3SnH-mediated protocol for radical cyclisations onto indole-3-carbaldehyde remain unclear, and the use of different solvents and temperatures for reactions with and without initiators, makes the drawing of definitive explanations difficult.

It is however well-documented that the addition-step of homolytic aromatic substitution (in this case the cyclisation) is slow and reversible[70] and it is plausible that initiator-derived radicals may intercept the cyclised radical intermediate leading to higher yields of the aromatic substitution product, in comparison to the non-cyclised reduced product.

It is noteworthy that the initiators had to be added over a relatively short-time of 5-15 minutes, in order to give the cyclised optimized yields reported. This supports the involvement of azo-initiator derived radicals in the aromatisation process due to the rapid breakdown of AIBN at this reaction temperature (AIBN, $t_{1/2} < 2$ min in toluene at 110 °C).[3]

The AIBN derived 2-cyano-2-propyl radical may be involved in either hydrogen abstraction from the cyclised radical to give directly the aromatic substitution product and/or via thermal breakdown of cyclised non-aromatic intermediates trapped by the 2-cyano-2-propyl radical.[2] The latter may account for the requirement of prolonged (3 hour) heating of the reaction mixture in toluene under reflux after the addition of most of the initiators was completed, as previously observed in our related radical cyclisations.[14]



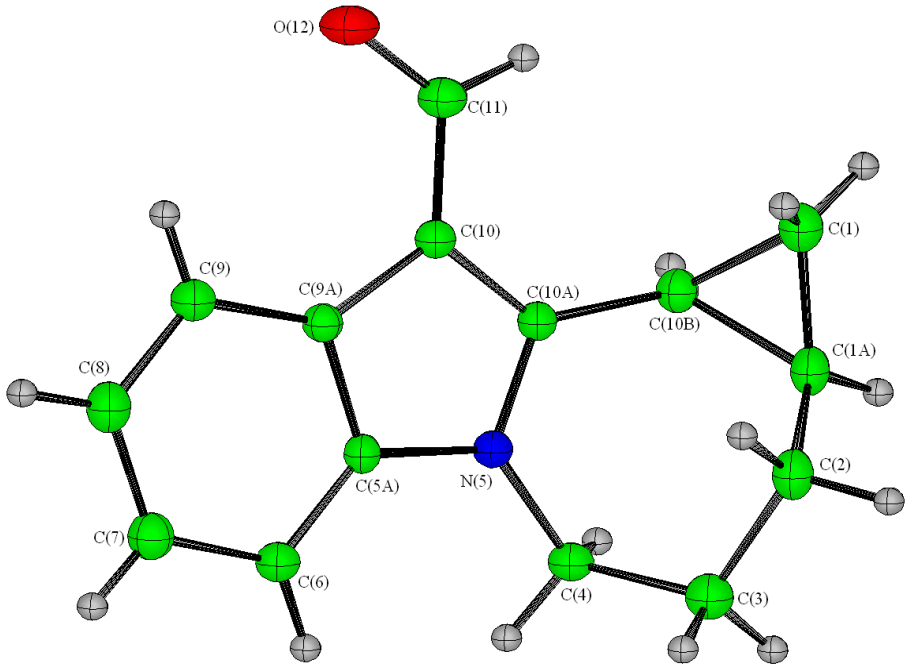
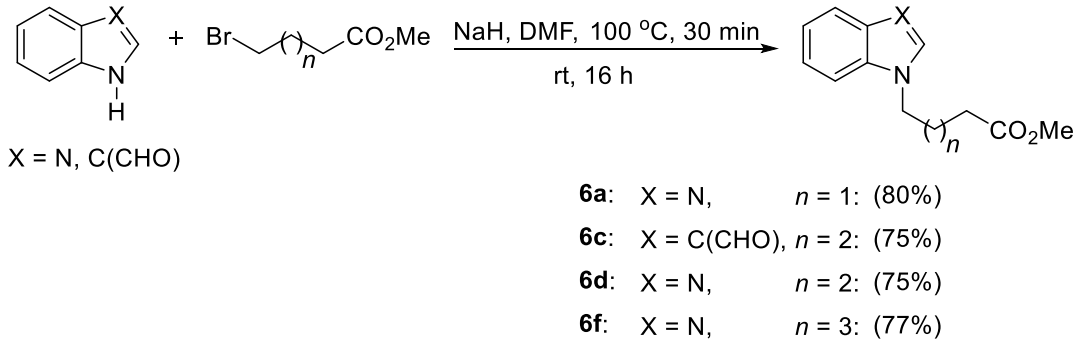


Figure 2.1. X-ray crystal structure of (1a*R*,10b*S*)-1,1*a*,2,3,4,10*b*-hexahydrocyclopropa[3,4]azepino[1,2-*a*]indole-10-carbaldehyde **(3l)**

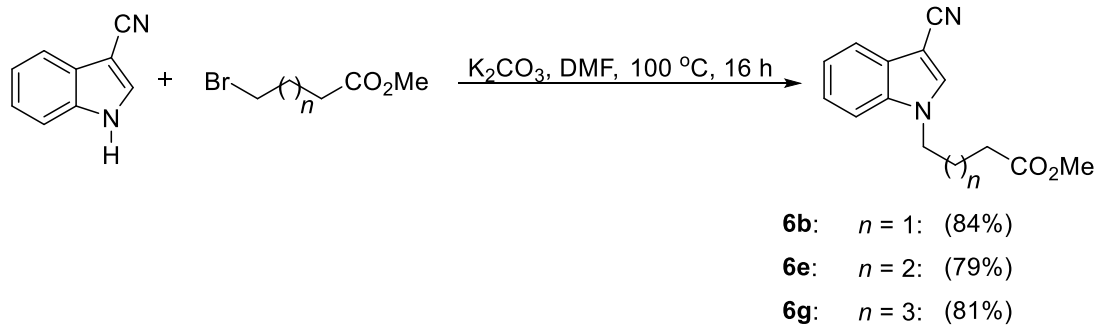
2.2.2 Alkyl radical cyclisations

2.2.2.1 Synthesis of alkyl radical precursors



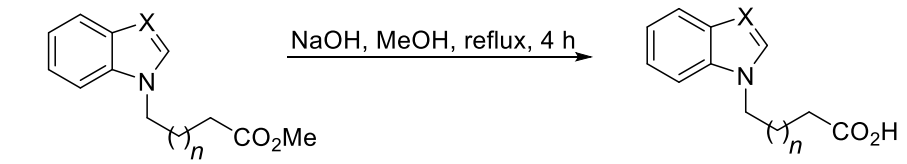
Scheme 2.10. *N*-Alkylation of benzimidazole and indole-3-carbaldehyde

Benzimidazole and indole-3-carbaldehyde underwent *N*-alkylation following treatment with NaH in DMF, while indole-3-carbonitrile required treatment with K_2CO_3 in DMF, prior to addition of the appropriate bromide.



Scheme 2.11. *N*-Alkylation of indole-3-carbonitrile

Saponification of the methyl esters **6a**–**g** gave the carboxylic acids **7a**–**g**, which were isolated in high purity, and required no further purification (Scheme 2.12).



6a-6g
X= N, C(CN), C(CHO)

7a:	X = N,	*n* = 1:	(66%)
7b:	X = C(CN),	*n* = 1:	(74%)
7c:	X = C(CHO),	*n* = 2:	(66%)
7d:	X = N,	*n* = 2:	(75%)
7e:	X = C(CN),	*n* = 2:	(73%)
7f:	X = N,	*n* = 3:	(73%)
7g:	X = C(CN),	*n* = 3:	(72%)

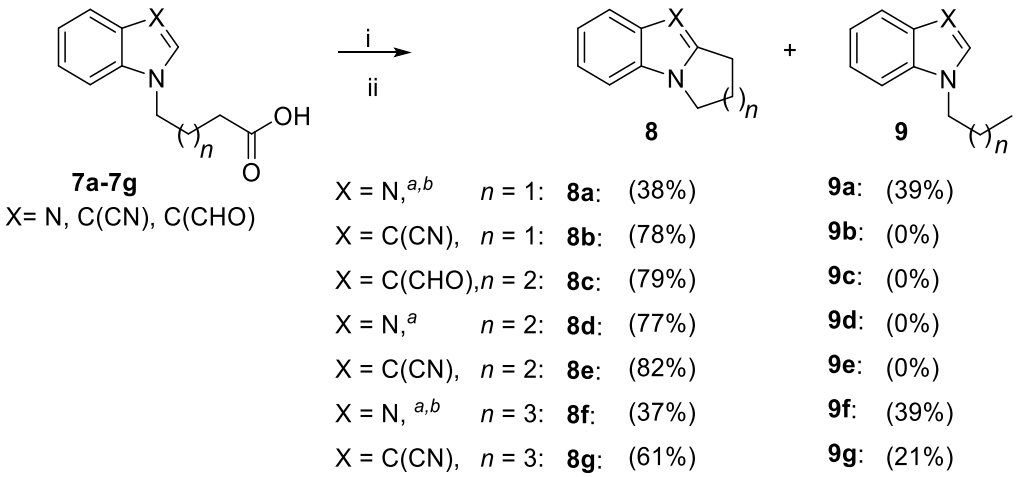
Scheme 2.12. Saponification of alkyl carboxylic acids

2.2.2.2 Initiator-free alkyl radical cyclisation

Therefore alicyclic ring-fused indoles and benzimidazoles can be accessed via a straight forward three-step synthesis with facile synthesis of the carboxylic acid, and new initiator-free radical cyclisation protocol (Scheme 2.13).

Six-membered alkyl radical cyclisation onto indoles and benzimidazole proceeded to give only the substitution product (**8c**–**8e**) in 77–82% yield, and without CSA activation for benzimidazole **8d**.

As with the cyclopropane series, five-membered alkyl radical cyclisation onto indole-3-carbonitrile **7b** was effective in giving only the substitution product **8b** in 78% yield, and radical reduction competed with the analogous cyclisation onto benzimidazole **7a**. However, the seven-membered alkyl radical cyclisation onto **7g** was also favoured (unlike cyclopropyl analogue **2k** or benzimidazole analogue **7f**) giving a good yield of 61% of novel azepino[1,2-*a*]indole **8g**, with non-cyclised **9g** separated in 21% yield.



Scheme 2.13. One pot Barton ester formation and initiator-free alkyl radical cyclisation. Conditions: (i) HOTT (1.5 equiv.), Et_3N (3 equiv.), THF–MeCN 3 : 1 (0.1 M), rt, 40 min, [a](DMAP 0.1 equiv.) (ii) MeCN (0.01 M), reflux, 2 × 100 W, 6 h, [b](CSA 4 equiv.) added.

2.3 Conclusions

Tin-free intramolecular homolytic aromatic substitutions via Barton esters that circumvent the requirement for harmful radical initiators have been realised. Efficient formation of the Barton ester intermediate is achieved using HOTT. Eleven favoured cyclisations onto indoles and benzimidazoles from the carboxylic acid give exclusively (or overwhelmingly in the case of **7g**) the substitution product. The reactivity of the cyclopropyl radical is shown to be similar to that of the alkyl radical with generally constrained cyclisations onto indole-3-carbonitrile being more facile than onto indole-3-carbaldehyde and benzimidazole. Alternative annulations using this new Barton ester cyclisation protocol are anticipated.

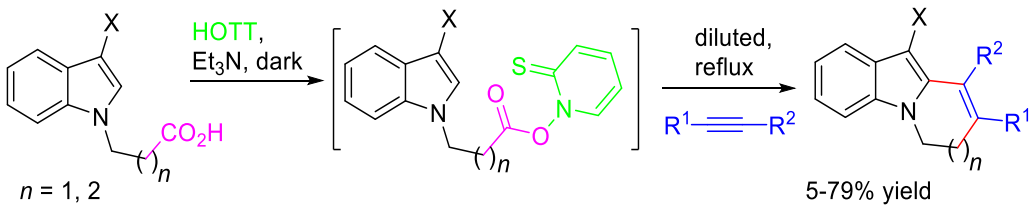
Bu_3SnH/AIBN-mediated seven-membered cyclopropyl radical cyclisation was used to access azepino[1,2-*a*]indole in respectable yield. The transformation is another example of "oxidative" aromatic substitutions mediated by the "reductant" Bu_3SnH. Included in this Chapter is a first crystal structure of the cyclopropane-fused azepino[1,2-*a*]indole heterocyclic system.

Overall, our radical cyclisation pathways via Barton esters compare favourably with alternative cycloaddition protocols for making these cyclopropane-fused heterocyclic systems.[40-47]

Chapter 3

Tandem reactions via Barton esters with intermolecular addition and vinyl radical substitution onto indole

Most of this Chapter is published in one publication:



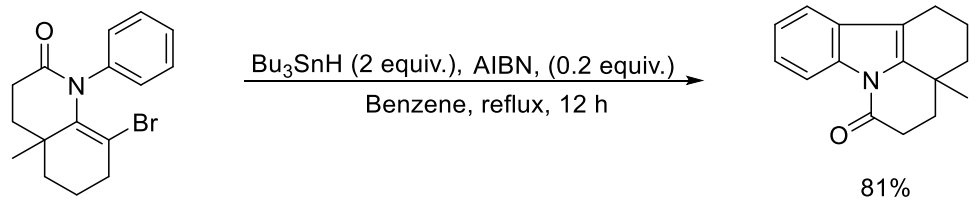
Tandem reactions *via* Barton esters with intermolecular addition and vinyl radical substitution onto indole,

Robert Coyle, Patrick McArdle and Fawaz Aldabbagh,

J. Org. Chem. **2014**, *79*, 5903-5907.

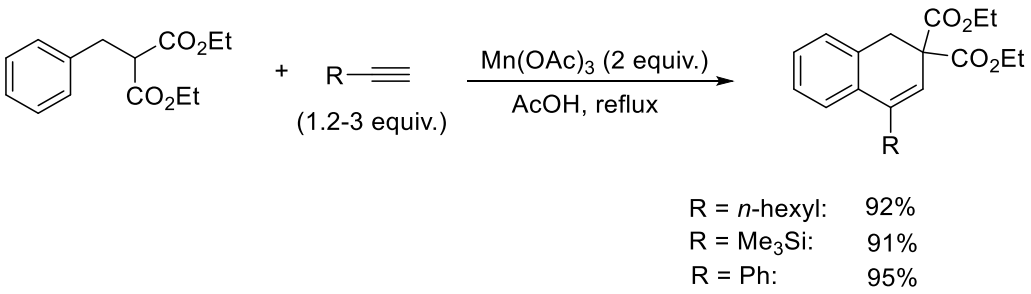
3.1 Introduction

Stork and Baine first demonstrated the synthetic utility of vinyl radicals by carrying out reductive cyclisations to form five and six-membered rings.[71] Bu_3SnH and azobisisobutyronitrile (AIBN) were used to carry out vinyl radical cyclisations onto indole yielding mainly reduced adducts.[7] Later vinyl radical cyclisation with aromatic substitution was achieved using a tin-free chain reaction, where displacement of indole-2-sulfonyl substituent occurs.[9] Effective five and six-membered intramolecular aromatic substitutions of vinyl radicals using Bu_3SnH and AIBN were reported by Padwa et al.[72] Although, usually the use of the "reductant" Bu_3SnH is not conducive with efficient aromatic substitution, where net-loss of $H^{\bullet}$ or "oxidation" occurs.[1,4]



Scheme 3.1. Bu_3SnH and AIBN mediated intramolecular aromatic substitutions of vinyl radicals

Where prior to the substitution the vinyl radical is generated via an intermolecular addition onto alkynes,[73] yields of aromatic product are traditionally modest.[74-78] The first synthetically viable tandem process containing an intermolecular addition onto alkynes was reported by Santi *et al.* using Mn(III)-mediated oxidation of benzylmalonates with the subsequent vinyl radical aromatic substitution giving naphthalene derivatives in moderate to good yields.[79-80]



Scheme 3.2. Mn(III)-mediated oxidation of benzylmalonates leading to vinyl radical aromatic substitution

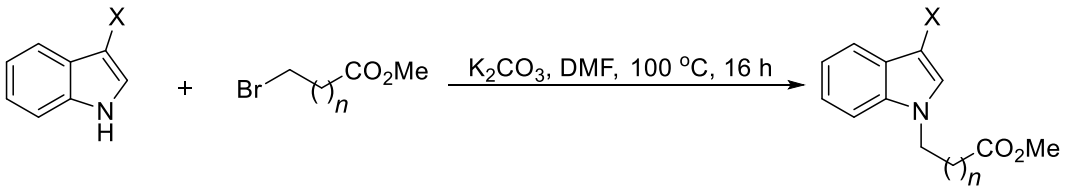
Most recently, Zhou and co-workers used a photo-redox catalytic system to synthesize 2-trifluoromethyl quinolines with imidoyl radical addition onto alkyne followed by aromatic substitution,[81] and Li and co-workers reported benzothiophenes under oxidative catalytic conditions with an initial sulfanyl radical addition onto but-2-ynedioates.[82]

The decomposition of Barton esters {*O*-acyl thiohydroxamate ester or pyridine-2-thione-*N*-oxycarbonyl (PTOC)}[31-32] provides a means of achieving aromatic substitution under mild initiator-free conditions,[5,83,84] as demonstrated by Barton et al for intermolecular substitution of nucleophilic alkyl radicals onto heteroaromatic salts.[5] Most recently we used Barton esters in radical cyclisations resulting in some high yielding five to seven-membered alkyl and cyclopropyl annulations of indoles and benzimidazoles (See Schemes 2.7, 2.13).[83,84]

In this chapter we report a new use of Barton esters, as precursors for one-pot initiator-free cascade/tandem reactions. The tandem reaction involves intermolecular addition of alkyl radicals onto alkyl propiolates or phenylacetylene followed by intramolecular substitution of vinyl radicals onto indoles. Investigations into the use of disubstituted (internal) alkynes with two different substituents are also presented with substitution products demonstrating the selectivity of the radical addition onto the alkyne.

3.2 Results and discussion

3.2.1 Synthesis of radical precursors

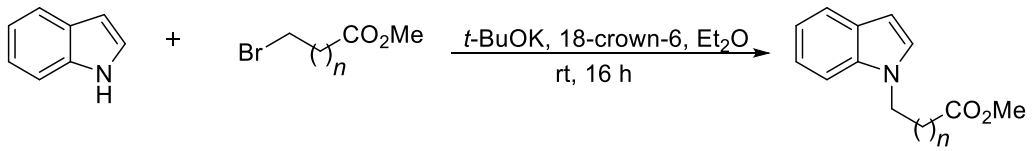


X = CN, CHO

10a: X = CN, *n* = 1: 84%
10b: X = CHO, *n* = 1: 81%
10c: X = CHO, *n* = 2: 88%

Scheme 3.3. *N*-Alkylation of indole-3-carbonitrile and indole-3-carbaldehyde

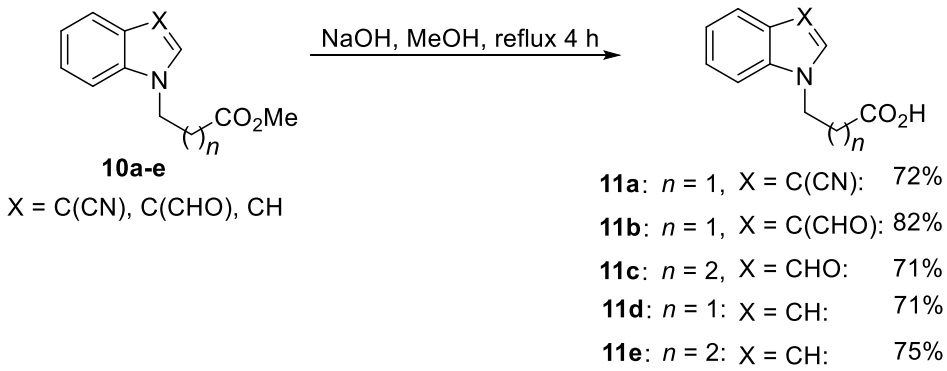
Indole-3-carbonitrile and indole-3-carbaldehyde underwent *N*-alkylation following treatment with K_2CO_3 (3 equiv.) in DMF.



10d: *n* = 1: 45%
10e: *n* = 2: 39%

Scheme 3.4. *N*-Alkylation of indole

N-Alkylation of indole was achieved through treatment with potassium *tert*-butoxide and 18-crown-6 in dry Et_2O with rapid stirring prior to addition of bromide with reactions proceeding in moderate yield.[50]



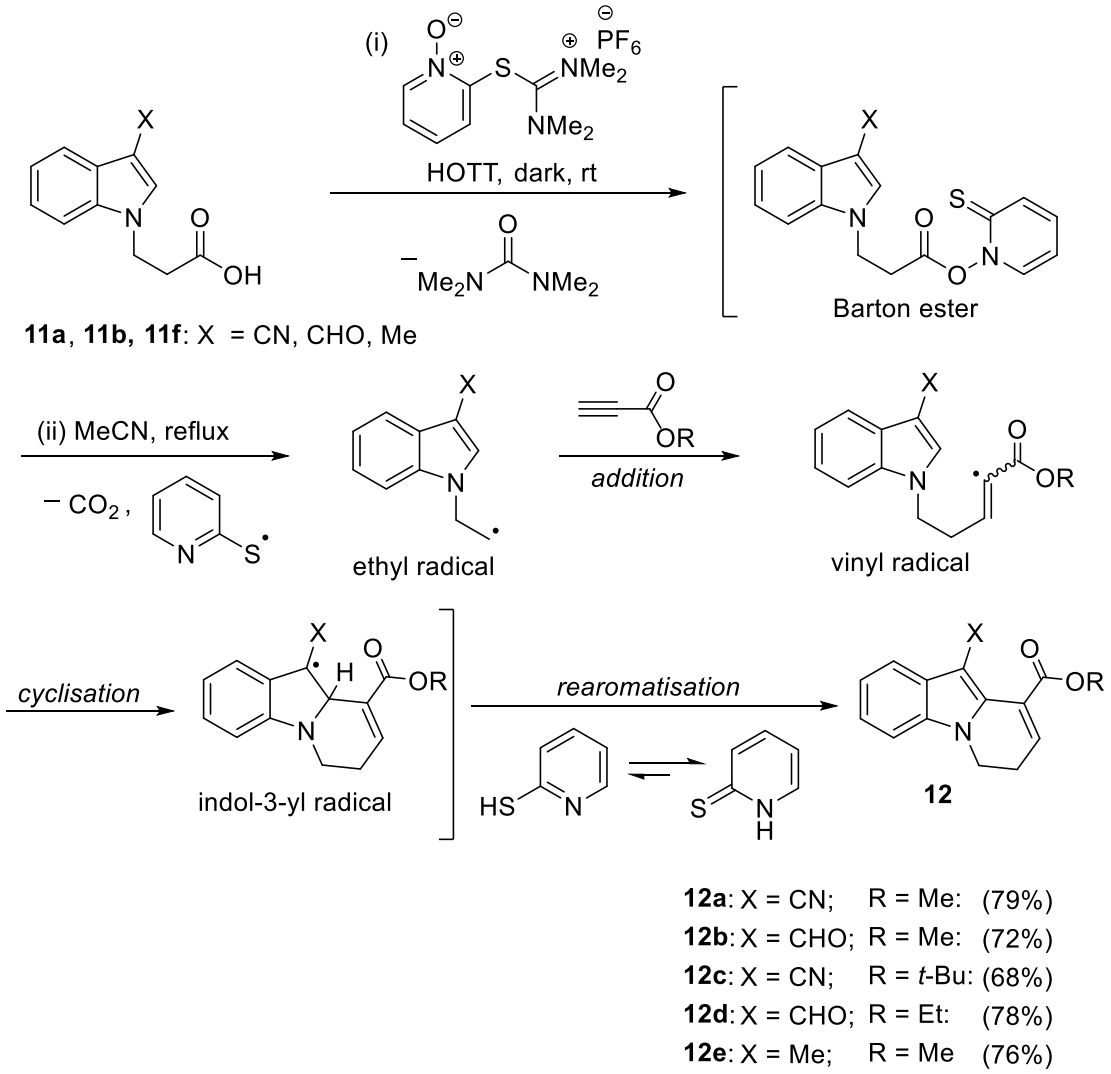
Scheme 3.5. Saponification of alkyl carboxylic acids

Though carboxylic acids **11b**, **11d** and **11e** are commercially available, saponification of the methyl esters **10a**–**e** gave the carboxylic acids **11a**–**e**, which were isolated in high purity, and required no purification (Scheme 3.5). The use of carboxylic acids is advantageous because of their robustness, unlike many conventional more labile radical cyclisation precursors.

3.2.2 Initiator free tandem radical reactions

The two-step one-pot protocol involves initial transformation of indole carboxylic acids (e.g. **11a** and **11b**) into Barton esters using Garner's HOTT (*S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethyl thiouronium hexafluorophosphate)[51] in the absence of light (Scheme 3.6).

HOTT is a useful coupling reagent for forming labile Barton esters from hindered or difficult carboxylic acids. The alkyne is present in excess (8 equivalents) in order to favour the intermolecular addition with reactions using terminal alkynes only proceeding efficiently by carrying out the radical generation and tandem reactions step under acidic conditions {4 equivalents of camphorsulfonic acid (CSA)}. CSA neutralizes remaining triethylamine from the Barton ester formation step, which would otherwise cause inadvertent dimerization of the alkyne.

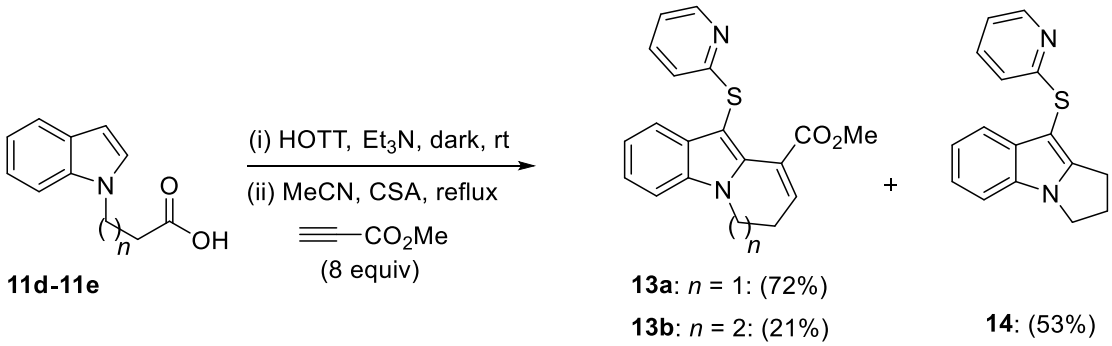


Scheme 3.6. One pot and initiator free radical cyclisation onto indole-3-carbonitrile and indole-3-carbaldehyde via tandem reaction and Barton ester. Conditions: (i) Barton ester formation: HOTT (1.5 equiv.), Et_3N (3 equiv.), THF-MeCN (3:1, 0.1 M), rt, dark, 40 min; (ii) radical generation and tandem reaction: MeCN (0.01M), propiolate (8 equiv.), CSA (4 equiv.), reflux, 6 h.

The one-pot reaction sequence begins with Barton ester thermal dissociation to give a nucleophilic ethyl radical that undergoes addition onto the unsubstituted carbon of the terminal alkyne resulting in a vinyl radical for aromatic substitution.

The yields for reactions with indole-3-carbonitrile **11a** and indole-3-carbaldehyde **11b** with methyl and ethyl propiolate to give 6,7-dihydropyrido[1,2-*a*]indoles **12a**, **12b**

and **12d** are 72-79%, with a smaller isolated yield obtained of adduct **12c** (68%) from the reaction of **11a** with *tert*-butyl propiolate. The tandem protocol is insensitive to substituents at the indole-3-position with 3-methylindole-1-propanoic acid (**11f**) giving 10-methyl-6,7-dihydropyrido[1,2-*a*]indole-9-carboxylate **12e** in 76% yield inferring a nonpolar cyclising radical. An efficient chain for vinyl radical aromatic substitution is indicated since no other indole adducts were observed.



Scheme 3.7. Radical cyclisation onto indole via tandem reaction and Barton ester

Though ESR data has suggested α-carboxy and α-phenyl vinylic radicals adopt close to linear π-type resonance stabilized structures,[85,86] a bent σ-type structure has been reported.[87-89] The conjugation of the vinyl radical with the adjacent substituent gives an electrophilic radical, while a nucleophilic or neutral radical would be expected if the σ-type structure is adopted.

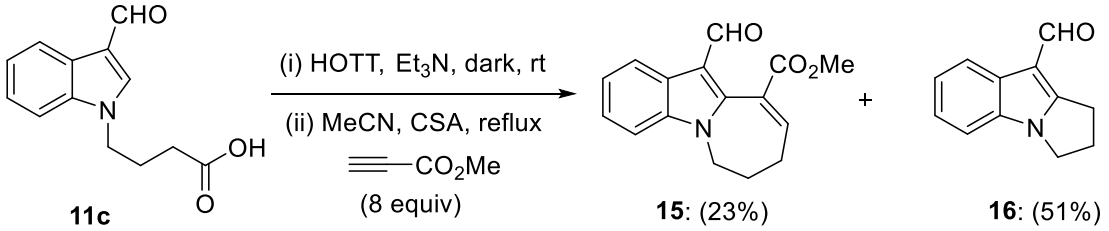
The isolation of only aromatic substitution product **13a** in 72% yield from the reaction of 3-unsubstituted 1-indolepropanoic acid **11d** with methyl propiolate (Scheme 3.7) indicates that the intermediate vinyl radical is not influenced by polar effects.

In agreement with the Barton et al chain proposal,[5] it can be inferred that the 2-thiopyridinyl *S*-radical traps the intermediate cyclised radical (the indol-3-yl radical in Scheme 3.6) prior to elimination of 2-pyridinethiol on rearomatisation.

In contrast to 3-substituted indoles, aromatic *S*-radical adduct **13a** is formed by oxidation during the reaction (presumably by the presence of adventitious oxygen), as confirmed by analysis of the reaction mixture. A mechanism similar to that proposed by Curran and Keller may be involved where hydrogen atom transfer to oxygen would

give $HO_2^{\bullet}$, which is used to explain the formation of "oxidised" aromatic substitution products from metal hydride-mediated reactions.[14,90]

A seven-membered vinyl radical cyclisation allowed access to the 7,8-dihydro-6*H*-azepino[1,2-*a*]indole system. Use of 3-formylindole-1-butanoic acid **11c** and methyl propiolate allowed isolation of seven-membered adduct 7,8-dihydro-6*H*-azepino[1,2-*a*]indole-10-carboxylate **15** albeit in 23% yield with 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole **16** predominating in 51% yield (Scheme 3.8).

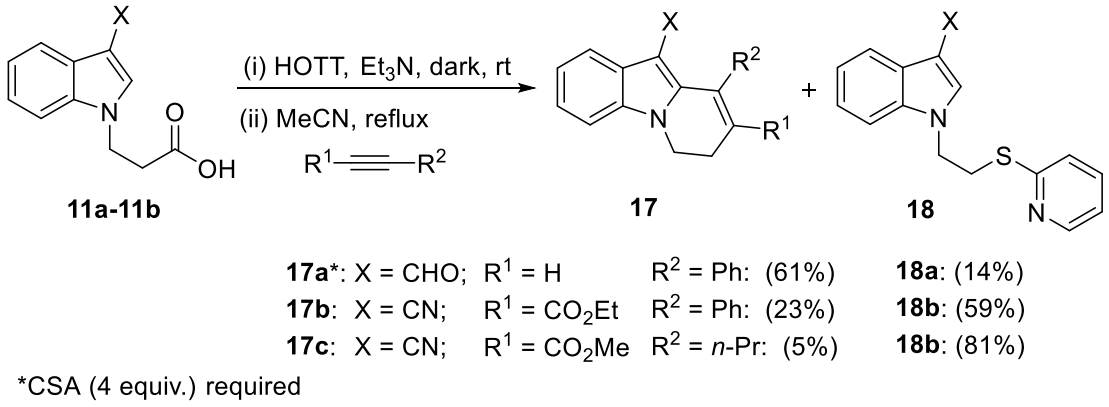


Scheme 3.8. 7,8-Dihydro-6*H*-azepino[1-2-*a*]indole via one-pot initiator-free tandem reactions

The higher yield for the propyl radical adduct **16** is in accordance with a more favourable five-membered cyclisation, where there is also compatible polar effects between the nucleophilic radical and the activated 2-position of indole-3-carbaldehyde. We previously reported a five-membered alkyl radical cyclisation occurring in 78% yield via the decomposition of the Barton ester of 4-(3-cyano-1*H*-indol-1-yl)butanoic acid.[83] Thus, it seemed that the tandem reaction via a cyclising seven-membered vinyl radical would be more favorable using non-activated indole **11e** (Scheme 3.7), however unexpectedly this gave 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole **14** as the major product in 53% yield with the desired 7,8-dihydro-6*H*-azepino[1,2-*a*]indole-10-carboxylate **13b** isolated in 21% yield. Therefore, it seems that cyclisations of alkyl radicals like vinyl radicals onto indoles are not significantly influenced by polar effects.

The addition of nucleophilic radicals (*t*-$Bu^{\bullet}$) onto electron-deficient alkyl propiolates is reported to be about ten times faster than onto phenylacetylene (~ $k = 2 \times 10^5$ $M^{-1}s^{-1}$ for alkyl propiolates in 1,2-epoxypropane in comparison to $k = 2.1 \times 10^4$ M^{-1} s^{-1} for

phenylacetylene in isopropanol at 300 K),[73,85] which may explain the higher yield for reaction of indole-3-carbaldehyde **11b** with alkyl propiolates (Scheme 3.6) in comparison with phenylacetylene to give the phenyl analogue **17a** in 61% yield, with 14% isolated of 2-thiopyridine **18a** (Scheme 3.9). Nevertheless this convenient tandem radical approach represents the first synthesis of 9-substituted 6,7-dihydropyrido[1,2-*a*]indoles.



Scheme 3.9 One-pot initiator-free tandem reactions with less reactive alkynes

Yields of 8,9-disubstituted 6,7-dihydropyrido[1,2-*a*]indoles **17b** and **17c** (5-23% in Scheme 3.9) were low from reactions of 3-cyanoindole-1-propanoic acid **(11a)** with internal alkynes under analogous Barton ester conditions to those used for terminal alkynes (Scheme 3.6).

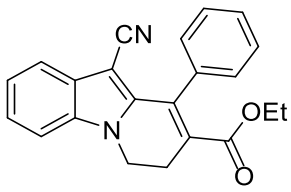
The major product was 1-[2-(pyridin-2-ylthio)ethyl]-1*H*-indole-3-carbonitrile **(18b)** (in 59-81% yield) indicative of a less competitive chain for the aromatic substitution.

The addition of the intermediate ethyl radical onto disubstituted alkynes is expected to be slow, as indicated by literature radical addition rates of nucleophilic radicals (*t*-Bu$^{\bullet}$) onto ethyl 3-phenylprop-2-ynoate and methyl but-2-ynoate, which are k = 4.2 x 10^4 M^{-1} s^{-1} and k = 5.2 x 10^2 M^{-1} s^{-1} respectively in 1,2-epoxypropane at 300 K,[73,85] factors of 10-1000 times slower than onto alkyl propiolates.

The selectivity of the ethyl radical addition onto ethyl 3-phenylprop-2-ynoate to give an α-styryl vinylic radical and onto methyl hex-2-ynoate to give an α-propyl vinylic radical respectively was confirmed by the X-ray crystal structures of the substitution

products; ethyl 10-cyano-9-phenyl-6,7-dihydropyrido[1,2-*a*]indole-8-carboxylate **(17b)** (Figure 3.1), and methyl 10-cyano-9-propyl-6,7-dihydropyrido[1,2-*a*]indole-8-carboxylate **(17c)**. (Figure 3.2).

The addition is thus dictated by steric factors in agreement with the ESR observation of α-phenyl vinyl radical formation from the addition of $Me_3C^{\bullet}$ onto alkyl 3-phenylprop-2-ynoates.[85] The lowest yielding tandem reaction to give adduct **17c** emphasizes the steric congestion about methyl hex-2-ynoate. The formation of sulfides **18a** and **18b** is only observed where the alkyne is less reactive, and can occur by alternative ethyl radical reactions such as combination with the 2-thiopyridinyl *S*-radical or from addition onto the Barton ester[5,91] to establish a chain.



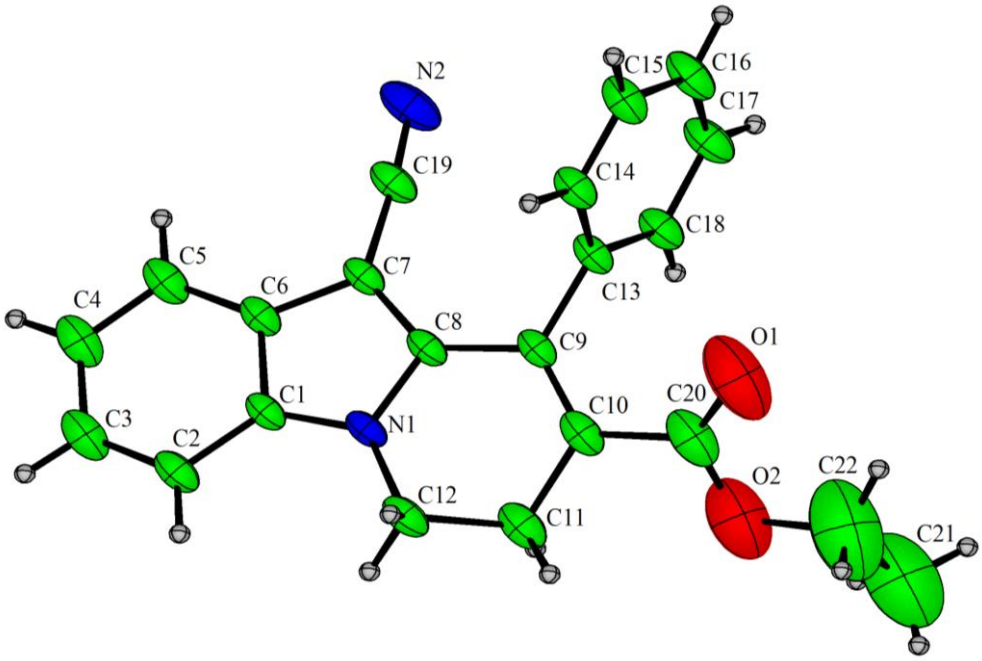
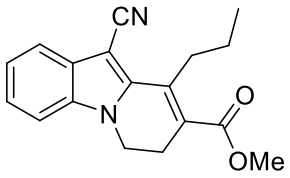


Figure 3.1. X-ray crystal structures of ethyl 10-cyano-9-phenyl-6,7-dihydropyrido [1,2-*a*] indole -8-carboxylate (**17b**)



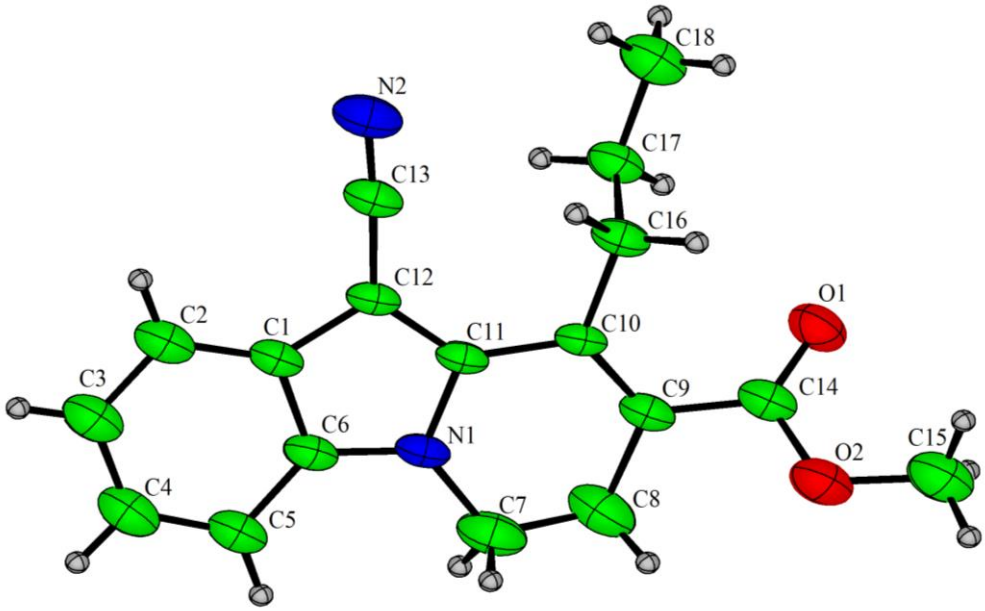


Figure 3.2. X-ray crystal structures of methyl 10-cyano-9-propyl-6,7-dihydropyrido[1,2-*a*]indole-8-carboxylate (**17c**)

3.3 Conclusion

One-pot initiator-free Barton ester decomposition, and tandem radical addition onto alkyl propiolates or phenylacetylene with aromatic substitution of the resultant vinyl radical allows convenient access to 9-substituted 6,7-dihydropyrido[1,2-*a*]indoles. Propyl radical cyclisations compete when forming the expanded 7,8-dihydro-6*H*-azepino[1,2-*a*]indole system.

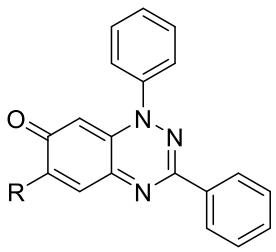
2-Thiopyridinyl *S*-radical is incorporated into aromatic adducts when using unsubstituted indole-1-alkanoic acid precursors.

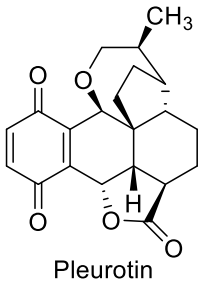
X-ray crystal structures of ethyl 10-cyano-9-phenyl-6,7-dihydropyrido [1,2-*a*] indole-8-carboxylate (**17b**) and methyl 10-cyano-9-propyl-6,7-dihydropyrido[1,2-*a*]indole-8-carboxylate (**17c**) allowed selectivity of the radical addition onto less reactive internal alkynes to be determined.

Chapter 4

Benzo[*e*][1,2,4]triazin-7-ones: Comparisons of anti-cancer activity with pleurotin

Most of this Chapter is to be submitted for publication:





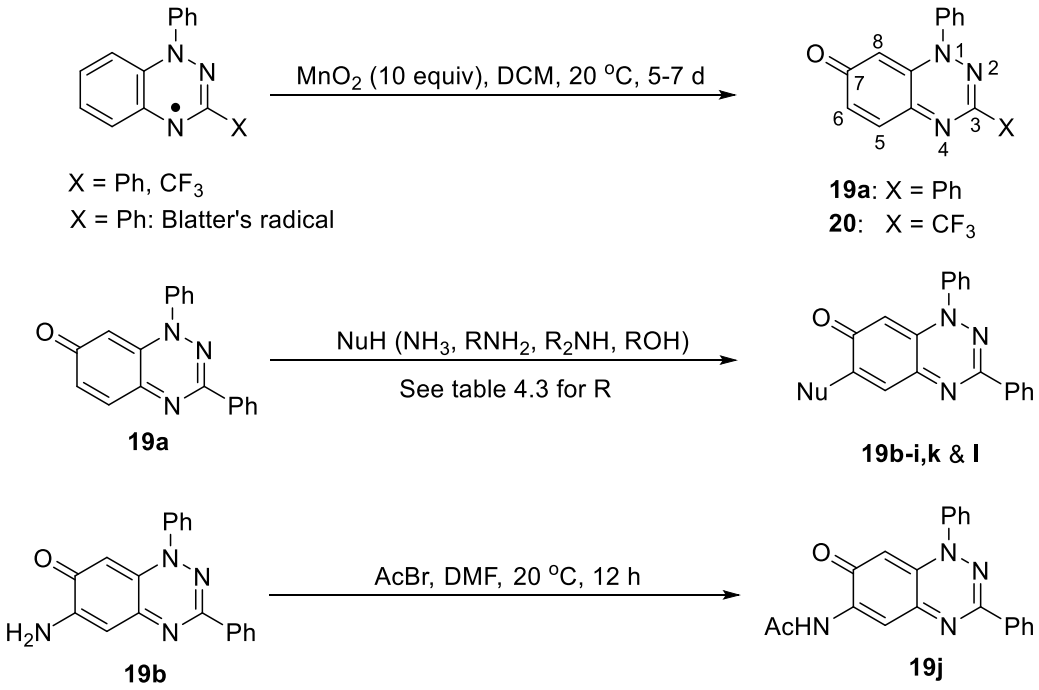
Pleurotin

Benzo[*e*][1,2,4]triazin-7-ones: New thioredoxin reductase inhibitors and comparisons of anti-cancer activity with pleurotin,

Robert Coyle, Martin Sweeney, Andrey A. Berezin, Daniele Lo Re, Panayiotis A. Koutentis, Michael P. Carty and Fawaz Aldabbagh

4.1 Introduction

4.1.1 Synthesis of benzo[*e*][1,2,4]triazin-7-ones

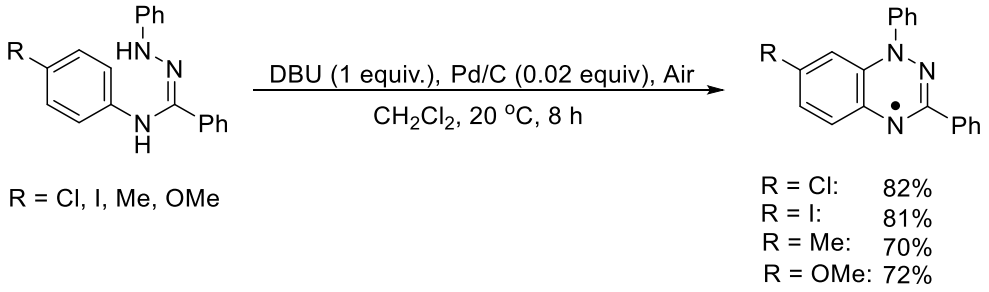


Scheme 4.1 Synthesis of benzotriazinones **19a** and **20** from benzotriazinyl radicals *via* oxidation with MnO_2 and conversion of benzotriazinone **19a** into 6-substituted analogues **19b-l**

First identified by Huisgen and Wulff in the late 1960s,[92] and isolated in 1980,[93] the rich chemistry of 1,3-diphenylbenzo-[*e*][1,2,4]triazin-7-ones **19** has only recently been explored.[94-96]

1,3-Diphenyl- and 1-phenyl-3-(trifluoromethyl)benzo[*e*][1,2,4]triazin-7(1*H*)-ones (**19a** and **20**) were prepared by mild oxidation of the readily available 1,3-diphenyl- and 1-phenyl-3-(trifluoromethyl)-1,4-dihydro-benzo[*e*][1,2,4]triazin-4-yl radicals [94,97] using MnO_2 (10 equiv) in DCM at *ca.* 20 °C (Scheme 4.1).

Described as indefinitely stable[98] benzotriazin-4-yl radicals such as Blatter's radical have recently been prepared in high yields *via* oxidative cyclisation using Pd-C and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in an air atmosphere from *N*-phenylamidrazone (Scheme 4.2).[94]



Scheme 4.2 Synthesis of various 1,3-diphenyl-1,4-dihydro-1,2,4-benzotriazin-4-yls from *N*-phenylamidrazones

Treatment of 1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (**19a**)[95,96] with a series of nitrogen and oxygen nucleophiles subsequently gave the corresponding 6-substituted benzotriazinones **19b-i**,**k** and **19l**,[96,99,100] while the 6-acetamido derivative **19j** was prepared from acetylation of the 6-aminobenzotriazinone **19b** using acetyl bromide in DMF, according to reported procedures[95,96,99-101] (Scheme 4.1).

4.1.2 Biological activity of 1,3-diphenylbenzo-[*e*][1,2,4]-triazine-7-(1*H*)ones and the link to thioredoxin reductase (TrxR)

Triazin-7-ones **19** (Figure 4.1) and derivatives have lately been implicated as multi-target inhibitors in Alzheimer's disease of beta-amyloid (Aβ) aggregation and acetyl-(AChE)/butyryl- (BChE) cholinesterase.[99]

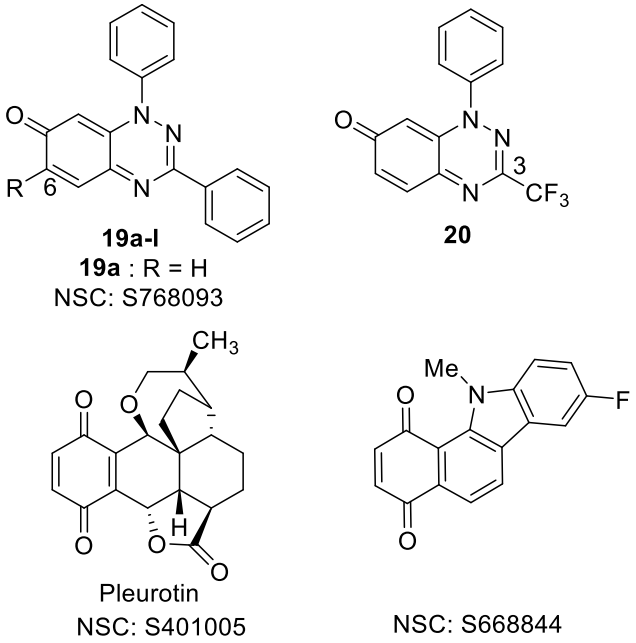


Figure 4.1 1,3-Diphenylbenzo-[*e*][1,2,4]-triazine-7-(1*H*)ones **19a-1** and 1-phenyl-3-(trifluoromethyl)-benzo[*e*][1,2,4]triazin-7(1*H*)-one **20** with correlated compounds pleurotin and 8-fluoro-11-methyl-1*H*-benzo[a]carbazole-1,4(11*H*)-dione using NCI COMPARE analysis

Scaffold **19** contains a highly conjugated iminoquinone motif. Recently an iminoquinone derivative of imidazo[5,4-*f*]benzimidazoles was shown to be a potent anti-cancer compound.[14,20]

Specificity of the latter towards NAD(P)H:quinone oxidoreductase 1 (NQO1) expression was demonstrated using COMPARE analysis of toxicity towards the 60 cell lines at the National Cancer Institute (NCI) Development Therapeutics Program (DTP) and using computational docking of iminoquines and quinones into the enzyme active site.[20]

We now report COMPARE analysis of toxicity of parent triazin-7-one **19a** leading to alternative correlations to synthetic and biomolecules, including the discovery of a very strong correlation to the naturally occurring antibiotic, pleurotin. This *para*-quinone with perhydroanthracene core was first isolated in the 1940s by Robbins *et al*. from the basidiomycete; Pleurotus griseus.[102] Though, pleurotin has been synthesized,[103] Shipley *et al.* reported a multi-gram fermentation process using *H. atrocaerulea* for supply of pleurotin to the NCI (LC_{50} of 42 mM by NCI).[104]

Pleurotin possesses antibacterial,[102] antifungal,[105] and anti-cancer activity, including inhibiting the hypoxia-induced factor (HIF-1α); a transcription factor associated with many aspects of tumour growth.[106] The underlying pathway to much of this antibiotic and anticancer activity is pleurotin's ability to act as a potent inhibitor (0.17 μM) of thioredoxin protein (Trx)-thioredoxin reductase (TrxR) system.[107,108]

Earlier reports more specifically describe pleurotin as an irreversible inhibitor of TrxR with a K_i of 0.28 μM.[23,106] TrxR is flavoprotein homodimer with each monomer containing FAD prosthetic group, NADPH binding domain, and a redox-active selenothiol active site.[109,110] TrxR is the only known enzyme to reduce Trx protein, which in turn provides reducing equivalents for a number of essential redox-dependent cellular processes, such as H_2O_2 metabolism, sulfate assimilation, DNA-signalling and signal transduction.[111,112]

Trx protein is however over-expressed in a number of cancers,[113] and is associated with increased cell proliferation, inhibition of apoptosis, and decreased patient survival.[111] Further the reduced form of Trx protein inhibits the tumour suppressor protein PTEN (protein tyrosine phosphatase and tensin homolog).[114,115]

Mutations in PTEN occur in a number of cancers, including in a number of prostate and breast cancer cell lines.[116] Thus negative regulation of Trx protein through TrxR inhibition is a highly significant strategy for the discovery of new anticancer agents.

The toxicity of 1,3-diphenylbenzo-[*e*][1,2,4]triazin-7-ones **19a-l** with variable substitution at C-6 and compound **20** where the 3-phenyl is replaced by a trifluoromethyl substituent is presented in order to determine key-structure activity relationships (Fig 4.1).

4.2 Results and discussion

4.2.1 Developmental Therapeutic Program (DTP) National Cancer Institute (NCI) 60 human tumour cell line screen and COMPARE analysis.

One dose (10μm) mean graph data of triazin-7-one **19a** showed strong growth inhibition against a number of cancer cell lines, particularly leukaemia, colon, melanoma and renal (Fig 4.2).

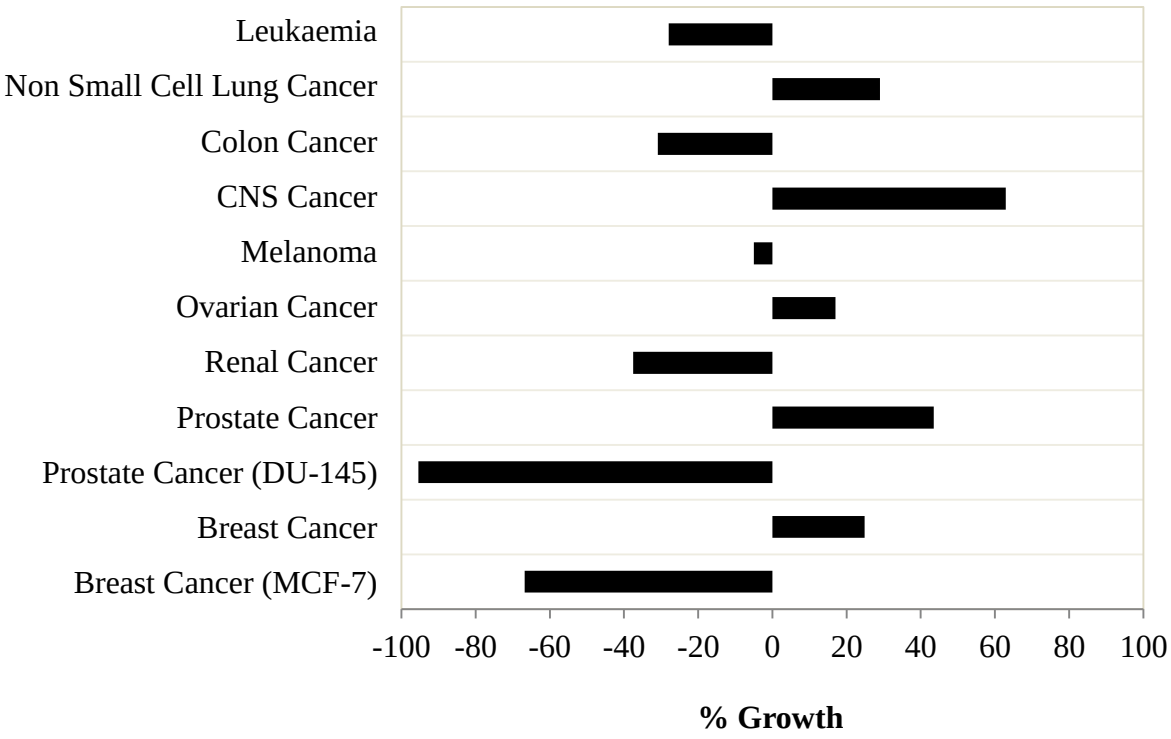


Figure 4.2 Summary of DTP NCI-60 single dose (10μm) screening results for compound **19a** expressed as average percent growth of each cancer type

The variable toxicity profile resulted in compound **19a** being selected for five dose testing; establishing the GI_{50}, LC_{50} and TGI. Naturally occurring anti-cancer agent pleurotin had the highest correlation coefficient (out of ~70000 compounds) in the NCI database to triazine **19a** at 0.84 (Table 4.1). Further a very strong correlation was noted between triazin-7- one **19a** (0.80) and carbazole *para*-quinone (NSC S668844, Figure 4.1), which was also strongly associated to pleurotin (0.87) indicating potential common mechanisms of action.

Entry	Compound	Pleurotin	NSC S668844
1	**19a**	0.84	0.80
2	Pleurotin	—	0.87

Table 4.1 COMPARE analysis to strongly correlated synthetic compounds in the NCI database expressed as Pearson correlation coefficients.

A negative correlation was obtained between compounds **19a**, pleurotin and NSC S668844 with TrxR (TXNRD1), indicating the three compounds exert a greater cytotoxic effect in cell lines with reduced TrxR activity. Medium to strong correlations (0.41-0.61) for all three compounds (**19a**, NSC S668844 and pleurotin) to alternative cancer markers (Table 4.2); the mitogen-activated protein kinase MAPK14 (also known as p38α) and high-mobility group AT-hook 2 (HMGA2) were obtained.

Entry	Compound	Biological (Cancer) Markers		
		MAPK14	HMGA2	TXNRD1
1	**19a**	0.45	0.50	-(0.25)
2	Pleurotin	0.61	0.41	-(0.21)
3	NSC S668844	0.60	0.56	-(0.22)

Table 4.2 COMPARE analysis to strongly correlated biological markers MAPK14 and HMGA2 in the NCI database expressed as Pearson correlation coefficients.

MAPKs form part of cellular signal pathways activated in response to extracellular stresses, although the MAPK pathway is also concerned with cell survival, differentiation and immune response.[117] A literature link between TrxR and MAPK exists in that PTEN tumour-suppressor protein inhibition (stimulated by the reduced form of Trx)[114,115] is reported, as a downstream blocker of the MAPK pathway in breast and prostate cancers.[118,119] The recent discovery of the 1,3-diphenylbenzo-[*e*][1,2,4]triazin-7-one scaffold in inhibition of Alzheimer's disease (AD)[99] can be linked to compound **19a** correlations with MAPK14 (Table 4.2); in that p38 MAPK-

signalling is a widely accepted cascade contributing to neurodegenerative processes of AD.[120-122]

HMGA2 gene expression is negligible in adult human healthy tissues with heightened expression occurring in a variety of cancers.[123,124] The precise mechanisms by which HMGA2 contributes to cancer are unknown, but its associated with metastasis and poor prognosis for the patient.

4.2.2. Cytotoxicity against normal and cancer cell lines using the MTT assay

Toxicity towards the prostate DU-145 and breast MCF-7 cancer cell lines was investigated further using benzo-[*e*][1,2,4]triazin-7-one analogues using the MTT assay. Both cell lines form part of the NCI-60 human tumour cell line screen with the response of a normal human-skin fibroblast (GM00637) cell line determined for comparison purposes.

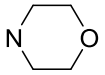
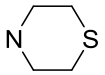
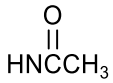
Pleurotin displayed sub-micromolar toxicity towards all three cell lines investigated with parent 1,3-diphenylbenzo-[*e*][1,2,4]triazin-7-ones **19a** showing comparable toxicity (Table 5.3). Substitution at the 6-position of the 1,3-diphenylbenzo-[*e*][1,2,4]triazin-7-one scaffold with amine, amide and alkoxy substituents was investigated (compounds **19a-l**).

Substitution with methoxy- and ethoxy-groups in compounds **19k** and **19l** and amide **19j** decreased toxicity to negligible values. The methoxy substituent (OMe) on indolequinones has previously been shown to lead to significant reductions in toxicity towards normal cells in comparison to its replacement with an aziridinyl substituent, with the trends in toxicity correlated to a less electron-affinic property, as a result of OMe.[125-126]

Cyclic amine substituents in **19f-19i** (pyrrolo-, piperidino-, morpholino-, thiomorpholino-) led to toxicity values 1.5-13 times smaller than the parent **19a**. For cyclic amine substituents, morpholino- and thiomorpholino of **19h** and **19l** toxicity is reduced in comparison to piperidinyl analogue **19g**.

Among the amines **19b-19e**, primary amine substituents in **19c** and **19d** gave sub-micromolar toxicity across all three cell lines with ethylamino- in **19d** resulting in similar potency to the parent **19a**, with an approximately two-fold reduced toxicity in comparison to **19a** towards the MCF-7 cell line.

The most selective compound towards the two cancer lines investigated was however compound **20**, where the 3-phenyl is replaced by a trifluoromethyl substituent. Benzo-[*e*][1,2,4]triazin-7-one **20** showed sub-micromolar toxicity towards the prostate (DU 145) and breast (MCF-7) cancer cell lines which were about 2-3 fold greater than towards the normal human cell line (GM00637).

Compd[c]	R	Cell Lines		
		GM00637	DU-145	MCF-7
Pleurotin		0.51 ± 0.12	0.43 ± 0.06	0.28 ± 0.03
19a	H	0.23 ± 0.01	0.23 ± 0.03	0.81 ± 0.08
19b	NH_2	2.04 ± 0.21	1.83 ± 0.08	0.95 ± 0.03[b]
19c	NHMe	0.93 ± 0.03	0.98 ± 0.06	0.69 ± 0.12[b]
19d	NHEt	0.24 ± 0.01	0.22 ± 0.01	1.62 ± 0.24
19e	NEt_2	2.73 ± 0.36	3.11 ± 0.08	>5.0
19f		1.79 ± 0.12	2.46 ± 0.19	0.36 ± 0.08[b]
19g		1.19 ± 0.02	0.61 ± 0.05	1.98 ± 0.06
19h		2.29 ± 0.06	3.21 ± 0.37	2.37 ± 0.07
19i		1.63 ± 0.31	1.22 ± 0.06	0.97 ± 0.16[b]
19j		>5.0	>5.0	>5.0
19k	OMe	>5.0	>5.0	>5.0
19l	OEt	>5.0	>5.0	>5.0[b]
20		1.61 ± 0.21	0.85 ± 0.04	0.60 ± 0.13

[a] IC_{50}(μM) represents the compound 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] IC_{50} values obtained by Martin Sweeney. [c] Compounds **19a**-**19l** & **20** were obtained from P. A. Koutentis, Associate Professor, Department of Chemistry, University of Cyprus

Table 4.3 Cytotoxicity evaluation using the MTT assay: IC_{50} values (μM)[a]

4.3. Conclusions

Developmental Therapeutic Program (DTP) National Cancer Institute (NCI) 60 human tumour cell line screen and COMPARE analysis of 1,3-diphenylbenzo-[*e*][1,2,4]-triazine-7-(1*H*)one yielded an excellent correlation to the natural occurring antibiotic pleurotin, and to cancer markers MAPK14 and HMGA2.

MTT cytotoxicity evaluations determined substitution at the 6-position of diphenylbenzo-[*e*][1,2,4]-triazine-7-(1*H*)ones led to reduce cytotoxicity across all three cell-lines with ethylamine substituted **19d**, the single exception. A large cytotoxicity drop-off was noted for alkoxy and amide substituted benzo-[*e*][1,2,4]-triazine-7-(1*H*)ones **19j-l**.

4.4. Future work

Given the now described strong correlation to pleurotin of triazin-7-one **19a**, an examination of the inhibitory activity of the latter compound and analogues towards thioredoxin reductase (TrxR) using the purified human enzyme is required.

The first comprehensive computational docking study of pleurotin into the human TrxR active site is envisioned, along with that of the selected benzo-[*e*][1,2,4]triazin-7-ones, in order to determine the substrate structural requirements for efficient TrxR reduction, and to assess the relationship between cytotoxicity and protein-ligand interactions.

Potent triazine-7ones **19d** and **20** will now be submitted to the (NCI) 60 human tumour cell line screen.

Chapter 5

Experimental

5.1 General

5.1.1 Instrumental

Melting points were determined on a Stuart Scientific melting point apparatus SMP3. IR spectra were obtained using a Perkin-Elmer Spectrum 1000 FT-IR spectrophotometer with ATR accessory. NMR spectra were recorded using a JOEL GXFT 400 MHz instrument equipped with a DEC AXP 300 computer workstation. Chemical shifts are reported relative to trimethylsilane as internal standard with NMR assignments supported by DEPT for all compounds and ^{1}H-^{13}C NMR 2D spectra for all compounds. Coupling constants (*J*) are expressed in Hertz (Hz). High resolution mass spectra (HRMS) for all compounds were carried out using electrospray ionization (ESI) on a Waters LCT Premier XE spectrometer by manual peak matching. The precision of all accurate mass measurements is better than 5 ppm.

5.1.2 Methods and Materials

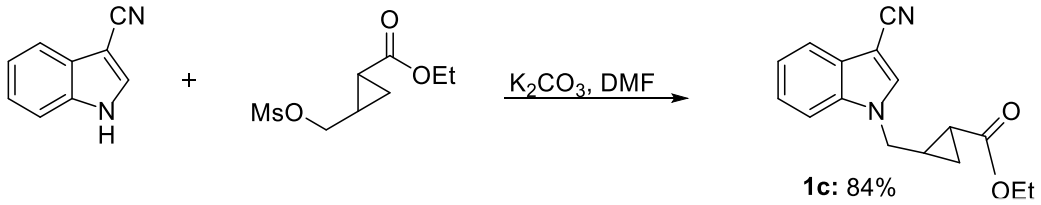
All commercially available reagents were obtained from Sigma-Aldrich. Ethyl *trans*-2′-{[(methylsulfonyl)oxy]methyl}cyclopropanecarboxylate, ethyl 2-(2-bromoethyl)cyclopropanecarboxylate and ethyl 2-(3-bromopropyl) cyclopropane-carboxylate were prepared in accordance with a previously reported preocedures.[48,49] Solvents were purified and dried prior to use according to conventional methods. All reactions were carried out under a nitrogen atmosphere apart from those involving aqueous solutions. NaH was obtained as 60% dispersion in oil and used without further purification. Monitoring of reactions by Thin Layer Chromatography (TLC) was carried out on aluminium-backed plates coated with silica gel (Merck Kieselgel 60 F_{254}). Column chromatography were carried out using Merck Kieselgel silica gel 60 (particle size 0.040-0.063 mm)

5.2 Experimental for Chapter 2

General Procedure for *N*-Alkylation of Indole-3-carbonitrile (Procedure 1.)

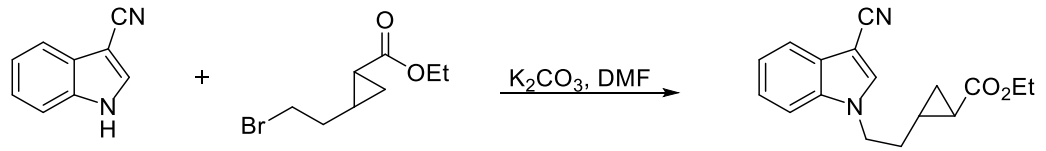
Indole-3-carbonitrile (0.700 g, 4.92 mmol), mesylate (1.175 g, 5.30 mmol) or bromide (5.30 mmol) and K_2CO_3 (1.955 g, 14.15 mmol) in DMF (125 mL) were heated at 100 °C for 16 h. The mixture was filtered, evaporated, dissolved in $CHCl_3$ (250 mL), and washed with water (3 x 100 mL). The organic extract was dried (Na_2SO_4), evaporated, and the residue purified by column chromatography using silica gel as absorbent with a gradient elution of hexanes and CH_2Cl_2.

Experiment 1: Ethyl *trans*-2′-[(3-cyano-1*H*-indol-1-yl)methyl]cyclopropane carboxylate (1c)



In accordance with procedure 1 gave (1.112 g, 84%), white solid, mp 85-86 ˚C, R_f 0.25 **(**CH_2Cl_2); ν_{max} (neat, cm^{-1}) 2983, 2218 (CN), 1719 (C=O), 1531, 1467, 1451, 1415, 1392, 1367, 1350, 1266, 1175, 1089, 1042; δ_H (400 MHz, $CDCl_3$) 0.95 (1H, ddd, *J* 5.0, 6.2, 8.5, 3′-H), 1.23 (3H, t, *J* 7.1, CH_3), 1.31 (1H, ddd, *J* 5.0, 5.0, 9.2, 3′-H), 1.67-1.71 (1H, m, 1′-H), 1.85-1.94 (1H, m, 2′-H), 4.02-4.17 (4H, m), 7.25-7.35 (2H, m), 7.40 (1H, d, *J* 7.8, 7-H), 7.65 (1H, s, 2-H), 7.73 (1H, d, *J* 7.8, 4-H); δ_C (100 MHz, $CDCl_3$) 14.0 (3′-CH_2), 14.3 (CH_3), 19.7 (1′-CH), 21.1 (2′-CH), 49.3 (NCH_2), 61.1 (OCH_2), 86.3 (3-C), 110.5 (7-CH), 115.9 (CN), 120.0 (4-CH), 122.4, 124.1 (5,6-CH), 127.9 (C), 134.3 (2-CH), 135.5 (C), 172.7 (C=O); HRMS (ESI): found $M+H^+$, 269.1283. $C_{16}H_{17}N_2O_2$ requires 269.1290.

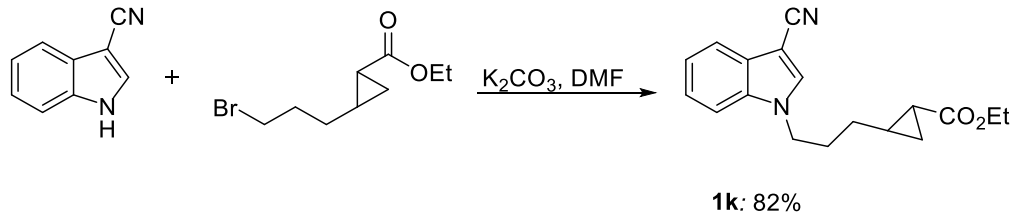
Experiment 2: Ethyl *trans*-2′-[2-(3-cyano-1*H*-indol-1-yl)ethyl]cyclopropane carboxylate (1g)



1g: 78%

In accordance with procedure 1 gave (1.086 g, 78%), yellow oil, R_f 0.28 **(**CH_2Cl_2); ν_{max} (neat, cm^{-1}) 2981, 2216 (CN), 1716 (C=O), 1532, 1468, 1411, 1394, 1368, 1336, 1266, 1176, 1087, 1045; δ_H (400 MHz, $CDCl_3$) 0.51 (1H, ddd, *J* 4.3, 6.2, 8.2, 3′-H), 1.02 (1H, ddd, *J* 4.3, 4.3, 8.7, 3′-H), 1.10-1.20 (5H, m, 1′-H, 2′-H & CH_3), 1.65-1.71 (1H, m), 1.76-1.83 (1H, m), 3.93-4.06 (2H, m, OCH_2), 4.18 (2H, t, *J* 6.9, NCH_2), 7.16-7.25 (2H, m), 7.32 (1H, d, *J* 7.8, 7-H), 7.53 (1H, s, 2-H), 7.64 (1H, d, *J* 7.8, 4-H); δ_C (100 MHz, $CDCl_3$) 13.8 (CH_3), 14.1 (3′-CH_2), 19.2, 19.3 (1′,2′-CH), 32.6 (CH_2), 46.3 (NCH_2), 60.3 (OCH_2), 85.1 (3-C), 110.2 (7-CH), 115.6 (CN), 119.4 (4-CH), 121.7, 123.4 (5,6-CH), 127.5 (C), 134.6 (2-CH), 134.8 (C), 173.1 (C=O); HRMS (ESI): found $M+H^+$, 283.1441. $C_{17}H_{19}N_2O_2$ requires 283.1447.

Experiment 3: Ethyl *trans*-2′-[3-(3-cyano-1*H*-indol-1-yl)propyl]cyclopropane carboxylate (1k)



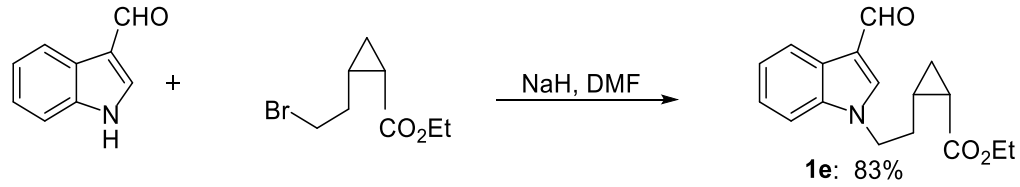
1k: 82%

In accordance with procedure 1 gave (1.196 g, 82%), yellow oil, R_f 0.45 **(**CH_2Cl_2); ν_{max} (neat, cm^{-1}) 2983, 2218 (CN), 1719 (C=O), 1532, 1468, 1411, 1396, 1367, 1335, 1269, 1173, 1086, 1048; δ_H (400 MHz, $CDCl_3$) 0.64-0.69 (1H, m, 3′-H), 1.15-1.19 (1H, m, 3′-H), 1.25 (3H, t, *J* 7.1, CH_3), 1.29-1.37 (4H, m), 1.95-2.03 (2H, m), 4.07-4.13 (2H, m, OCH_2), 4.18 (2H, t, *J* 7.1, NCH_2), 7.26-7.40 (3H, m), 7.59 (1H, s, 2-H), 7.76 (1H, d, *J* 7.8, 4-H); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 15.3 (3′-CH_2), 20.2, 21.7 (1′,2′-CH), 29.4, 30.1 (CH_2), 46.7 (NCH_2), 60.6 (OCH_2), 85.8 (3-C), 110.4 (7-CH), 115.9 (CN), 120.1 (4-CH), 122.1, 123.8 (5,6-CH), 127.9 (C), 134.4 (2-CH), 135.2 (C), 174.0 (C=O); HRMS (ESI): found $M+H^+$, 297.1602. $C_{18}H_{21}N_2O_2$ requires 297.1603.

General Procedure for *N*-Alkylation of Indole-3-carbaldehyde and benzimidazoles (Procedure 2.)

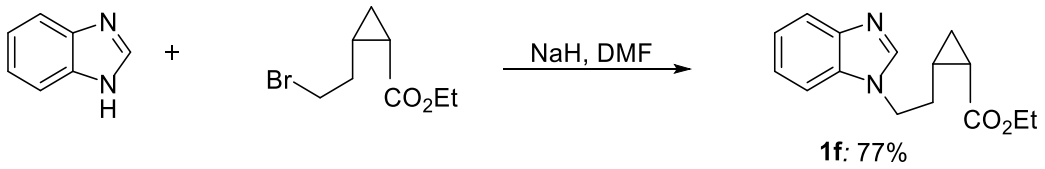
Indole-3-carbaldehyde or benzimidazoles (8.50 mmol) and NaH (0.224 g, 9.35 mmol) in DMF (25 mL) were heated at 100 °C for 30 min. A solution of mesylate (2.08 g, 9.35 mmol) or bromide (9.35 mmol) in DMF (10 mL) was added, and the mixture stirred at room temperature for 16 h. The mixture was evaporated, dissolved in $CHCl_3$ (50 mL), and washed with water (3 x 25 mL). The organic extract was dried (Na_2SO_4), evaporated and the residue purified by column chromatography using silica gel as absorbent with a gradient elution of hexanes and EtOAc.

Experiment 4: Ethyl *cis*-2′-[2-(3-formyl-1*H*-indol-1-yl)ethyl]cyclopropane carboxylate (1e)



In Accordance with procedure 2 gave (2.013 g, 83%), yellow oil, R_f 0.22 (CH_2Cl_2); ν_{max} (neat, cm^{-1}) 1714 (C=O ester), 1656 (C=O aldehyde), 1613, 1529, 1466, 1398, 1380, 1269, 1168, 1140, 1039; δ_H (400 MHz, $CDCl_3$) 0.92 (1H, ddd, *J* 5.3, 5.3, 7.1, 3′-H), 1.01-1.06 (1H, m, 3′-H), 1.09-1.18 (1H, m, 2′-H), 1.24 (3H, t, *J* 7.2, CH_3), 1.69 (1H, ddd, *J* 5.3, 8.3, 8.3, 1′-H), 2.12-2.27 (2H, m), 3.94-4.03 (1H, m, OCH*H*), 4.03-4.12 (1H, m, OC*H*H), 4.20 (2H, t, *J* 6.9, NCH_2), 7.28-7.36 (2H, m), 7.39-7.41 (1H, m, 7-H), 7.72 (1H, s, 2-H), 8.28-8.31 (1H, m, 4-H), 10.00 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$) 13.3 (3′-CH_2), 14.4 (CH_3), 17.8 (1′-CH), 18.8 (2′-CH), 27.3 (CH_2), 47.3 (NCH_2), 60.8 (OCH_2), 110.2 (7-CH), 118.3 (C), 122.2 (4-CH), 123.0, 124.1 (5,6-CH), 125.5, 137.3 (C), 138.4 (2-CH), 172.7 (COOEt), 184.6 (CHO); HRMS (ESI): found $M+H^+$, 286.1447. $C_{17}H_{20}NO_3$ requires 286.1443.

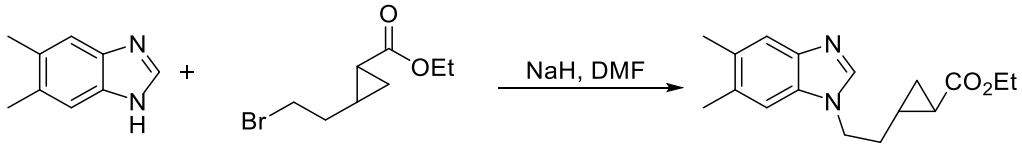
Experiment 5: Ethyl *cis*-2′-[2-(1*H*-benzimidazol-1-yl)ethyl]cyclopropane carboxylate (1f)



1f: 77%

In accordance with procedure 2 gave (1.691 g, 77%), yellow oil, R_f 0.51 (EtOAc); ν_{max} (neat, cm^{-1}) 1724 (C=O), 1610, 1499, 1456, 1398, 1383, 1284, 1178, 1089; δ_H (400 MHz, $CDCl_3$) 0.90 (1H, q, *J* 5.2, 3′-H), 0.98-1.04 (1H, m, 3′-H), 1.05-1.15 (1H, m, 2′-H), 1.23 (3H, t, *J* 7.2, CH_3), 1.68 (1H, ddd, *J* 5.2, 8.4, 8.4, 1′-H), 2.08-2.23 (2H, m), 3.95-4.03 (1H, m, OCH*H*), 4.03-4.11 (1H, m, OC*H*H), 4.18 (2H, t, *J* 6.9, NCH_2), 7.24-7.31 (2H, m), 7.42 (1H, d, *J* 7.6, 7-H), 7.78 (1H, d, *J* 7.1, 4-H), 7.91 (1H, s, 2-H); δ_C (100 MHz, $CDCl_3$) 13.2 (3′-CH_2), 14.4 (CH_3), 17.8 (1′-CH), 18.8 (2′-CH), 27.3 (CH_2), 45.0 (NCH_2), 60.7 (OCH_2), 109.9 (7-CH), 120.4 (4-CH), 122.2, 123.0 (5,6-CH), 133.9 (C), 143.1 (2-CH), 143.8 (C), 172.8 (C=O); HRMS (ESI): found $M+H^+$, 259.1439. $C_{15}H_{19}N_2O_2$ requires 259.1447.

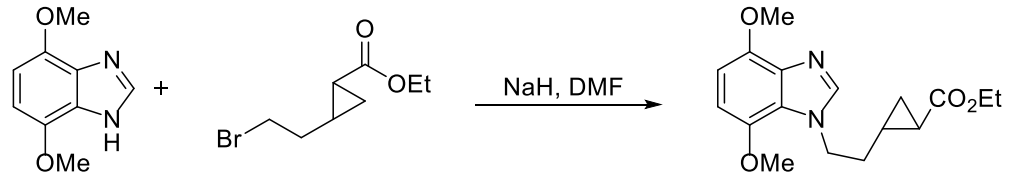
Experiment 6: Ethyl *trans*-2′-[2-(5,6-dimethyl-1*H*-benzimidazol-1-yl)ethyl] cyclopropanecarboxylate (1h)



1h: 81%

In accordance with procedure 2 gave (1.980 g, 81%), yellow oil, R_f 0.41 (EtOAc); ν_{max} (neat, cm^{-1}) 1717 (C=O), 1498, 1470, 1451, 1411, 1370, 1329, 1274, 1204, 1177, 1086, 1044; δ_H (400 MHz, $CDCl_3$) 0.50-0.55 (1H, m, 3′-H), 1.04-1.09 (1H, m, 3′-H), 1.16 (3H, t, *J* 7.1, CH_3), 1.21-1.26 (2H, m, 1′, 2′-H), 1.69-1.79 (2H, m), 2.30 (3H, s, CH_3), 2.32 (3H, s, CH_3), 3.97-4.03 (2H, m, OCH_2), 4.12 (2H, t, *J* 6.9, NCH_2), 7.06 (1H, s, 7-H), 7.50 (1H, s, 4-H), 7.69 (1H, s, 2-H); δ_C (100 MHz, $CDCl_3$) 13.9 (CH_3), 14.4 (3′-CH_2), 19.4, 19.5 (1′,2′-CH), 20.0, 20.3 (CH_3), 32.9 (CH_2), 44.2 (NCH_2), 60.3 (OCH_2), 109.4 (7-CH), 120.1 (4-CH), 130.6, 131.7, 131.9 (all C), 141.9 (2-CH), 142.3 (C), 173.3 (C=O); HRMS (ESI): found $M+H^+$, 287.1759. $C_{17}H_{23}N_2O_2$ requires 287.1760.

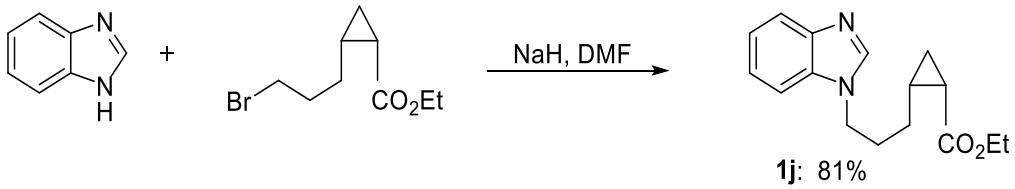
Experiment 7: Ethyl *trans*-2′-[2-(4,7-dimethoxy-1*H*-benzimidazol-1-yl)ethyl] cyclopropanecarboxylate (1i)



1i: 73%

In accordance with procedure 2 gave (1.980 g, 73%), yellow oil, R_f 0.50 (EtOAc); ν_{max} (neat, cm^{-1}) 1751 (C=O), 1523, 1456, 1443, 1371, 1265, 1207, 1116, 1088, 1077, 1038; δ_H (400 MHz, $CDCl_3$) 0.58 (1H, ddd, *J* 4.6, 6.4, 8.2 Hz, 3′-H), 1.12 (1H, ddd, *J* 4.6, 4.6, 8.9, 3′-H), 1.23 (3H, t, *J* 7.1, CH_3), 1.27-1.37 (2H, m, 1′,2′-H), 1.77-1.88 (2H, m), 3.89 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 4.03-4.12 (2H, m, NCH_2), 4.36-4.52 (2H, m, OCH_2), 6.52 (1H, d(AB-q), *J* 8.4, 5,6-H), 6.56 (1H, d(AB-q), *J* 8.4, 5,6-H), 7.70 (1H, s, 2-H); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 14.8 (3′-CH_2), 19.6, 19.8 (1′,2′-CH), 35.2 (CH_2), 46.6 (NCH_2), 55.7, 56.1 (OCH_3), 60.6 (OCH_2), 101.8, 103.1 (5,6-CH), 124.7, 136.2, 141.6 (all C), 142.2 (2-CH), 146.3 (C), 173.9 (C=O); HRMS (ESI): found $M+H^+$, 319.1654. $C_{17}H_{23}N_2O_4$ requires 319.1658.

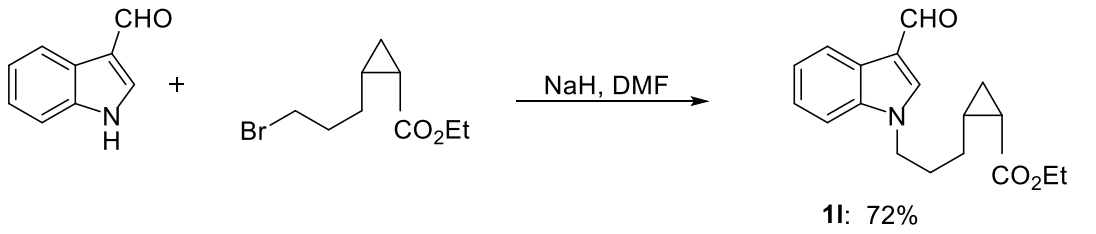
Experiment 8: Ethyl *cis*-2′-[3-(1*H*-benzimidazol-1-yl)propyl]cyclopropane carboxylate (1j)



1j: 81%

In accordance with procedure 2 gave (1.880 g, 81%), yellow oil, R_f 0.35 (EtOAc); ν_{max} (neat, cm^{-1}) 1717 (C=O), 1613, 1492, 1456, 1381, 1328, 1285, 1254, 1166, 1090, 1044; δ_H (400 MHz, $CDCl_3$) 0.85-0.88 (1H, m, 3′-H), 0.97 (1H, ddd, *J* 4.6, 8.2, 8.2, 3′-H), 1.16 (3H, t, *J* 7.3, CH_3), 1.12-1.21 (1H, m), 1.50-1.66 (3H, m), 1.77-1.92 (2H, m), 4.01 (2H, q, *J* 7.3, OCH_2), 4.09 (2H, t, *J* 7.3, NCH_2), 7.19-7.25 (2H, m), 7.31-7.34 (1H, m, 7-H), 7.73-7.76 (1H, m, 4-H), 7.82 (1H, s, 2-H); δ_C (100 MHz, $CDCl_3$) 13.6 (3′-CH_2), 14.4 (CH_3), 18.1, 21.0 (1′,2′-CH), 24.5, 29.9 (CH_2), 44.8 (NCH_2), 60.5 (OCH_2), 109.7 (7-CH), 120.4 (4-CH), 122.1, 122.8 (5,6-CH), 133.8 (C), 142.9 (2-CH), 144.0 (C), 172.9 (C=O); HRMS (ESI): found $M+H^+$, 273.1598. $C_{16}H_{21}N_2O_2$ requires 273.1603.

Experiment 9 Ethyl *cis*-2′-[3-(3-formyl-1*H*-indol-1-yl)propyl]cyclopropane carboxylate (1l)



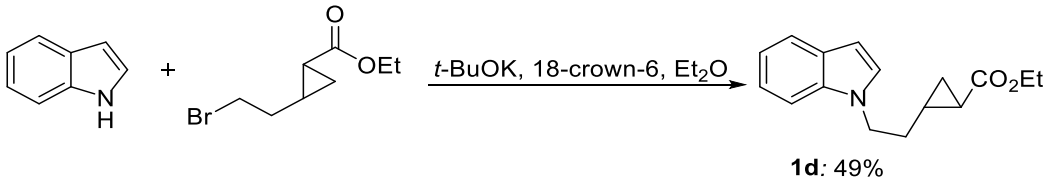
1l: 72%

In accordance with procedure 2 gave (1.840 g, 72%), yellow oil, R_f 0.51 (hexanes-EtOAc 3:2); IR (ν_{max}, neat/cm^{-1}) 2933, 2249, 1718 (C=O ester), 1659 (C=O aldehyde), 1615, 1578, 1533, 1468, 1402, 1389, 1178, 1136, 1095, 1048; δ_H (400 MHz, $CDCl_3$) 0.92 (1H, ddd, *J* 4.6, 6.9, 6.9, 3′-H), 1.03 (1H, ddd, *J* 4.6, 8.2, 8.2, 3′-H), 1.20 (3H, t, *J* 7.1, CH_3), 1.23-1.26 (1H, m, 2′-H), 1.55-1.71 (3H, m), 1.82-2.00 (2H, m), 4.02-4.08 (2H, m, OCH_2), 4.15 (2H, t, *J* 7.3, NCH_2), 7.29-7.33 (3H, m), 7.69 (1H, s, 2-H), 8.27-8.29 (1H, m, 4-H), 9.97 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$) 13.6 (3′-CH_2), 14.4 (CH_3), 18.1, 21.1 (1′,2′-CH), 24.5, 29.9 (CH_2), 47.1 (NCH_2), 60.5 (OCH_2), 110.1 (7-CH), 118.2 (C), 122.2 (4-CH), 123.0, 124.0 (5,6-CH), 125.6 (C), 137.2 (3-C), 138.3 (2-CH), 172.9 (COOEt), 184.6 (CHO); HRMS (ESI): found $M+H^+$, 300.1598. $C_{18}H_{22}NO_3$ requires 300.1600.

General Procedure for *N*-Alkylation of Indole (Procedure 3.)

Indole (0.500 g, 4.26 mmol), *t*-BuOK (0.500 g, 4.46 mmol) and 18-crown-6 (0.120 g, 0.45 mmol) in Et_2O (50 mL) were stirred vigorously at room temperature for 10 min. Ethyl *trans*-2'-(2-bromoethyl)cyclopropanecarboxylate (1.000 g, 4.52 mmol) was added and the reaction stirred at room temperature for 16 h. Water (50 mL) was added, the Et_2O layer extracted, evaporated and purified by column chromatography using silica gel as absorbent with a gradient elution of hexanes and EtOAc.

Experiment 10: Ethyl-*trans*-2'-[2-(1*H*-indol-1-yl)ethyl] cyclopropanecarboxylate (1d)



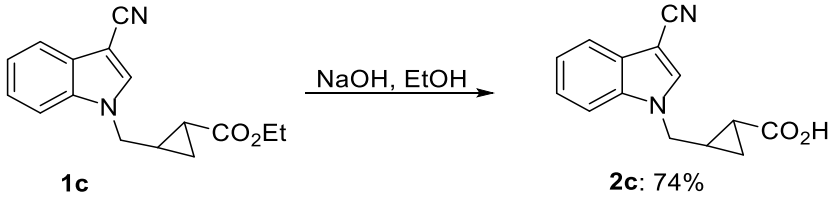
1d: 49%

In accordance with procedure 3 gave (0.537 g, 49%), colourless oil, R_f 0.65 (hexanes-EtOAc 4:1); ν_{max} (neat, cm^{-1}) 1718 (C=O), 1512, 1464, 1411, 1369, 1335, 1314, 1265, 1244, 1201, 1176, 1085, 1045, 1012; δ_H (400 MHz, $CDCl_3$) 0.61 (1H, ddd, *J* 4.6, 6.2, 8.2, 3′-H), 1.13 (1H, ddd, *J* 4.6, 4.6, 8.9, 3′-H), 1.24 (3H, t, *J* 6.8, CH_3), 1.26-1.33 (2H, m, 1′-H & 2′-H), 1.77-1.83 (2H, m), 4.04-4.10 (2H, m, OCH_2), 4.22 (2H, t, *J* 6.8, NCH_2), 6.49 (1H, d, *J* 2.3, 3-H), 7.07-7.12 (2H, m), 7.18-7.22 (1H, m), 7.31-7.33 (1H, m), 7.64 (1H, d, *J* 7.8 Hz); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 14.8 (3′-CH_2), 19.9, 20.1 (1′,2′-CH), 33.6 (CH_2), 45.8 (NCH_2), 60.5 (OCH_2), 101.2 (3-CH), 109.1, 119.1, 121.0, 121.4, 127.7 (all CH), 128.6, 135.8 (C), 173.8 (C=O); HRMS (ESI): found $M+H^+$, 258.1485. $C_{16}H_{20}NO_2$ requires 258.1494.

General Procedure for Hydrolysis of Esters (Procedure 4.)

A mixture of ethyl ester (5.80 mmol) and NaOH (2.5 M, 3.5 mL) in EtOH (30 mL) was refluxed for 4 h. The solution was evaporated, dissolved in water (20 mL) and washed with EtOAc (2 x 10 mL) to remove traces of unreacted ester. The aqueous solution was acidified with HCl (2.8 M) to pH 4, extracted with EtOAc (2 x 30 mL), dried (Na_2SO_4), and evaporated to give the acid.

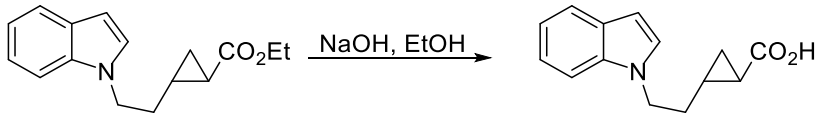
Experiment 11: 2′-[(3-Cyano-1*H*-indol-1-yl)methyl]-*trans*-cyclopropane carboxylic acid (2c)



1c **2c**: 74%

In accordance with procedure 4 gave (1.030 g, 74%), brown solid, mp 59-60 ˚C; ν_{max} (neat, cm^{-1}) 2924, 2218 (CN), 1695 (C=O), 1531, 1466, 1451, 1432, 1392, 1336, 1264, 1230, 1184, 1086, 1024, 1013; δ_H (400 MHz, MeOH–d_4) 1.04 (1H, ddd, *J* 4.6, 6.2, 8.7, 3′-H), 1.19 (1H, ddd, *J* 4.6, 4.6, 9.2, 3′-H), 1.72 (1H, ddd, *J* 4.6, 4.6, 8.7, 1′-H), 1.82-1.91 (1H, m), 4.20 (2H, d, *J* 6.9, NCH_2), 7.23-7.35 (2H, m, 5,6-H), 7.57-7.64 (2H, m, 4,7-H), 7.98 (1H, s, 2-H), OH not observed; δ_C (100 MHz, MeOH–d_4) 14.3 (3′-CH_2), 20.1 (1′-CH), 22.8 (2′-CH), 49.9 (NCH_2), 85.9 (3-C), 112.1 (7-CH), 116.9 (CN), 120.2 (4-CH), 123.3, 124.9 (5,6-CH), 129.1 (C), 136.8 (2-CH), 137.0 (C), 176.8 (C=O); HRMS (ESI): found $M+H^+$, 241.0976. $C_{14}H_{13}N_2O_2$ requires 241.0977.

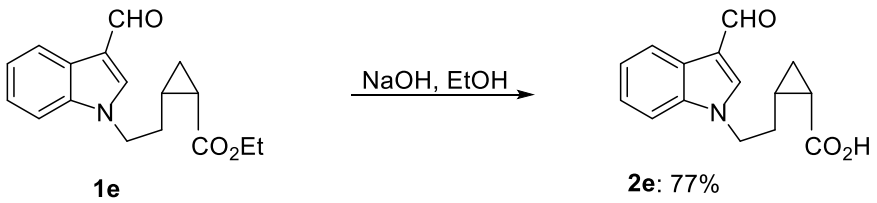
Experiment 12: 2'-[2-(1*H*-indol-1-yl)ethyl]-*trans*-cyclopropanecarboxylic acid (2d)



1d **2d**: 82%

In accordance with procedure 4 gave (1.093 g, 82%), white solid, mp 106-107 ˚C; ν_{max} (neat, cm^{-1}) 2927, 1687 (C=O), 1512, 1463, 1432, 1336, 1314, 1230, 1203, 1086, 1012; δ_H (400 MHz, MeOH–d_4) 0.59 (1H, ddd, *J* 4.4, 6.3, 8.4, 3′-H), 0.97 (1H, ddd, *J* 4.4, 4.4, 8.7, 3′-H), 1.14-1.22 (1H, m), 1.26 (1H, ddd, *J* 4.4, 4.4, 8.4, 1′-H), 1.66-1.82 (2H, m), 4.21 (2H, t, *J* 6.8, NCH_2), 6.39 (1H, dd, *J* 0.7, 3.2, 3-H), 6.96-7.00 (1H, m), 7.08-7.12 (1H, m), 7.14 (1H, d, *J* 3.2, 2-H), 7.34 (1H, dd, *J* 0.7, 8.2, 7-H), 7.50 (1H, d, *J* 7.8, 4-H), OH not observed; δ_C (100 MHz, MeOH–d_4) 14.2 (3′-CH_2), 19.2 (1′-CH), 20.0 (2′-CH), 33.3 (CH_2), 45.2 (NCH_2), 100.6 (3-CH), 109.0 (7-CH), 118.7, 120.4, 120.9 (all CH), 127.7 (2-CH), 128.8, 136.1 (C), 176.6 (C=O). HRMS (ESI): found $M+H^+$, 230.1188. $C_{14}H_{16}NO_2$ requires 230.1181.

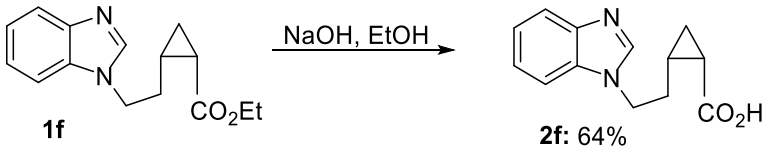
Experiment 13: 2′-[2-(3-Formyl-1*H*-indol-1-yl)ethyl]-*cis*-cyclopropane carboxylic acid (2e)



1e **2e**: 77%

In accordance with procedure 4 gave (1.149 g, 77%), brown solid, mp 133-134 ˚C; ν_{max} (neat, cm^{-1}) 1699 (C=O acid), 1605 (C=O aldehyde), 1572, 1532, 1469, 1456, 1393, 1302, 1274, 1206, 1175, 1140, 1100, 1074, 1044, 1024, 1014; δ_H (400 MHz, $CDCl_3$) 0.95-1.00 (1H, m), 1.12-1.14 (1H, m), 1.18-1.28 (1H, m), 1.74 (1H, ddd, *J* 5.5, 8.3, 8.3, 1′-H), 2.13-2.29 (2H, m), 4.22 (2H, t, *J* 6.8, NCH_2), 7.27-7.34 (2H, m), 7.36-7.40 (1H, m, 7-H), 7.73 (1H, s, 2-H), 8.27-8.30 (1H, m, 4-H), 9.98 (1H, s, CHO), OH not observed; δ_C (100 MHz, $CDCl_3$) 14.0 (3′-CH_2), 17.5, 19.6 (1′,2′-CH), 27.3 (CH_2), 46.9 (NCH_2), 110.1 (7-CH), 118.0 (C), 122.0 (4-CH), 123.0, 124.0 (5,6-CH), 125.3 (C), 137.2 (2-CH), 138.7 (C), 178.3 (COOH), 184.9 (CHO); HRMS (ESI): found $M+H^+$, 258.1137. $C_{15}H_{16}NO_3$ requires 258.1130.

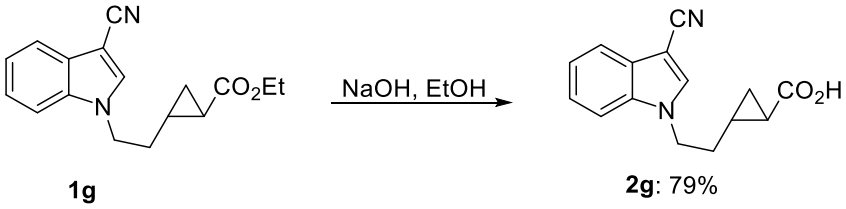
Experiment 14: 2′-[2-(1*H*-benzimidazol-1-yl)ethyl]-*cis*-cyclopropane carboxylic acid (2f).



1f **2f:** 64%

In accordance with procedure 4 gave (0.855 g, 64%), yellow solid, mp 155-156 ˚C; ν_{max} (neat, cm^{-1}) 1696 (C=O), 1608, 1496, 1456, 1380, 1322, 1304, 1274, 1261, 1183, 1140, 1079, 1001; δ_H (400 MHz, DMSO–d_6) 0.60-0.64 (1H, m, 3′-H), 0.89 (1H, ddd, *J* 4.1, 8.2, 8.2, 3′-H), 1.07-1.18 (1H, m), 1.57-1.63 (1H, m), 1.94-2.00 (2H, m), 4.14-4.30 (2H, m, NCH_2), 7.14-7.23 (2H, m), 7.55 (1H, d, *J* 7.8, 7-H), 7.63 (1H, d, *J* 7.8, 4-H), 8.18 (1H, s, 2-H), 12.30 (1H, bs, OH); δ_C (100 MHz, DMSO–d_6) 13.2 (3′-CH_2), 17.7, 18.4 (1′,2′-CH), 27.8 (CH_2), 44.6 (NCH_2), 110.9 (7-CH), 120.0 (4-CH), 122.0, 122.8 (5,6-CH), 134.3, 143.9 (C), 144.5 (2-CH), 174.4 (C=O); HRMS (ESI): found $M+H^+$, 231.1124. $C_{13}H_{15}N_2O_2$ requires 231.1134.

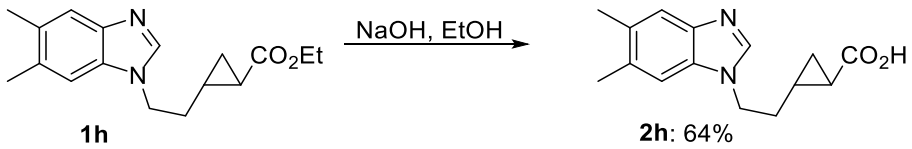
Experiment 15: 2′-[2-(3-Cyano-1*H*-indol-1-yl)ethyl]-*trans*-cyclopropane carboxylic acid (2g)



1g **2g**: 79%

In accordance with procedure 4 gave (1.168 g, 79%), pale yellow oil, ν_{max} (neat, cm^{-1}) 2926, 2216 (CN), 1690 (C=O), 1531, 1467, 1394, 1359, 1336, 1183, 1085, 1014; δ_H (400 MHz, MeOH–d_4) 0.52 (1H, ddd, *J* 4.2, 7.3, 7.3, 3′-H), 0.94 (1H, ddd, *J* 4.2, 4.2, 8.8, 3′-H), 1.10-1.19 (2H, m, 1′, 2′-H), 1.60-1.76 (2H, m), 4.17 (2H, t, *J* 6.8, NCH_2), 7.14-7.25 (2H, m), 7.43 (1H, d, *J* 8.2, 7-H), 7.55 (1H, d, *J* 7.8, 4-H), 7.76 (1H, s, 2-H), OH not observed; δ_C (100 MHz, MeOH–d_4) 15.1 (3′-CH_2), 20.3, 20.7 (1′, 2′-CH), 33.8 (CH_2), 47.3 (NCH_2), 85.4 (3-C), 112.0 (7-CH), 117.0 (CN), 120.0 (4-CH), 123.0, 124.7 (5,6-CH), 128.9, 136.6 (C), 137.0 (2-CH), 177.5 (C=O); HRMS (ESI): found $M+H^+$, 255.1124. $C_{15}H_{15}N_2O_2$ requires 255.1134.

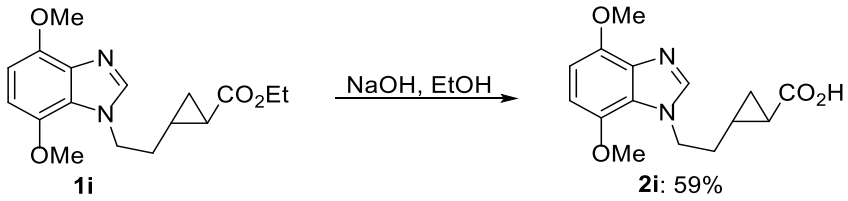
Experiment 16: 2′-[2-(5,6-Dimethyl-1*H*-benzimidazol-1-yl)ethyl]-*trans*-cyclopropanecarboxylic acid (2h).



1h **2h**: 64%

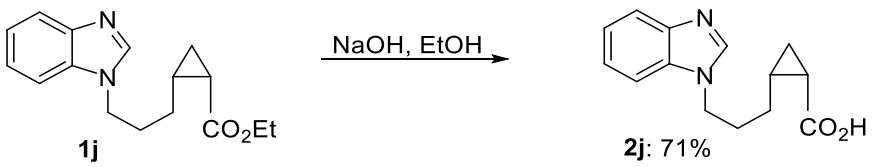
In accordance with procedure 4 gave (0.961 g, 64%), white solid, mp 205-206 ˚C; ν_{max} (neat, cm^{-1}) 1696 (C=O), 1497, 1472, 1449, 1378, 1329, 1276, 1224, 1199, 1141, 1008; δ_H (400 MHz, DMSO–d_6) 0.59 (1H, ddd, *J* 4.1, 6.2, 8.0, 3′-H), 0.84 (1H, ddd, *J* 4.1, 4.1, 8.5, 3′-H), 1.08 (1H, bs), 1.31 (1H, bs), 1.64-1.82 (2H, m), 2.26 (3H, s, CH_3), 2.29 (3H, s, CH_3), 4.21 (2H, t, *J* 6.9, NCH_2), 7.33-7.37 (2H, m), 8.01 (1H, s, 2-H), 12.07 (1H, bs, OH); δ_C (100 MHz, DMSO–d_6) 14.2 (3′-CH_2), 19.0, 19.2 (1′,2′-CH), 19.9, 20.1 (CH_3), 32.3 (CH_2), 43.7 (NCH_2), 110.4 (7-CH), 119.4 (4-CH), 129.7, 130.9, 132.3, 142.0 (all C), 143.1 (2-CH), 174.8 (C=O); HRMS (ESI): found $M+H^+$, 259.1443. $C_{15}H_{19}N_2O_2$ requires 259.1447.

Experiment 17: 2′-[2-(4,7-Dimethoxy-1*H*-benzimidazol-1-yl)ethyl]-*trans*-cyclopropanecarboxylic acid (2i)



In accordance with procedure 4 gave (1.000 g, 59%), white solid, mp 186-187 ˚C; ν_{max} (neat, cm^{-1}) 1690 (C=O), 1526, 1499, 1457, 1442, 1381, 1358, 1338, 1286, 1261, 1228, 1092, 1067; δ_H (400 MHz, DMSO–d_6) 0.54 (1H, ddd, *J* 3.9, 6.2, 8.2, 3′-H), 0.81-0.88 (1H, m, 3′-H), 1.02-1.08 (1H, m), 1.24 (1H, ddd, *J* 4.5, 4.5, 8.2, 1′-H), 1.65-1.79 (2H, m), 3.81 (6H, s, OCH_3), 4.36 (2H, t, *J* 7.0, NCH_2), 6.51 (1H, d(AB-q), *J* 8.7, 5,6-H), 6.60 (1H, d(AB-q), *J* 8.7, 5,6-H), 7.95 (1H, s, 2-H), 12.00 (1H, bs, OH); δ_C (100 MHz, DMSO–d_6) 15.2 (3′-CH_2), 19.9, 20.1 (1′, 2′-CH), 35.3 (CH_2), 46.8 (NCH_2), 56.8, 57.0 (OCH_3), 103.5, 104.4 (5,6-CH), 125.5, 136.6, 142.4 (all C), 144.1 (2-CH), 146.7 (C), 175.9 (C=O); HRMS (ESI): found $M+H^+$, 291.1347. $C_{15}H_{19}N_2O_4$ requires 291.1345.

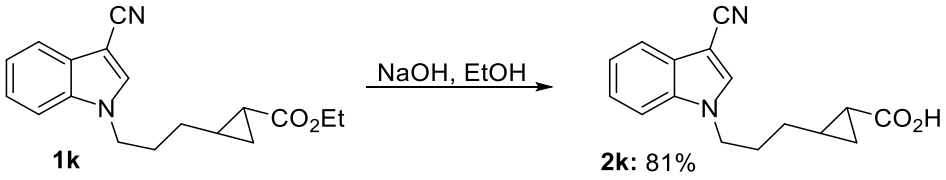
Experiment 18: 2′-[3-(1*H*-benzimidazol-1-yl)propyl]-*cis*-cyclopropane carboxylic acid (2j)



1j **2j**: 71%

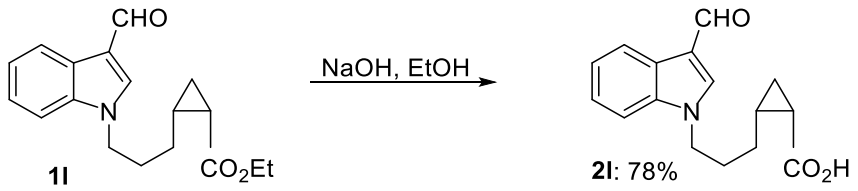
In accordance with procedure 4 gave (1.001 g, 71%), white solid, mp 165–166 ˚C; ν_{max} (neat, cm^{-1}) 1694 (C=O), 1611, 1499, 1456, 1363, 1290, 1239, 1204, 1183, 1138, 1034; δ_H (400 MHz, MeOH–d_4) 0.81-0.85 (1H, m, 3′-H), 1.03 (1H, ddd, *J* 4.1, 8.2, 8.2, 3′-H), 1.30 (1H, ddd, *J* 8.2, 15.4, 15.4, 1′-H), 1.54-1.70 (3H, m), 1.88-2.02 (2H, m), 4.29 (2H, t, *J* 7.1, NCH_2), 7.25-7.33 (2H, m), 7.54-7.56 (1H, m, 7-H), 7.65-7.68 (1H, m, 4-H), 8.18 (1H, s, 2-H), OH not observed; δ_C (100 MHz, MeOH–d_4) 14.0 (CH_2), 19.0, 21.9 (1′, 2′-CH), 25.5, 30.8 (CH_2), 45.8 (NCH_2), 111.5 (7-CH), 120.0 (4-CH), 123.5, 124.3 (5,6-CH), 134.9, 143.8 (C), 144.5 (2-CH), 176.8 (C=O); HRMS (ESI): found $M+H^+$, 245.1292. $C_{14}H_{17}N_2O_2$ requires 245.1290.

Experiment 19: 2′-[3-(3-Cyano-1*H*-indol-1-yl)propyl]-*trans*-cyclopropane carboxylic acid (2k)



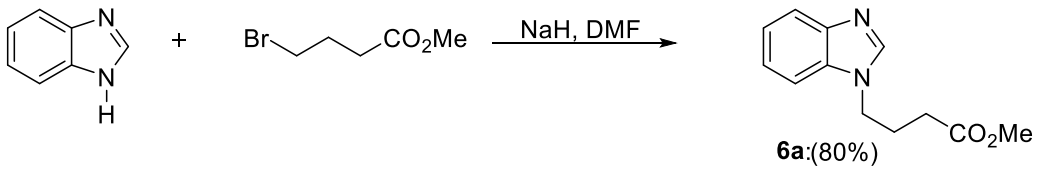
In accordance with procedure 4 gave (1.264 g, 81%), brown oil, ν_{max} (neat, cm^{-1}) 2925, 2216 (CN), 1689 (C=O), 1530, 1454, 1395, 1361, 1335, 1228, 1264, 1180, 1087, 1045; δ_H (400 MHz, MeOH–d_4) 0.60-0.65 (1H, m, 3′-H), 1.03-1.07 (1H, m, 3′-H), 1.18-1.28 (4H, m), 1.81-1.89 (2H, m), 4.12 (2H, t, *J* 7.3, NCH_2), 7.16-7.27 (2H, m), 7.43 (1H, d, *J* 8.3, 7-H), 7.56 (1H, d, *J* 7.8, 4-H), 7.81 (1H, s, 2-H), OH not observed; δ_C (100 MHz, MeOH–d_4) 14.7 (3′-CH_2), 19.6, 22.0 (1′, 2′-CH), 29.2, 29.7 (CH_2), 46.2 (NCH_2), 84.2 (3-C), 110.8 (7-CH), 115.8 (CN), 118.9 (4-CH), 121.9, 123.5 (5,6-CH), 127.8, 135.5 (C), 135.7 (2-CH), 176.8 (C=O); HRMS (ESI): found $M+H^+$, 269.1297. $C_{16}H_{17}N_2O_2$ requires 269.1290.

Experiment 20: 2′-[3-(3-Formyl-1*H*-indol-1-yl)propyl]-*cis*-cyclopropane carboxylic acid (2l)



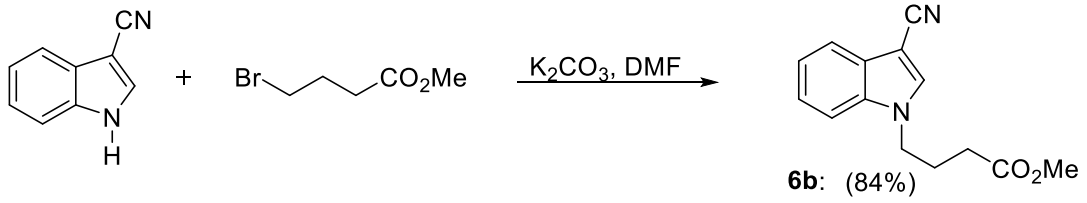
In accordance with procedure 4 gave (1.231 g, 78%), brown oil, ($\nu_{max,}$ neat/cm^{-1}) 1689 (C=O acid), 1651 (C=O aldehyde), 1613, 1575, 1527, 1459, 1396, 1388, 1171, 1133, 1070, 1042. δ_H (400 MHz, $CDCl_3$) 0.94-0.99 (1H, m, 3′-H), 1.11 (1H, ddd, *J* 4.6, 8.0, 8.0, 3′-H), 1.26-1.32 (1H, m), 1.59-1.75 (3H, m), 1.87-1.98 (2H, m), 4.11 (2H, t, *J* 7.3, NCH_2), 7.25-7.33 (3H, m), 7.67 (1H, s, 2-H), 8.26-8.28 (1H, m, 4-H), 9.90 (1H, s, CHO), 10.90 (1H, bs, OH). δ_C (100 MHz, $CDCl_3$) 14.6 (3′-CH_2), 18.0, 22.1 (1′,2′-CH), 24.4, 29.7 (CH_2), 47.0 (NCH_2), 110.2 (7-CH), 118.0 (C), 122.2, 123.1, 124.1 (all CH), 125.5 (C), 137.3 (C), 138.9 (2-CH), 178.9 (COOH), 185.0 (CHO). HRMS (ESI) found M+H$^+$ 272.1284. $C_{16}H_{18}NO_3$ requires 272.1287.

Experiment 21: Methyl 4-(1*H*-benzimidazol-1-yl)butanoate (6a)



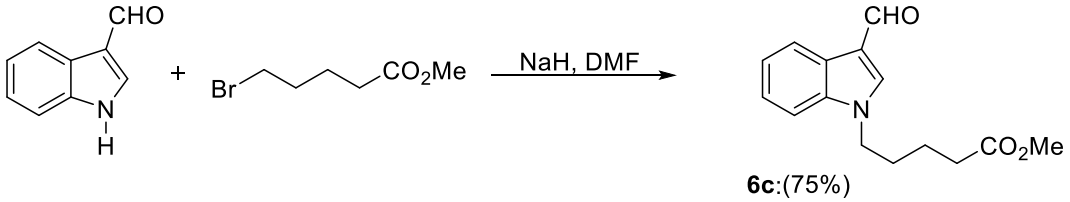
In accordance with procedure 2 except using benzimidazole (8.50 mmol) and methyl 4-bromobutanoate (9.35 mmol) gave (1.480 g, 74%), pale yellow oil, R_f 0.40 (EtOAc); ν_{max} (neat, cm^{-1}) 1729 (C=O), 1615, 1496, 1459, 1438, 1365, 1332, 1286, 1255, 1201, 1162, 1122 1094, 1061, 1007; δ_H (400 MHz, $CDCl_3$) 1.90-1.99 (2H, m, CH_2), 2.09 (2H, t, *J* 7.0, CH_2CO), 3.45 (3H, s, OCH_3), 3.98 (2H, t, *J* 7.1, NCH_2), 7.07-7.10 (2H, m, 5,6-H), 7.20-7.23 (1H, m, 7-H), 7.58 (1H, s, 2-H), 7.61-7.64 (1H, m, 4-H); δ_C (100 MHz, $CDCl_3$) 24.9 (CH_2), 30.4 (CH_2CO), 43.8 (NCH_2), 51.7 (OCH_3), 109.7 (7-CH), 120.2 (4-CH), 122.1, 122.9 (5,6-CH), 143.0 (2-CH), 143.8 (C), 172.7 (C=O); HRMS (ESI): found $M+H^+$, 219.1140. $C_{12}H_{15}N_2O_2$ requires 219.1134.

Experiment 22: Methyl 4-(3-cyano-1*H*-indol-1-yl)butanoate (6b)



In accordance with procedure 1 exept using indole-3-carbonitrile (4.92 mmol) and methyl 4-bromobutanoate (5.30 mmol) gave (0.996 g, 84%), colourless oil, R_f 0.68 (CH_2Cl_2); ν_{max} (neat, cm^{-1}) 2953, 2217 (CN), 1731 (C=O), 1532, 1468, 1437, 1395, 1364, 1243, 1196, 1165, 1045; δ_H (400 MHz, $CDCl_3$) 2.12-2.19 (2H, m, CH_2), 2.31 (2H, t, *J* 7.0, CH_2CO), 3.66 (3H, s, OCH_3), 4.23 (2H, t, *J* 7.1, NCH_2), 7.24-7.35 (2H, m, 5,6-H), 7.43 (1H, d, *J* 8.2, 7-H), 7.58 (1H, s, 2-H), 7.71-7.74 (1H, m, 4-H); δ_C (100 MHz, $CDCl_3$) 24.9 (CH_2), 30.3 (CH_2CO), 46.0 (NCH_2), 51.8 (OCH_3), 85.7 (3-C), 110.5 (7-CH), 115.8 (CN), 119.8 (4-CH), 122.1, 123.8 (5,6-CH), 127.8 (C), 134.6 (2-CH), 135.2 (C), 172.7 (C=O); HRMS (ESI): found $M+H^+$, 243.1140. $C_{14}H_{15}N_2O_2$ requires 243.1134.

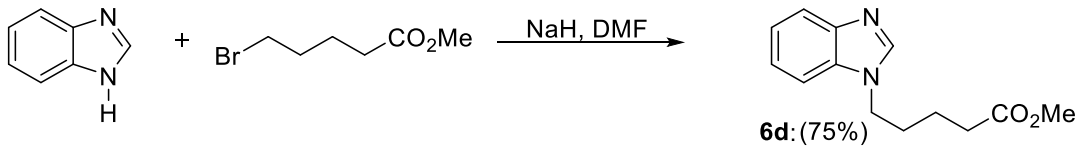
Experiment 23: Methyl 5-(3-formyl-1*H*-indol-1-yl)pentanoate (6c)



6c:(75%)

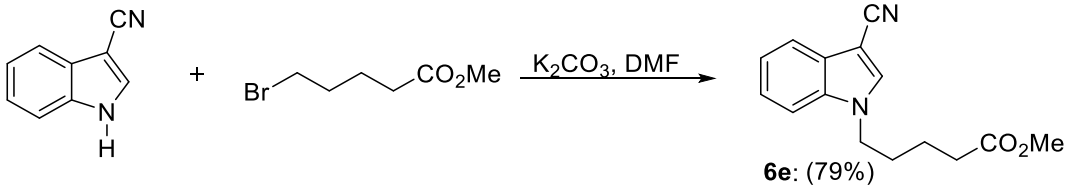
In accordance with procedure 2 except using indole-3-carbaldehyde (8.50 mmol) and methyl 5-bromopentanoate (9.35 mmol) gave (1.651 g, 75%), yellow oil, R_f 0.31 (CH_2Cl_2); ν_{max} (neat, cm^{-1}) 2950, 1732 (C=O ester), 1654 (C=O aldehyde), 1532, 1468, 1437, 1401, 1388, 1254, 1166, 1089, 1013; δ_H (400 MHz, $CDCl_3$) 1.56-1.66 (2H, m), 1.82-1.89 (2H, m), 2.28 (2H, t, *J* 7.3, CH_2CO), 3.59 (3H, s, OCH_3), 4.11 (2H, t, *J* 7.1, NCH_2), 7.21-7.32 (3H, m), 7.67 (1H, s, 2-H), 8.22-8.25 (1H, m, 4-H), 9.90 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$) 21.9, 28.9 (CH_2), 33.0 (CH_2CO), 46.7 (NCH_2), 51.4 (OCH_3), 109.9 (7-CH), 117.8 (C), 121.9, 122.7 123.7 (CH), 125.2, 136.9 (C), 138.3 (2-CH), 173.1 (*C*OOMe), 184.3 (CHO); HRMS (ESI): found $M+H^+$, 260.1292. $C_{15}H_{18}NO_3$ requires 260.1287.

Experiment 24: Methyl 5-(1*H*-benzimidazol-1-yl)pentanoate (6d)



In accordance with procedure 2 except using benzimidazole (8.50 mmol) and methyl 5-bromopentanoate (9.35 mmol) gave (1.480 g, 75%), yellow oil, R_f 0.40 (EtOAc); ν_{max} (neat, cm^{-1}) 1729 (C=O), 1615, 1496, 1458, 1437, 1365, 1331, 1287, 1252, 1200, 1174; δ_H (400 MHz, $CDCl_3$) 1.56-1.64 (2H, m), 1.82-1.90 (2H, m), 2.28 (2H, t, *J* 7.3, CH_2CO), 3.59 (3H, s, OCH_3), 4.11 (2H, t, *J* 7.1, NCH_2), 7.20-7.27 (2H, m), 7.32-7.35 (1H, m, 7-H), 7.75-7.77 (1H, m, 4-H), 7.83 (1H, s, 2-H); δ_C (100 MHz, $CDCl_3$) 22.2, 29.3 (CH_2), 33.3 (CH_2CO), 44.8 (NCH_2), 51.7 (OCH_3), 109.7 (7-CH), 120.5 (4-CH), 122.1, 122.9 (5,6-CH), 133.8 (C), 143.0 (2-CH), 143.9 (C), 173.4 (C=O); HRMS (ESI): found $M+H^+$, 233.1280. $C_{13}H_{17}N_2O_2$ requires 233.1290.

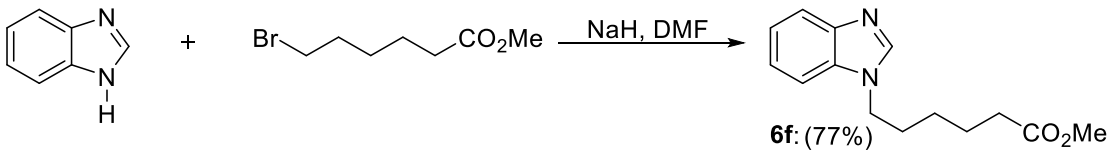
Experiment 25: Methyl 5-(3-cyano-1*H*-indol-1-yl)pentanoate (6e)



6e: (79%)

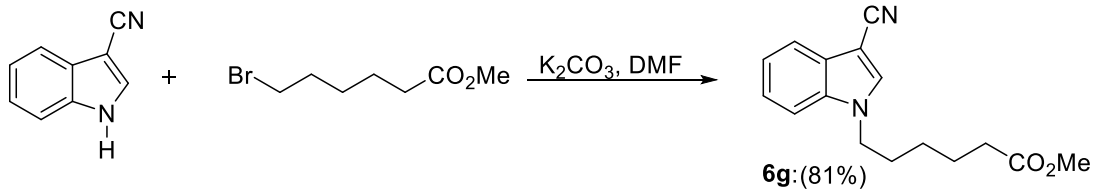
In accordance with procedure 1 except using indole-3-carbonitrile (4.92 mmol) and methyl 5-bromopentanoate (5.30 mmol) gave (1.000 g, 79%), white solid, mp 62-64 ˚C, R_f 0.60 (CH_2Cl_2); ν_{max} (neat, cm^{-1}) 3120, 2952, 2211 (CN), 1736 (C=O), 1527, 1471, 1457, 1436, 1396, 1358, 1189, 1168, 1076; δ_H (400 MHz, $CDCl_3$) 1.50-1.59 (2H, m), 1.76-1.84 (2H, m), 2.25 (2H, t, *J* 7.2, CH_2CO), 3.56 (3H, s, OCH_3), 4.08 (2H, t, *J* 7.1, NCH_2), 7.16-7.26 (2H, m), 7.33 (1H, d, *J* 8.3, 7-H), 7.55 (1H, s, 2-H), 7.63 (1H, d, *J* 7.8, 4-H); δ_C (100 MHz, $CDCl_3$) 22.1, 29.2 (CH_2), 33.3 (CH_2CO), 46.9 (NCH_2), 51.7 (OCH_3), 85.3 (3-C), 110.7 (7-CH), 116.1 (CN), 119.8 (4-CH), 122.1, 123.8 (5,6-CH), 127.9 (C), 135.0 (2-CH), 135.3 (C), 173.4 (C=O); HRMS (ESI): found $M+H^+$, 257.1283. $C_{15}H_{17}N_2O_2$ requires 257.1290.

Experiment 26: Methyl 6-(1*H*-benzimidazol-1-yl)hexanoate (6f)



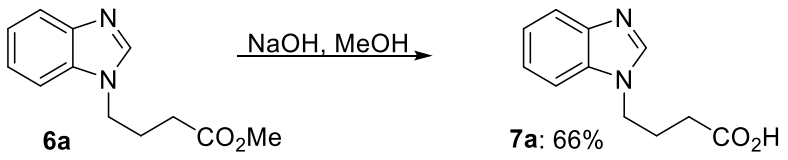
In accordance with procedure 2 except using benzimidazole (8.50 mmol) and methyl 6-bromohexanoate (9.35 mmol) gave (1.610 g, 77%), yellow oil, R_f 0.41 (EtOAc); ν_{max} (neat, cm^{-1}) 2945, 2863, 1730 (C=O), 1615, 1496, 1459, 1437, 1365, 1331, 1286, 1243, 1200, 1172, 1155, 1099, 1007; δ_H (400 MHz, $CDCl_3$) 1.17-1.25 (2H, m), 1.49-1.57 (2H, m), 1.70-1.78 (2H, m), 2.17 (2H, t, *J* 7.3, CH_2CO), 3.53 (3H, s, OCH_3), 4.01 (2H, t, *J* 7.1, NCH_2), 7.13-7.20 (2H, m), 7.24-7.28 (1H, m, 7-H), 7.69-7.72 (1H, m, 4-H), 7.77 (1H, s, 2-H); δ_C (100 MHz, $CDCl_3$) 24.3, 26.2, 29.4 (CH_2), 33.7 (CH_2CO), 44.8 (NCH_2), 51.5 (OCH_3), 109.7 (7-CH), 120.3 (4-CH), 122.0, 122.8 (5,6-CH), 133.8 (C), 143.0 (2-CH), 143.9 (C), 173.7 (C=O); HRMS (ESI): found $M+H^+$, 247.1447. $C_{14}H_{19}N_2O_2$ requires 247.1447.

Experiment 27: Methyl 6-(3-cyano-1*H*-indol-1-yl)hexanoate (6g)



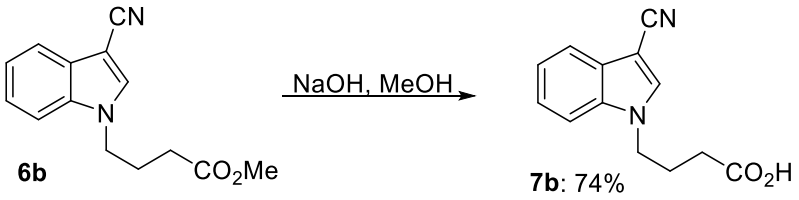
In accordance with procedure 1 except using indole-3-carbonitrile (4.92 mmol) and methyl 6-bromohexanoate (5.30 mmol) gave (1.076 g, 81%), yellow oil, R_f 0.53 (CH_2Cl_2); ν_{max} (neat, cm^{-1}) 2947, 2215 (CN), 1731 (C=O), 1531, 1467, 1436, 1395, 1361, 1336, 1242, 1252, 1193, 1162, 1013; δ_H (400 MHz, $CDCl_3$) 1.24-1.32 (2H, m), 1.56-1.64 (2H, m), 1.77-1.85 (2H, m), 2.24 (2H, t, *J* 7.3, CH_2CO), 3.59 (3H, s, OCH_3), 4.10 (2H, t, *J* 7.1, NCH_2), 7.19-7.29 (2H, m), 7.35 (1H, d, *J* 8.2, 7-H), 7.55 (1H, s, 2-H), 7.66-7.69 (1H, m, 4-H); δ_C (100 MHz, $CDCl_3$) 24.0, 25.9, 29.2 (CH_2), 33.4 (CH_2CO), 46.7 (NCH_2), 51.3 (OCH_3), 85.0 (3-C), 110.3 (7-CH), 115.8 (CN), 119.5 (4-CH), 121.8, 123.5 (5,6-CH), 127.6 (C), 134.6 (2-CH), 135.0 (C), 173.5 (C=O); HRMS (ESI): found $M+H^+$, 271.1444. $C_{16}H_{19}N_2O_2$ requires 271.1447.

Experiment 28: 4-(1-*H*-benzimidazol-1-yl)butanoic acid (7a)



In accordance with procedure 4 except using NaOH in MeOH gave (0.781 g, 66%), white solid, mp 137-139 ˚C, lit mp 146-147 ˚C. Physical and spectroscopic data were consistant with that previously reported.[127]

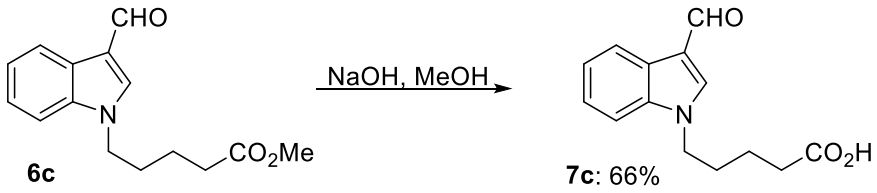
Experiment 29: 4-(3-Cyano-1*H*-indol-1-yl)butanoic acid (7b)



6b **7b**: 74%

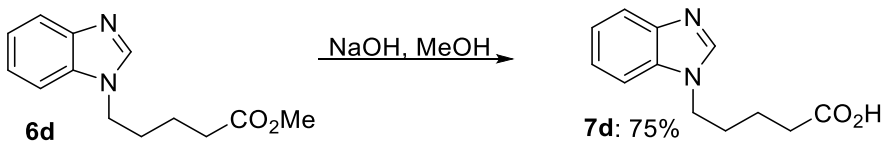
In accordance with procedure 4 except using NaOH in MeOH gave (0.979 g, 74%), white solid, mp 82-84 ˚C, lit mp 91-93 ˚C. Physical and spectroscopic data were consistant with that previously reported.[129]

Experiment 30: 5-(3-Formyl-1*H*-indol-1-yl)pentanoic acid (7c)



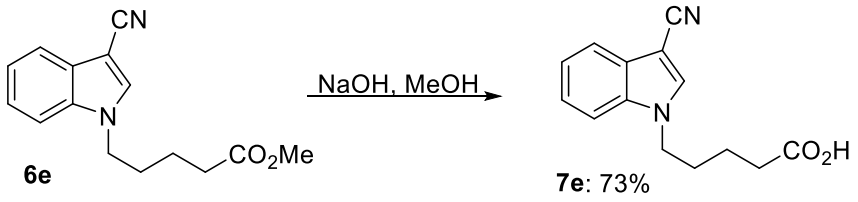
In accordance with procedure 4 except using NaOH in MeOH gave (0.942 g, 66%), brown solid, mp 126-129 ˚C; ν_{max} (neat, cm^{-1}) 3116, 2935, 2590, 1703 (C=O acid), 1610 (C=O aldehyde), 1578, 1524, 1491, 1475, 1465, 1449, 1393, 1381, 1347, 1218, 1174, 1142, 1077, 1014; δ_H (400 MHz, MeOH–d_4) 1.57-1.65 (2H, m), 1.88-1.96 (2H, m), 2.32 (2H, t, *J* 7.4, CH_2CO), 4.29 (2H, t, *J* 7.1, NCH_2), 7.23-7.33 (2H, m, 5,6-H), 7.52 (1H, d, *J* 8.2, 7-H), 8.12 (1H, s, 2-H), 8.15 (1H, d, *J* 7.8, 4-H), 9.83 (1H, s, CHO), OH not observed; δ_C (100 MHz, MeOH–d_4) 23.2, 30.3 (CH_2), 34.2 (CH_2CO), 47.8 (NCH_2), 111.7 (7-CH), 119.1 (C), 122.8, 123.9, 125.1 (CH), 126.5, 138.9 (C), 142.2 (2-CH), 177.0 (COOH), 185.7 (CHO); HRMS (ESI): found $M+H^+$, 246.1125. $C_{14}H_{16}NO_3$ requires 246.1130.

Experiment 31: 5-(1*H*-benzimidazol-1-yl)pentanoic acid (7d)



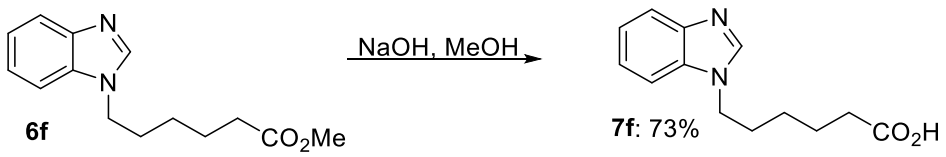
In accordance with procedure 4 except using NaOH in MeOH gave (0.949 g, 75%), white solid, mp 154-157 ˚C; ν_{max} (neat, cm^{-1}) 3102, 2944, 2872, 1687 (C=O), 1615, 1504, 1464, 1453, 1420, 1372, 1317, 1291, 1251, 1183; δ_H (400 MHz, MeOH–d_4) 1.55-1.63 (2H, m), 1.86-1.94 (2H, m), 2.31 (2H, t, *J* 7.3, CH_2CO), 4.28 (2H, t, *J* 7.1, NCH_2), 7.23-7.33 (2H, m), 7.56 (1H, d, *J* 7.8, 7-H), 7.65 (1H, d, *J* 8.3, 4-H), 8.19 (1H, s, 2-H), OH not observed; δ_C (100 MHz, MeOH–d_4) 21.9, 29.0 (CH_2), 33.0 (CH_2CO), 44.4 (NCH_2), 110.2 (7-CH), 118.7 (4-CH), 122.3, 123.0 (5,6-CH), 133.6, 142.5 (C), 143.3 (2-CH), 175.8 (C=O); HRMS (ESI): found $M+H^+$, 219.1127. $C_{12}H_{15}N_2O_2$ requires 219.1134.

Experiment 32: 5-(3-Cyano-1*H*-indol-1-yl)pentanoic acid (7e)



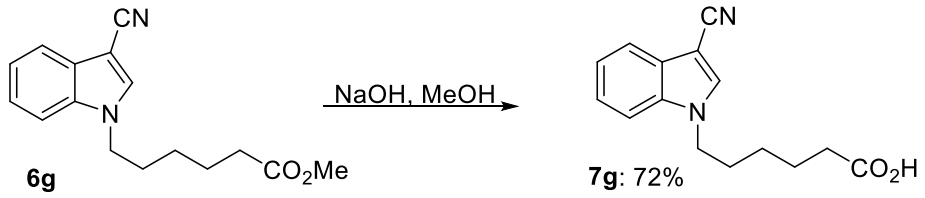
In accordance with procedure 4 except using NaOH in MeOH gave (1.029 g, 73%), white solid, mp 117-118 ˚C; ν_{max} (neat, cm^{-1}) 3120, 2943, 2875, 2212 (CN), 1701 (C=O), 1532, 1470, 1392, 1323, 1310, 1285, 1259, 1228, 1205, 1151, 1113, 1083; δ_H (400 MHz, MeOH–d_4) 1.44-1.52 (2H, m), 1.71-1.79 (2H, m), 2.22 (2H, t, *J* 7.4, CH_2CO), 4.08 (2H, t, *J* 7.1, NCH_2), 7.14-7.25 (2H, m, 5,6-H), 7.41 (1H, d, *J* 8.2, 7-H), 7.54 (1H, d, *J* 8.0, 4-H), 7.78 (1H, s, 2-H), OH not observed; δ_C (100 MHz, MeOH–d_4) 24.5, 31.7 (CH_2), 35.6 (CH_2CO), 49.0 (NCH_2), 86.7 (3-C), 113.5 (7-CH), 118.5 (CN), 121.5, 124.5, 126.1 (CH), 130.4, 138.1 (C), 138.4 (2-CH), 178.4 (C=O); HRMS (ESI): found $M+H^+$, 243.1134. $C_{14}H_{15}N_2O_2$ requires 243.1134.

Experiment 33: 6-(1*H*-benzimidazol-1-yl)hexanoic acid (7f)



In accordance with procedure 4 except using NaOH in MeOH gave (0.982 g, 73%), white solid, mp 110-112 ˚C; ν_{max} (neat, cm^{-1}) 2953, 2457, 1906, 1694 (C=O), 1505, 1465, 1400, 1292, 1276, 1238, 1209, 1187, 1042, 1006; δ_H (400 MHz, MeOH–d_4) 1.30-1.39 (2H, m), 1.59-1.67 (2H, m), 1.86-1.94 (2H, m), 2.26 (2H, t, *J* 7.3, CH_2CO), 4.29 (2H, t, *J* 7.1, NCH_2), 7.24-7.33 (2H, m), 7.56 (1H, d, *J* 8.3, 7-H), 7.66 (1H, d, *J* 7.8, 4-H), 8.18 (1H, s, 2-H), OH not observed; δ_C (100 MHz, MeOH–d_4) 25.5, 27.2, 30.6 (CH_2), 34.7 (CH_2CO), 45.9 (NCH_2), 111.5 (7-CH), 120.0 (4-CH), 123.6, 124.3 (5,6-CH), 134.9, 143.8 (C), 144.6 (2-CH), 177.5 (C=O); HRMS (ESI): found $M+H^+$, 233.1295. $C_{13}H_{17}N_2O_2$ requires 233.1290.

Experiment 34: 6-(3-Cyano-1*H*-indol-1-yl)hexanoic acid (7g)



6g **7g**: 72%

In accordance with procedure 4 except using NaOH in MeOH gave (1.073 g, 72%), white precipitate, mp 90-91 ˚C; ν_{max} (neat, cm^{-1}) 3127, 2952, 2874, 2212 (CN), 1705 (C=O), 1524, 1466, 1450, 1410, 1364, 1298, 1252, 1189, 1010; δ_H (400 MHz, MeOH–d_4) 1.28-1.36 (2H, m), 1.57-1.65 (2H, m), 1.81-1.89 (2H, m), 2.25 (2H, t, *J* 7.3, CH_2CO), 4.24 (2H, t, *J* 7.1, NCH_2), 7.22-7.34 (2H, m), 7.55 (1H, d, *J* 8.2, 7-H), 7.62 (1H, d, *J* 8.0, 4-H), 7.96 (1H, s, 2-H), OH not observed; δ_C (100 MHz, MeOH–d_4) 24.2, 25.9, 29.3 (CH_2), 33.3 (CH_2CO), 46.5 (NCH_2), 84.0 (3-C), 110.8 (7-CH), 115.7 (CN), 118.8 (4-CH), 121.8, 123.4 (5,6-CH), 127.9, 135.6 (C), 135.9 (2-CH), 176.1 (C=O); HRMS (ESI): found $M+H^+$, 257.1293. $C_{15}H_{17}N_2O_2$ requires 257.1290.

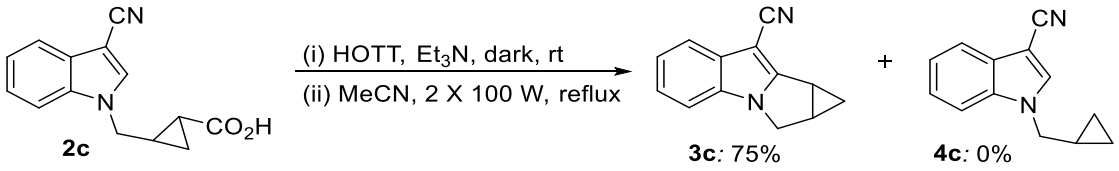
General Procedure for One-Pot Barton Ester Formation and Radical Cyclisations onto Indole-3-Carbonitrile and Indole-3-Carbaldehyde (Procedure 5.)

Et_3N (0.32 mL, 2.30 mmol) in THF (5.7 mL) was added to a mixture of carboxylic acid (0.76 mmol) and HOTT (0.424 g, 1.14 mmol) in MeCN (1.9 mL). The solution was stirred at room temperature in the absence of light for 40 min. MeCN (68 mL) was added, and the mixture illuminated with two 100 W light bulbs, and heated under reflux for 6 h. The solution was evaporated, dissolved in CH_2Cl_2 (10 mL) and washed with H_2O (2 x 10 mL). The organic extract evaporated and purified by column chromatography using silica gel as absorbent with a gradient elution of hexanes and CH_2Cl_2, Et_2O or EtOAc.

General Procedure for One-Pot Barton Ester Formation and Radical Cyclisations onto Benzimidazoles (Procedure 6.)

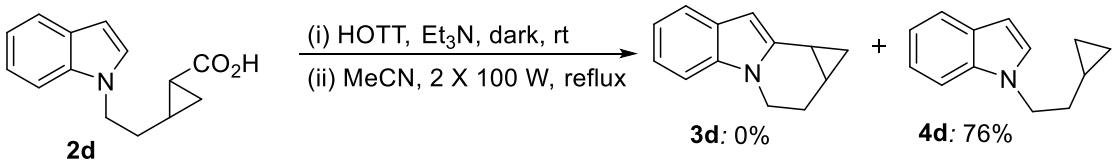
Et_3N (0.32 mL, 2.30 mmol) in THF (5.7 mL) was added to a mixture of carboxylic acid (0.76 mmol), HOTT (0.424 g, 1.14 mmol) and (DMAP 9.3 mg, 0.08 mmol) in MeCN (1.9 mL). The solution was stirred at room temperature in the absence of light for 40 min. MeCN (68 mL) was added or a solution of CSA (0.711 g, 3.06 mmol) in MeCN (68 mL) for selected benzimidazoles and the mixture illuminated with two 100 W light bulbs, and heated under reflux for 6 h. The solution was evaporated, dissolved in CH_2Cl_2 (10 mL) and washed with H_2O (2 x 10 mL). The organic extract evaporated and purified by column chromatography using silica gel as absorbent with a gradient elution of hexanes and EtOAc.

Experiment 35: 1,1*a*,2,8*b*-Tetrahydrocyclopropa[3,4]pyrrolo[1,2-*a*]indole-8-carbonitrile (3c)



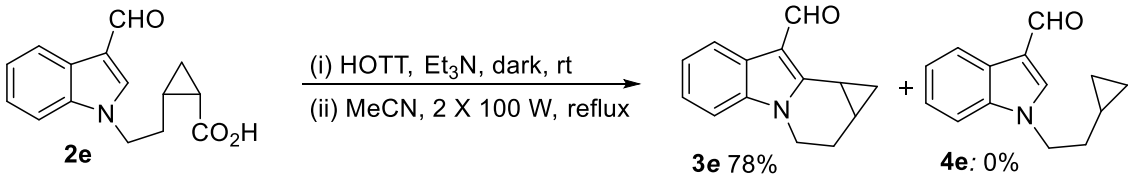
In accordance with procedure 5 gave (0.111 g, 75%), white solid, mp 117-118 ˚C, R_f 0.70 (CH_2Cl_2); ν_{max} (neat, cm^{-1}) 2922, 2208 (CN), 1617, 1567, 1475, 1458, 1418, 1360, 1327, 1306, 1279, 1247, 1175, 1124; δ_H (400 MHz, $CDCl_3$) 0.73 (1H, q, *J* 4.6, 1-H), 1.40-1.46 (1H, m), 2.46-2.53 (1H, m), 2.64-2.69 (1H, m), 4.11 (1H, d, *J* 11.0, 2-H), 4.19 (1H, dd, *J* 5.7, 11.0, 2-H), 7.12-7.20 (3H, m), 7.58-7.61 (1H, m, 7-H); δ_C (100 MHz, $CDCl_3$) 16.3 (CH), 17.4 (1-CH_2), 21.6 (CH), 47.8 (2-CH_2), 77.7 (8-C), 110.0 (4-CH), 116.4 (CN), 119.6 (7-CH), 121.7, 122.8 (5,6-CH), 131.7, 132.1, 154.5 (all C); HRMS (ESI): found $M+H^+$, 195.0919. $C_{13}H_{11}N_2$ requires 195.0922.

Experiment 36: 1-(2-Cyclopropylethyl)-1*H*-indole (4d)



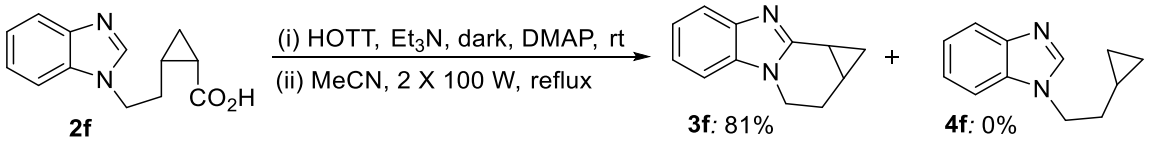
In accordance with procedure 5 gave (0.108 g, 76%), colourless oil, R_f 0.26 (hexane); ν_{max} (neat, cm^{-1}) 2924, 2854, 1559, 1512, 1463, 1332, 1313, 1247, 1178; δ_H (400 MHz, $CDCl_3$) 0.00-0.04 (2H, m), 0.40-0.44 (2H, m), 0.58-0.63 (1H, m, CH), 1.66-1.73 (2H, m), 4.20 (2H, t, *J* 7.1, NCH_2), 6.47 (1H, d, *J* 2.3, 3-H), 7.06-7.12 (2H, m), 7.16-7.21 (1H, m), 7.35-7.37 (1H, m), 7.61 (1H, d, *J* 8.2, 4-H); δ_C (100 MHz, $CDCl_3$) 4.3 (2 x CH_2), 8.7 (CH), 35.3 (CH_2), 46.5 (NCH_2), 100.8 (3-CH), 109.4 (7-CH), 119.1 (4-CH), 120.9, 121.2, 127.9, (all CH), 128.5, 135.9 (C); HRMS (ESI): found $M+H^+$, 186.1280. $C_{13}H_{16}N$ requires 186.1283.

Experiment 37: 1*a*,2,3,9*b*-Tetrahydro-1*H*-cyclopropa[3,4]pyrido[1,2-*a*]indole-9-carbaldehyde (3e)



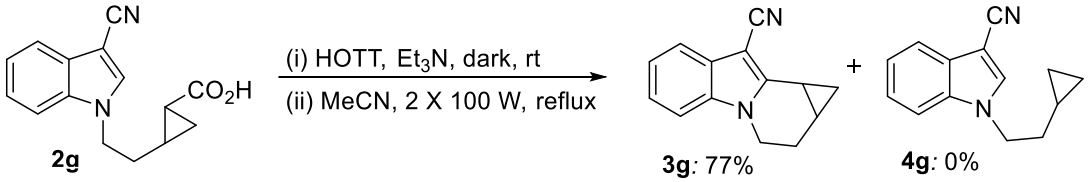
In accordance with procedure 5 gave (0.125 g, 78%), brown solid, mp 121-122 ˚C, R_f 0.52 (Et_2O); ν_{max} (neat, cm^{-1}) 1643 (C=O), 1605, 1580, 1532, 1459, 1436, 1393, 1373, 1317, 1257, 1231, 1194, 1128, 1080, 1062; δ_H (400 MHz, $CDCl_3$) 1.13 (1H, q, *J* 5.5, 1-H), 1.29-1.35 (1H, m, 1-H), 1.85-1.91 (1H, m), 2.12-2.22 (1H, m), 2.34-2.39 (1H, m), 2.76-2.83 (1H, m), 3.55 (1H, dt, *J* 5.0, 12.8, 3-H), 4.25 (1H, dd, *J* 6.0, 12.8, 3-H), 7.19-7.28 (3H, m), 8.20-8.23 (1H, m, 8-H), 10.21 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$) 6.3 (CH), 8.7 (1-CH_2), 11.1 (CH), 17.8 (2-CH_2), 34.9 (3-CH_2), 106.2 (5-CH), 111.4 (C), 118.1 (8-CH), 120.3 (6 & 7-CH), 123.4, 133.6, 147.9 (all C), 180.9 (CHO); HRMS (ESI): found $M+H^+$, 212.1074. $C_{14}H_{14}NO$ requires 212.1075.

Experiment 38: 1*a*,2,3,9*b*-Tetrahydro-1*H*-cyclopropa[3,4]pyrido[1,2-*a*] benzimidazole (3f)



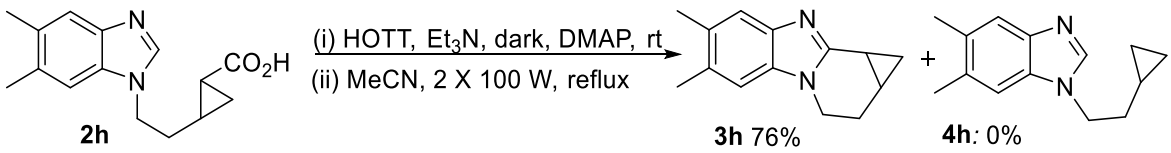
In accordance with procedure 6 gave (0.113 g, 81%), white solid, mp 122-123 ˚C, lit mp 123-124 ˚C, R_f 0.50 (EtOAc-MeOH 9:1). Physical and spectroscopic data were consistant with that previously reported.[45]

Experiment 39: 1*a*,2,3,9*b*-Tetrahydro-1*H*-cyclopropa[3,4]pyrido[1,2-*a*]indole-9-carbonitrile (3g)



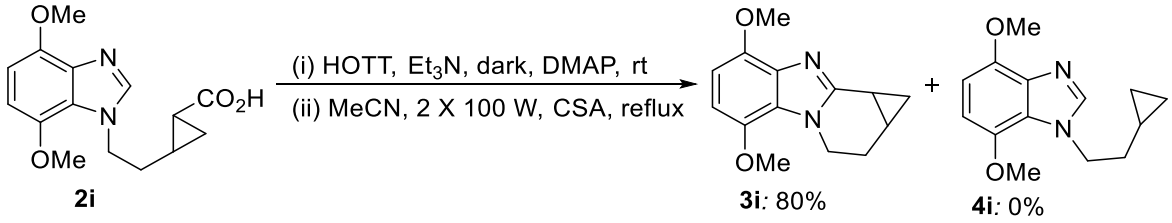
In accordance with procedure 5 gave (0.122 g, 77%), white solid, mp 91-93 ˚C, R_f 0.68 (CH_2Cl_2); ν_{max} (neat, cm^{-1}) 2929, 2206 (CN), 1551, 1464, 1456, 1435, 1363, 1337, 1324, 1260, 1193, 1049; δ_H (400 MHz, $CDCl_3$) 1.08 (1H, q, *J* 5.6, 1-H), 1.29 (1H, ddd, *J* 5.7, 8.5, 8.5, 1-H), 1.84-1.91 (1H, m), 2.10-2.19 (1H, m), 2.33-2.38 (1H, m), 2.50 (1H, ddd, *J* 4.3, 8.5, 8.5, 9b-H), 3.55 (1H, dt, *J* 5.0, 13.1, 3-H), 4.27 (1H, dd, *J* 6.0, 13.1, 3-H), 7.20-7.26 (3H, m), 7.61-7.66 (1H, m, 8-H); δ_C (100 MHz, $CDCl_3$) 10.0 (9b-CH), 10.8 (1-CH_2), 13.4 (1a-CH), 20.6 (2-CH_2), 37.5 (3-CH_2), 82.7 (9-C), 109.1 (5-CH), 116.9 (CN), 118.8 (8-CH), 121.9, 122.6 (6,7-CH), 127.4, 135.1, 148.2 (all C); HRMS (ESI): found $M+H^+$, 209.1072. $C_{14}H_{13}N_2$ requires 209.1079.

Experiment 40: 6,7-Dimethyl-1*a*,2,3,9*b*-tetrahydro-1*H*-cyclopropa[3,4]pyrido [1,2-*a*]benzimidazoles (3h)



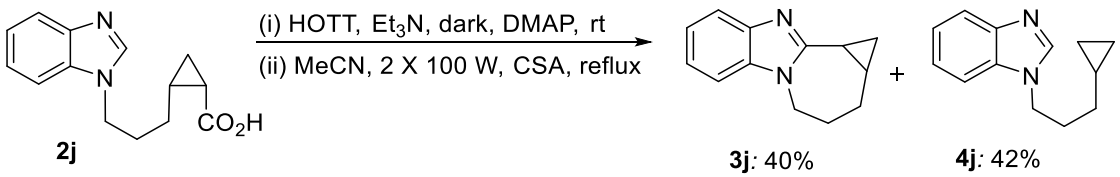
In accordance with procedure 6 gave (0.122 g, 76%), brown solid, mp 135-136 ˚C, lit mp 136-137 ˚C, R_f 0.25 (EtOAc). Physical and spectroscopic data were consistant with that previously reported.[47]

Experiment 41: 5,8-Dimethoxy-1*a*,2,3,9*b*-tetrahydro-1*H*-cyclopropa[3,4] pyrido[1,2-*a*]benzimidazole (3i)



In accordance with procedure 6 gave (0.148 g, 80%), white solid, mp 144-145 ˚C, lit mp 145-146 ˚C, R_f 0.36 (EtOAc). Physical and spectroscopic data were consistant with that previously reported.[46]

Experiment 42: 1,1a,2,3,4,10b-Hexahydrocyclopropa[3,4]azepino[1,2-*a*] benzimidazole (3j)

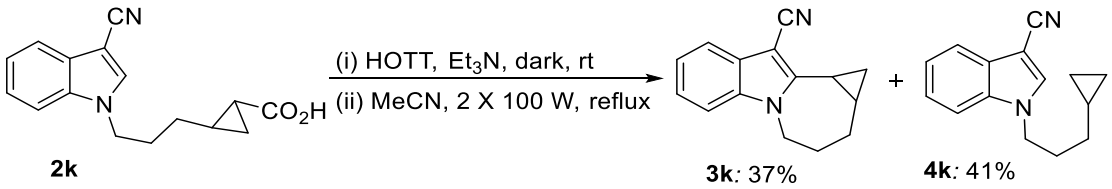


In accordance with procedure 6 gave (60 mg, 40%), white solid, mp 144-145 ˚C, R_f 0.47 (EtOAc); ν_{max} (neat, cm^{-1}) 2928, 1524, 1455, 1404, 1359, 1325, 1287, 1270, 1239, 1177, 1155; δ_H (400 MHz, $CDCl_3$) 0.35-0.45 (1H, m), 0.72 (1H, q, *J* 4.8, 1-H), 1.19-1.29 (2H, m), 1.72-1.89 (2H, m), 2.15-2.25 (2H, m), 4.26-4.32 (1H, m, 4-H), 4.36-4.45 (1H, m, 4-H), 7.15-7.26 (3H, m), 7.67-7.70 (1H, m, 9-H); δ_C (100 MHz, $CDCl_3$) 11.9, 12.3 (CH), 13.4 (1-CH_2), 23.6, 27.0 (CH_2), 40.8 (4-CH_2), 108.7 (6-CH), 119.4 (9-CH), 121.6, 122.2 (7,8-CH), 134.1, 143.0, 154.4 (all C); HRMS (ESI): found $M+H^+$, 199.1226. $C_{13}H_{15}N_2$ requires 199.1235.

1-(3-cyclopropylpropyl)-1*H*-benzimidazole (4j)

(64 mg, 42%), yellow oil, R_f 0.65 (EtOAc); ν_{max} (neat, cm^{-1}) 2982, 2932, 1494, 1459, 1393, 1360, 1325, 1282, 1242, 1199, 1161; δ_H (400 MHz, $CDCl_3$) (-0.01)-0.01 (2H, m), 0.41-0.45 (2H, m), 0.62-0.72 (1H, m, CH), 1.22-1.28 (2H, m), 1.96-2.04 (2H, m), 4.20 (2H, t, *J* 7.4, NCH_2), 7.26-7.33 (2H, m), 7.40-7.42 (1H, m, 7-H), 7.79-7.82 (1H, m, 4-H), 7.98 (1H, s, 2-H); δ_C (100 MHz, $CDCl_3$) 4.6 (2 x CH_2), 10.3 (CH), 29.9, 31.9 (CH_2), 45.2 (NCH_2), 110.0 (7-CH), 119.9 (4-CH), 122.6, 123.2 (5,6-CH), 133.7 (C), 142.8 (2-CH), 142.9 (C); HRMS (ESI): found $M+H^+$, 201.1400. $C_{13}H_{17}N_2$ requires 201.1392.

Experiment 43: 1,1*a*,2,3,4,10*b*-Hexahydrocyclopropa[3,4]azepino[1,2-*a*]indole -10-carbonitrile (3k)



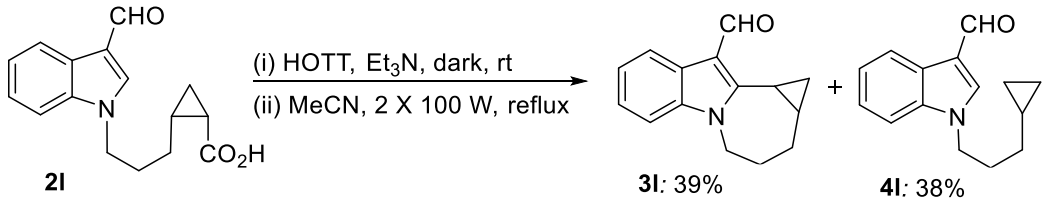
2k **3k***:* 37% **4k***:* 41%

In accordance with procedure 5 gave (63 mg, 37%), white solid, mp 90-91 ˚C, R_f 0.66 (CH_2Cl_2); ν_{max} (neat, cm^{-1}) 2927, 2213 (CN), 1546, 1460, 1418, 1355, 1326, 1278, 1248, 1192, 1042, 1011; δ_H (400 MHz, $CDCl_3$) 0.25-0.37 (1H, m), 0.74 (1H, q, *J* 5.0, 1-H), 1.24-1.32 (1H, m), 1.38-1.43 (1H, m, 1-H), 1.76-1.90 (2H, m), 2.10-2.16 (1H, m), 2.18-2.25 (1H, m), 4.37-4.52 (2H, m, 4-H), 7.19-7.33 (3H, m), 7.67 (1H, d, *J* 7.8, 9-H); δ_C (100 MHz, $CDCl_3$) 10.4, 12.1 (CH), 14.5 (1-CH_2), 23.7, 26.9 (CH_2), 41.4 (4-CH_2), 86.2 (10-C), 109.6 (6-CH), 116.6 (CN), 119.3 (9-CH), 121.7, 123.3 (7,8-CH), 127.6, 134.5, 148.4 (all C); HRMS (ESI): found $M+H^+$, 223.1237. $C_{15}H_{15}N_2$ requires 223.1235.

1-(3-cyclopropylpropyl)-1*H*-indole-3-carbonitrile (4k)

(70 mg, 41%), colourless oil, R_f 0.69 (CH_2Cl_2); ν_{max} (neat, cm^{-1}) 2998, 2929, 2215 (CN), 1530, 1465, 1394, 1360, 1247, 1184, 1141; δ_H (400 MHz, $CDCl_3$) (-0.01)-0.01 (2H, m), 0.42-0.47 (2H, m), 0.62-0.70 (1H, m, CH), 1.20-1.26 (2H, m), 1.93-2.01 (2H, m), 4.18 (2H, t, *J* 7.3, NCH_2), 7.25-7.35 (2H, m), 7.41 (1H, d, *J* 7.8, 7-H), 7.60 (1H, s, 2-H), 7.75 (1H, d, *J* 7.8, 4-H); δ_C (100 MHz, $CDCl_3$) 4.5 (2 x CH_2), 10.2 (CH), 30.0, 31.7 (CH_2), 47.0 (NCH_2), 85.5 (3-C), 110.5 (7-CH), 116.0 (CN), 120.0 (4-CH), 122.0, 123.7 (5,6-CH), 127.9 (C), 134.5 (2-CH), 135.3 (C); HRMS (ESI): found $M+H^+$, 225.1391. $C_{15}H_{17}N_2$ requires 225.1392.

Experiment 44: 1,1a,2,3,4,10*b*-Hexahydrocyclopropa[3,4]azepino[1,2-*a*]indole-10-carbaldehyde (3l)



In accordance with procedure 5 gave (67 mg, 39%), yellow solid, mp 124-125 ˚C, R_f 0.29 (hexane-EtOAc 3:7); IR (ν_{max}, neat/cm^{-1}) 1638 (C=O), 1608, 1573, 1535, 1459, 1428, 1368, 1328, 1282, 1252, 1211, 1188, 1168, 1125, 1077; δ_H (400 MHz, $CDCl_3$) 0.32-0.47 (1H, m), 0.68 (1H, q, *J* 5.0, 1-H), 1.23-1.34 (1H, m), 1.45-1.51 (1H, m, 1-H), 1.79-1.94 (2H, m), 2.16-2.27 (2H, m), 4.37-4.53 (2H, m, 4-H), 7.23-7.31 (3H, m), 8.27-8.31 (1H, m, 9-H), 10.31 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$) 9.4, 11.6 (CH), 15.6 (1-CH_2), 23.5, 26.7 (CH_2), 41.0 (4-CH_2), 108.8 (6-CH), 115.6 (C), 121.7 (9-CH), 122.5, 123.3 (7,8-CH), 125.2, 135.3, 150.9 (all C), 185.6 (CHO); HRMS (ESI): found M+H$^+$, 226.1231. $C_{15}H_{16}NO$ requires 226.1232.

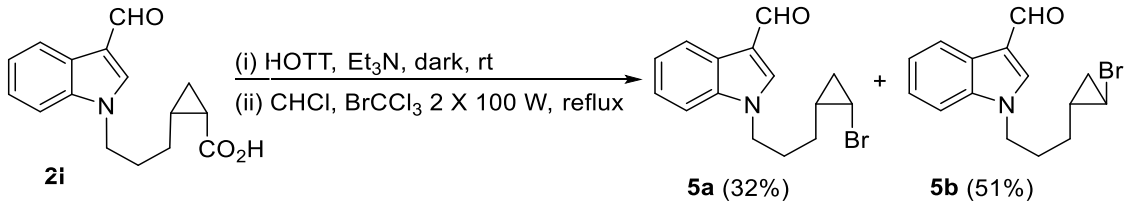
1-(3-cyclopropylpropyl)-1H-indole-3-carbaldehyde (4l)

(66 mg, 38%), yellow oil, R_f 0.36 (hexane-EtOAc 3:7); IR (ν_{max}, neat/cm^{-1}) 1656 (C=O), 1611, 1605, 1578, 1532, 1467, 1398, 1388, 1257, 1170, 1133; δ_H (400 MHz, $CDCl_3$) (-0.01)-0.01 (2H, m), 0.42-0.47 (2H, m), 0.62-0.73 (1H, m), 1.23-1.28 (2H, m), 1.96-2.04 (2H, m), 4.19 (2H, t, *J* 7.3, NCH_2), 7.28-7.38 (3H, m), 7.71 (1H, s, 2-H), 8.28-8.31 (1H, m, 4-H), 9.99 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$) 4.5 (2 x CH_2), 10.3 (CH), 29.8, 31.8 (CH_2), 47.0 (NCH_2), 110.0 (7-CH), 118.0 (C), 122.1, 122.8, 123.9 (all CH), 125.5, 137.2 (C), 138.1 (2-CH), 184.5 (CHO); HRMS (ESI): found M+H$^+$, 228.1380. $C_{15}H_{18}NO$ requires 228.1388.

Procedure for the HOTT-mediated formation of bromides (Procedure 7.)

Et_3N (0.32 mL, 2.30 mmol) in THF (5.7 mL) was added to a mixture of acid **10l** (0.76 mmol) and HOTT (0.424 g, 1.14 mmol) in MeCN (1.9 mL). The solution was stirred at room temperature in the absence of light for 40 min. $BrCCl_3$ (3.7 mL, 38.00 mmol) in $CHCl_3$ (40 mL) was added, and the solution was heated under reflux for 4 h. The solution was evaporated, dissolved in CH_2Cl_2 (10 mL) and washed with H_2O (2 x 10 mL). The organic extract was evaporated and purified by column chromatography using silica gel as absorbent with a gradient elution of hexanes and Et_2O.

Experiment 45: 1-[3-(2′-Bromocyclopropyl)-*cis*-propyl]-1*H*-indole-3-carbaldehyde (5a)



In accordance with procedure 7 gave (74 mg, 32%), yellow oil, R_f 0.74 (Et_2O); IR (ν_{max}, neat/cm^{-1}) 2934, 1653 (C=O), 1614, 1576, 1533, 1486, 1469, 1402, 1390, 1258, 1173, 1135; δ_H (400 MHz, $CDCl_3$) 0.50-0.54 (1H, m, 3′-H), 0.79–0.89 (1H, m, 1′-H), 1.16-1.22 (1H, m, 3′-H), 1.48-1.55 (1H, m), 1.56-1.66 (1H, m), 1.98-2.16 (2H, m, CH_2), 3.03-3.08 (1H, m, 2′-H), 4.21-4.25 (2H, m, NCH_2), 7.29-7.41 (3H, m), 7.74 (1H, s, 2-H), 8.29-8.31 (1H, m, 4-H), 9.99 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$) 15.1 (3′-CH_2), 16.2 (2′-CH), 23.4 (1′-CH), 28.6, 29.2 (CH_2), 47.1 (NCH_2), 110.1 (7-CH), 118.2 (C), 122.3 (4-CH), 123.0, 124.1 (5,6-CH), 125.5, 137.3 (C), 138.2 (2-CH), 184.6 (CHO); HRMS (ESI): found $M+H^+$, 306.0504. $C_{15}H_{17}{}^{79}BrNO$ requires 306.0494.

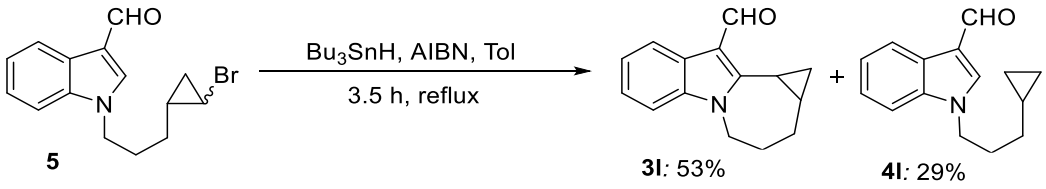
1-[3-(2′-bromocyclopropyl)-*trans*-propyl]-1*H*-indole-3-carbaldehyde (5b)

(0.118 g, 51%), yellow oil, R_f 0.70 (Et_2O); IR (ν_{max}, neat/cm^{-1}) 2931, 1656 (C=O), 1614, 1577, 1532, 1469, 1401, 1389, 1245, 1173, 1134, 1037; δ_H (400 MHz, $CDCl_3$) 0.74-0.79 (1H, m, 3′-H), 1.03 (1H, ddd, *J* 3.7, 6.2, 9.8, 3′-H), 1.18-1.26 (1H, m, 1′-H), 1.31-1.37 (2H, m, CH_2), 2.00–2.08 (2H, m, CH_2), 2.56 (1H, ddd, *J* 3.7, 3.7, 7.4, 2′-H), 4.19-4.24 (2H, m, NCH_2), 7.29-7.40 (3H, m), 7.71 (1H, s, 2-H), 8.29-8.32 (1H, m, 4-H), 10.00 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$) 16.0 (3′-CH_2), 19.3 (2′-CH), 22.3 (1′-CH), 29.1, 30.0 (CH_2), 46.8 (NCH_2), 110.1 (7-CH), 118.3 (C), 122.3 (4-CH), 123.1, 124.1 (5,6-CH), 125.6, 137.2 (C), 138.0 (2-CH), 184.6 (CHO); HRMS (ESI): found $M+H^+$, 306.0493. $C_{15}H_{17}{}^{79}BrNO$ requires 306.0494,

Procedure for the Bu_3SnH-mediated radical cyclisation (Procedure 8.)

A solution of Bu_3SnH (0.116 mL, 0.431 mmol) and AIBN (60 mg, 0.360 mmol) in toluene (4.6 mL) was added to a solution of bromides **14** (0.110 g, 0.360 mmol) in toluene (3.4 mL) under reflux using a syringe pump over 15 min. The reaction was stirred under reflux for 3 h, and a further portion of Bu_3SnH (38 µL, 0.141 mmol) and AIBN (20 mg, 0.120 mmol) in toluene (2 mL) was added over 5 min. The reaction was stirred under reflux for 15 min, and the cooled solution evaporated. EtOAc (5 mL), water (5 mL), and excess KF were added, and the mixture stirred overnight. The organic extract was evaporated and purified by column chromatography using silica gel as absorbant with gradient elution of hexanes and EtOAc.

Experiment 46: 1,1a,2,3,4,10*b*-Hexahydrocyclopropa[3,4]azepino[1,2-*a*]indole-10-carbaldehyde (3l)

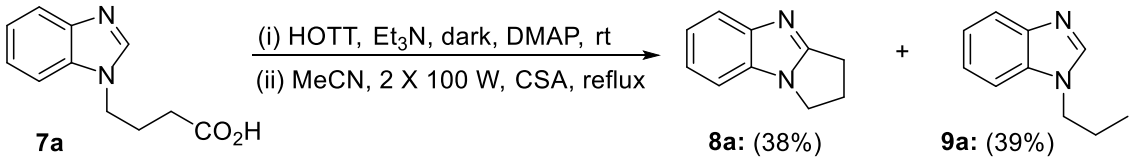


In accordance with procedure 8 gave (43 mg, 53%), yellow solid, mp 124-125 ˚C, R_f 0.29 (hexane-EtOAc 3:7). Physical and spectroscopic data were consistent with that previously reported in experiment 44.

1-(3-cyclopropylpropyl)-1H-indole-3-carbaldehyde (4l)

(24 mg, 29%), yellow oil, R_f 0.36 (hexane-EtOAc 3:7). Physical and spectroscopic data were consistent with that previously reported in experiment 44.

Experiment 47: 2,3-Dihydro-1-pyrrolo[1,2-*a*]benzimidazole (8a)

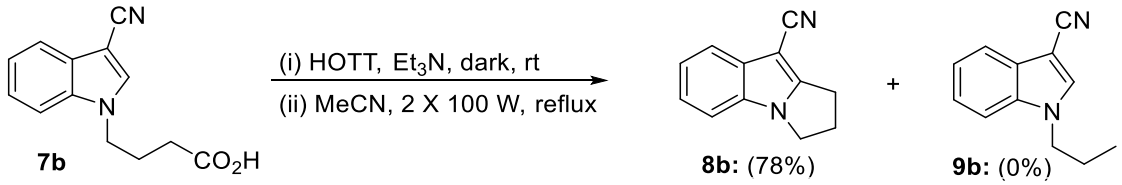


In accordance with procedure 6 gave (46 mg, 38%), off-white solid, mp 110-111 ˚C, lit mp 114-115 ˚C, R_f 0.22 (EtOAc). Physical and spectroscopic data were consistent with that previously reported. [10]

1-Propyl-1*H*-benzimidazole (9a)

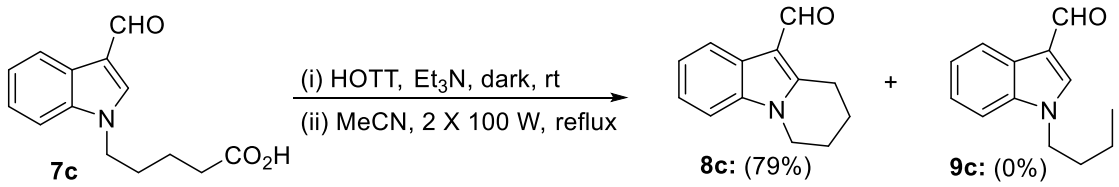
(47 mg, 39%), yellow oil, R_f 0.26 (EtOAc). Physical and spectroscopic data were consistent with that previously reported [10]

Experiment 48: 2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carbonitrile (8b)



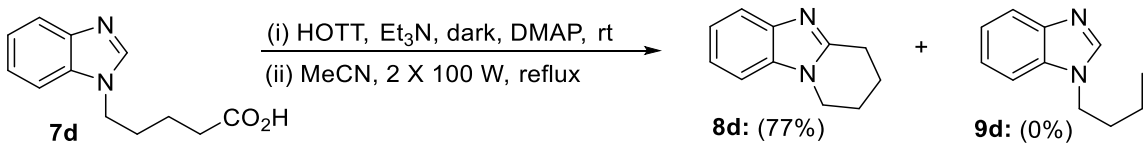
In accordance with procedure 5 gave (0.108 g, 78%), off-white solid, mp 124-126 ˚C, lit[129] mp 126-127 ˚C, R_f 0.57 (CH_2Cl_2); ν_{max} (neat, cm^{-1}) 2894, 2203 (CN), 1551, 1454, 1424, 1366, 1302, 1243, 1174, 1121, 1028; δ_H (400 MHz, $CDCl_3$) 2.66-2.74 (2H, m, 2-CH_2), 3.20 (2H, t, *J* 7.4, 1-CH_2), 4.15 (2H, t, *J* 7.1, 3-CH_2), 7.20-7.29 (3H, m), 7.65-7.67 (1H, m, 8-H); δ_C (100 MHz, $CDCl_3$) 24.8 (2-CH_2), 27.0 (1-CH_2), 45.0 (3-CH_2), 78.0 (9-C), 110.6 (5-CH), 116.6 (CN), 119.8 (8-CH), 121.9, 122.8 (6,7-CH), 132.0, 132.3, 152.9 (all C); HRMS (ESI): found $M+H^+$, 183.0924. $C_{12}H_{11}N_2$ requires 183.0922.

Experiment 49: 6,7,8,9-Tetrahydropyrido[1,2-*a*]indole-10-carbaldehyde (8c)



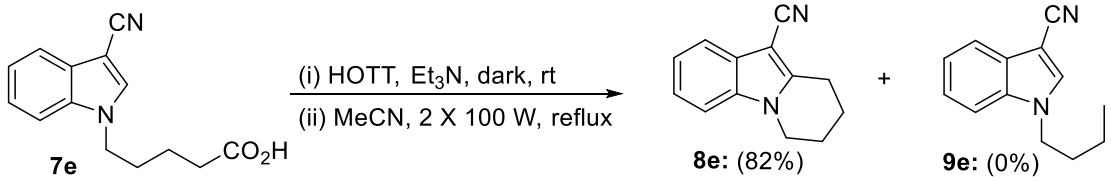
In accordance with procedure 5 gave (0.119 g, 79%), off-white solid, mp 120-122 ˚C, lit mp 121-125 ˚C, R_f 0.17 (CH_2Cl_2). Physical and spectroscopic data were consistent with that previously reported.[130]

Experiment 50: 1,2,3,4-Tetrahydropyrido[1,2-*a*]benzimidazole (8d)



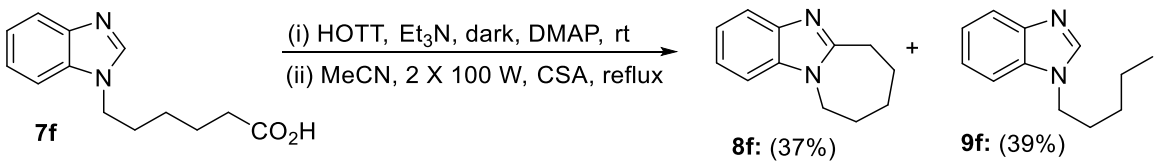
In accordance with procedure 6 gave (0.101 g, 77%), off-white solid, mp 101-103 ˚C, lit mp 98-100 ˚C, R_f 0.32 (EtOAc). Physical and spectroscopic data were consistent with that previously reported. [10]

Experiment 51: 6,7,8,9-Tetrahydropyrido[1,2-*a*]indole-10-carbonitrile (8e)



In accordance with procedure 5 gave (0.122 g, 82%), off-white solid, mp 89-91 ˚C, R_f 0.62 (CH_2Cl_2); ν_{max} (neat, cm^{-1}) 2950, 2203 (CN), 1534, 1491, 1477, 1458, 1424, 1358, 1318, 1245, 1164, 1045; δ_H (400 MHz, $CDCl_3$) 1.93-2.00 (2H, m), 2.09-2.16 (2H, m), 3.11 (2H, t, *J* 6.4, 9-CH_2), 4.08 (2H, t, *J* 6.2, 6-CH_2), 7.21-7.27 (2H, m), 7.29-7.34 (1H, m, 4-H), 7.63-7.68 (1H, m, 1-H); δ_C (100 MHz, $CDCl_3$) 19.9, 22.7 (CH_2), 23.3 (9-CH_2), 42.6 (6-CH_2), 82.6 (10-C), 109.6 (4-CH), 116.6 (CN), 119.0 (1-CH), 122.3, 122.7 (2,3-CH), 127.4, 135.5, 146.3 (all C); HRMS (ESI): found $M+H^+$, 197.1072. $C_{13}H_{13}N_2$ requires 197.1079.

Experiment 52: 7,8,9,10-Tetrahydro-6*H*-azepino[1,2-*a*]benzimidazole (8f)

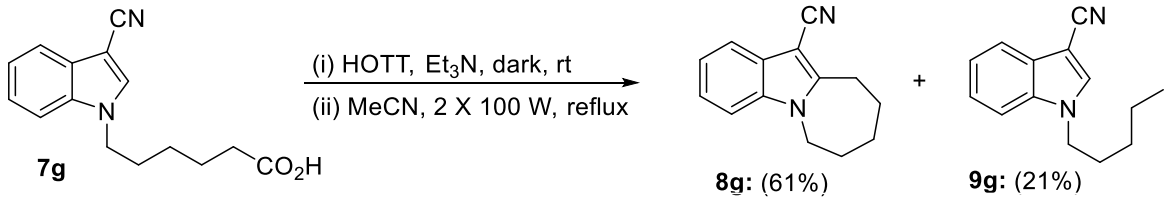


In accordance with procedure 6 gave (52 mg, 37%), off-white solid, mp 118-119 ˚C, lit mp 124-125 ˚C, R_f 0.23 (EtOAc). Physical and spectroscopic data were consistent with that previously reported. [10]

1-Pentyl-1*H*-benzimidazole (9f)

(56 mg, 39%), yellow oil, R_f 0.27 (EtOAc). Physical and spectroscopic data were consistent with that previously reported. [131]

Experiment 53: 7,8,9,10-Tetrahydro-6*H*-azepino[1,2-*a*]indole-11-carbonitrile (8g)



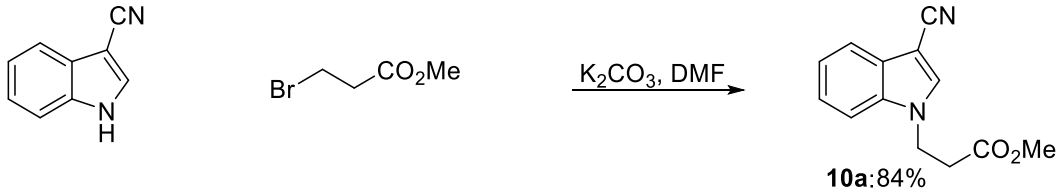
In accordance with procedure 5 gave (98 mg, 61%), off-white solid, mp 112-114 ˚C, R_f 0.64 (CH_2Cl_2); ν_{max} (neat, cm^{-1}) 2931, 2854, 2210 (CN), 1543, 1473, 1461, 1426, 1361, 1331, 1206; δ_H (400 MHz, $CDCl_3$) 1.75-1.82 (4H, m), 1.89-1.95 (2H, m), 3.08 (2H, t, *J* 5.5, 10-CH_2), 4.20 (2H, t, *J* 4.8, 6-CH_2), 7.19-7.33 (3H, m), 7.64-7.67 (1H, m, 1-H); δ_C (100 MHz, $CDCl_3$) 26.7, 27.5, 28.6 (CH_2), 30.8 (10-CH_2), 45.5 (6-CH_2), 84.2 (11-C), 109.7 (4-CH), 116.8 (CN), 119.4 (1-CH), 121.7, 123.0 (2,3-CH), 127.1, 136.0, 151.7 (all C); HRMS (ESI): found $M+H^+$, 211.1234. $C_{14}H_{15}N_2$ requires 211.1235.

1-pentyl-1*H*-indole-3-carbonitrile (9g)

(34 mg, 21%), off-white solid, mp 48-51 ˚C, R_f 0.67 (CH_2Cl_2); ν_{max} (neat, cm^{-1}) 2957, 2931, 2861, 2215 (CN), 1531, 1467, 1394, 1362, 1335, 1244, 1182, 1159, 1138; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.9, CH_3), 1.22-1.37 (4H, m), 1.79-1.87 (2H, m), 4.12 (2H, t, *J* 7.2, NCH_2), 7.24-7.34 (2H, m), 7.39-7.41 (1H, m, 7-H), 7.56 (1H, s, 2-H), 7.72-7.75 (1H, m, 4-H); δ_C (100 MHz, $CDCl_3$) 13.7 (CH_3), 22.0, 28.7, 29.3 (CH_2), 47.1 (NCH_2), 85.1 (3-C), 110.5 (7-CH), 116.0 (CN), 119.6 (4-CH), 121.8, 123.5 (5,6-CH), 127.7 (C), 134.6 (2-CH), 135.1 (C); HRMS (ESI): found $M+H^+$, 213.1387. $C_{14}H_{17}N_2$ requires 213.1392.

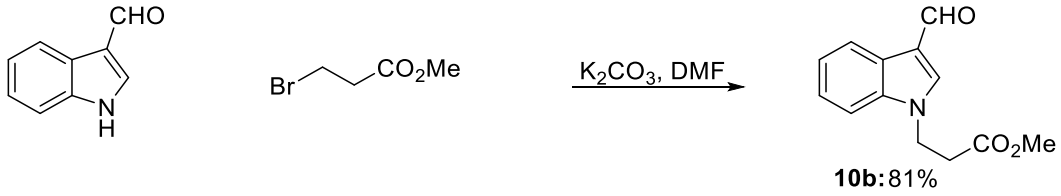
5.3 Experimental for Chapter 3

Experiment 54: Methyl 3-(3-cyano-1*H*-indol-1-yl)propanoate (10a)



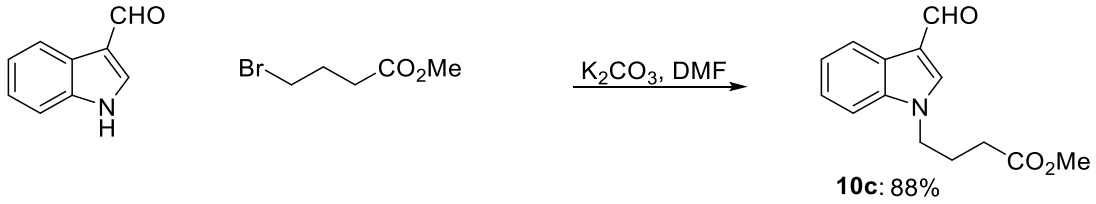
In accordance with procedure 1 gave (0.942 g, 84%), colourless oil, R_f 0.70 **(**Et_2O); IR ν_{max} (neat, cm^{-1}) 3121, 2954, 2216 (CN), 1732 (C=O), 1533, 1468, 1437, 1395, 1363, 1335, 1264, 1197, 1171, 1013; δ_H (400 MHz, $CDCl_3$) 2.84 (2H, t, *J* 6.4 Hz, CH_2), 3.64 (3H, s, OCH_3), 4.46 (2H, t, *J* 6.4 Hz, NCH_2), 7.24-7.34 (2H, m, 5,6-H), 7.40 (1H, d, *J* 8.2 Hz, 7-H), 7.67 (1H, s, 2-H), 7.71 (1H, d, *J* 8.0 Hz, 4-H); δ_C (100 MHz, $CDCl_3$) 34.2 (CH_2), 42.5 (NCH_2), 52.3 (OCH_3), 86.0 (C), 110.4 (7-CH), 115.9 (C), 120.1 (4-CH), 122.4, 124.1 (5,6-CH), 128.0 (C), 135.0 (C), 135.5 (2-CH), 171.2 (C=O); HRMS (ESI): found $M+H^+$, 229.0972. $C_{13}H_{13}N_2O_2$ requires 229.0977.

Experiment 55: Methyl 3-(3-formyl-1*H*-indol-1-yl)propanoate (10b)



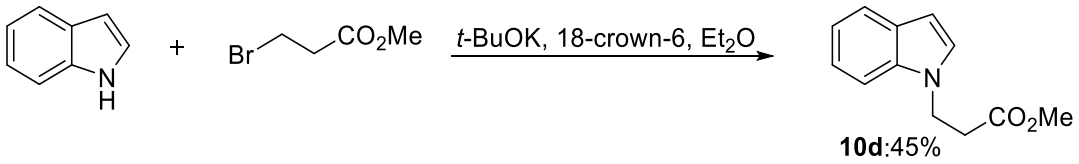
In accordance with procedure 1 gave (0.921 g, 81%), pale yellow oil, R_f 0.29 **(**Et_2O); IR ν_{max} (neat, cm^{-1}) 3109, 2953, 2812, 1732 (C=O ester), 1653 (C=O aldehyde), 1614, 1578, 1531, 1468, 1437, 1401, 1389, 1196, 1166, 1137, 1047; δ_H (400 MHz, $CDCl_3$) 2.86 (2H, t, *J* 6.5 Hz, CH_2), 3.64 (3H, s, OCH_3), 4.46 (2H, t, *J* 6.5 Hz, NCH_2), 7.27-7.33 (3H, m, 5,6,7-H), 7.72 (1H, s, 2-H), 8.27-8.29 (1H, m, 4-H), 9.94 (1H, s, CHO), δ_C (100 MHz, $CDCl_3$) 34.1 (CH_2), 42.6 (NCH_2), 52.2 (OCH_3), 109.8 (7-CH), 118.4 (C), 122.4 (4-CH), 123.1, 124.2 (5,6-CH), 125.5 (C), 136.8 (C), 139.3 (2-CH), 171.3 (COOH), 184.8 (CHO); HRMS (ESI): found $M+H^+$, 232.0963. $C_{13}H_{14}NO_3$ requires 232.0974.

Experiment 56: Methyl 4-(3-formyl-1*H*-indol-1-yl)butanoate (10c)



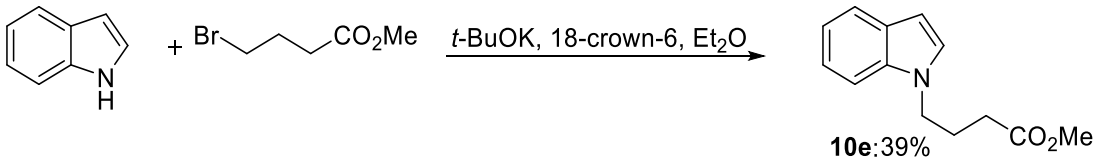
In accordance with procedure 1 gave (1.061 g, 88%), yellow oil, R_f 0.31 (Et_2O); ν_{max} (neat, cm^{-1}) 2951, 1731 (C=O ester), 1653 (C=O aldehyde), 1531, 1468, 1437, 1401, 1388, 1257, 1165, 1152 1074; δ_H (400 MHz, $CDCl_3$) 1.99-2.06 (2H, m, CH_2), 2.20 (2H, t, *J* 7.0 Hz, CH_2), 3.54 (3H, s, OCH_3), 4.07 (2H, t, *J* 7.1 Hz, NCH_2), 7.15-7.22 (2H, m, 5,6-H), 7.26-7.30 (1H, m, 7-H), 7.59 (1H, s, 2-H), 8.17-8.21 (1H, m, 4-H), 9.82 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$) 24.9 (CH_2), 30.5 (CH_2), 46.1 (NCH_2), 51.8 (OCH_3), 110.3 (7-CH), 118.1 (C), 122.0 (4-CH), 122.9, 124.0 (5,6-CH), 125.3 (C), 137.2 (C), 138.9 (2-CH), 172.8 (COOMe), 184.6 (CHO); HRMS (ESI): found $M+H^+$, 246.1139.$C_{14}H_{16}NO_3$ requires 246.1130.

Experiment 57: Methyl 3-(1*H*-indol-1-yl)propanoate (10d)



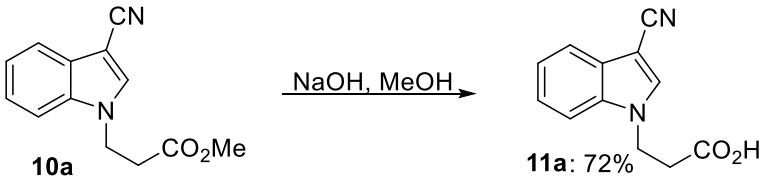
In accordance with procedure 3 gave (0.389 g, 45%), colourless oil, R_f 0.65 **(**CH_2Cl_2); Physical and spectroscopic data were consistent with that previously reported. [132]

Experiment 58: Methyl 4-(1*H*-indol-1-yl)butanoate (10e)



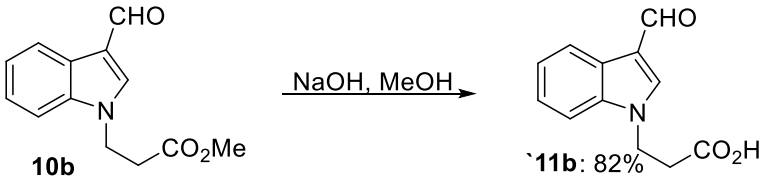
In accordance with procedure 3 gave (0.361 g, 39%), colourless oil, R_f 0.64 **(**CH_2Cl_2); Physical and spectroscopic data were consistent with that previously reported. [132]

Experiment 59: 3-(3-cyano-1*H*-indol-1-yl)propanoic acid (11a)



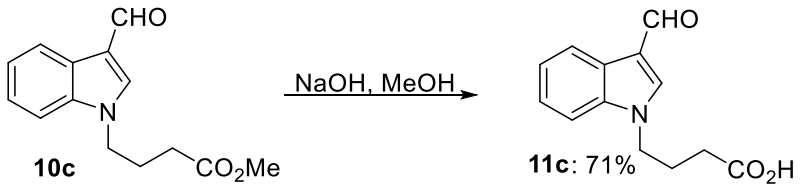
In accordance with procedure 4 except using NaOH in MeOH gave (0.89 g, 72%), off white solid, mp 123-124 ˚C; IR ν_{max} (neat, cm^{-1}) 3123, 2894, 2221 (CN), 1701 (C=O), 1531, 1477, 1445, 1419, 1374, 1334, 1312, 1297, 1242, 1224, 1200, 1066, 1010; δ_H (400 MHz, DMSO-d_6) 2.79 (2H, t, *J* 6.8 Hz, CH_2), 4.44 (2H, t, *J* 6.8 Hz, NCH_2), 7.21-7.32 (2H, m, 5,6-H), 7.60 (1H, d, *J* 7.8 Hz, 7-H), 7.69 (1H, d, *J* 8.2 Hz, 4-H), 8.24 (1H, s, 2-CH);δ_C (100 MHz, DMSO-d_6) 34.6 (CH_2), 42.9 (NCH_2), 84.1 (C), 112.2 (7-CH), 116.5 (C), 119.3 (4-CH), 122.6, 124.0 (5,6-CH), 127.6 (C), 135.5 (C), 137.6 (2-CH), 172.7 (C=O); HRMS (ESI): found $M+H^+$, 215.0820. $C_{12}H_{11}N_2O_2$ requires 215.0821.

Experiment 60: 3-(3-formyl-1*H*-indol-1-yl)propanoic acid (11b)



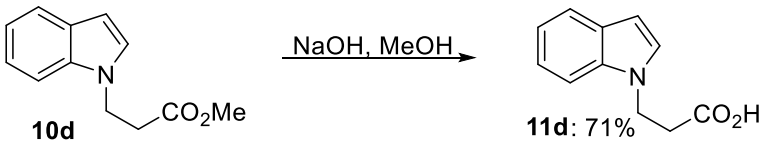
In accordance with procedure 4 except using NaOH in MeOH gave (1.03 g, 82%), yellow brown solid, mp 179-180; Physical and spectroscopic data were consistent with that previously reported.[133]

Experiment 61: 4-(3-Formyl-1*H*-indol-1-yl)butananoic acid (11c)



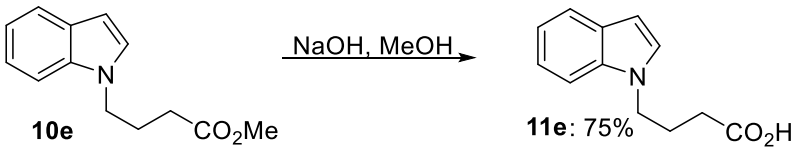
In accordance with procedure 4 except using NaOH in MeOH gave (0.951 g, 71%), yellow solid, mp 139-140 ˚C; ν_{max} (neat, cm^{-1}) 3117, 2935, 2814, 1721 (C=O acid), 1622 (C=O aldehyde), 1575, 1534, 1462, 1398, 1267, 1250, 1185, 1164, 1153, 1080, 1067, 1036, 1012; δ_H (400 MHz, DMSO-d_6) 1.96-2.05 (2H, m, CH_2), 2.24 (2H, t, *J* 7.3 Hz, CH_2), 4.28 (2H, t, *J* 7.1 Hz, NCH_2), 7.22-7.30 (2H, m, 5,6-H), 7.62 (1H, d, *J* 8.2 Hz, 7-H), 8.10 (1H, d, *J* 7.6 Hz, 4-H), 8.30 (1H, s, 2-CH), 9.89 (1H, s, CHO), 12.22 (1H, bs, OH), δ_C (100 MHz, DMSO-d_6) 25.4 (CH_2), 31.1 (CH_2), 46.1 (NCH_2), 111.5 (7-CH), 117.7 (C), 121.6 (4-CH), 123.0, 124.1 (5,6-CH), 125.2, 137.5 (both C), 141.2 (2-CH), 174.3 (COOH), 185.1 (CHO),HRMS (ESI): found $M+H^+$, 232.0963. $C_{13}H_{14}NO_3$ requires 232.0974.

Experiment 62: 3-(1*H*-indol-1-yl)propanoic acid (11d)



In accordance with procedure 4 except using NaOH in MeOH gave (0.778 g, 71%), off white solid, mp 83-84 ˚C; IR Physical and spectroscopic data were consistent with that previously reported. [134]

Experiment 63: 4-(1*H*-indol-1-yl)butanoic acid (11e)

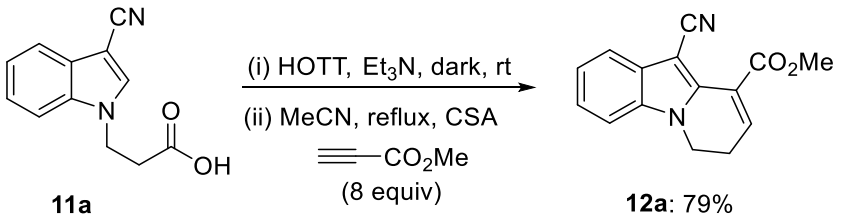


In accordance with procedure 4 except using NaOH in MeOH gave (0.883 g, 75%), yellow oil, Physical and spectroscopic data were consistent with that previously reported. [132]

General Procedure for One-Pot Barton Ester Formation, Alkyne Addition and Aromatic Substitution (Procedure 9.)

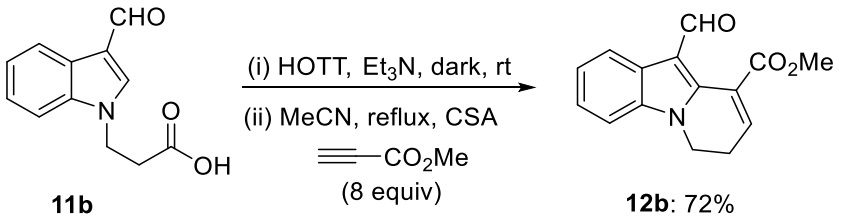
Et_3N (0.32 mL, 2.30 mmol) in THF (5.7 mL) was added to a mixture of carboxylic acid (0.76 mmol) and HOTT (0.424 g, 1.14 mmol) in MeCN (1.9 mL). The solution was stirred at room temperature in the absence of light for 40 min. Alkyne (6.08 mmol) in MeCN (40 mL) and containing CSA (0.711 g, 3.06 mmol) for propiolates was added, and heated under reflux for 6 h. The solution was evaporated, dissolved in CH_2Cl_2 (10 mL) and washed with H_2O (2 x 10 mL). The organic extract evaporated and purified by column chromatography using silica gel as absorbent with a gradient elution of hexanes and CH_2Cl_2 or Et_2O.

Experiment 64: Methyl 10-cyano-6,7-dihydropyrido[1,2-*a*]indole-9-carboxylate (12a)



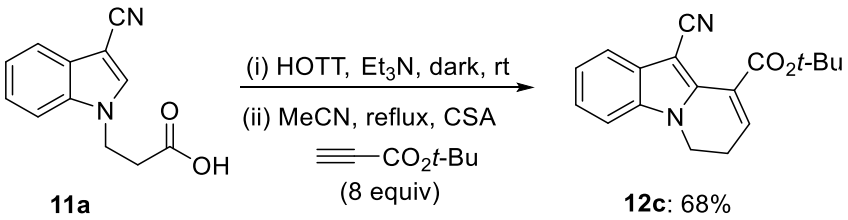
In accordance with procedure 9 gave (0.151 g, 79%), off-white solid, mp 125-126 ˚C, R_f 0.62 (Et_2O); IR ν_{max} (neat, cm^{-1}) 2952, 2215 (CN), 1724 (C=O), 1623, 1473, 1457, 1439, 1337, 1276, 1198, 1082, 1017; δ_H (400 MHz, $CDCl_3$) 2.77-2.83 (2H, m, 7-CH_2), 3.98 (3H, s, OCH_3), 4.17 (2H, t, *J* 7.1 Hz, 6-CH_2), 7.25-7.32 (4H, m), 7.77 (1H, d, *J* 8.2 Hz, 1-H); δ_C (100 MHz, $CDCl_3$) 24.3 (7-CH_2), 39.0 (6-CH_2), 52.2 (OCH_3), 85.1 (CN), 109.6 (4-CH), 115.8 (C), 120.2 (1-CH), 122.4, 124.8 (2,3-CH), 125.7, 128.9, 135.2 (all C), 138.7 (8-CH), 164.4 (C=O); HRMS (ESI): found $M+H^+$, 253.0973. $C_{15}H_{13}N_2O_2$ requires 253.0977.

Experiment 65: Methyl 10-formyl-6,7-dihydropyrido[1,2-*a*]indole-9-carboxylate (12b)



In accordance with procedure 9 gave (0.140 g, 72%), yellow solid, mp 119-120 ˚C, R_f 0.32 (Et_2O); IR ν_{max} (neat, cm^{-1}) 2952, 1724 (C=O ester), 1623(C=O aldehyde), 1473, 1457, 1439, 1337, 1276, 1198, 1082, 1017; δ_H (400 MHz, $CDCl_3$) 2.76 (2H, q, 7.0 Hz, 7-CH_2), 3.88 (3H, s, OCH_3), 4.14 (2H, t, *J* 7.0 Hz, 6-CH_2), 7.24-7.33 (4H, m), 8.36 (1H, d, *J* 7.7 Hz, 1-H), 10.13 (1H, s, CHO), ; δ_C (100 MHz, $CDCl_3$) 24.2 (7-CH_2), 38.6 (6-CH_2), 52.8 (OCH_3), 109.2 (4-CH), 113.5 (C), 122.5 (1-CH), 123.2, 124.5 (2,3-CH), 126.2, 127.1, 136.0, 136.7 (all C), 138.6 (8-CH), 166.3 (COOMe), 186.0 (CHO); HRMS (ESI): found $M+H^+$, 256.0971. $C_{15}H_{14}NO_3$ requires 256.0974.

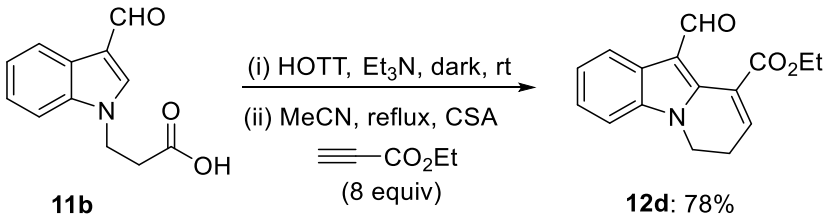
Experiment 66: *tert*-Butyl 10-cyano-6,7-dihydropyrido[1,2-*a*]indole-9-carboxylate (12c)



11a **12c**: 68%

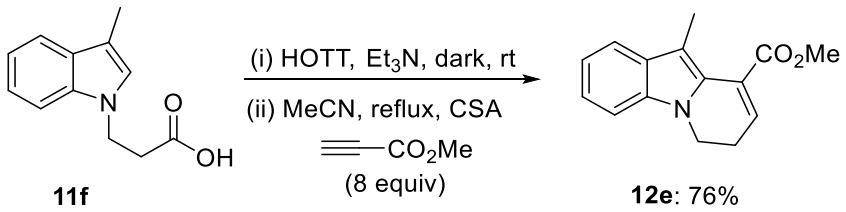
In accordance with procedure 9 gave (0.152 g, 68%), yellow oil, R_f 0.76 (Et_2O); IR ν_{max} (neat, cm^{-1}) 2978, 2217 (CN), 1715 (C=O), 1533, 1457, 1428, 1393, 1368, 1287, 1254, 1163, 1080, 1016; δ_H (400 MHz, $CDCl_3$) 1.65 (9H, s, *t*Bu), 2.73-2.78 (2H, m, 7-CH_2), 4.16 (2H, t, *J* 7.1 Hz, 6-CH_2), 7.17 (1H, t, *J* 4.8 Hz, 8-H), 7.24-7.34 (3H, m), 7.79 (1H, d, *J* 7.8 Hz, 1-H); δ_C (100 MHz, $CDCl_3$) 24.1 (7-CH_2), 28.0 ((*CH*$_3$)C)), 38.8 (6-CH_2), 83.4 (CN), 109.5 (4-CH), 115.9 (C), 120.1 (1-CH), 122.1 124.5, (2,3-CH), 127.5, 128.7, 135.0, 135.7 (all C), 137.3 (8-CH), 163.1 (C=O), HRMS (ESI): found $M+H^+$, 295.1439. $C_{18}H_{19}N_2O_2$ requires 295.1447.

Experiment 67: Ethyl 10-formyl-6,7-dihydropyrido[1,2-*a*]indole-9-carboxylate (12d)



In accordance with procedure 9 (0.160 g, 78%), yellow brown solid, mp 149-151 ˚C, R_f 0.49 (Et_2O); IR ν_{max} (neat, cm^{-1}) 1719 (C=O ester), 1649 (C=O aldehyde), 1456, 1436, 1400, 1333, 1271, 1185, 1130, 1085; δ_H (400 MHz, $CDCl_3$) 1.35 (3H, t, *J* 7.1 Hz, CH_3), 2.73-2.78 (2H, m, 7-CH_2), 4.14 (2H, t, *J* 7.1 Hz, 6-CH_2), 4.36 (2H, q, *J* 7.1 Hz, CH_2), 7.22-7.33 (4H, m), 8.36-8.39 (1H, m, 1-H), 10.15 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 24.2 (7-CH_2), 38.6 (6-CH_2), 62.0 (OCH_2), 109.2 (4-CH), 113.5 (C), 122.6 (1-CH), 123.2, 124.5 (2,3-CH), 126.2, 127.4, 136.0, 136.9 (all C), 138.4 (8-CH), 165.9 (COOMe), 186.1 (CHO); HRMS (ESI): found $M+H^+$, 270.1132. $C_{16}H_{16}NO_3$ requires 270.1130.

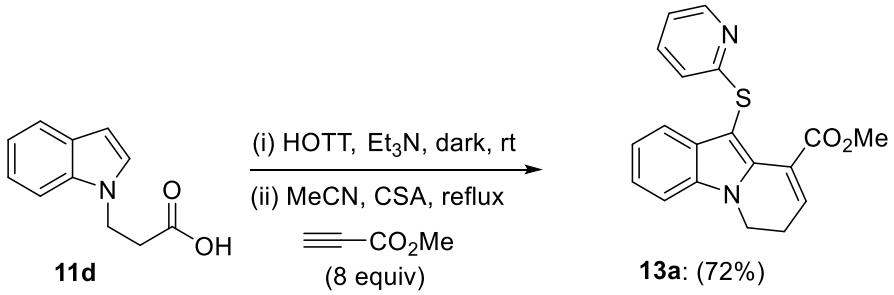
Experiment 68: Methyl 10-methyl-6,7-dihydropyrido[1,2-a]indole-9-carboxylate (12e)



11f **12e**: 76%

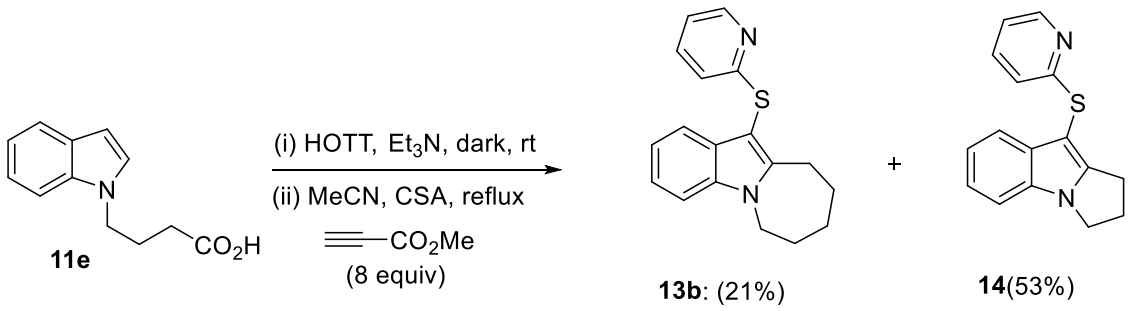
In accordance with procedure 9 (0.139 g, 76%), yellow oil, R_f 0.43 (CH_2Cl_2); IR ν_{max} (neat, cm^{-1}) 2949, 1726 (C=O), 1464, 1438, 1385, 1334, 1271, 1195, 1179, 1077, 1016; δ_H (400 MHz, $CDCl_3$) 2.30 (3H, s, CH_3), 2.63-2.68 (2H, m, 7-CH_2), 3.90 (3H, s, OCH_3), 4.07 (2H, t, *J* 6.6 Hz, 6-CH_2), 6.79 (2H, t, *J* 5.0 Hz, 8-H), 7.05-7.10 (1H m), 7.21-7.22 (2H m), 7.57 (1H, d, *J* 7.8 Hz, 1-H); δ_C (100 MHz, $CDCl_3$) 10.0 (CH_3), 24.8 (7-CH_2), 38.7 (6-CH_2), 52.1 (OCH_3), 108.4 (4-CH), 109.1 (C), 119.0 (CH), 119.3 (1-CH), 122.7 (CH), 127.2, 127.9, 129.0 (all C), 131.8 (8-CH), 135.8 (C), 167.1 (C=O); HRMS (ESI): found $M+H^+$, 242.1178. $C_{15}H_{16}NO_2$ requires 242.1181.

Experiment 69: Methyl 10-(pyridine-2-ylthio)-6,7-dihydropyrido[1,2-*a*]indole-9-carboxylate (13a)



In accordance with procedure 9 gave (0.183 g, 72%), yellow oil, R_f 0.45 (Et_2O); IR ν_{max} (neat, cm^{-1}) 3052, 2947,2983, 1726 (C=O), 1574, 1559, 1448, 1435, 1417, 1341, 1272, 1194, 1170, 1127, 1070; δ_H (400 MHz, $CDCl_3$) 2.72-2.77 (2H, m, 7-CH_2), 3.50 (3H, s, OCH_3), 4.22 (2H, t, *J* 6.8 Hz, 6-CH_2), 6.75 (1H, d, *J* 8.0 Hz, pyr-3-H), 6.78 (1H, t, *J* 4.9 Hz, 8-H), 6.92-6.95 (1H, m, pyr-5-H), 7.11-7.15 (1H, m), 7.28-7.37 (3H, m), 7.56 (1H, d, *J* 8.0 Hz, 1-H), 8.39-8.41 (1H, m, pyr-6-H); δ_C (100 MHz, $CDCl_3$) 24.4 (7-CH_2), 39.3 (6-CH_2), 52.1 (OCH_3), 98.3 (C), 109.2 (4-CH), 119.2 (pyr-5-CH), 120.2 (CH), 121.1, 123.9 (both CH), 128.0, 130.0 (both C), 133.1 (8-CH), 135.1 (C), 136.5 (pyr-4-CH), 149.2 (pyr-6-CH), 162.6 (pyr-2-C), 167.3 (C=O); HRMS (ESI): found $M+H^+$, 337.1003. $C_{19}H_{17}NO_2S$ requires 337.1011.

Experiment 70: Methyl 11-(pyridin-2-ylthio)-7,8-dihydro-6*H*-azepino[1,2-*a*]indole-10-carboxylate (13b)

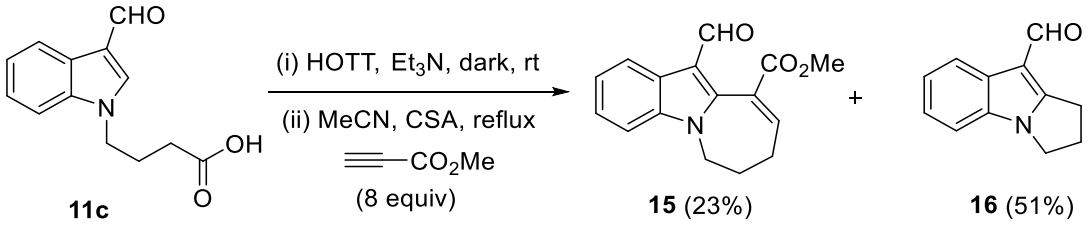


In accordance with procedure 9 gave (56 mg, 21%), yellow oil, R_f 0.55 (Et_2O); IR ν_{max} (neat, cm^{-1}) 2949, 1719 (C=O), 1577, 1559, 1449, 1417, 1265, 1126, 1045; δ_H (400 MHz, $CDCl_3$) 2.21-2.28 (2H, m, 7-CH_2), 2.29-2.35 (2H, m, 8-CH_2), 3.43 (3H, s, OCH_3), 4.28 (2H, t, *J* 6.3 Hz, 6-CH_2), 6.69 (1H, d, *J* 8.3 Hz, pyr-3-H), 6.89-6.92 (1H, m, pyr-5-H), 7.12-7.17 (1H, m), 7.28-7.33 (2H, m), 7.36 (1H, t, *J* 7.0 Hz, 9-H), 7.41 (1H, d, *J* 8.5 Hz, 4-H), 7.57 (1H, d, *J* 8.0 Hz, 1-H), 8.37-8.39 (1H, m, pyr-6-H); δ_C (100 MHz, $CDCl_3$) 25.3, 29.7 (both CH_2), 41.9 (6-CH_2), 52.0 (OCH_3), 99.9 (C), 109.3 (4-CH), 119.0 (pyr-5-H), 119.9 (CH), 120.9, 123.1 (all CH), 128.4, 129.1 (both C), 136.3 (pyr-4-CH), 136.6, 139.3 (both C), 144.0 (9-CH), 149.1 (pyr-6-CH), 162.3 (pyr-2-C), 166.4 (C=O), HRMS (ESI): found $M+H^+$, 351.1180. $C_{20}H_{19}N_2O_2S$ requires 351.1167.

9-(Pyridin-2-ylthio)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole (14)

(107 mg, 53%), off white solid, mp 147-148 ˚C, R_f 0.68 (Et_2O); IR ν_{max} (neat, cm^{-1}) 2953, 1574, 1558, 1449, 1417, 1339, 1298, 1229, 1125, 1010; δ_H (400 MHz, $CDCl_3$) 2.62-2.70 (2H, m, 2-CH_2), 3.08 (2H, t, *J* 7.6 Hz, 1-CH_2), 4.19 (2H, t, *J* 7.1 Hz, 3-CH_2), 6.70 (1H, d, *J* 8.3 Hz, pyr-3-H), 6.89-6.92 (1H, m, pyr-5-H), 7.11-7.15 (1H, m), 7.18-7.22 (1H, m), 7.28-7.33 (2H, m), 7.55 (1H, d, *J* 8.0 Hz, 8-H), 8.39-8.41 (1H, m, pyr-6-H), δ_C (100 MHz, $CDCl_3$) 24.0 (1-CH_2), 27.0 (2-CH_2), 44.8 (3-CH_2), 90.3 (C), 109.9 (5-CH), 118.9 (pyr-5-H), 119.1, 119.2, 120.4, 121.5 (all CH), 133.3, 134.1 (both C), 136.4 (pyr-4-CH), 149.3 (pyr-6-CH), 151.0 (C), 163.3 (pyr-2-C); HRMS (ESI): found $M+H^+$, 267.0963. $C_{16}H_{15}N_2S$ requires 267.0956.

Experiment 71: Methyl 11-formyl-7,8-dihydro-6*H*-azepino[1,2-*a*]indole-10-carboxylate (15)

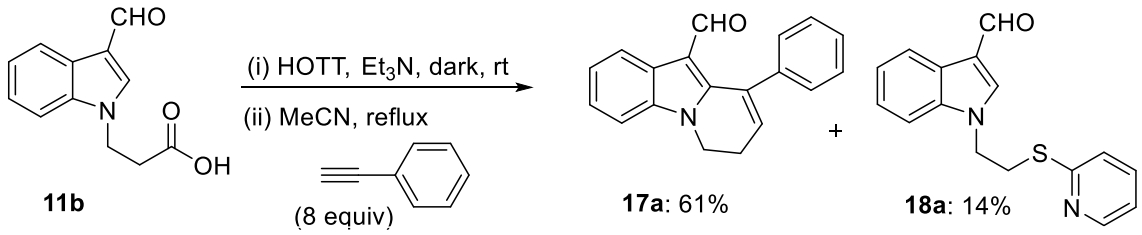


In accordance with procedure 9 gave (47 mg, 23%), yellow oil, R_f 0.33 (Et_2O); IR ν_{max} (neat, cm^{-1}) 2952, 1720 (C=O ester), 1653 (C=O aldehyde), 1575, 1518, 1458, 1438, 1393, 1376, 1267, 1246, 1210, 1128, 1072, 1051; δ_H (400 MHz, $CDCl_3$) 2.31-2.33 (4H, m), 3.82 (3H, s, OCH_3), 4.24 (2H, t, *J* 6.4 Hz, 6-CH_2), 7.30-7.40 (3H, m), 7.69 (1H, t, *J* 7.3 Hz, 9-H), 8.31-8.34 (1H, m, 1-H), 10.03 (1H, s, CHO), δ_C (100 MHz, $CDCl_3$) 24.7, 30.4 (both CH_2), 41.5 (6-CH_2), 52.6 (OCH_3), 109.2 (4-CH), 114.9 (C), 121.7 (1-CH), 123.0, 123.9 (2,3-CH), 125.8, 127.8, 136.2, 142.1 (all C), 147.0 (9-CH), 165.5 (COOMe), 184.8 (CHO), HRMS (ESI): found $M+H^+$, 270.1136. $C_{16}H_{16}NO_3$ requires 270.1130.

2,3-Dihydro-1H-pyrrolo[1,2-*a*]indole-9-carbaldehyde (16)

(72 mg, 51%), off white solid, mp 134-135 °C, lit mp 136 °C. Physical and spectroscopic data were consistent with that previously reported [12]

Experiment 72: 9-Phenyl-6,7-dihydropyrido[1,2-*a*]indole-10-carbaldehyde (17a)

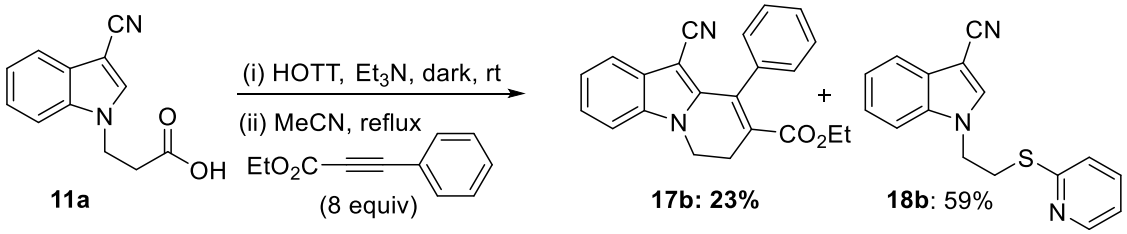


In accordance with procedure 9 gave (0.127 g, 61%), yellow solid, 123-124 °C, R_f 0.65 (Et_2O); IR ν_{max} (neat, cm^{-1}) 2978, 1643 (C=O), 1576, 1469, 1456, 1428, 1394, 1368, 1331, 1300, 1175, 1127, 1067, 1020; δ_H (400 MHz, $CDCl_3$) 2.74-2.80 (2H, m, 7-CH_2), 4.22 (2H t, *J* 7.1 Hz, , 6-CH_2), 6.33 (1H, t, *J* 5.0 Hz, 8-H), 7.26-7.29 (1H, m), 7.30-7.45 (7H, m), 8.41 (1H, d, *J* 7.8 Hz, 1-H), 9.20 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$) 24.0 (7-CH_2), 39.4 (6-CH_2), 109.0 (4-CH), 113.8 (C), 122.1, 123.2, 124.4 (1,2,3-CH), 126.2 (C), 128.3, 128.6 (Ph-CH), 129.0 (8-CH, Ph-CH), 134.5, 136.2, 139.9, 142.2 (all C), 186.9 (CHO), HRMS (ESI): found $M+H^+$, 274.1229. $C_{19}H_{16}NO$ requires 274.1232.

1-[2-(pyridin-2-ylthio)ethyl]-1*H*-indole-3-carbaldehyde (**18a**)

(30 mg, 14%), pale yellow oil, R_f 0.35 (**E**t_2O); IR ν_{max}(neat, cm^{-1}) 3046, 2809, 1655 (C=O), 1558, 1577, 1531, 1467, 1454, 1415, 1400, 1388, 1164, 1151, 1125, 1043; δ_H (400 MHz, $CDCl_3$) 3.55 (2H, t, *J* 7.1 Hz, CH_2), 4.48 (2H, t, *J* 7.1 Hz, NCH_2), 6.98-7.02 (1H, m, pyr-5-H), 7.14 (1H, d, *J* 8.2 Hz, pyr-3-H), 7.27-7.36 (2H, m, 5,6-H), 7.43-7.48 (1H, m, pyr-4-H), 7.56 (1H, d, *J* 8.3 Hz, 7-H), 7.72 (1H, s, 2-H), 8.28 (1H, d, *J* 7.8 Hz, 4-H), 8.41-8.43 (1H, m, pyr-6-H), 9.95 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$) 29.3 (CH_2), 47.1 (NCH_2), 110.4 (7-CH), 118.3 (C), 120.1 (pyr-5-CH), 122.2 (4-CH), 122.7, 123.0 (5-6-CH), 124.1 (pyr-3-CH), 125.5 (C), 136.3 (pyr-4-CH), 137.2 (C), 139.0 (2-CH), 149.6 (pyr-6-CH), 156.9 (pyr-2-C), 184.7 (CHO); HRMS (ESI): found $M+H^+$, 283.0911. $C_{16}H_{15}N_2OS$ requires 283.0905.

Experiment 73: ethyl 10-cyano-9-phenyl-6,7-dihydropyrido[1,2-*a*]indole-8-carboxylate (**17b**)

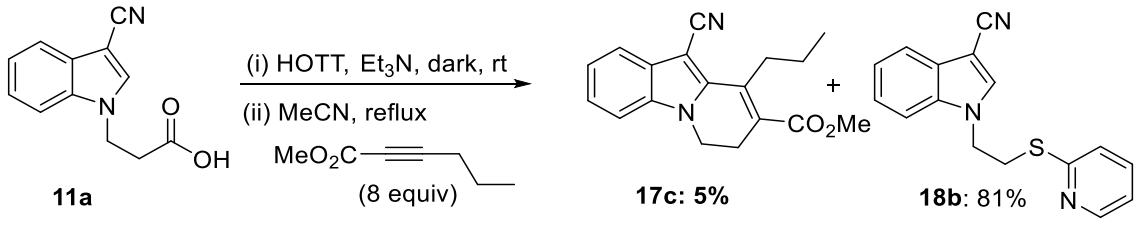


In accordance with procedure 9 gave (60 mg, 23%), off-white solid, mp 119-120 ˚C, R_f 0.31 **(**CH_2Cl_2); IR ν_{max}(neat, cm^{-1}) 2980, 2213 (CN), 1696 (C=O), 1475, 1426, 1378, 1296, 1247, 1216, 1130, 1110, 1017; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.2 Hz, CH_3), 3.11 (2H, t, *J* 7.2 Hz, 7-CH_2), 3.98 (2H, q, *J* 7.2 Hz, OCH_2), 4.31 (2H, t, *J* 7.2 Hz, 6-CH_2), 7.21-7.30 (3H, m), 7.35-7.40 (2H, m), 7.43-7.53 (3H, m), 7.68 (1H, d, *J* 8.0 Hz, 1-H), δ_C (100 MHz, $CDCl_3$) 13.6 (CH_3), 25.7 (7-CH_2), 40.0 (6-CH_2), 61.0 (OCH_2), 88.3 (C), 109.9 (4-CH), 113.6 (CN), 120.3 (1-CH), 122.5, 125.5 (2,3-CH), 126.6 (C), 128.5, 129.0 129.1 (Ph-CH), 129.2, 135.8, 135.9, 137.5 (C), 140.1 (C), 167.3 (C=O), HRMS (ESI): found $M+H^+$, 343.1444. $C_{22}H_{19}N_2O_2$ requires 343.1447.

1-[2-(Pyridin-2-ylthio)ethyl]-1*H*-indole-3-carbonitrile (**18b**)

(0.125 g, 59%), pale yellow oil, R_f 0.28 **(**CH_2Cl_2); IR ν_{max}(neat, cm^{-1}) 2927, 2217 (CN), 1578, 1558, 1533, 1467, 1455, 1415, 1392, 1349, 1283, 1250, 1167, 1125, 1015; δ_H (400 MHz, $CDCl_3$) 3.55 (2H, t, *J* 7.1 Hz, CH_2), 4.50 (2H, t, *J* 7.1 Hz, NCH_2), 7.00-7.04 (1H, m, pyr-5-H), 7.15 (1H d, *J* 7.8 Hz, , pyr-3-H), 7.26-7.37 (2H, m, 5,6-H), 7.46-7.52 (1H, m, 7-H), 7.61 (1H, d, *J* 8.2 Hz, 4-H), 7.64 (1H, s, 2-H), 7.73 (1H, d, *J* 8.3 Hz, pyr-4-H), 8.42 (1H, d, *J* 5.0 Hz, pyr-6-H), δ_C (100 MHz, $CDCl_3$) 29.4 (CH_2), 47.1 (NCH_2), 85.8 (3-C), 110.9 (7-CH), 116.1 (CN), 120.0 (4-CH), 120.1 (pyr-5-CH), 122.3, 122.8 (5,6-CH), 124.0 (ppy-3-CH), 128.0 (C), 135.3 (2-CH), 135.4 (C), 136.4 (pyr-4-CH), 149.4 (pyr-6-CH), 156.7 (pyr-2-C), HRMS (ESI): found $M+H^+$, 280.0905. $C_{16}H_{14}N_3S$ requires 280.0908.

Experiment 74: Methyl 10-cyano-9-propyl-6,7-dihydropyrido[1,2-*a*]indole-8-carboxylate (17c)



In accordance with procedure 9 gave (11 mg, 5%), pale yellow solid, mp 166-167 ˚C, R_f 0.63 **(**Et_2O); IR ν_{max}(neat, cm^{-1}) 2925, 2215 (CN), 1715 (C=O), 1596, 1457, 1423, 1292, 1272, 1245, 1213, 1086; δ_H (400 MHz, $CDCl_3$) 1.08 (3H, t, *J* 7.3 Hz, CH_3), 1.66-1.76 (2H, m, CH_2), 2.93 (2H, t, *J* 7.1 Hz, 7-CH_2), 3.18 (2H, t, *J* 8.0 Hz, CH_2), 3.85 (3H, s, OCH_3), 4.15 (2H, t, *J* 7.1 Hz, 6-CH_2), 7.25-7.29 (1H, m), 7.33-7.39 (2H, m), 7.77 (1H, d, *J* 8.0 Hz, 1-H); δ_C (100 MHz, $CDCl_3$) 13.9 (CH_3), 23.8, 25.6, 31.2 (all CH_2), 39.9 (6-CH_2), 52.1 (OCH_3), 85.4 (C), 109.9 (4-CH), 116.3 (CN), 120.1 (1-CH), 121.9 (C), 122.6, 125.3 (2,3-CH), 128.9 (C), 135.4 (C), 139.9 (C), 149.9 (C), 167.5 (C=O); HRMS (ESI): found $M+H^+$, 295.1445. $C_{18}H_{19}N_2O_2$ requires 295.1447.

1-[2-(pyridin-2-ylthio)ethyl]-1H-indole-3-carbonitrile (**18b**)

(0.172 g, 81%), pale yellow oil, R_f 0.28 **(**CH_2Cl_2). Physical and spectroscopic data were consistent with that previously reported in experiment 73.

5.4 Experimental for Chapter 4

5.4.1 Cell culture and cytotoxicity evaluation

5.4.1.1 Cell lines

DU145 prostate cancer cell line (ATCC repository number HTB-81) was obtained from Prof. William Watson, School of Medicine & Medical Science, University College Dublin, Ireland. SV40-transformed human normal skin fibroblast cell line (repository number GM00637) was obtained from the National Institute for General Medical Sciences (NIGMS) Human Genetic Cell Repository (Coriell Institute for Medical Research, New Jersey, USA). The MCF-7 breast cancer cell line was obtained from Dr. Adrienne Gorman, Biochemistry, School of Natural Sciences, National University of Ireland, Galway.

Cell culture reagents were obtained from Sigma-Aldrich and sterile plastic ware was obtained from Sarstedt AG (Numbrecht, Germany).

The SV40-transformed human normal skin fibroblast cell line (GM00637) was grown in Minimum Essential Media (MEM) Eagle-Earle's BSS supplemented with 15% non heat-inactivated fetal bovine serum (FBS), 1% penicillin-streptomycin, 2mM $_{L}$-glutamine, 2X essential and non-essential amino acids and 2X vitamins. MCF-7 breast cancer cells were cultured in Dulbecco's modified Eagle's medium (DMEM) containing high glucose (4.5g/mL) and supplemented with 10% heat-inactivated FBS and 1% penicillin-streptomycin. DU145 prostate cancer cells were grown in RPMI-1640 medium supplemented with 10% non heat-inactivated fetal bovine serum, penicillin-streptomycin and 2 mM L-glutamine. All cell lines grew as adherent cultures.

Cell culture procedures were carried out in a Class III Bio-Safety Cabinet (Medical Supply Company, Dublin, Ireland). Disposable sterile plastic ware was used for all cell culture protocols. Surfaces were sprayed with 70% ethanol prior to carrying out procedures. Cells were grown in 75 cm^3 flasks in 20 mL of medium, and incubated in an autoflow CO_2 water-jacket incubator at 37 °C and 5% CO_2

When cells were approximately 80% confluent, they were subcultured by treatment with 2X trypsin-EDTA in Hanks balanced salt solution for five minutes. Cells were centrifuged at 1,200 rpm in a Rotanta 300 centrifuge and the cell pellet was re-suspended in fresh culture medium. The total cell number was determined using a Kova® Glasstic® Slide 10 combination coverslip-microslip slide. When cells did not need to be counted the GM00637 stock was seeded at 1/4, MCF-7 at 1/10 and DU145 at 1/6 and were added to 20 mL of pre warmed medium in a sterile 75 cm^3 flask and incubated at 37 °C and 5% CO_2. Cell culture medium was changed every two-three days.

5.4.1.2 Cell resuscitation

All cell lines were resuscitated by rapid thawing of the cell suspension at 37 °C. 1 mL of pre-warmed culture medium was added to a 25 cm^3 sterile culture flask followed by the thawed cell suspension, and a further 5 mL of pre warmed culture medium was added. The cells were incubated at 37 °C and 5% CO_2 and the culture medium was changed the following day.

5.4.1.3 Cytotoxicity measurements using the MTT assay

Cell viability was determined using the MTT colorimetric assay.[135] Cells were plated into 96-well plates at a density of 10,000 cells per well (GM00637, 200 µL per well), 1,000 cells per well (MCF-7, 200 µL per well) and 2,000 cells per well (DU145, 200 µL per well) and allowed to adhere over a period of 24 hours. Drug solutions were applied in DMSO. All cells were incubated at 37 °C under a humidified atmosphere containing 5% CO_2 for 72 hours. Control cells were exposed to an equivalent concentration of DMSO control alone. MTT (20µL, 5mg/mL solution) was added and the cells were incubated for a further 4 hours. The supernatant was then removed by careful pipetting. The resultant MTT formazan crystals were dissolved in 100 µL of DMSO and absorbance was determined using a Wallac Victor 2 1420 multilabel counter plate reader at 550 nm with a reference at 690 nm. Cell viability is expressed as a percentage of the DMSO-only treated control value. Dose-response curves were analyzed by nonlinear regression analysis and IC_{50} values were estimated by using GraphPad Prism software, v.5.02 (GraphPad Inc., San Diego, CA, USA). The *in vitro* activity of the drugs towards all cell lines is expressed as IC_{50} (i.e. concentration required for the reduction of the mean cell viability to 50%).

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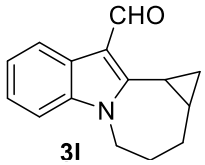
Appendix

A.1 X-Ray crystallographic data

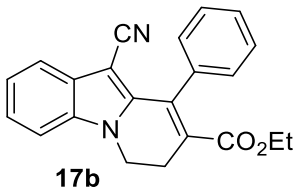
Table A.1; X-ray crystallographic data and structure refinement for 1,1a,2,3,4,10*b*-hexahydrocyclopropa[3,4]azepino[1,2-*a*]indole-10-carbaldehyde (**3l**).



3l

CCDC reference number	936651
Empirical formula	$C_{15}H_{15}NO$
Formula weight	225.28
Temperature	297.5 K
Wavelength	0.7107 Å
Crystal system	Monoclinic
Space group	P21/n
Unit cell dimensions	a = 11.5247 34)Å α = 90.00 º
	b = 8.3392(2)Å β = 90.631(3) º
	12.1937(4) (3) Å 90.00 º
Volume	1171.82(6) $Å^3$
Z	4
Density (calculated)	1.277 Mg/m^3
Absorption coefficient	0.080 mm^{-1}
F(000)	480
Crystal size	0.50 x 0.40 x 0.20 mm
Theta range for data collection	2.9534 to 29.0568 º.
Index ranges	-15<=h<=14; -10<=k<=10; -16<=l<=10
Reflections collected	2994
Independent reflections	2139 [R_{int} = 0.0177]
Reflections observed (>2□)	1885
Data Completeness	0.998
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.98902
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1805 / 1 / 142
Goodness-of-fit on F^2	1.071
Final R indices [I>2□(I)]	R_1 = 0.0428 wR_2 = 0.0993
R indices (all data)	R_1 = 0.0369 wR_2 = 0.0988
Largest diff. peak and hole	0.240 and -0.196 e.$Å^{-3}$

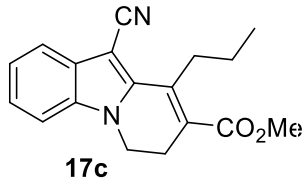
Table A.2; X-ray crystallographic data and structure refinement for ethyl 10-cyano-9-phenyl-6,7-dihydropyrido[1,2-*a*]indole-8-carboxylate (**17b**).



17b

CCDC reference number	996100
Empirical formula	$C_{22}H_{18}N_2O_2$
Formula weight	342.38
Temperature	297.0 K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 9.2424(14) Å α = 66.357(16) º
	b = 10.0425(19) Å β = 76.443(13) º
	c = 11.6734(18) Å γ = 63.890(16) º
Volume	889.0(3) $Å^3$
Z	2
Density (calculated)	1.279 Mg/m^3
Absorption coefficient	0.081 mm^{-1}
F(000)	362
Crystal size	0.50 x 0.40 x 0.20 mm
Theta range for data collection	3.7610 to 24.9830 º.
Index ranges	-11<=h<=9; -10<=k<=12; -14<=l<=14
Reflections collected	3247
Independent reflections	2118 [R_{int} = 0.0280]
Reflections observed (>2□)	1248
Data Completeness	0.998
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.98965
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1911 / 0 / 163
Goodness-of-fit on F^2	1.049
Final R indices [I>2□(I)]	R_1 = 0.1187 wR_2 = 0.2810
R indices (all data)	R_1 = 0.0840 wR_2 = 0.2505
Largest diff. peak and hole	0.412 and -0.318 e.$Å^{-3}$

Table A.3; X-ray crystallographic data and structure refinement for Methyl 10-cyano-9-propyl-6,7-dihydropyrido[1,2-*a*]indole-8-carboxylate (**17c**).



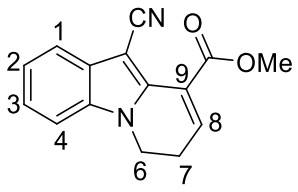
17c

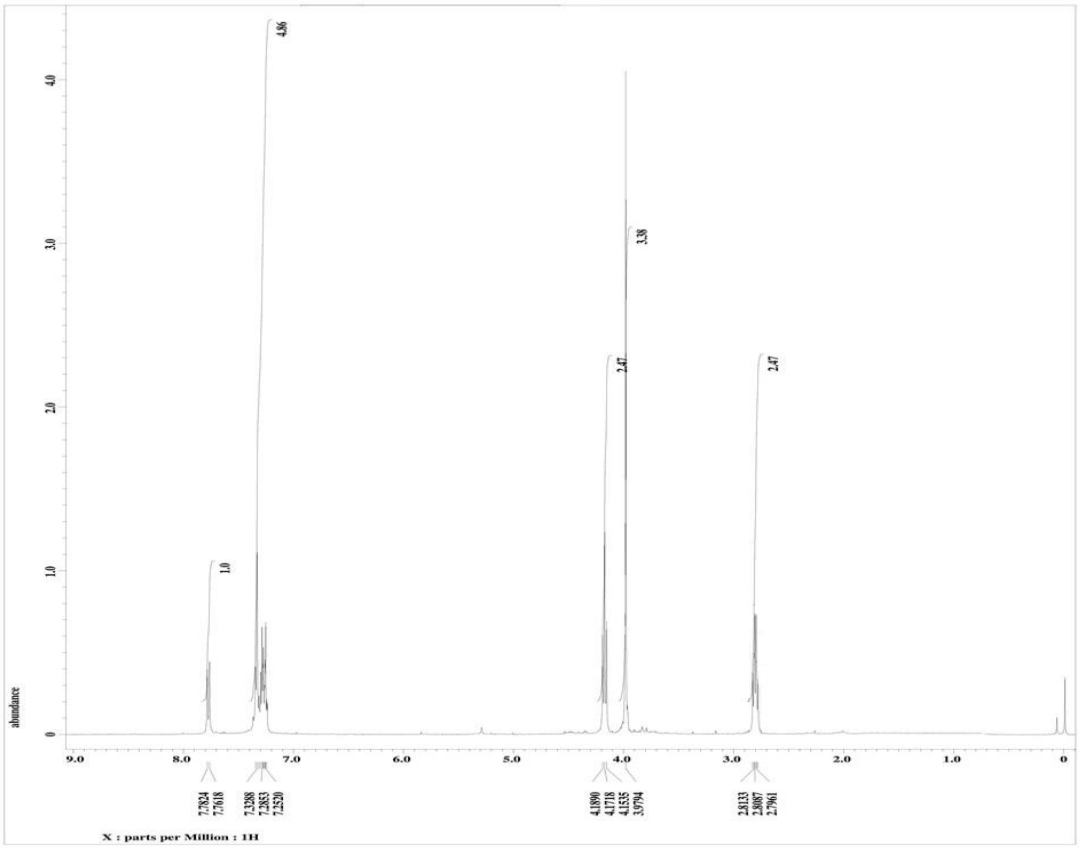
CCDC reference number	996099
Empirical formula	$C_{18}H_{18}N_2O_2$
Formula weight	294.34
Temperature	297.8 K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P -1
Unit cell dimensions	a = 9.088(4) Å α= 101.612(20)°.
	b = 12.184(3) Å β= 90.49(3)°.
	c = 15.086(3) Å γ = 107.47(3)°.
Volume	1556.7(9) $Å^3$
Z	4
Density (calculated)	1.256 Mg/m^3
Absorption coefficient	0.083 mm^{-1}
F(000)	624
Crystal size	5.00 x 0.10 x 0.02 mm^3
Theta range for data collection	3.373 to 25.349°.
Index ranges	-10<=h<=6, -14<=k<=14, -18<=l<=18
Reflections collected	10701
Independent reflections	5638 [R(int) = 0.0866]
Reflections observed (>2□)	1406
Data Completeness	99.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.83332
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5638 / 348 / 401
Goodness-of-fit on F^2	0.940
Final R indices [I>2□(I)]	R_1 = 0.1188, wR_2 = 0.1879
R indices (all data)	R_1 = 0.2932, wR_2 = 0.2696
Largest diff. peak and hole	0.216 and -0.215 $e.Å^{-3}$

A.2 NMR for Chapter 3

***Methyl 10-cyano-6,7-dihydropyrido[1,2-a]indole-9-carboxylate* (12a)**

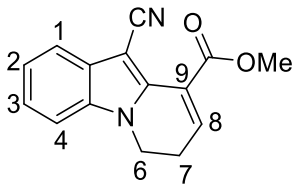
^{1}H NMR, 400 MHz, $CDCl_3$

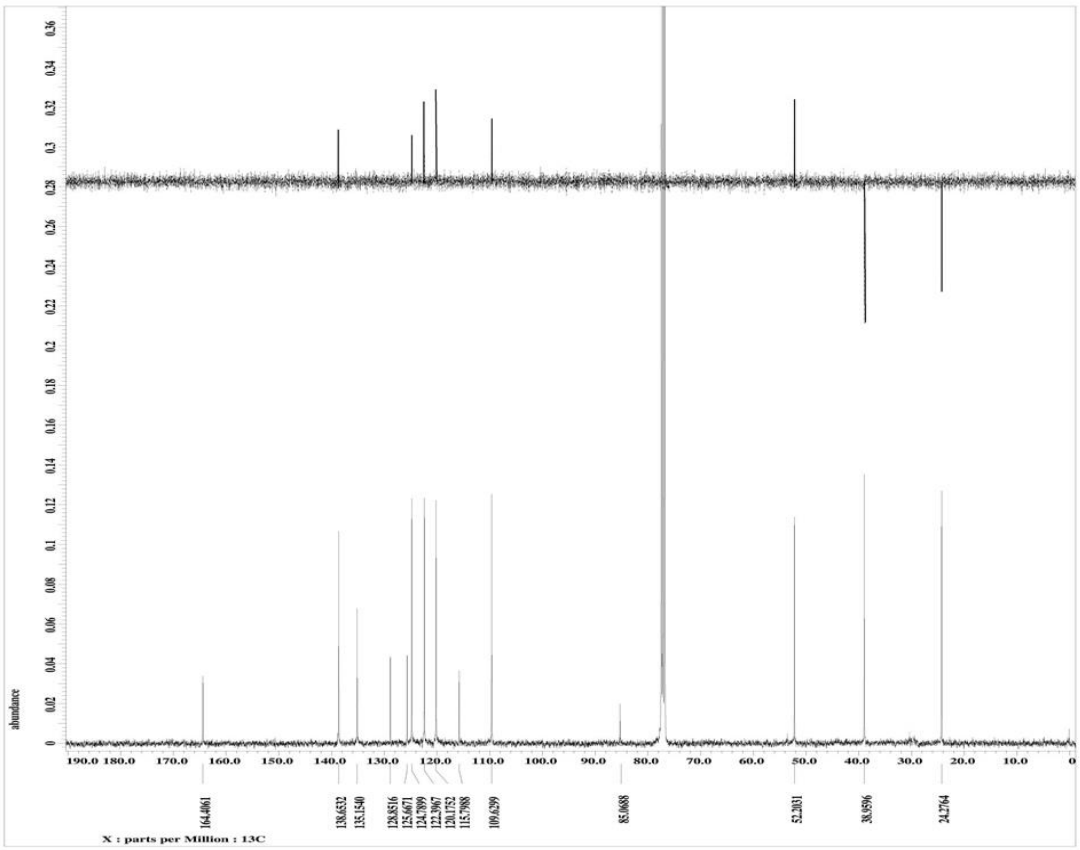




Methyl 10-cyano-6,7-dihydropyrido[1,2-a]indole-9-carboxylate **(12a)**

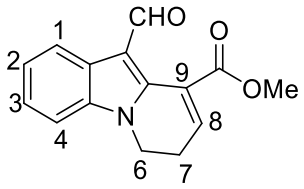
^{13}C NMR, 100 MHz, $CDCl_3$

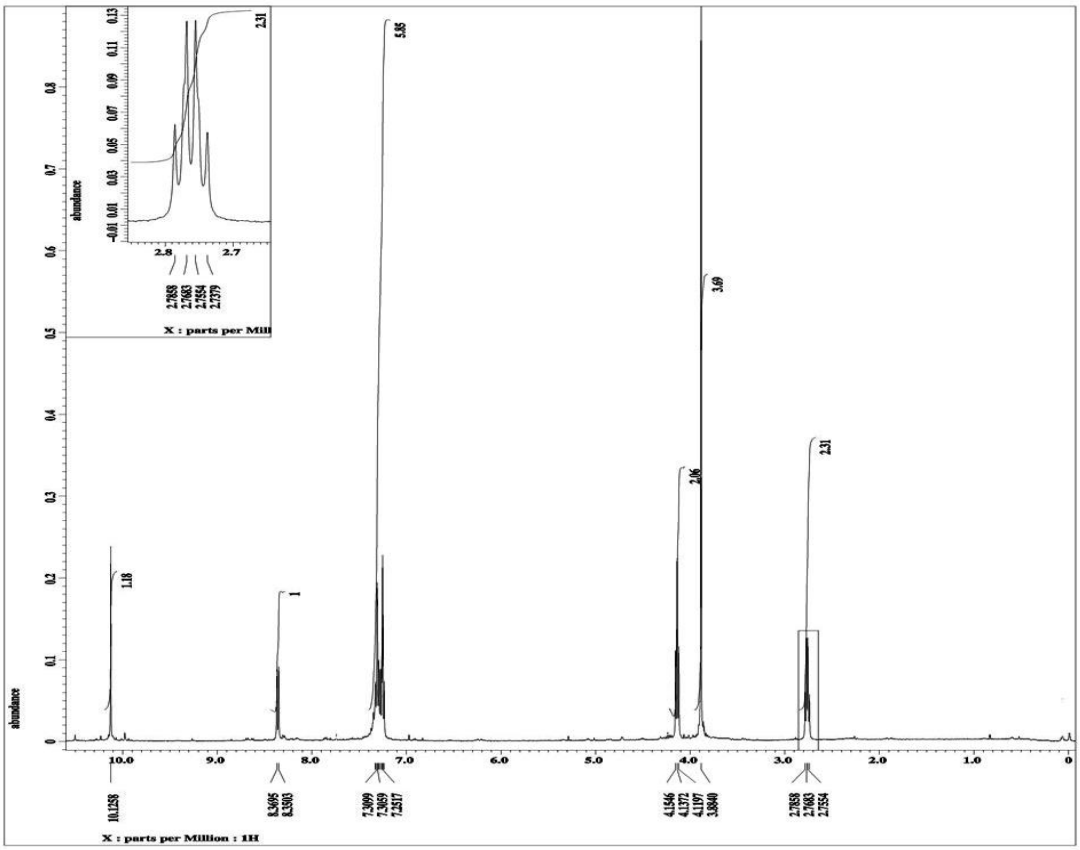




Methyl 10-formyl-6,7-dihydropyrido[1,2-a]indole-9-carboxylate **(12b)**

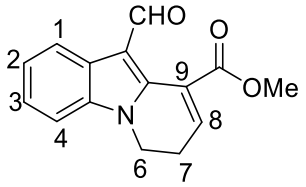
^{1}H NMR, 400 MHz, $CDCl_3$

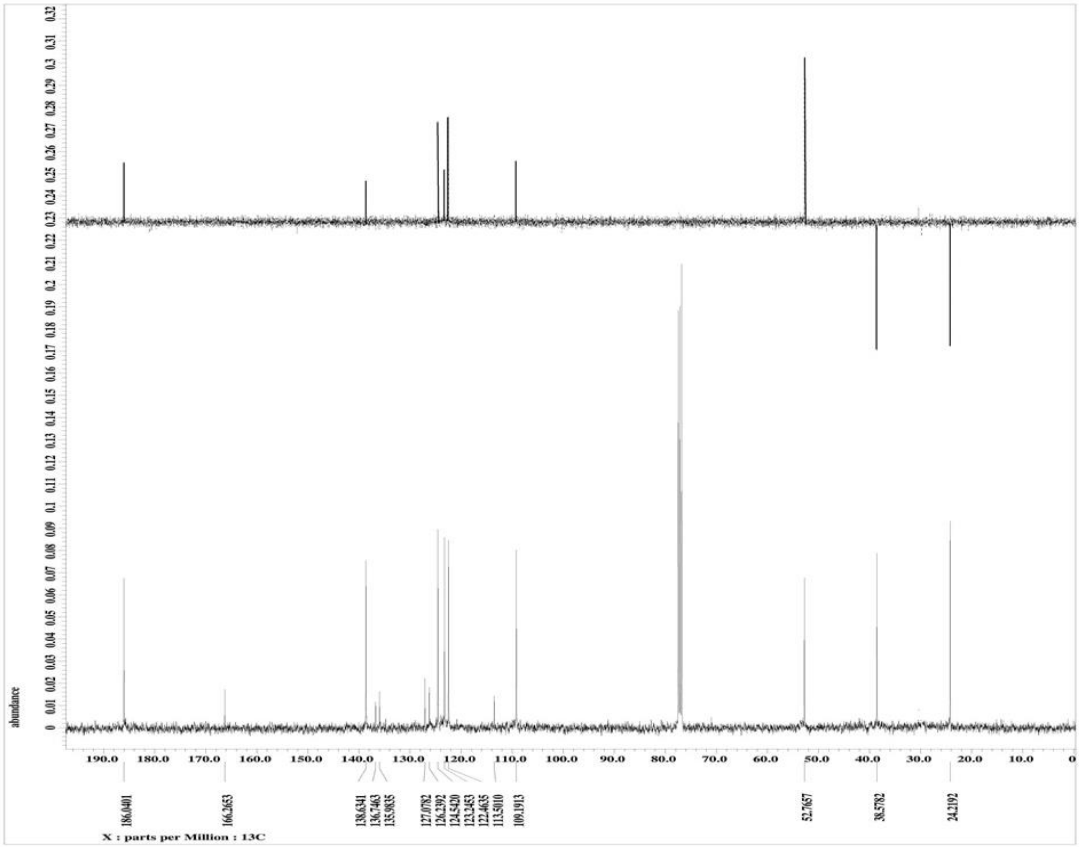




Methyl 10-formyl-6,7-dihydropyrido[1,2-a]indole-9-carboxylate **(12b)**

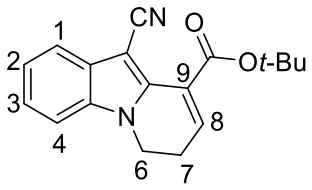
^{13}C NMR, 100 MHz, $CDCl_3$

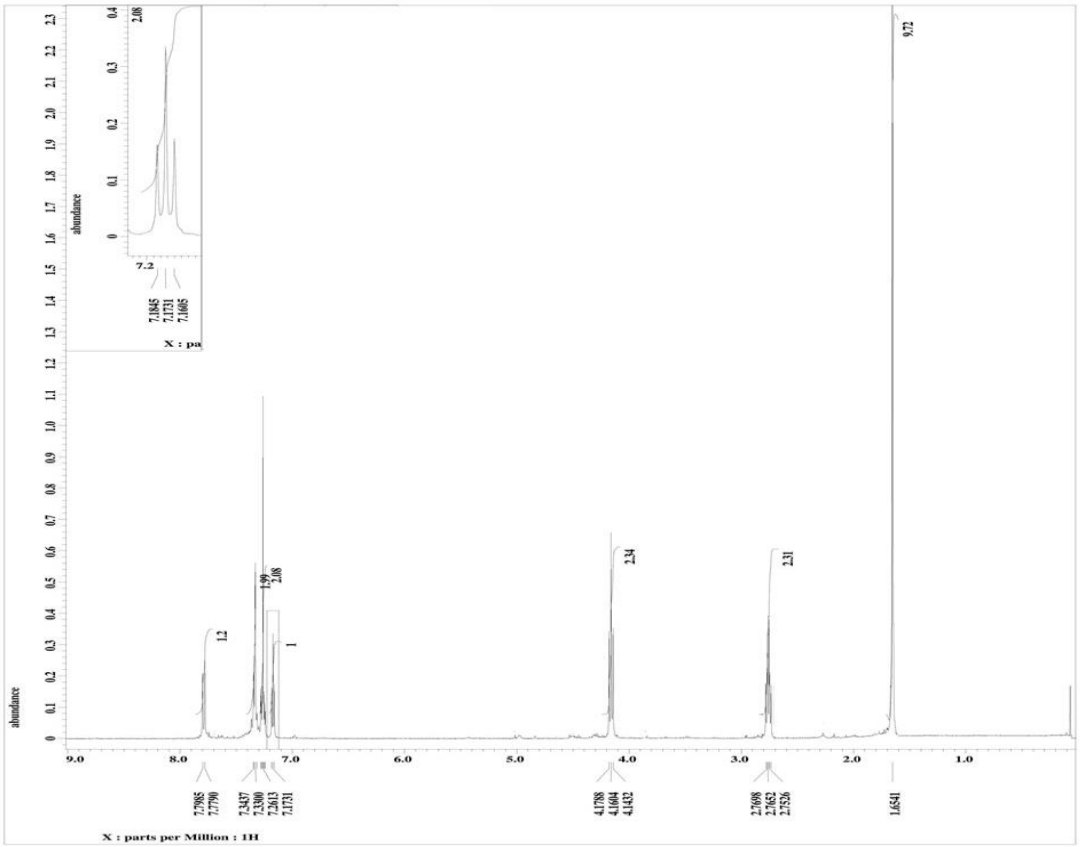




tert-Butyl 10-cyano-6,7-dihydropyrido[1,2-a]indole-9-carboxylate **(12c)**

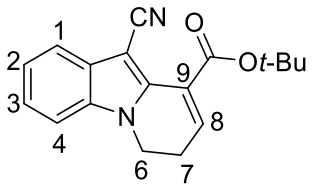
^{1}H NMR, 400 MHz, $CDCl_3$

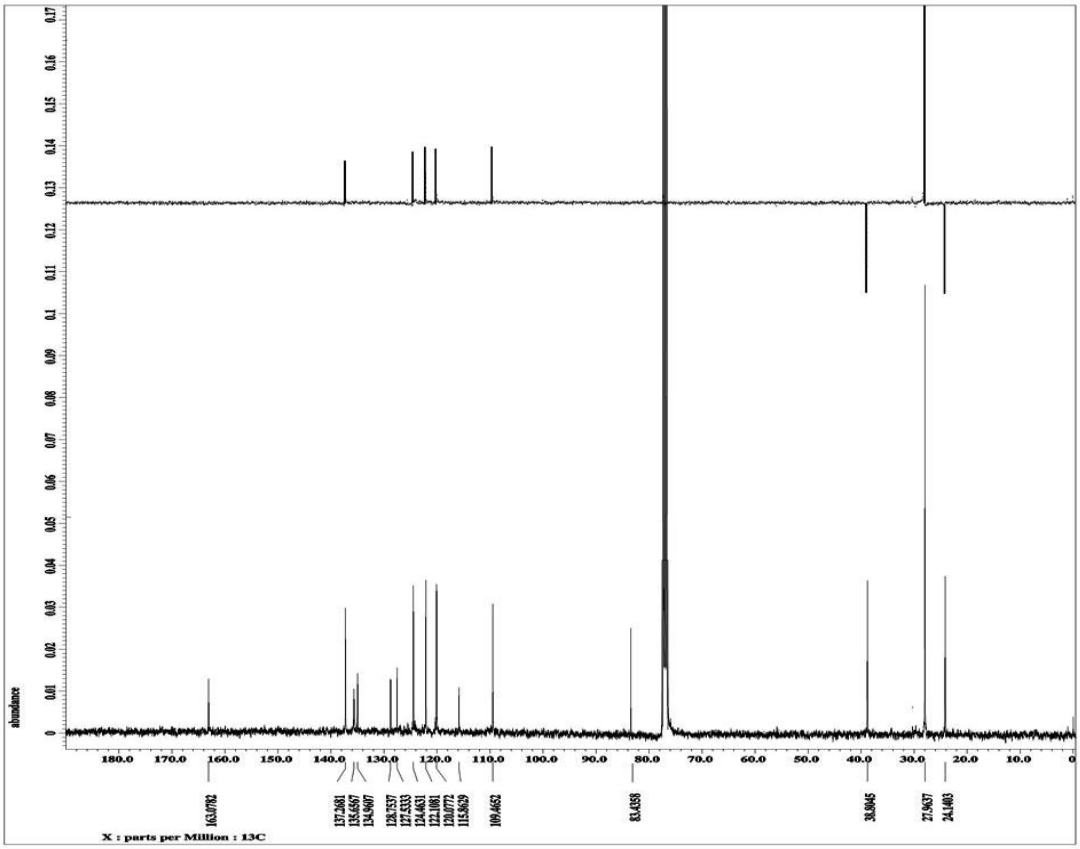




tert-Butyl 10-cyano-6,7-dihydropyrido[1,2-a]indole-9-carboxylate **(12c)**

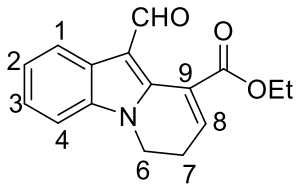
^{13}C NMR, 100 MHz, $CDCl_3$

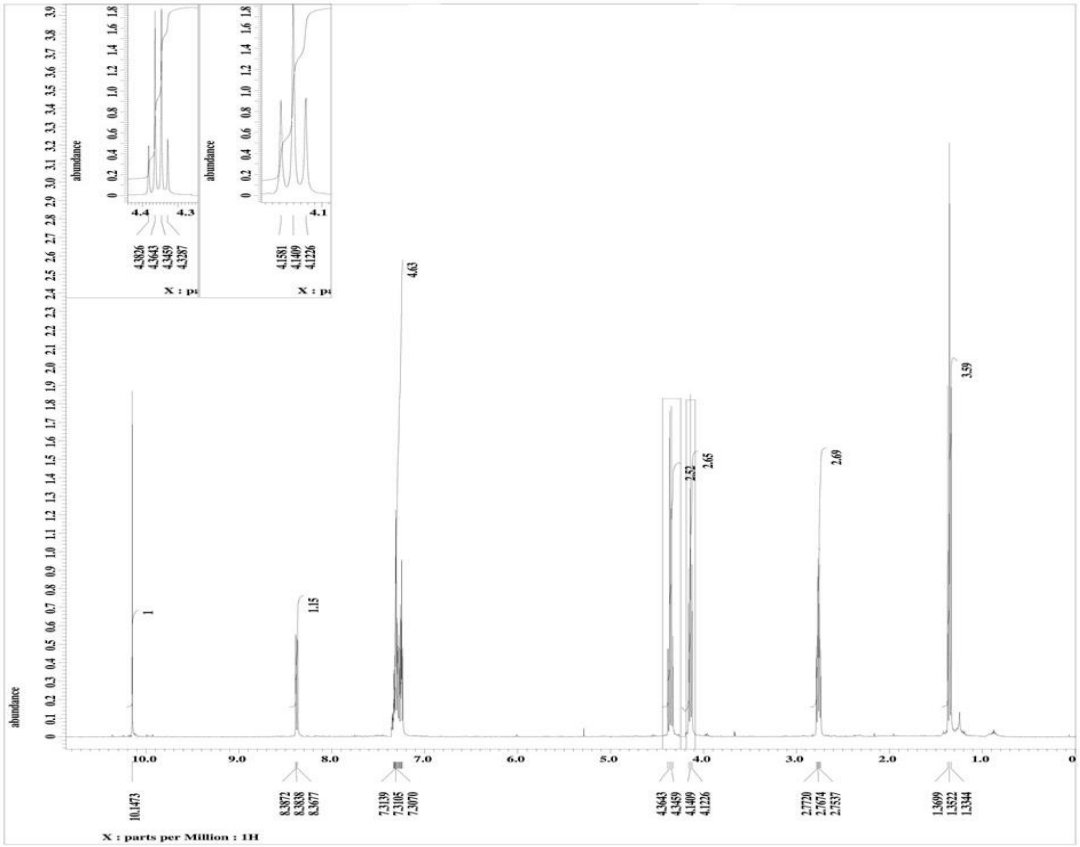




Ethyl 10-formyl-6,7-dihydropyrido[1,2-a]indole-9-carboxylate **(12d)**

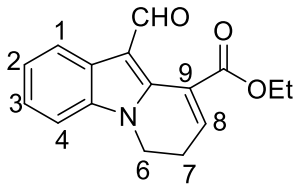
^{1}H NMR, 400 MHz, $CDCl_3$

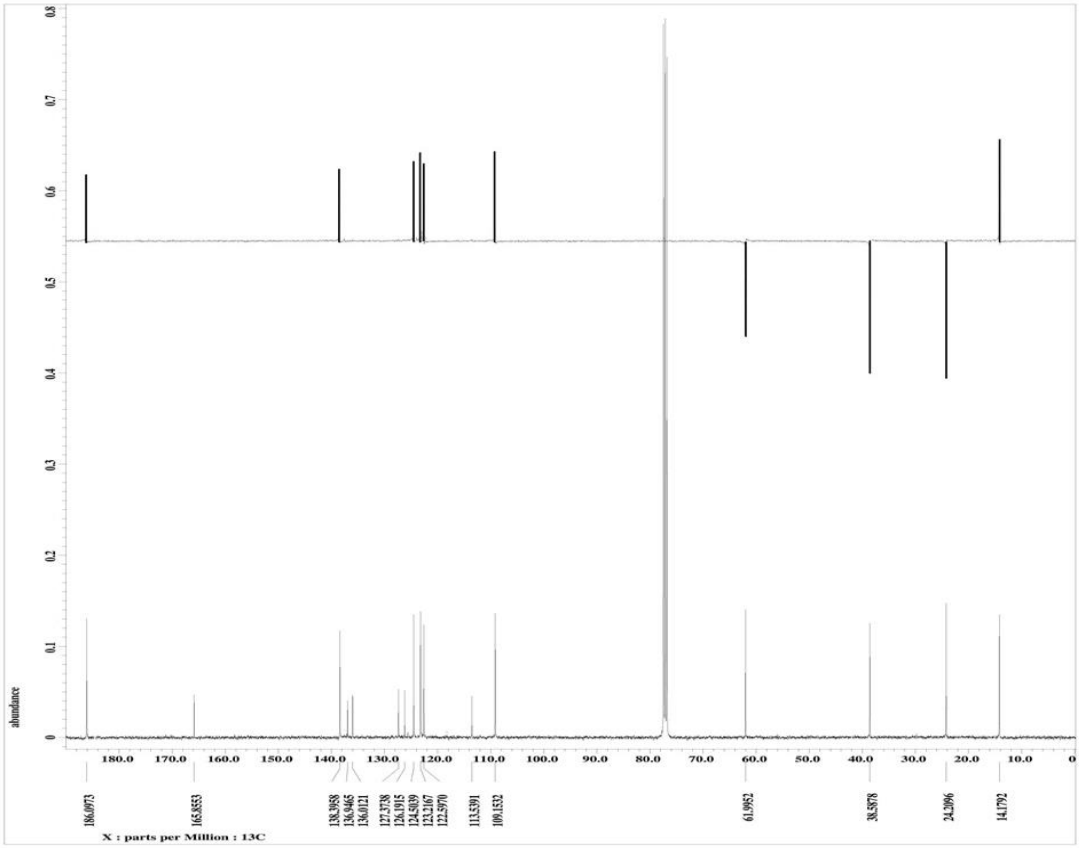




Ethyl 10-formyl-6,7-dihydropyrido[1,2-a]indole-9-carboxylate **(12d)**

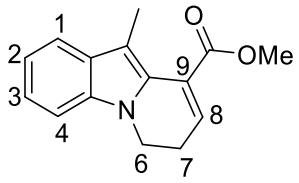
^{13}C NMR, 100 MHz, $CDCl_3$

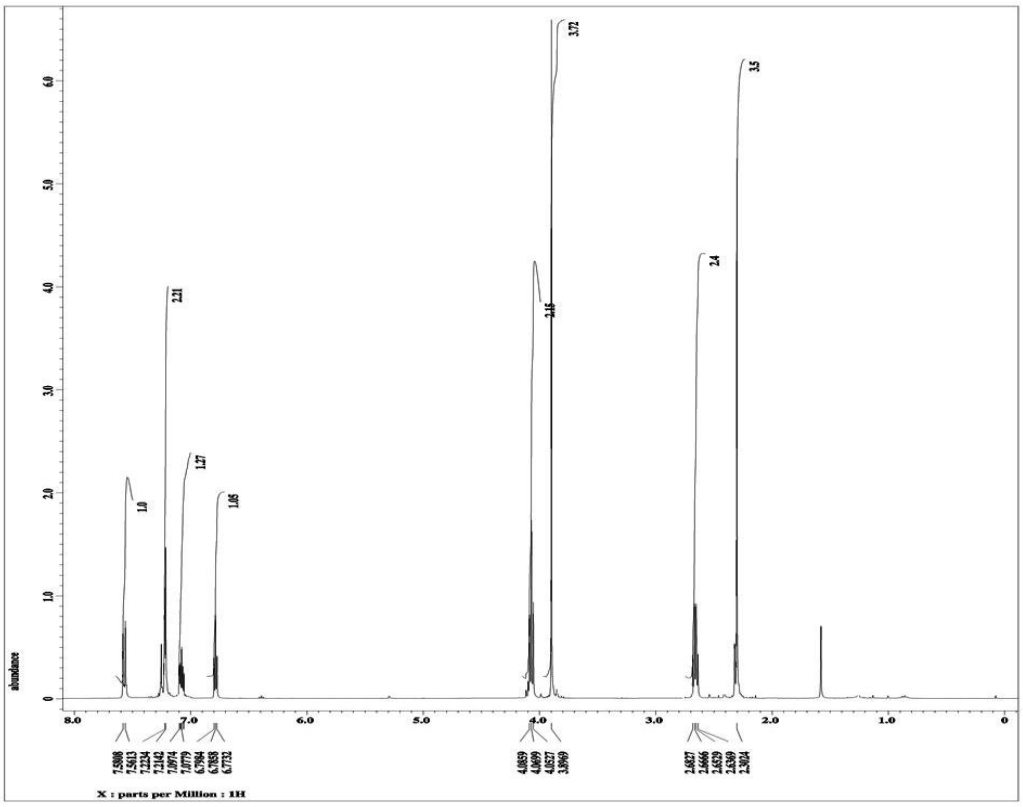




Methyl 10-methyl-6,7-dihydropyrido[1,2-a]indole-9-carboxylate **(12e)**

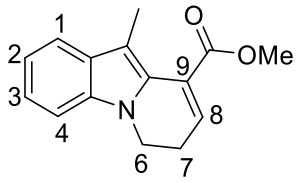
^{1}H NMR, 400 MHz, $CDCl_3$

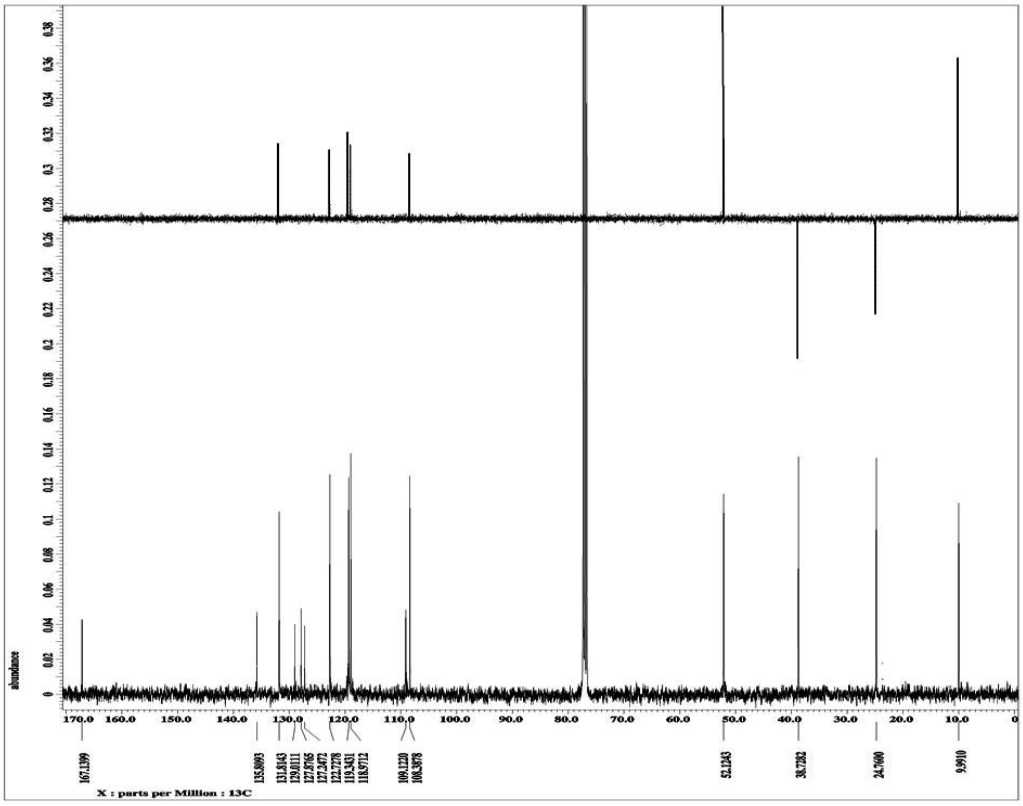




Methyl 10-methyl-6,7-dihydropyrido[1,2-a]indole-9-carboxylate **(12e)**

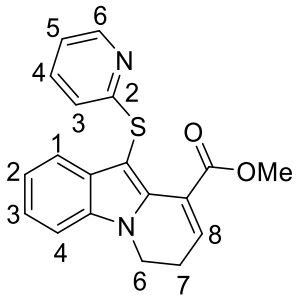
^{13}C NMR, 100 MHz, $CDCl_3$

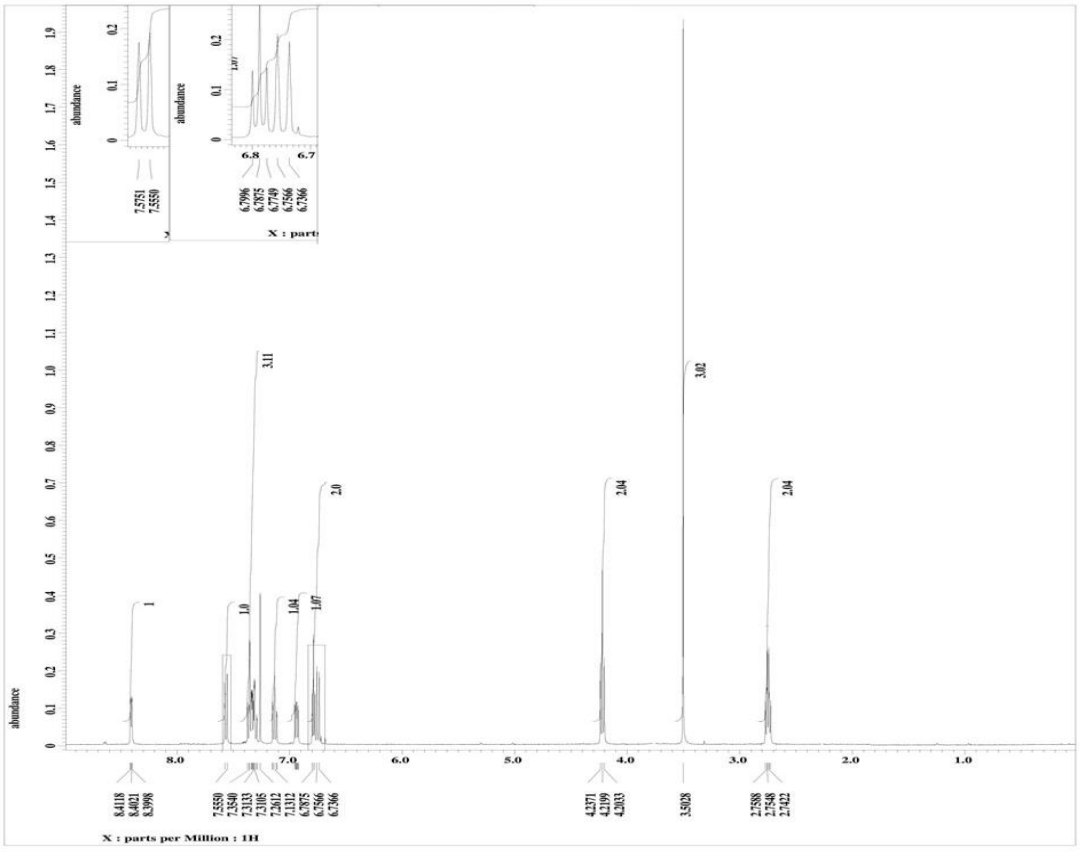




Methyl 10-(pyridine-2-ylthio)-6,7-dihydropyrido[1,2-a]indole-9-carboxylate **(13a)**

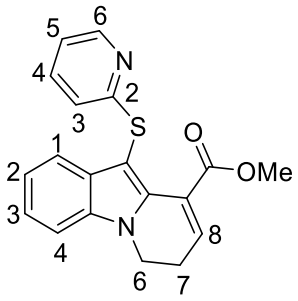
^{1}H NMR, 400 MHz, $CDCl_3$

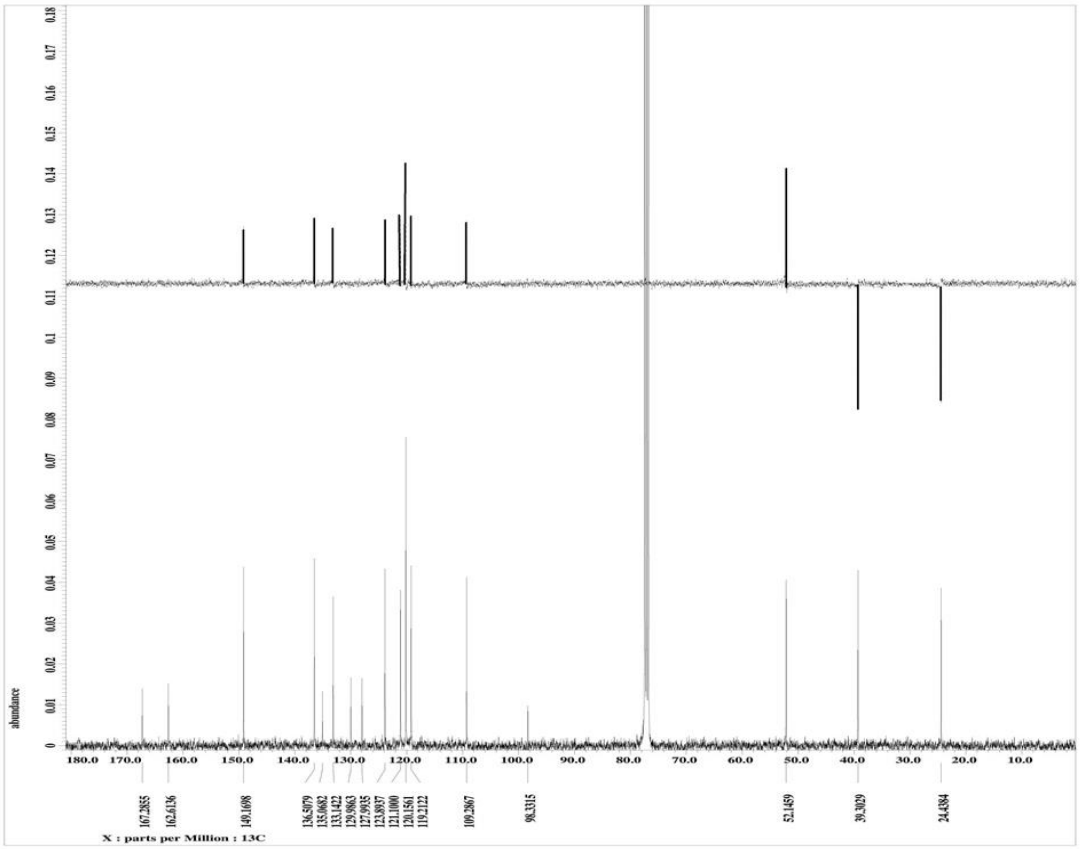




Methyl 10-(pyridine-2-ylthio)-6,7-dihydropyrido[1,2-a]indole-9-carboxylate **(13a)**

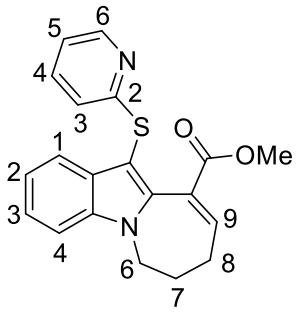
^{13}C NMR, 100 MHz, $CDCl_3$

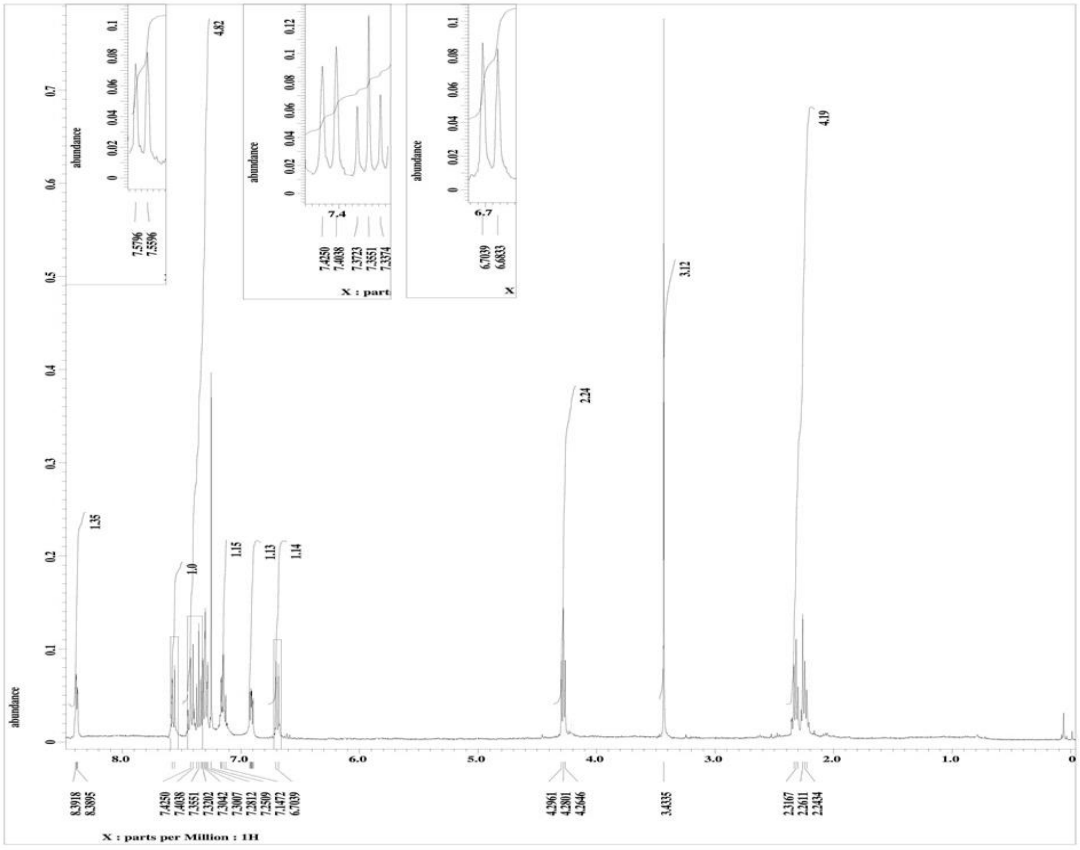




Methyl 11-(pyridin-2-ylthio)-7,8-dihydro-6H-azepino[1,2-a]indole-10-carboxylate **(13b)**

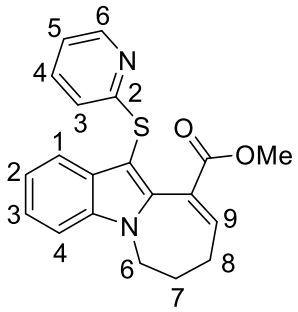
^{1}H NMR, 400 MHz, $CDCl_3$

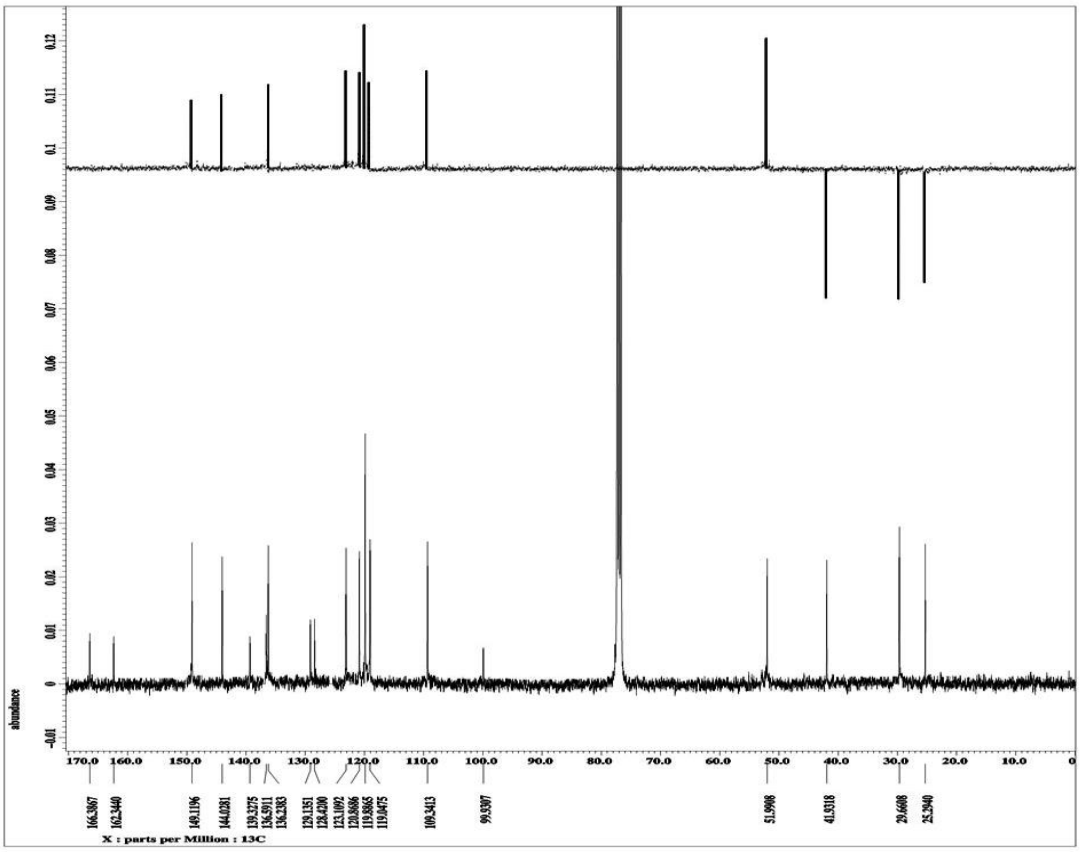




Methyl 11-(pyridin-2-ylthio)-7,8-dihydro-6H-azepino[1,2-a]indole-10-carboxylate **(13b)**

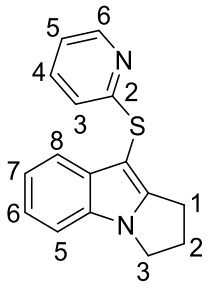
^{13}C NMR, 100 MHz, $CDCl_3$

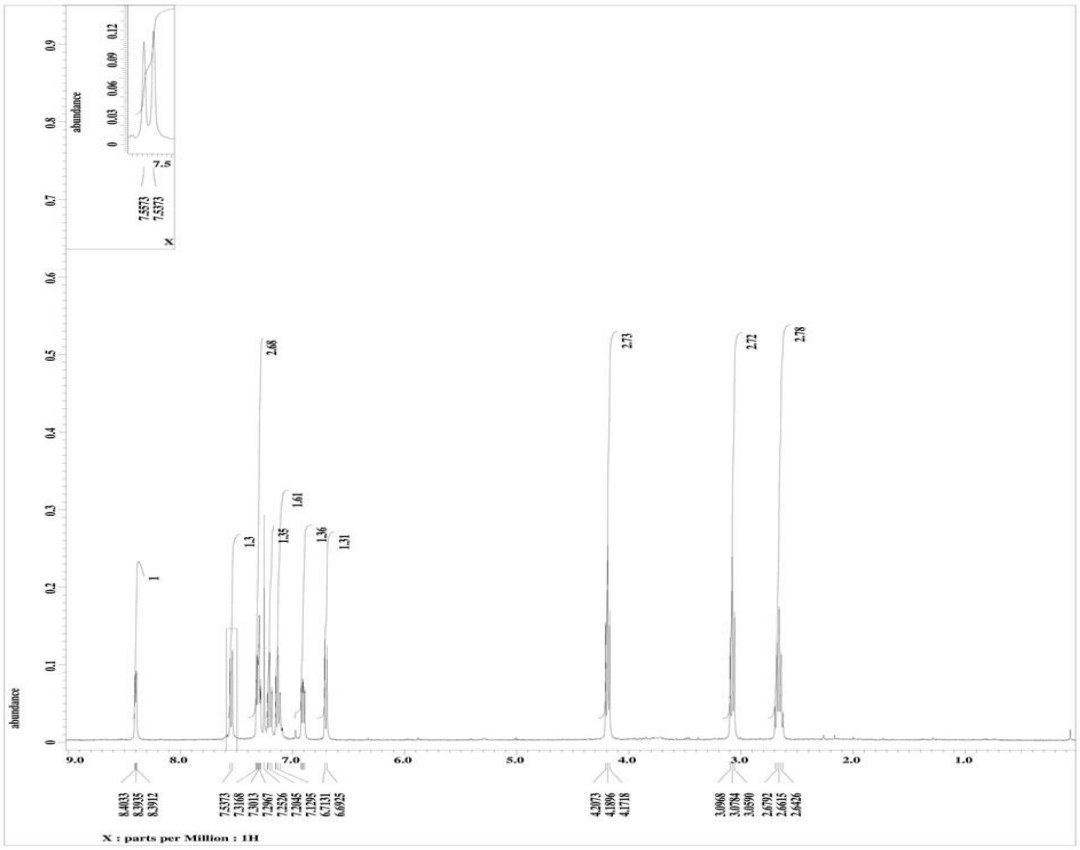




9-(Pyridin-2-ylthio)-2,3-dihydro-1H-pyrrolo[1,2-a]indole **(14)**

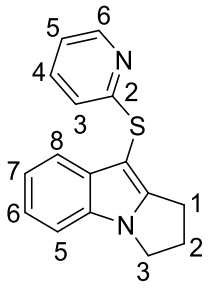
^{1}H NMR, 400 MHz, $CDCl_3$

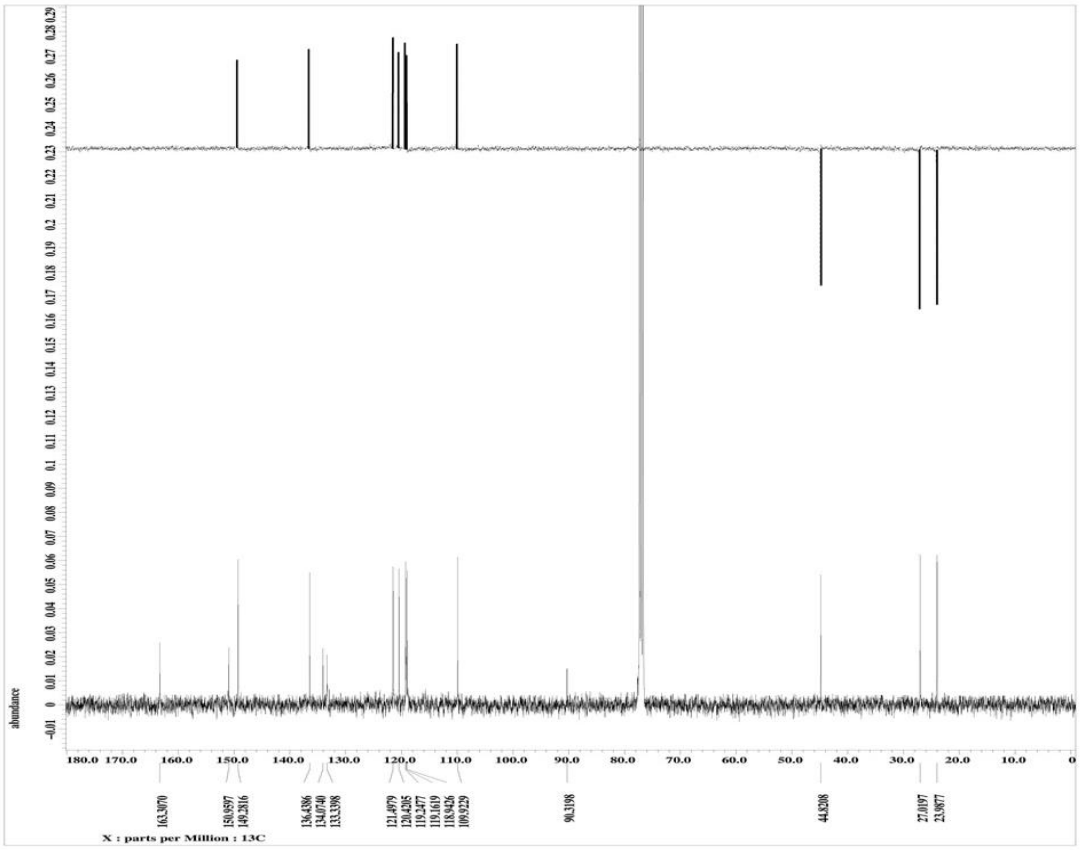




***9-(Pyridin-2-ylthio)-2,3-dihydro-1H-pyrrolo[1,2-a]indole* (14)**

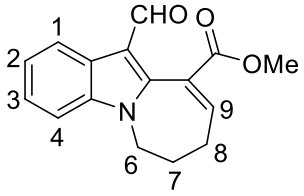
^{13}C NMR, 100 MHz, $CDCl_3$

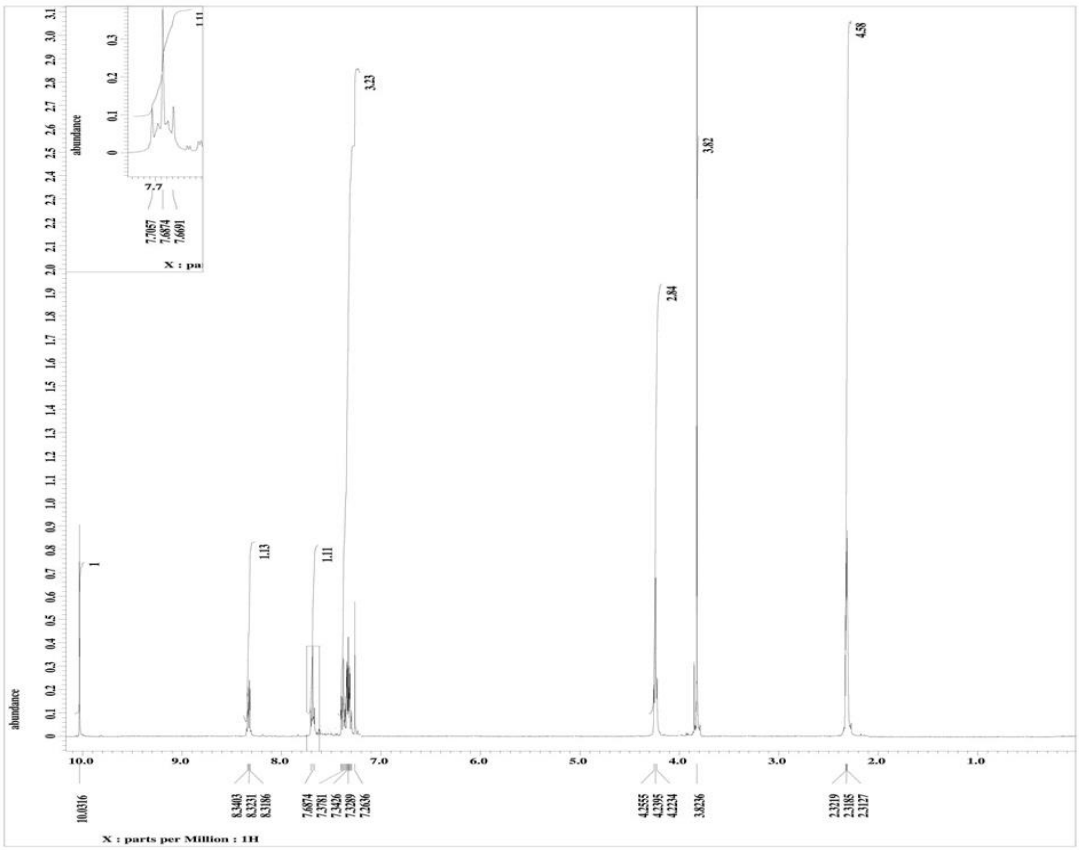




Methyl 11-formyl-7,8-dihydro-6H-azepino[1,2-a]indole-10-carboxylate **(15)**

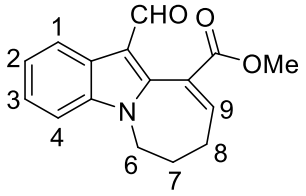
^{1}H NMR, 400 MHz, $CDCl_3$

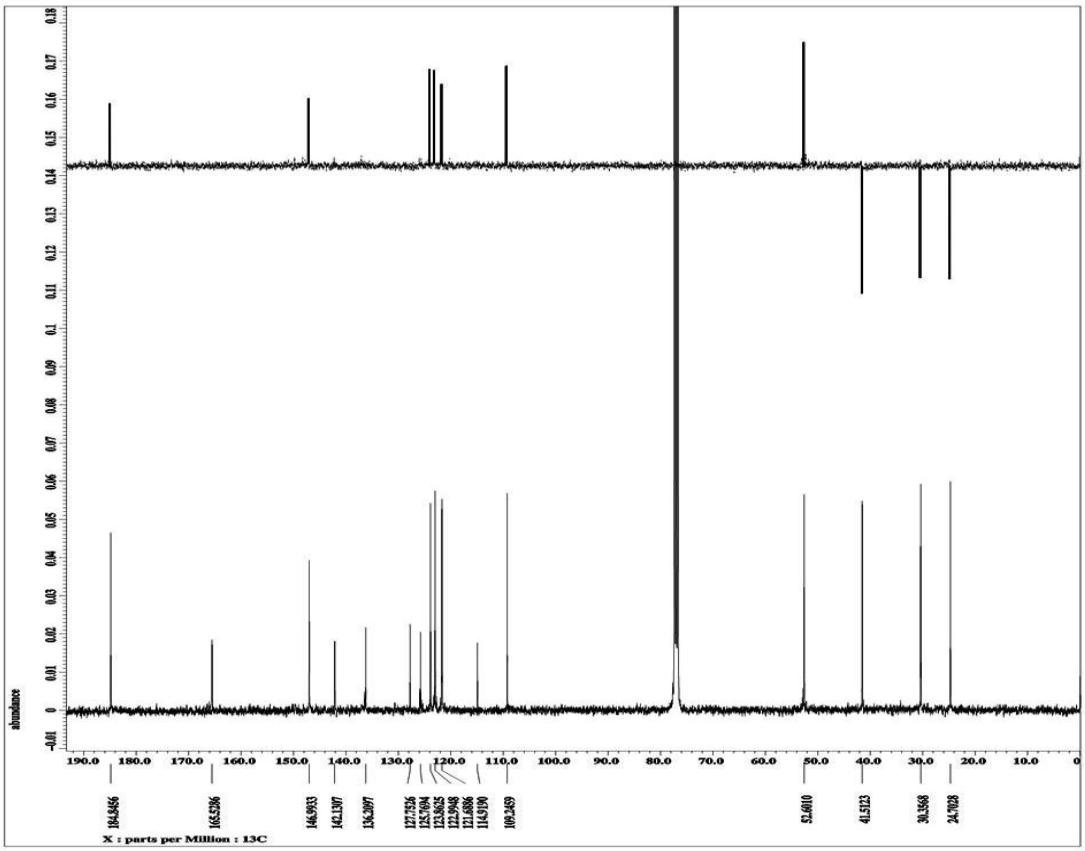




Methyl 11-formyl-7,8-dihydro-6H-azepino[1,2-a]indole-10-carboxylate **(15)**

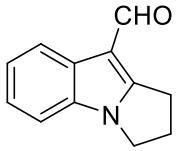
^{13}C NMR, 100 MHz, $CDCl_3$

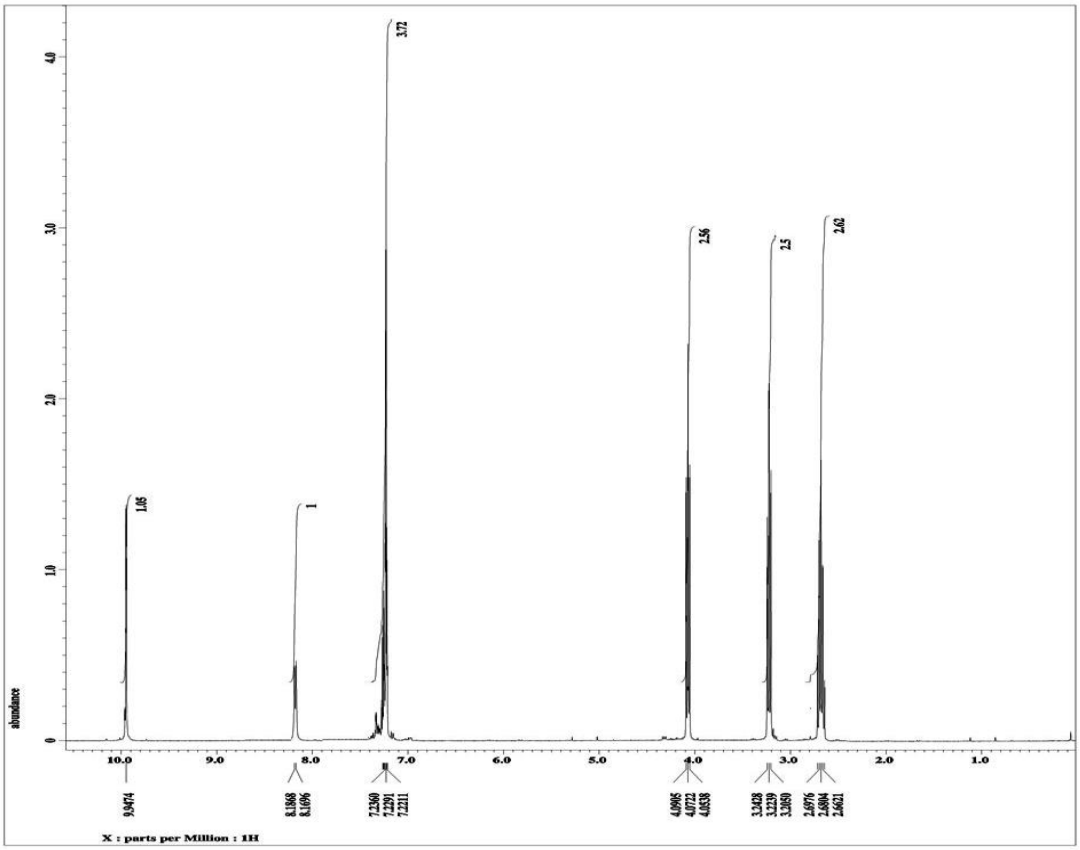




2,3-Dihydro-1H-pyrrolo[1,2-a]indole-9-carbaldehyde **(16)**

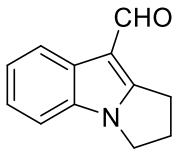
^{1}H NMR, 400 MHz, $CDCl_3$

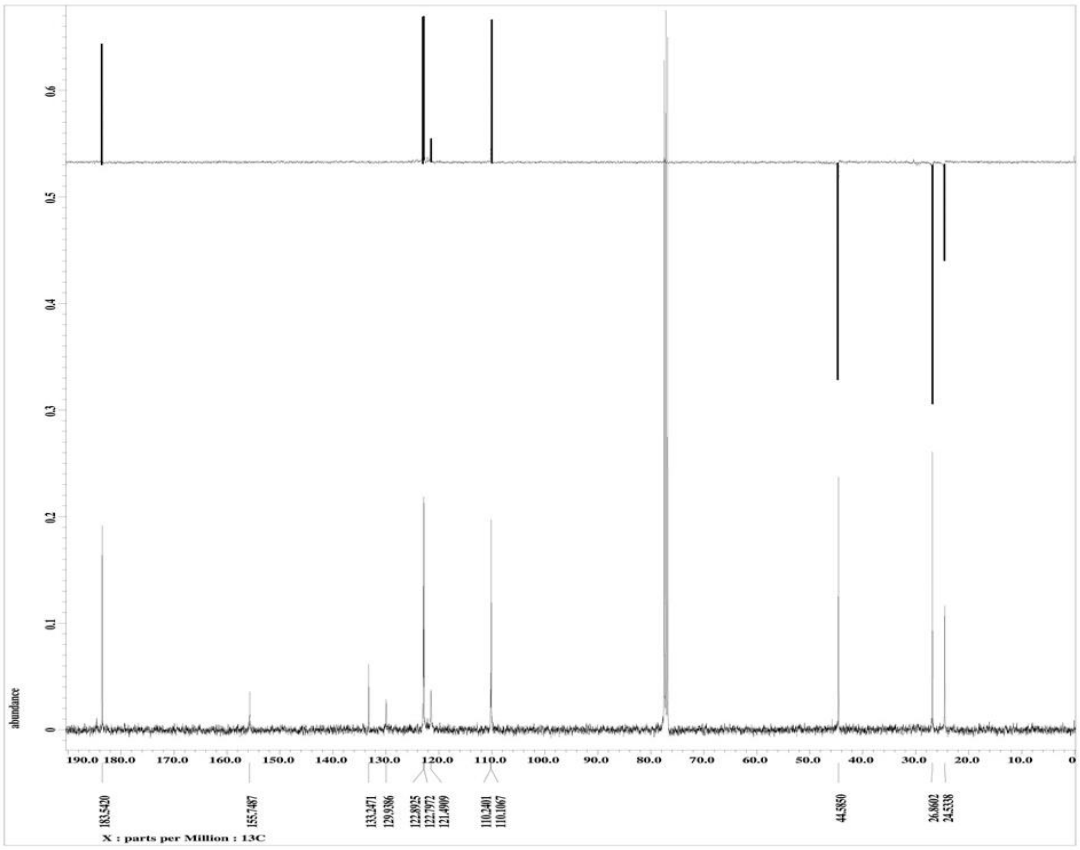




2,3-Dihydro-1H-pyrrolo[1,2-a]indole-9-carbaldehyde **(16)**

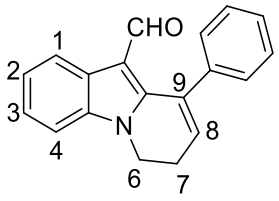
^{13}C NMR, 100 MHz, $CDCl_3$

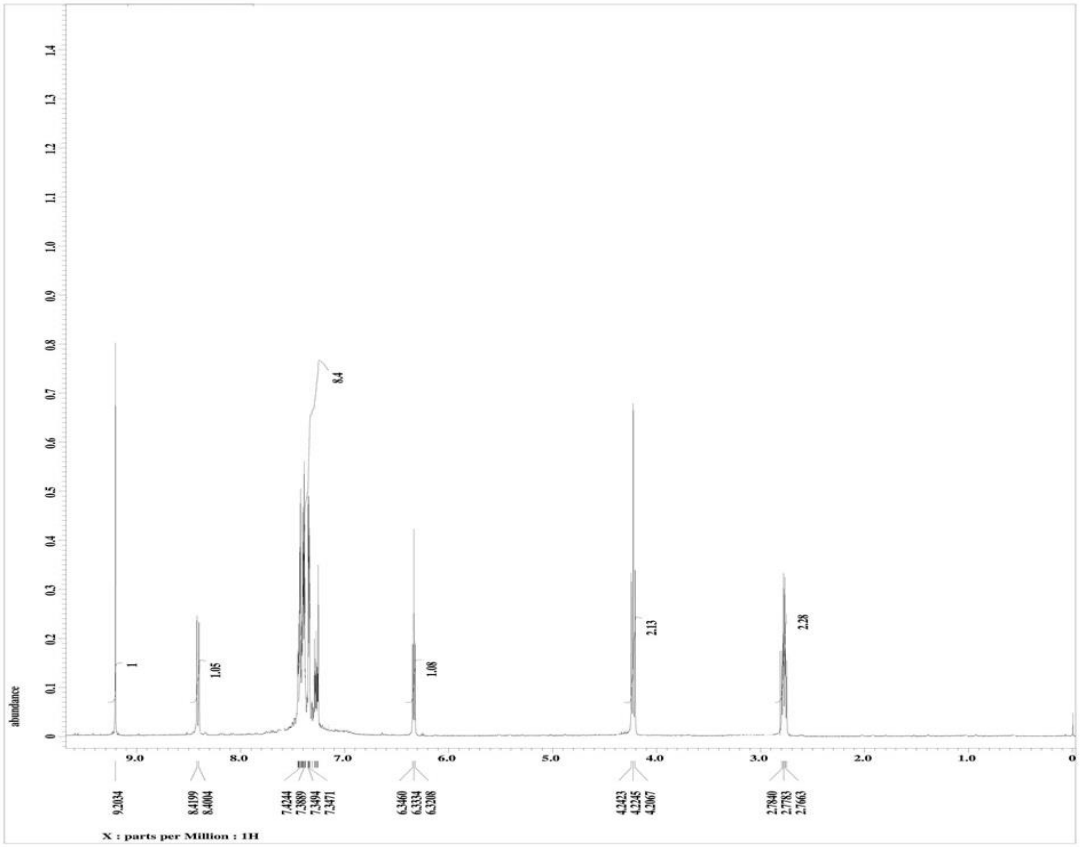




9-Phenyl-6,7-dihydropyrido[1,2-a]indole-10-carbaldehyde **(17a)**

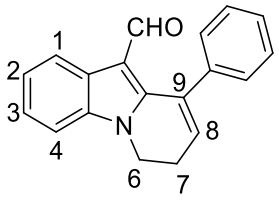
^{1}H NMR, 400 MHz, $CDCl_3$

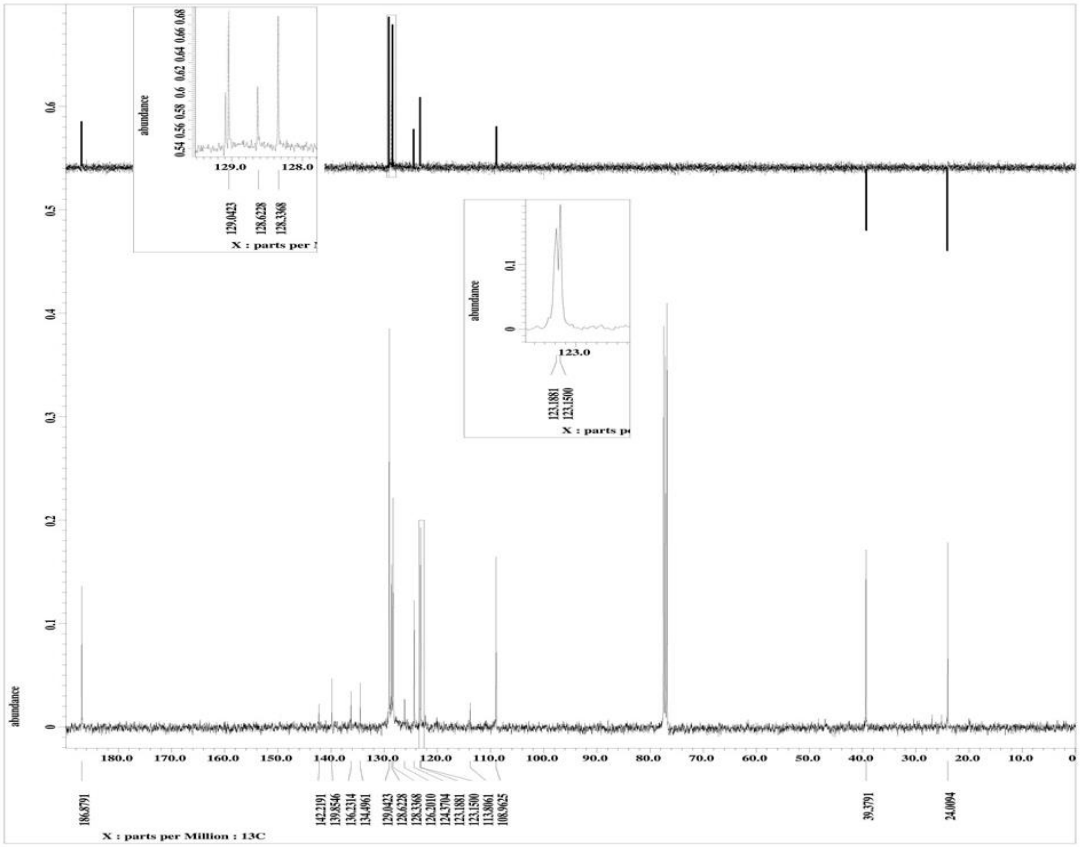




9-Phenyl-6,7-dihydropyrido[1,2-a]indole-10-carbaldehyde **(7a)**

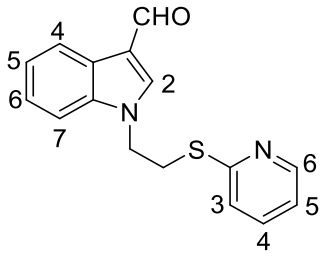
^{13}C NMR, 100 MHz, $CDCl_3$

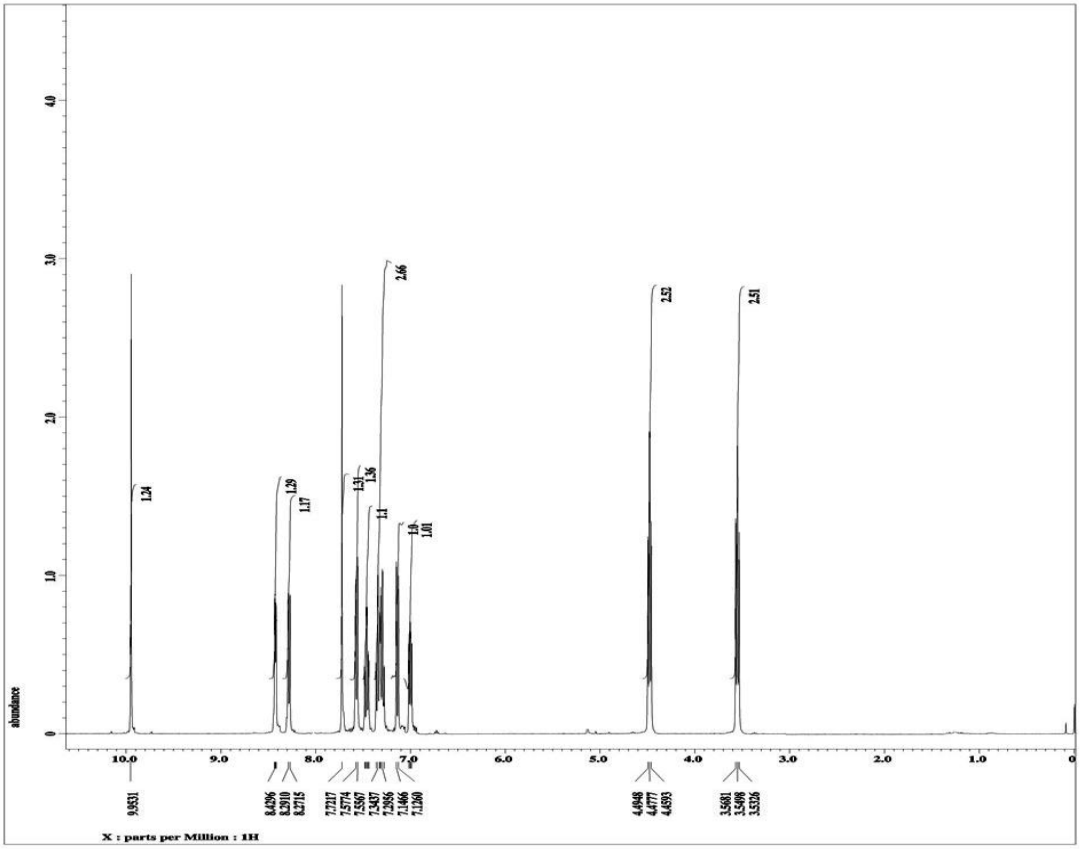




1-[2-(Pyridin-2-ylthio)ethyl]-1H-indole-3-carbaldehyde **(18a)**

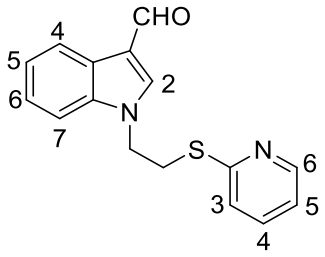
^{1}H NMR, 400 MHz, $CDCl_3$

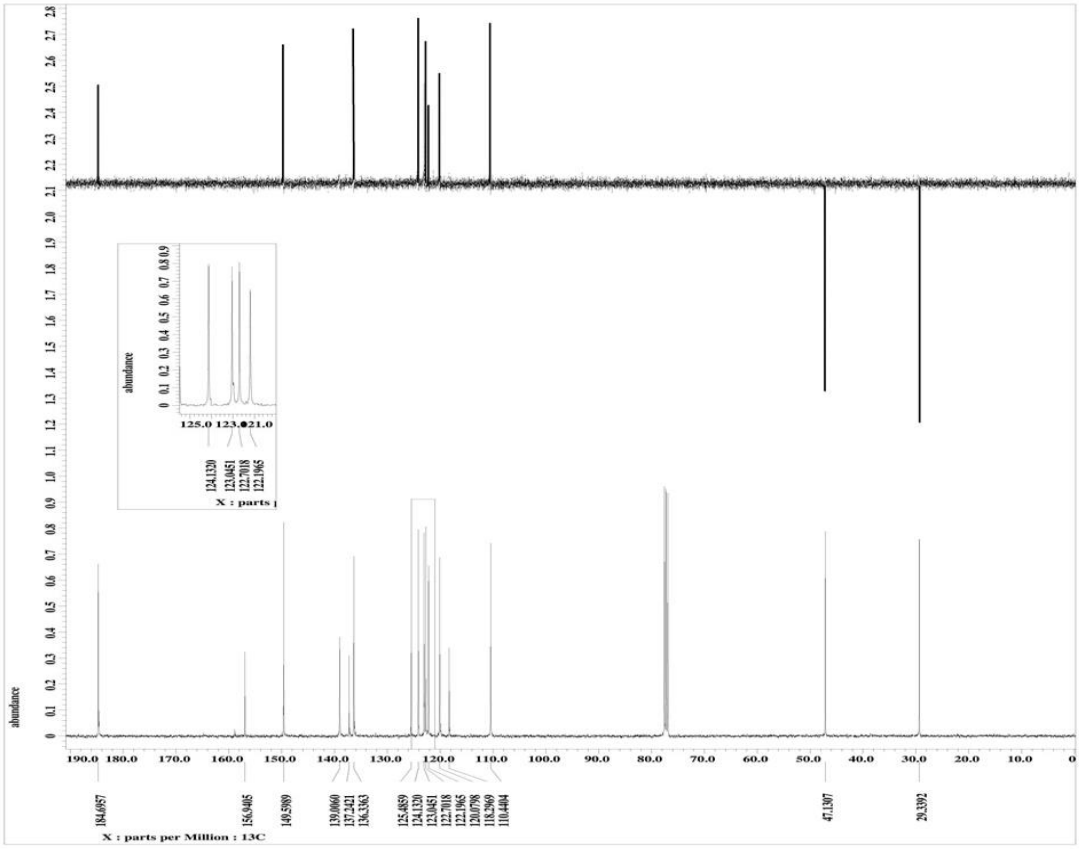




1-[2-(Pyridin-2-ylthio)ethyl]-1H-indole-3-carbaldehyde **(18a)**

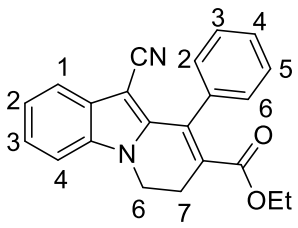
^{13}C NMR, 100 MHz, $CDCl_3$

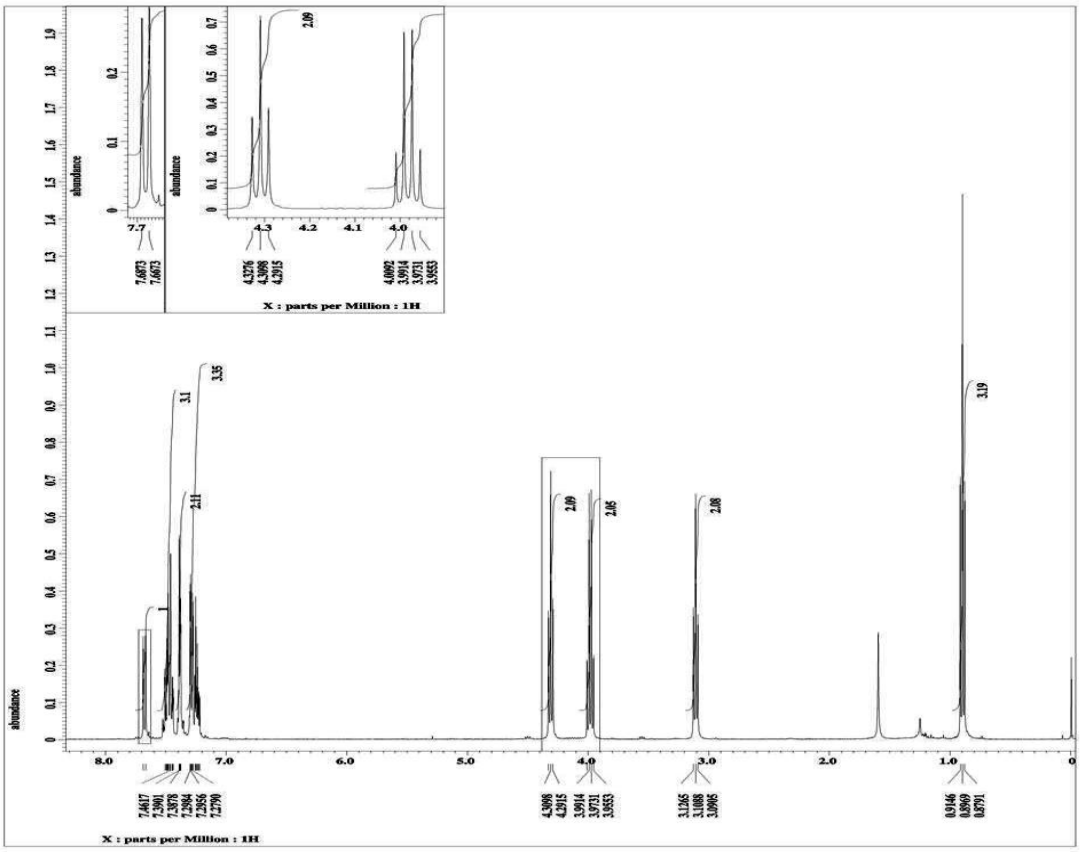




Ethyl 10-cyano-9-phenyl-6,7-dihydropyrido[1,2-a]indole-8-carboxylate **(17b)**

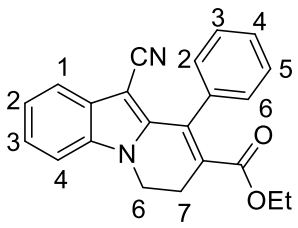
^{1}H NMR, 400 MHz, $CDCl_3$

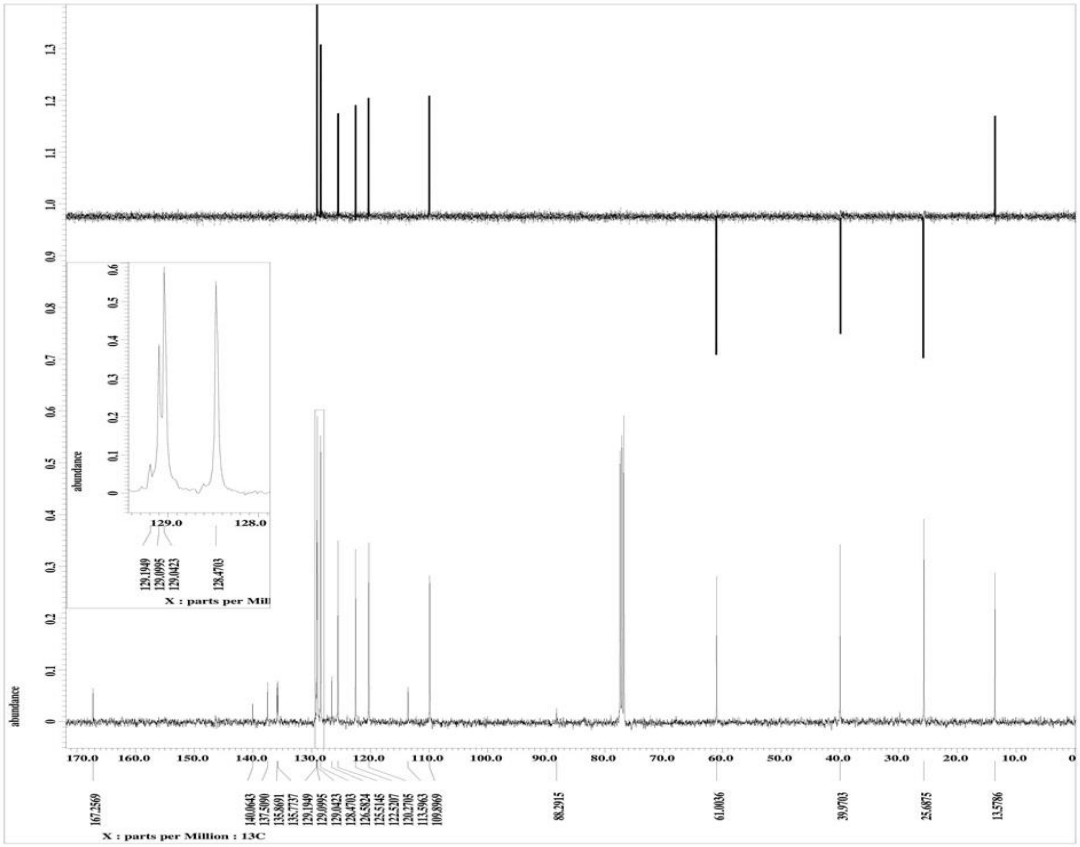




Ethyl 10-cyano-9-phenyl-6,7-dihydropyrido[1,2-a]indole-8-carboxylate **(17b)**

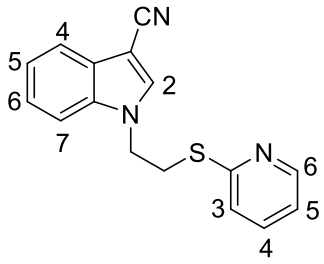
^{13}C NMR, 100 MHz, $CDCl_3$

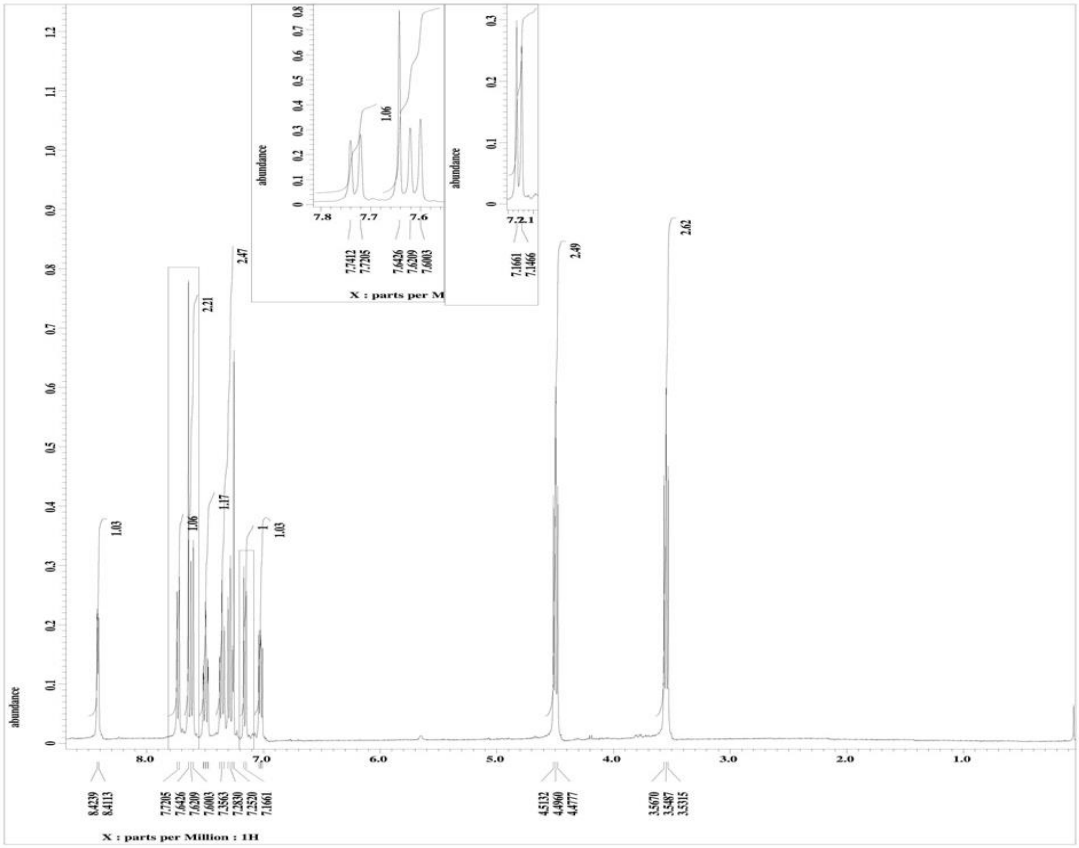




1-[2-(Pyridin-2-ylthio)ethyl]-1H-indole-3-carbonitrile **(18b)**

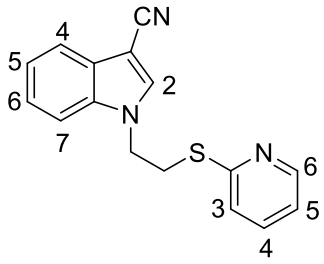
^{1}H NMR, 400 MHz, $CDCl_3$

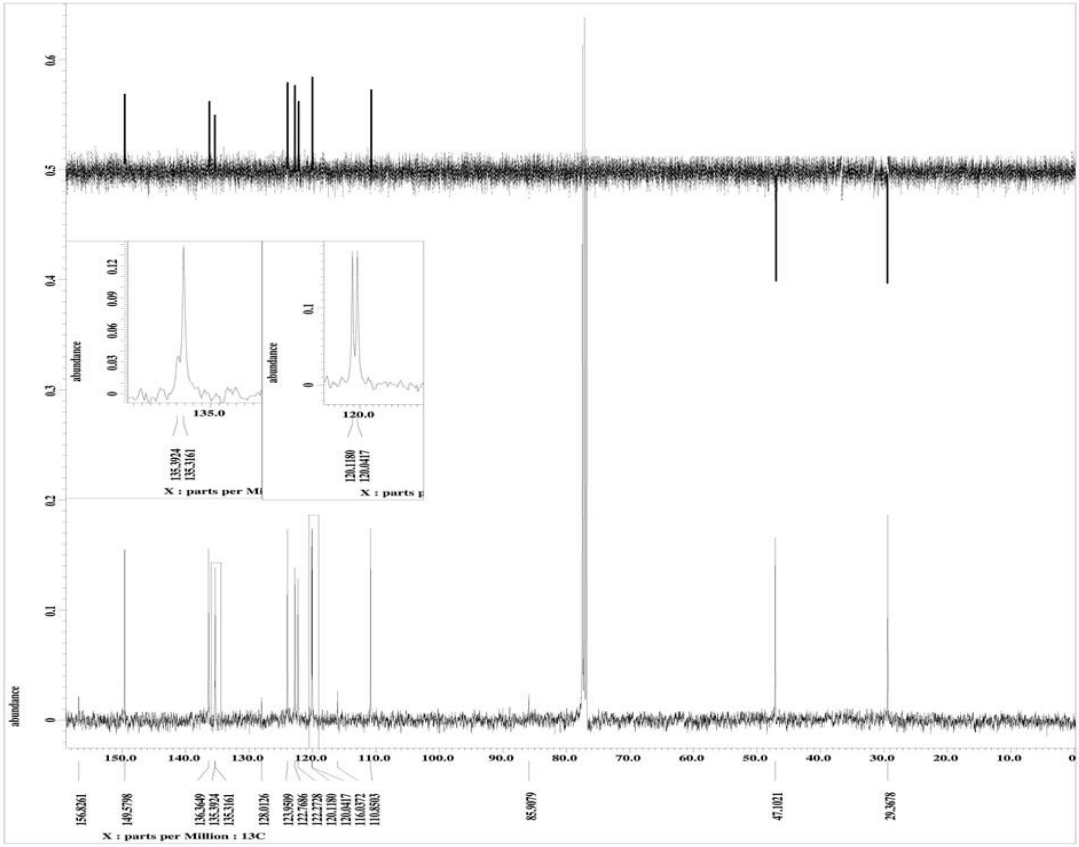




1-[2-(Pyridin-2-ylthio)ethyl]-1H-indole-3-carbonitrile **(18b)**

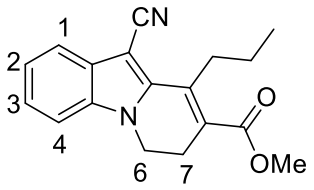
^{13}C NMR, 100 MHz, $CDCl_3$

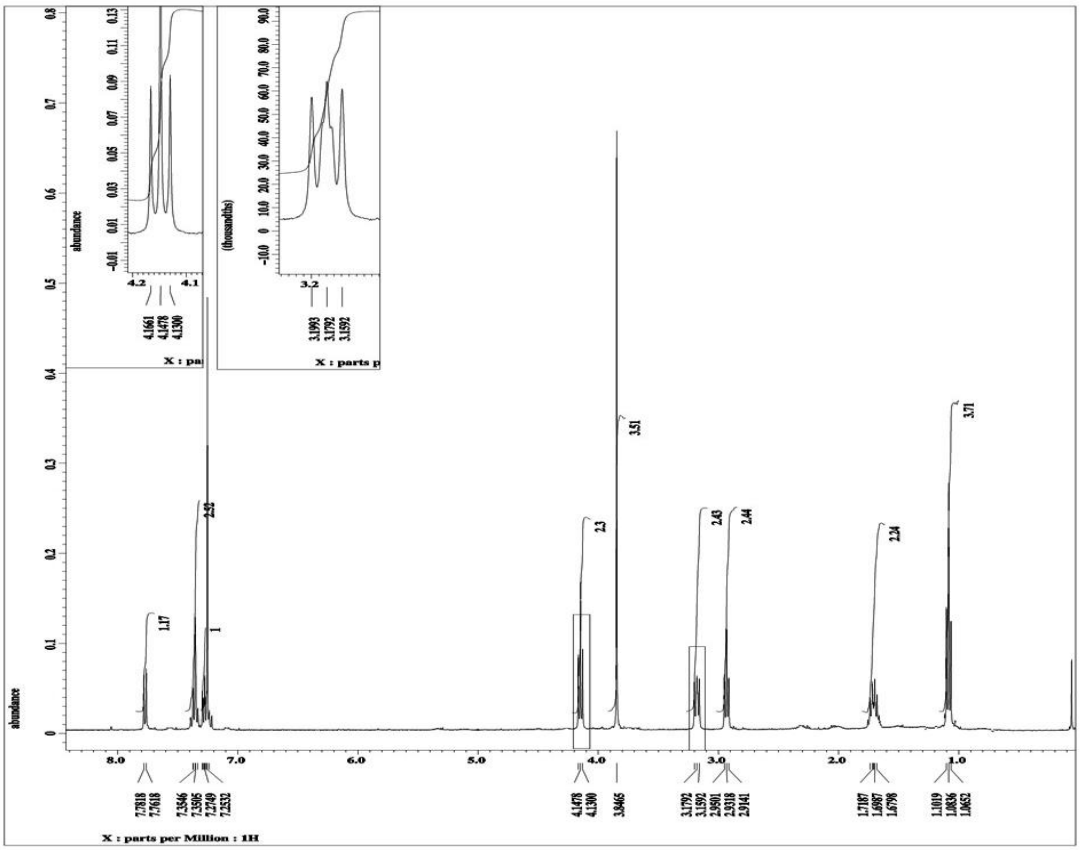




Methyl 10-cyano-9-propyl-6,7-dihydropyrido[1,2-a]indole-8-carboxylate **(17c)**

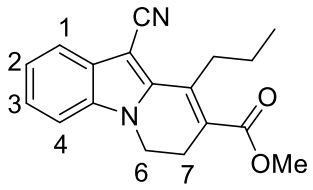
^{1}H NMR, 400 MHz, $CDCl_3$

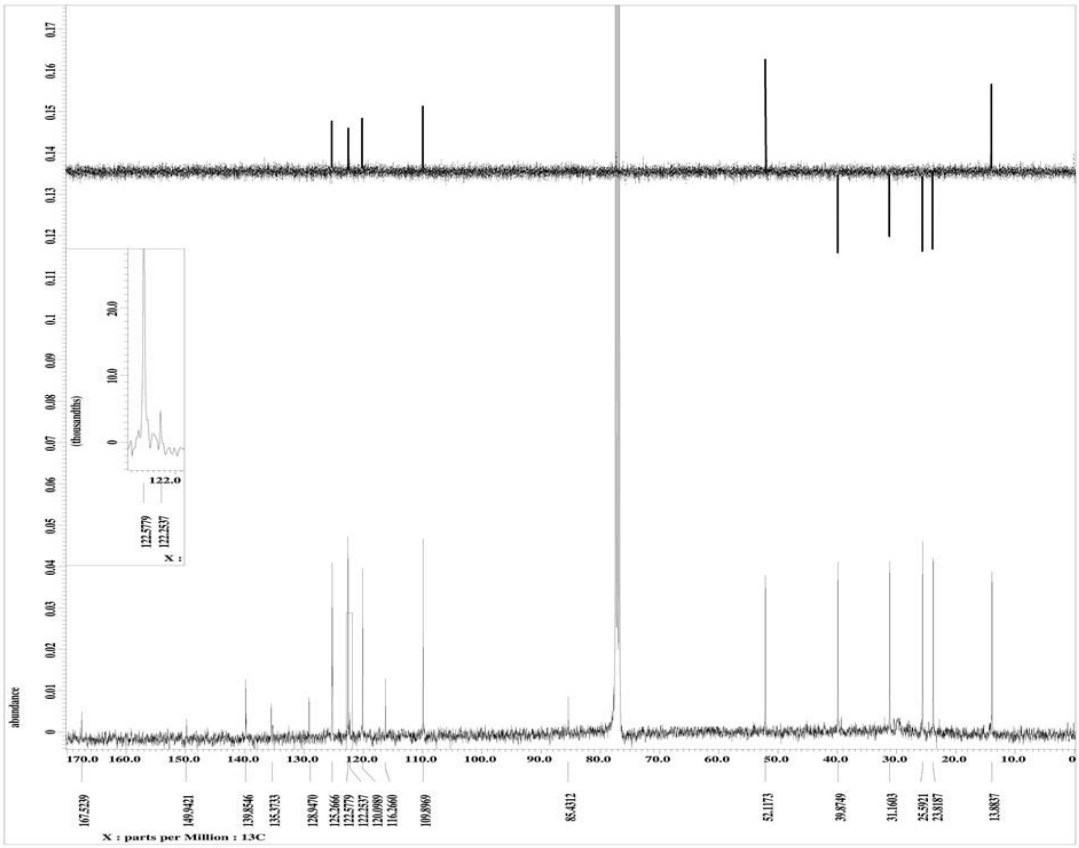




Methyl 10-cyano-9-propyl-6,7-dihydropyrido[1,2-a]indole-8-carboxylate **(17c)**

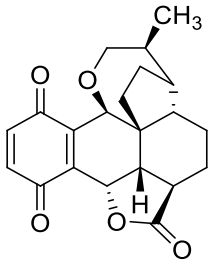
^{13}C NMR, 100 MHz, $CDCl_3$

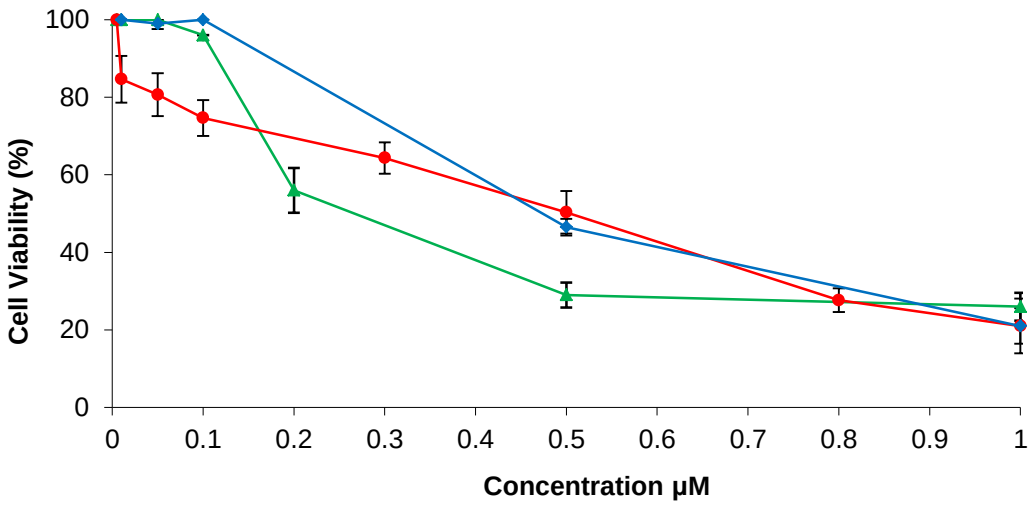




A.3.1 MTT assay cell viability graphs

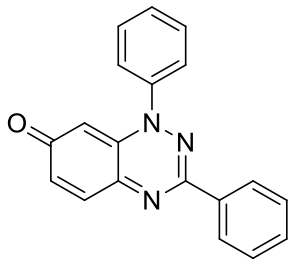
Pleurotin

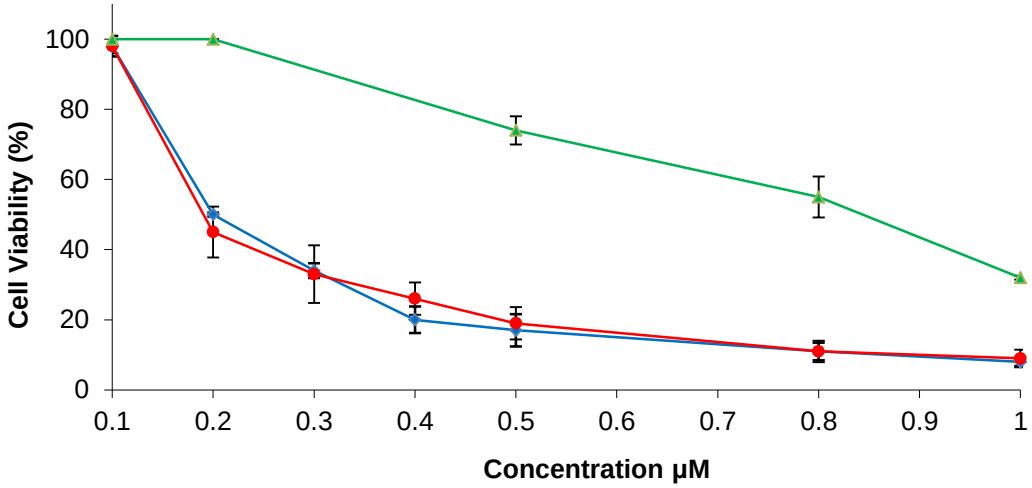




Viability of normal human skin fibroblast (GM00637) (♦), prostate cancer (DU145) (●) and breast cancer (MCF7) (▲) cell lines determined using the MTT assay following treatment with pleurotin under aerobic conditions for 72 h at 37°C. Each data point is the mean of at least three independent experiments. The lines shown are trend lines.

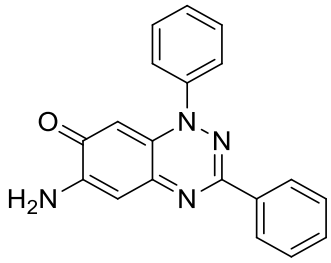
1,3-Diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (19a)

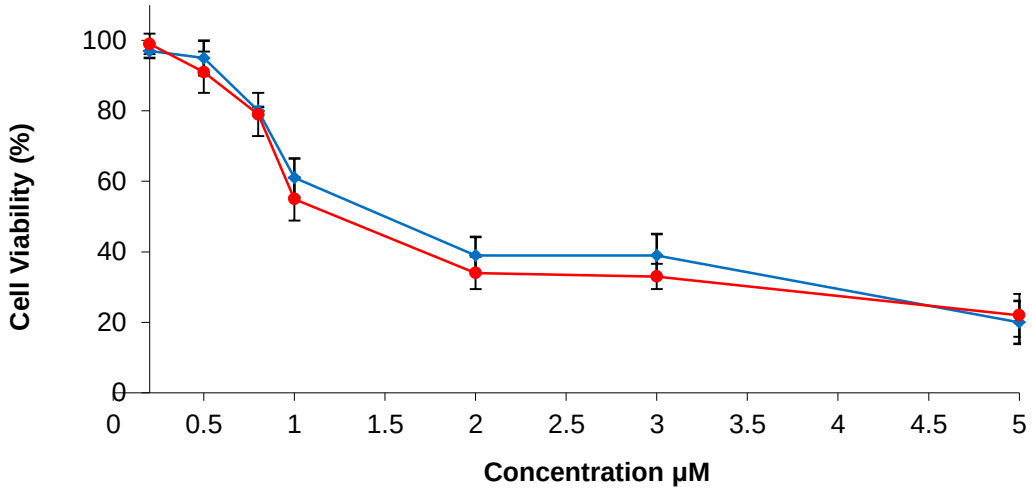




Viability of normal human skin fibroblast (GM00637) (♦), prostate cancer (DU145) (●) and breast cancer (MCF7) (▲) cell lines determined using the MTT assay following treatment with 1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (**19a)** under aerobic conditions for 72 h at 37°C. Each data point is the mean of at least three independent experiments. The lines shown are trend lines.

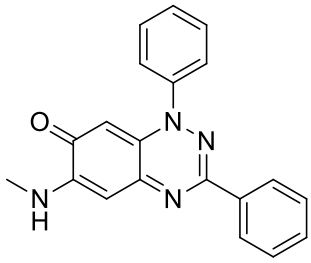
6-Amino-1,3-Diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (19b)

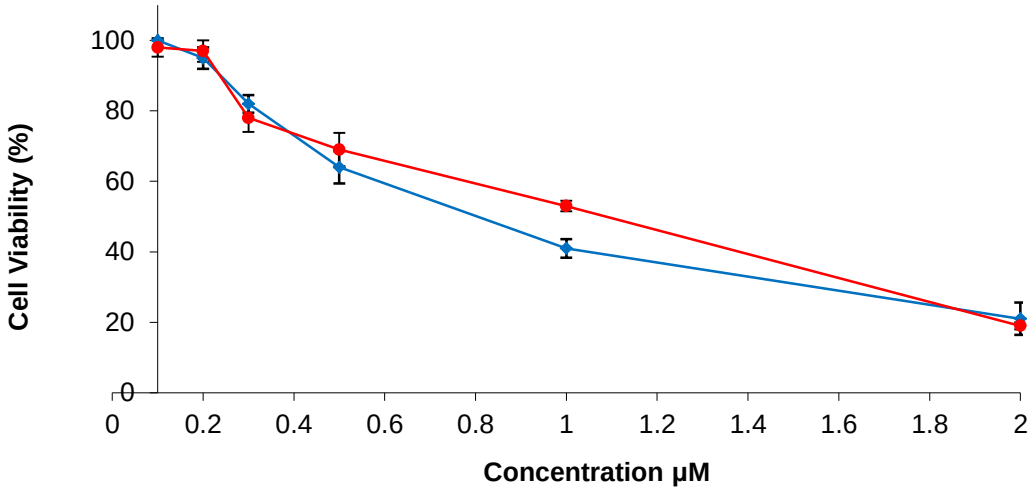




Viability of normal human skin fibroblast (GM00637) (♦) and prostate cancer (DU145) (●) cell lines determined using the MTT assay following treatment with 6-amino-1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (**19b)** under aerobic conditions for 72 h at 37°C. Each data point is the mean of at least three independent experiments. The lines shown are trend lines.

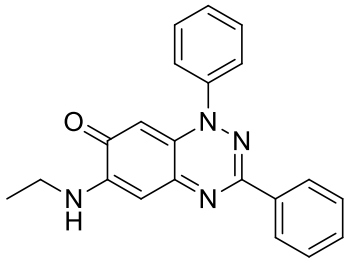
6-(Methylamino)-1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (19c)

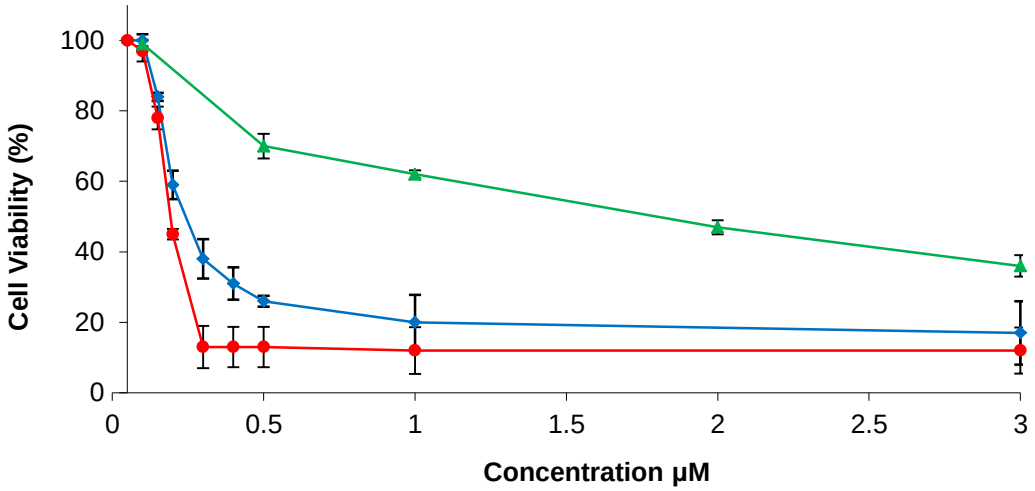




Viability of normal human skin fibroblast (GM00637) (♦) and prostate cancer (DU145) (●) cell lines determined using the MTT assay following treatment with 6-(methylamino)-1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (**19c)** under aerobic conditions for 72 h at 37°C. Each data point is the mean of at least three independent experiments. The lines shown are trend lines.

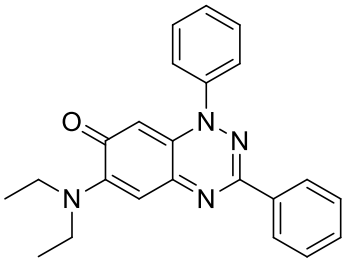
6-(Ethylamino)-1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (19d)

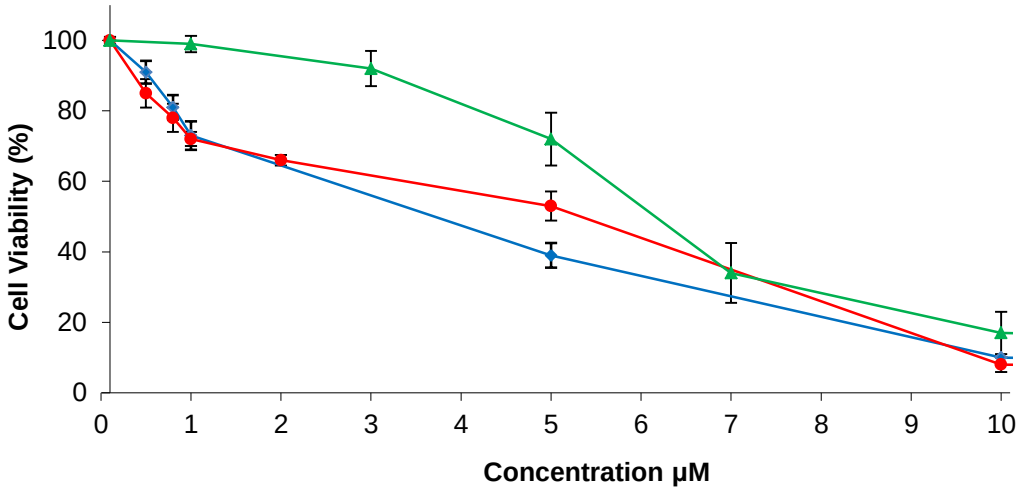




Viability of normal human skin fibroblast (GM00637) (♦), prostate cancer (DU145) (●) and breast cancer (MCF7) (▲) cell lines determined using the MTT assay following treatment with 6-(ethylamino)-1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (**19d)** under aerobic conditions for 72 h at 37°C. Each data point is the mean of at least three independent experiments. The lines shown are trend lines.

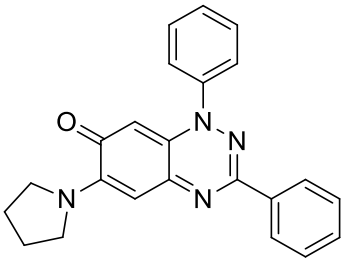
6-(Diethylamino)-1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (19e)

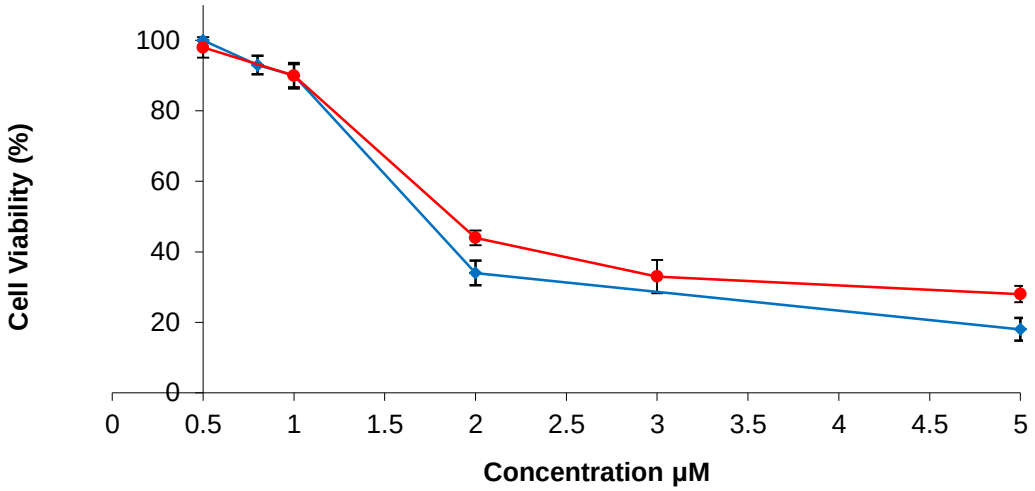




Viability of normal human skin fibroblast (GM00637) (♦), prostate cancer (DU145) (●) and breast cancer (MCF7) (▲) cell lines determined using the MTT assay following treatment with 6-(diethylamino)-1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (**19e)** under aerobic conditions for 72 h at 37°C. Each data point is the mean of at least three independent experiments. The lines shown are trend lines.

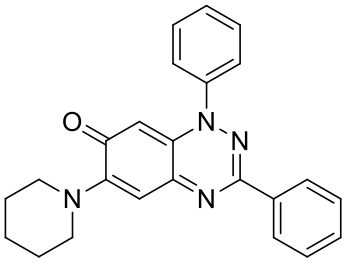
1,3-Diphenyl-6-(pyrrolidin-1-yl)-benzo[*e*][1,2,4]triazin-7(1*H*)-one (19f)

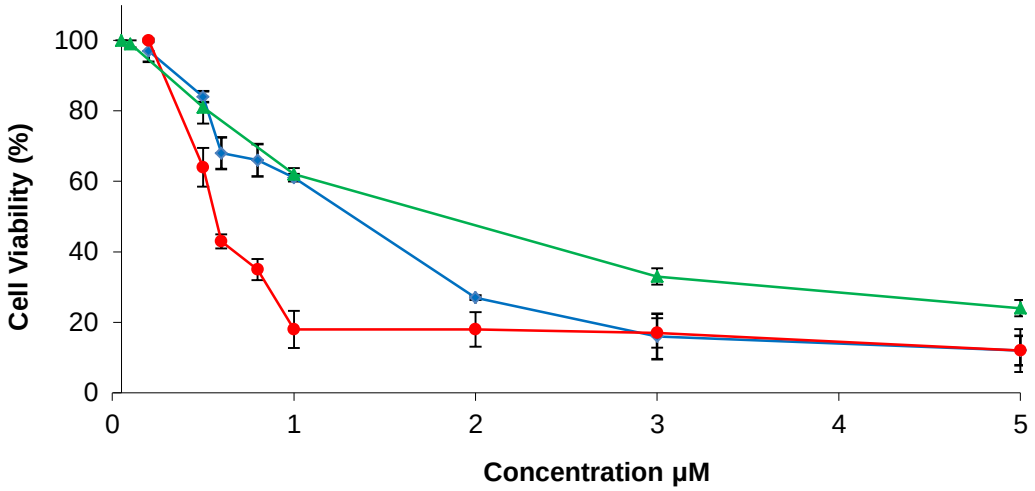




Viability of normal human skin fibroblast (GM00637) (♦) and prostate cancer (DU145) (●) cell lines determined using the MTT assay following treatment with 1,3-diphenyl-6-(pyrrolidin-1-yl)-benzo[*e*][1,2,4]triazin-7(1*H*)-one (**19f)** under aerobic conditions for 72 h at 37°C. Each data point is the mean of at least three independent experiments. The lines shown are trend lines.

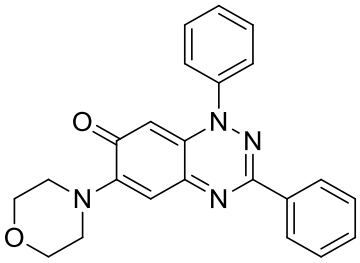
1,3-Diphenyl-6-(piperidin-1-yl)-benzo[*e*][1,2,4]triazin-7(1*H*)-one (19g)

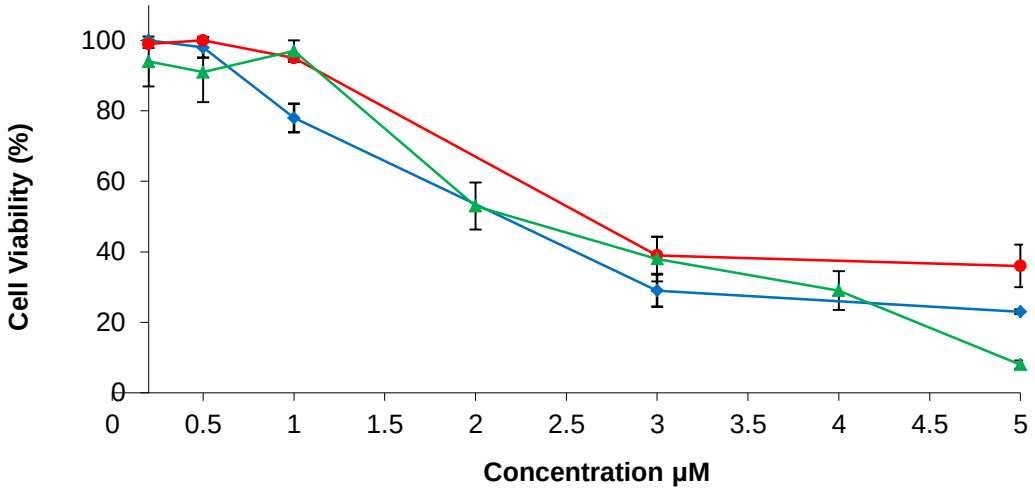




Viability of normal human skin fibroblast (GM00637) (♦), prostate cancer (DU145) (●) and breast cancer (MCF7) (▲) cell lines determined using the MTT assay following treatment with 1,3-diphenyl-6-(piperidin-1-yl)-benzo[*e*][1,2,4]triazin-7(1*H*)-one (**19g)** under aerobic conditions for 72 h at 37°C. Each data point is the mean of at least three independent experiments. The lines shown are trend lines.

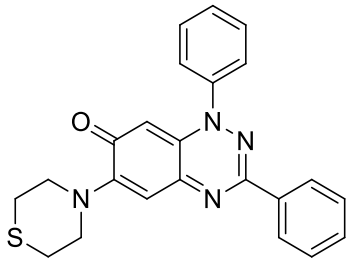
6-Morpholino-1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (19h)

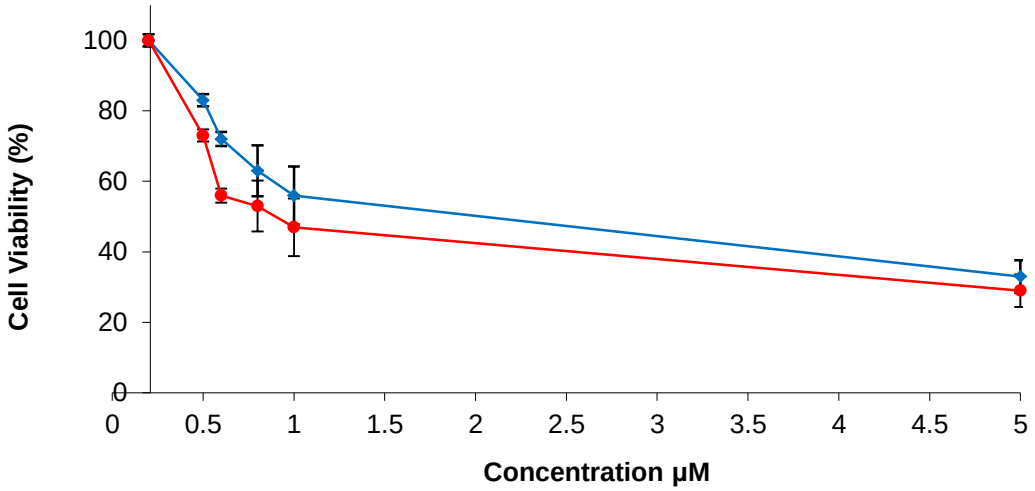




Viability of normal human skin fibroblast (GM00637) (♦), prostate cancer (DU145) (●) and breast cancer (MCF7) (▲) cell lines determined using the MTT assay following treatment with 6-morpholino-1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (**19h)** under aerobic conditions for 72 h at 37°C. Each data point is the mean of at least three independent experiments. The lines shown are trend lines.

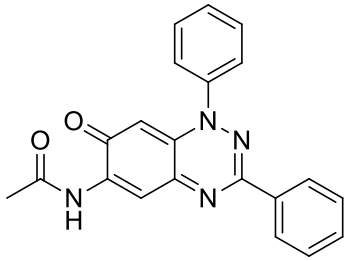
6-Thiomorpholino-1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (19i)

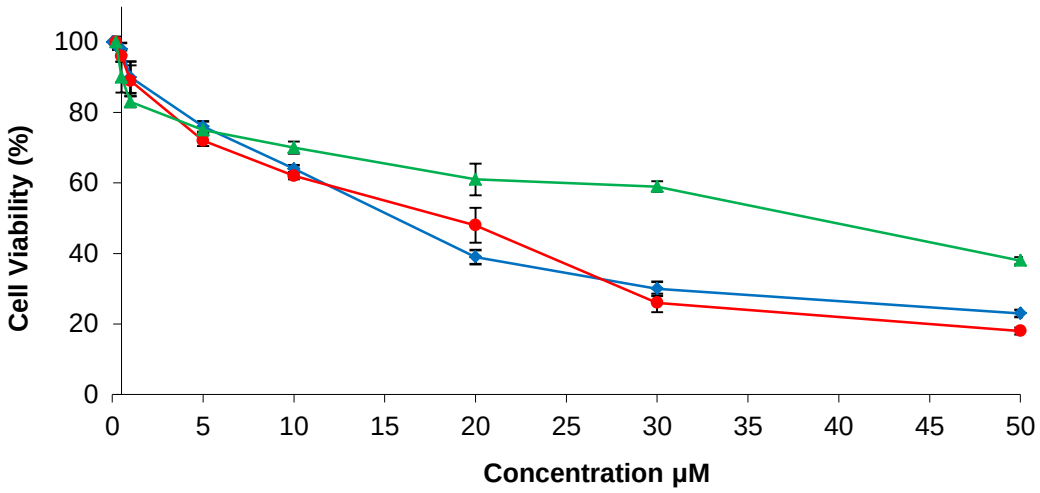




Viability of normal human skin fibroblast (GM00637) (♦) and prostate cancer (DU145) (●) cell lines determined using the MTT assay following treatment with 6-thiomorpholino-1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (**19i)** under aerobic conditions for 72 h at 37°C. Each data point is the mean of at least three independent experiments. The lines shown are trend lines.

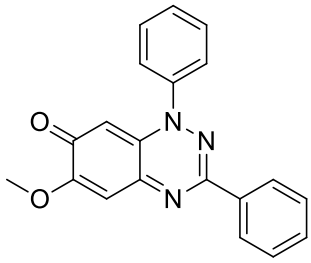
***N*-(7-oxo-1,3-diphenyl-1,7-dihydrobenzo[*e*][1,2,4]triazin-6-yl)acetamide (19j)**

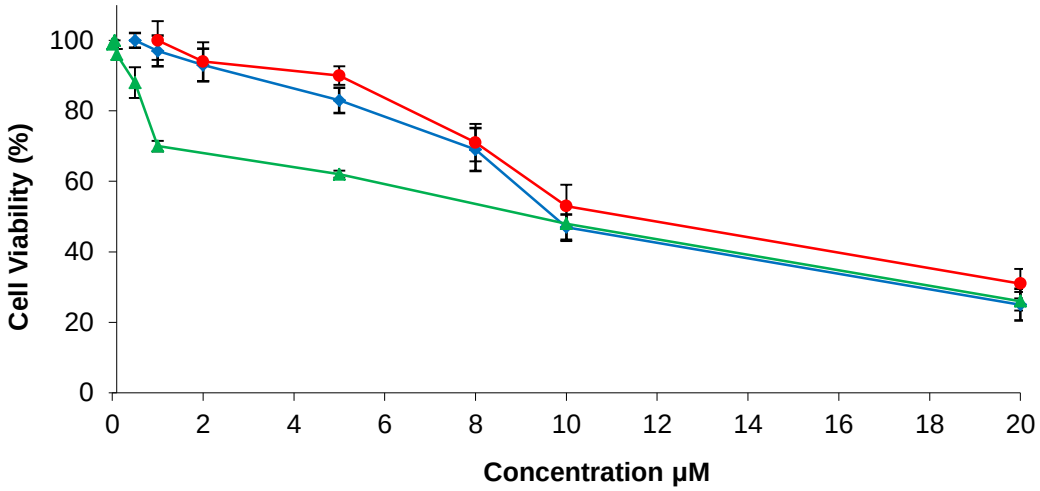




Viability of normal human skin fibroblast (GM00637) (♦), prostate cancer (DU145) (●) and breast cancer (MCF7) (▲) cell lines determined using the MTT assay following treatment with *N*-(7-oxo-1,3-diphenyl-1,7-dihydrobenzo[*e*][1,2,4]triazin-6-yl) acetamide **(19j)** under aerobic conditions for 72 h at 37°C. Each data point is the mean of at least three independent experiments. The lines shown are trend lines.

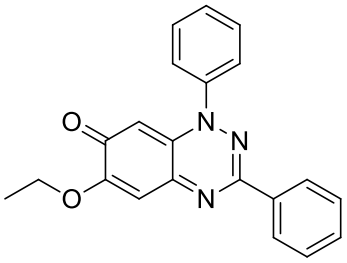
6-Methoxy-1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (19k)

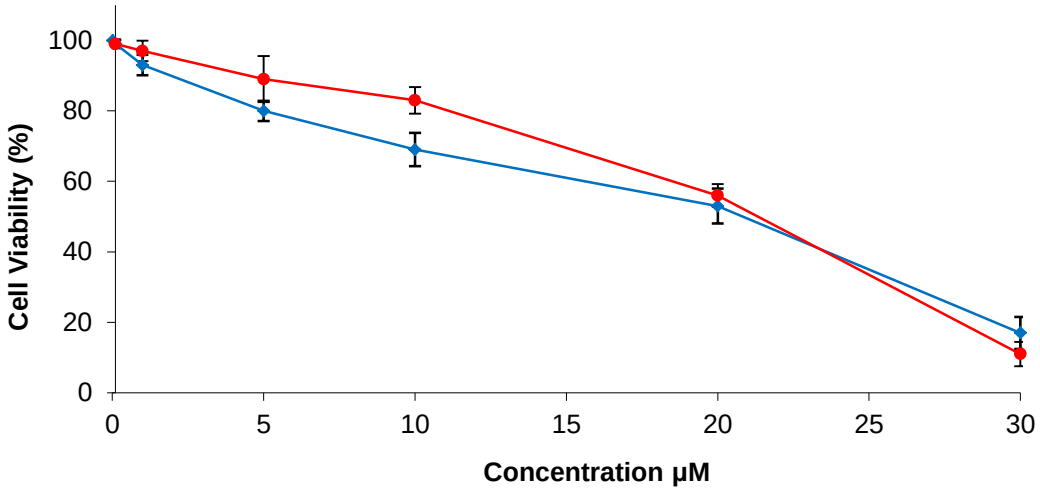




Viability of normal human skin fibroblast (GM00637) (♦), prostate cancer (DU145) (●) and breast cancer (MCF7) (▲) cell lines determined using the MTT assay following treatment with 6-methoxy-1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (**19k)** under aerobic conditions for 72 h at 37°C. Each data point is the mean of at least three independent experiments. The lines shown are trend lines.

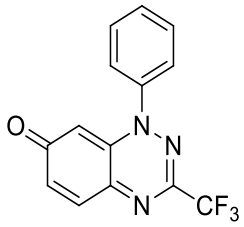
6-Ethoxy-1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (19l)

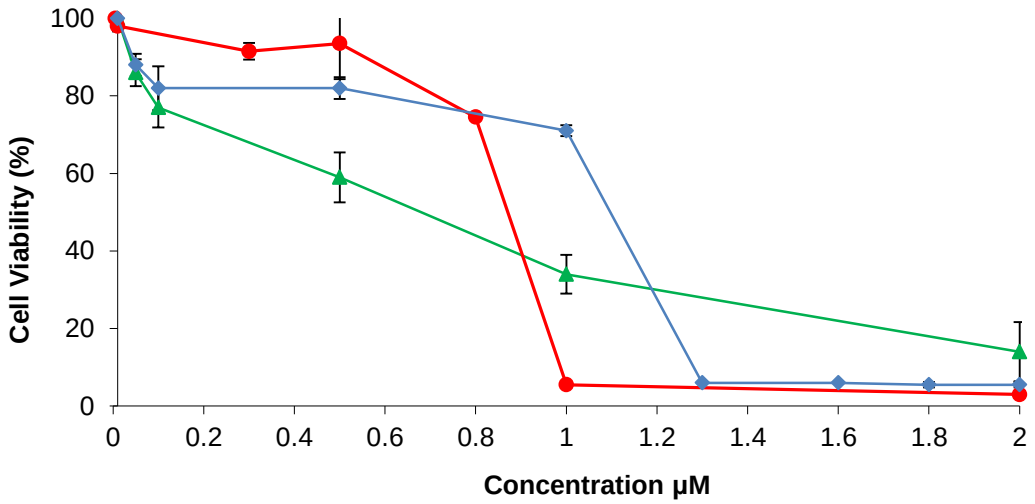




Viability of normal human skin fibroblast (GM00637) (♦) and prostate cancer (DU145) (●) cell lines determined using the MTT assay following treatment with 6-ethoxy-1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (**19l)** under aerobic conditions for 72 h at 37°C. Each data point is the mean of at least three independent experiments. The lines shown are trend lines.

1-Phenyl-3-(trifluoromethyl)-benzo[*e*][1,2,4]triazin-7(1*H*)-one (20)

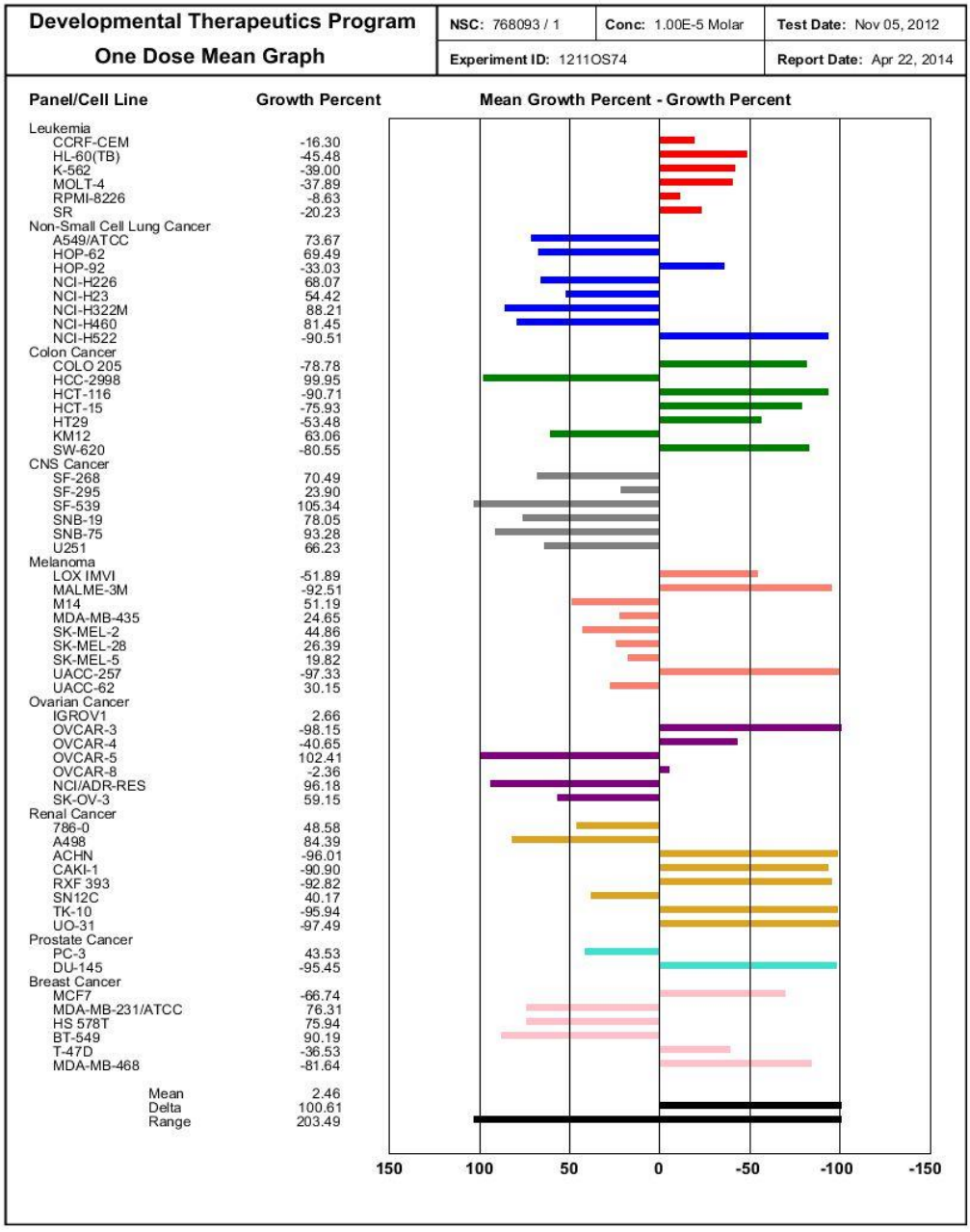




Viability of normal human skin fibroblast (GM00637) (♦), prostate cancer (DU145) (●) and breast cancer (MCF7) (▲) cell lines determined using the MTT assay following treatment with 1-phenyl-3-(trifluoromethyl)-benzo[*e*][1,2,4]triazin-7(1*H*)-one (**20)** under aerobic conditions for 72 h at 37°C. Each data point is the mean of at least three independent experiments. The lines shown are trend lines.

A.3.2 DTP NCI-60 mean growth percent graphs

A.3.2.1 One dose testing for 1,3-Diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (19a)



Developmental Therapeutics Program
One Dose Mean Graph

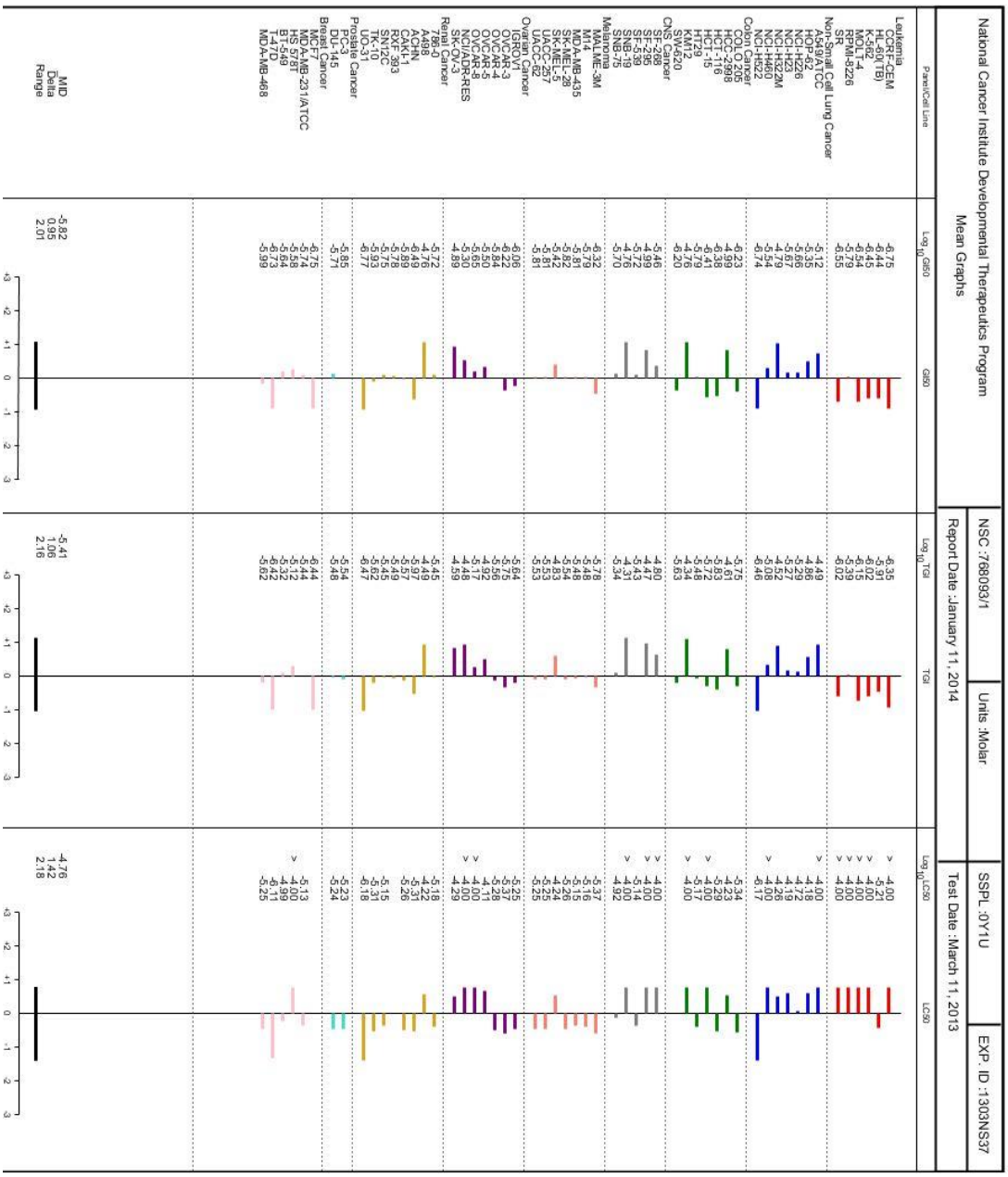
NSC: 768093 / 1	Conc: 1.00E-5 Molar	Test Date: Nov 05, 2012
Experiment ID: 1211OS74		Report Date: Apr 22, 2014

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	-16.30
HL-60(TB)	-45.48
K-562	-39.00
MOLT-4	-37.89
RPMI-8226	-8.63
SR	-20.23
Non-Small Cell Lung Cancer	
A549/ATCC	73.67
HOP-62	69.49
HOP-92	-33.03
NCI-H226	68.07
NCI-H23	54.42
NCI-H322M	88.21
NCI-H460	81.45
NCI-H522	-90.51
Colon Cancer	
COLO 205	-78.78
HCC-2998	99.95
HCT-116	-90.71
HCT-15	-75.93
HT29	-53.48
KM12	63.06
SW-620	-80.55
CNS Cancer	
SF-268	70.49
SF-295	23.90
SF-539	105.34
SNB-19	78.05
SNB-75	93.28
U251	66.23
Melanoma	
LOX IMVI	-51.89
MALME-3M	-92.51
M14	51.19
MDA-MB-435	24.65
SK-MEL-2	44.86
SK-MEL-28	26.39
SK-MEL-5	19.82
UACC-257	-97.33
UACC-62	30.15
Ovarian Cancer	
IGROV1	2.66
OVCAR-3	-98.15
OVCAR-4	-40.65
OVCAR-5	102.41
OVCAR-8	-2.36
NCI/ADR-RES	96.18
SK-OV-3	59.15
Renal Cancer	
786-0	48.58
A498	84.39
ACHN	-96.01
CAKI-1	-90.90
RXF 393	-92.82
SN12C	40.17
TK-10	-95.94
UO-31	-97.49
Prostate Cancer	
PC-3	43.53
DU-145	-95.45
Breast Cancer	
MCF7	-66.74
MDA-MB-231/ATCC	76.31
HS 578T	75.94
BT-549	90.19
T-47D	-36.53
MDA-MB-468	-81.64
Mean	2.46
Delta	100.61
Range	203.49

Mean Growth Percent - Growth Percent

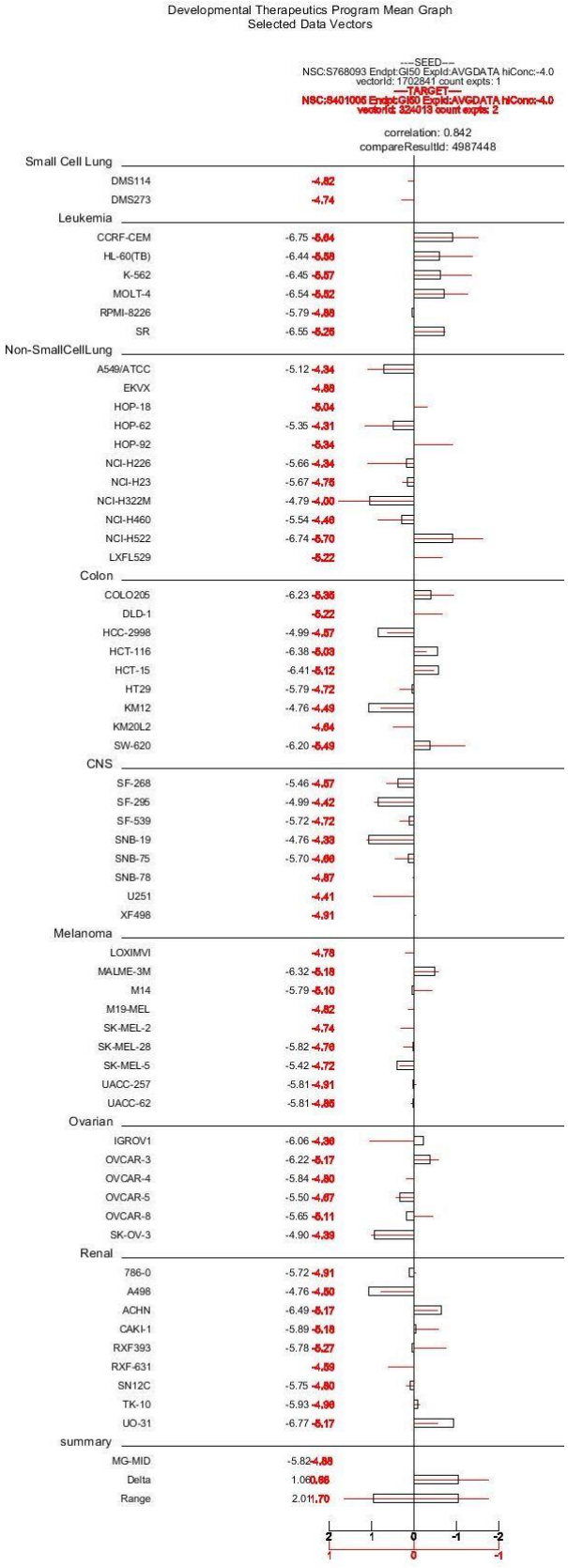
150 100 50 0 -50 -100 -150

A.3.2.2 Five dose testing for 1,3-Diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (19a)

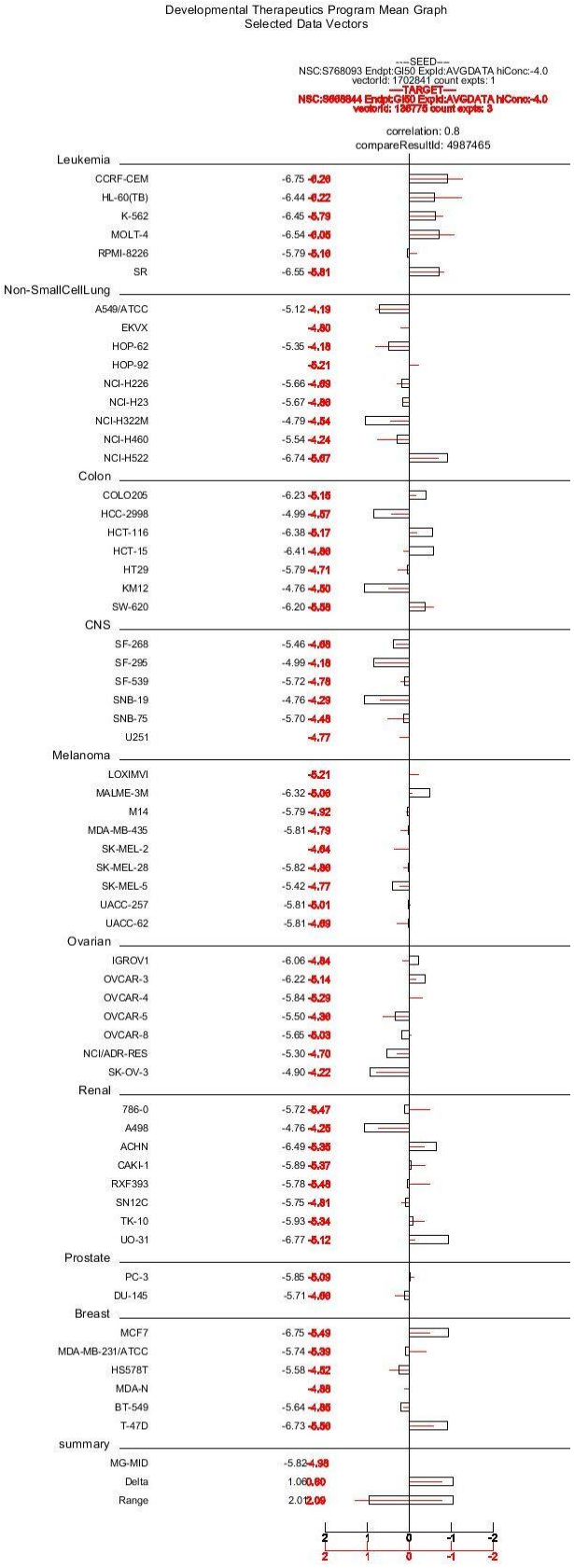


A.3.3 COMPARE correlations

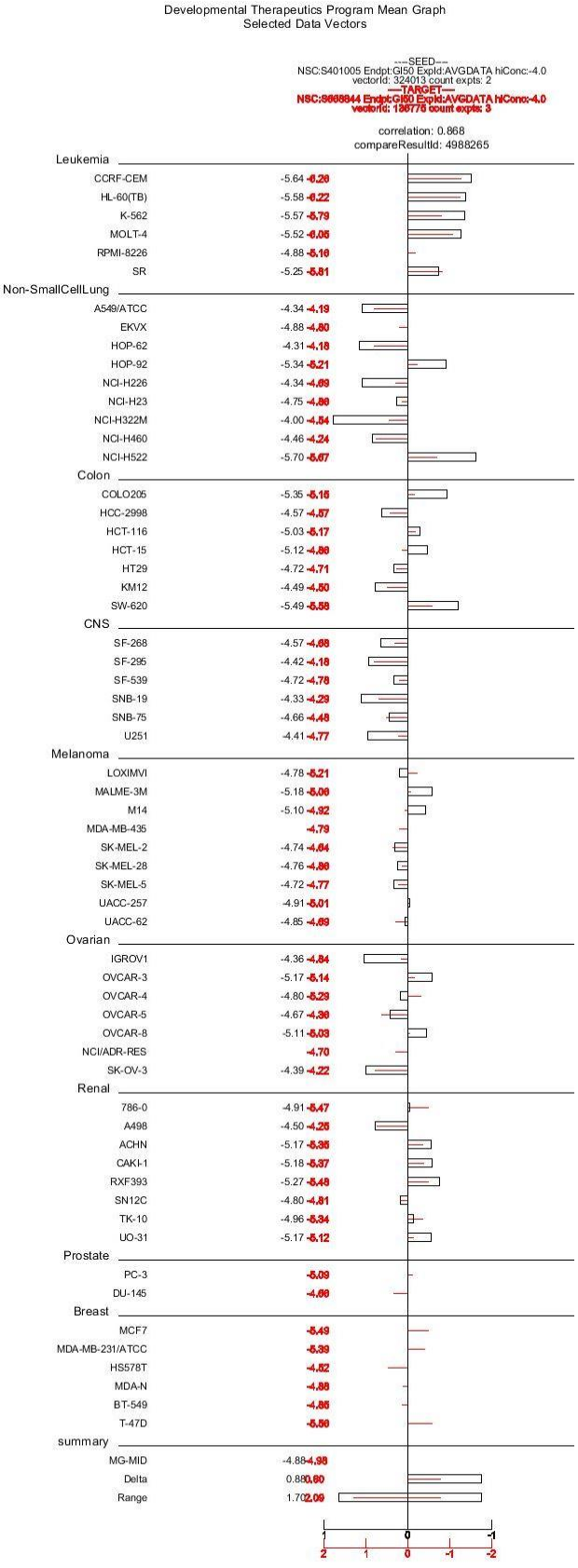
Correlation of compound 19a to pleurotin



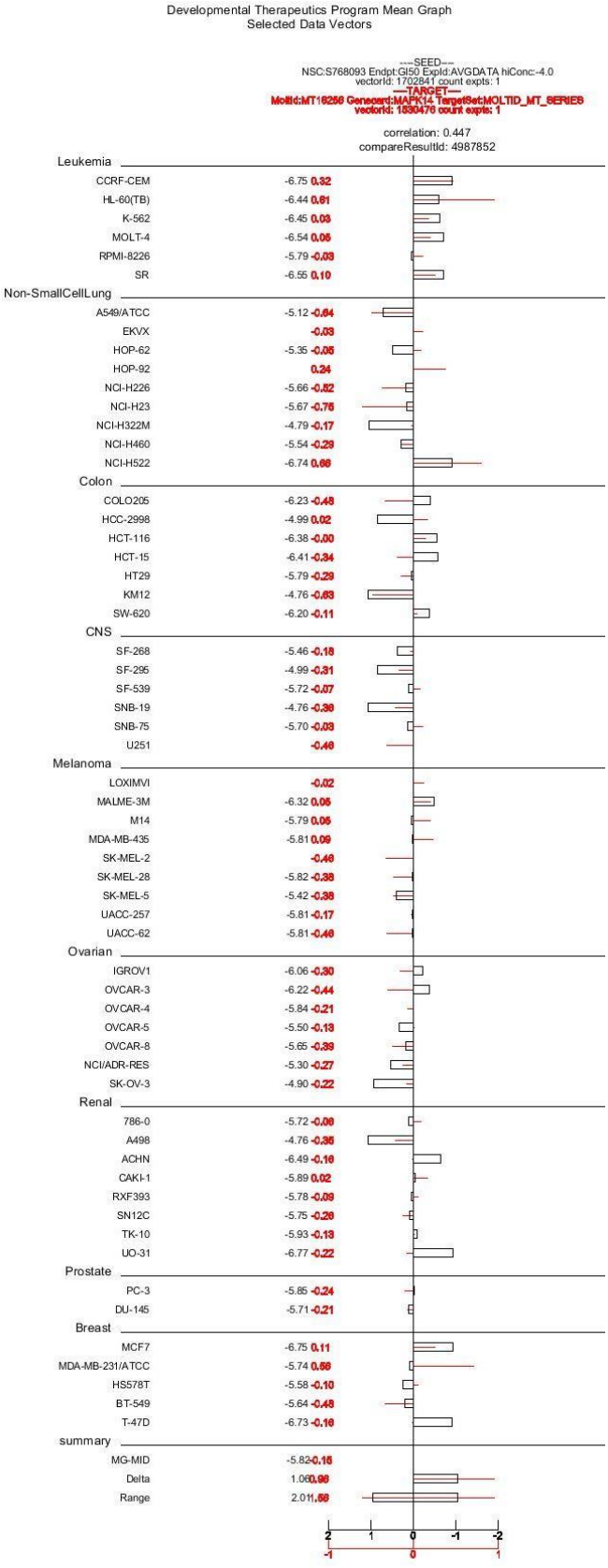
Correlation of compound 19a to NSC668844



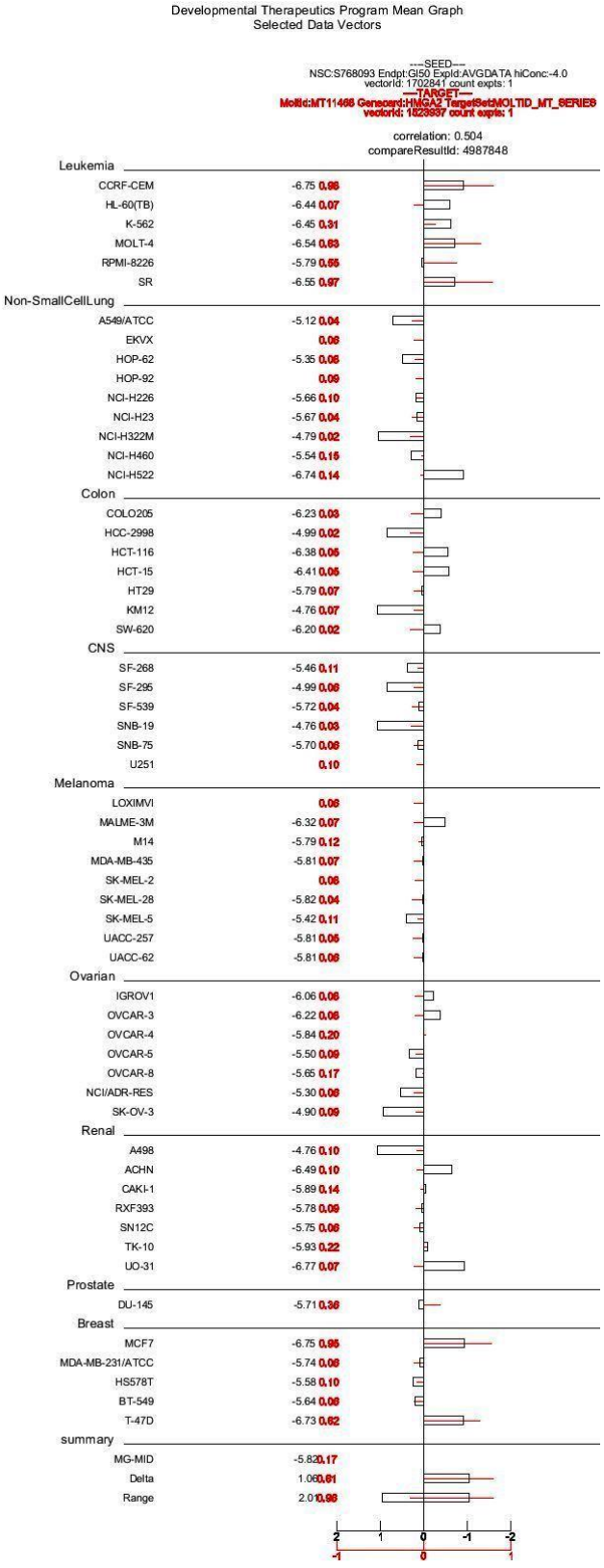
Correlation of pleurotin to NSC668844



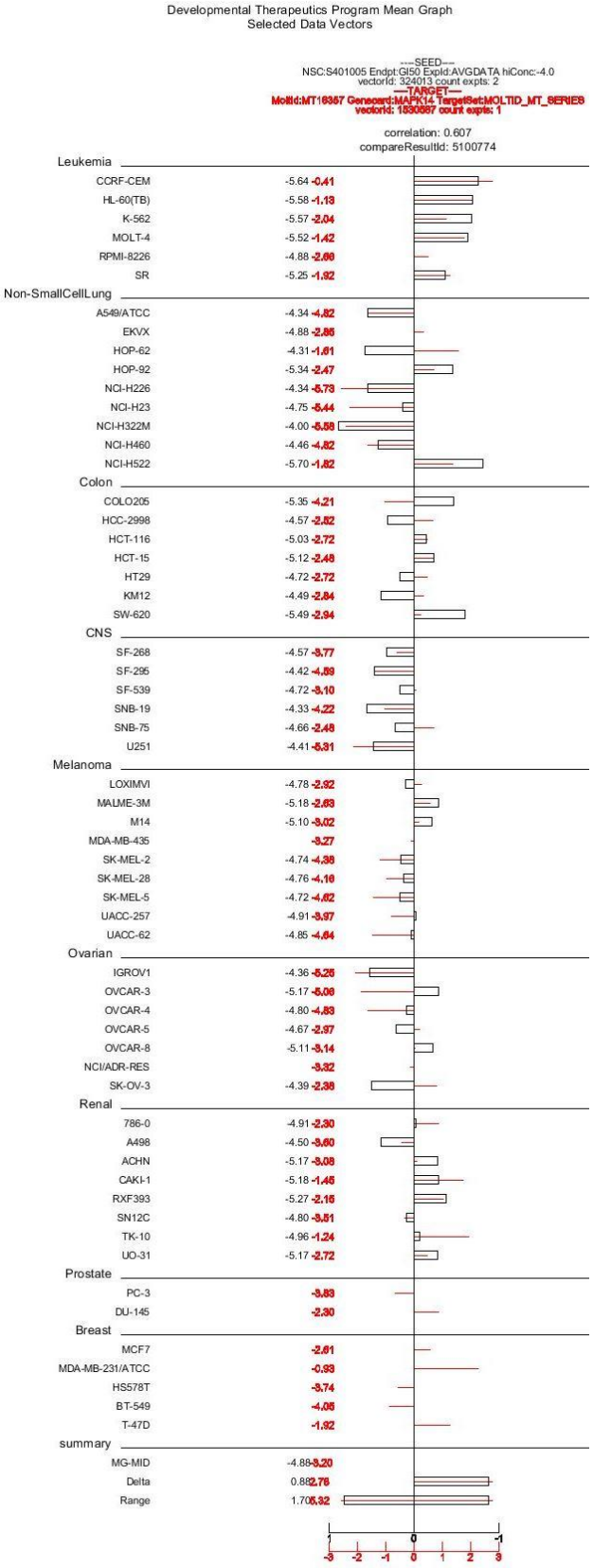
Correlation of compound 19a to MAPK14



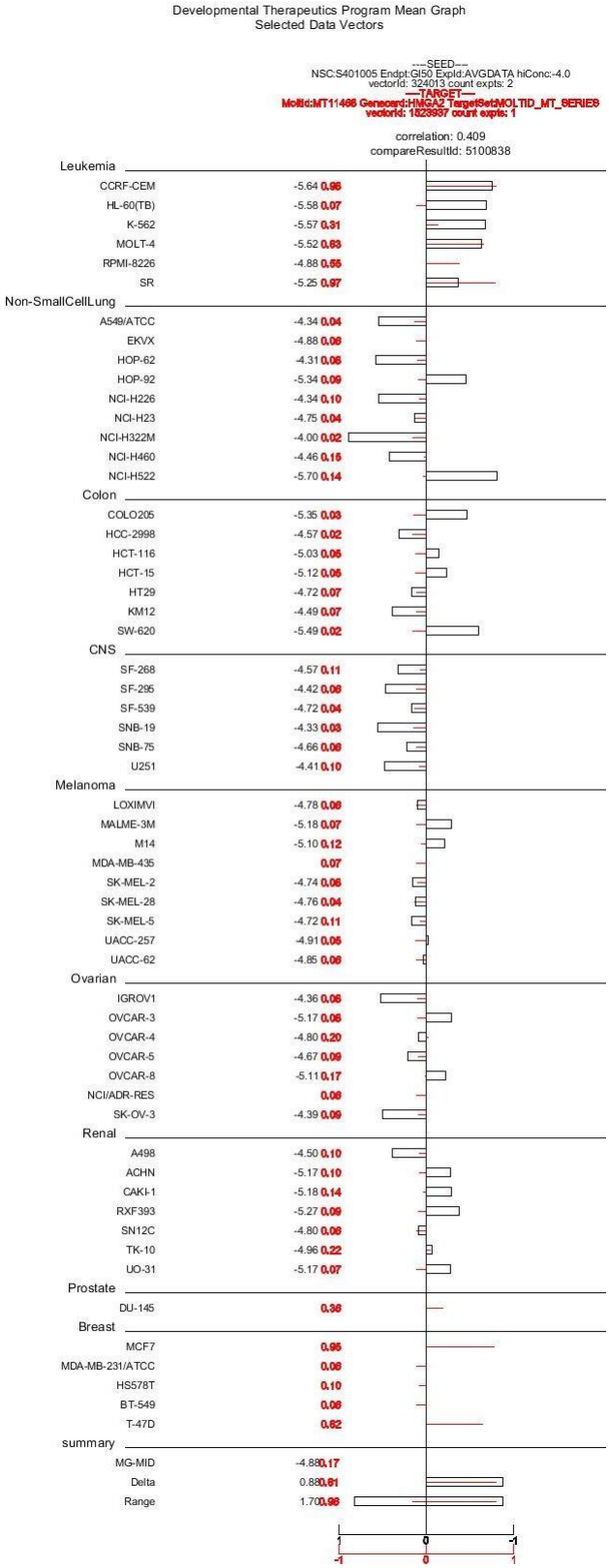
Correlation of compound 19a to HMGA2



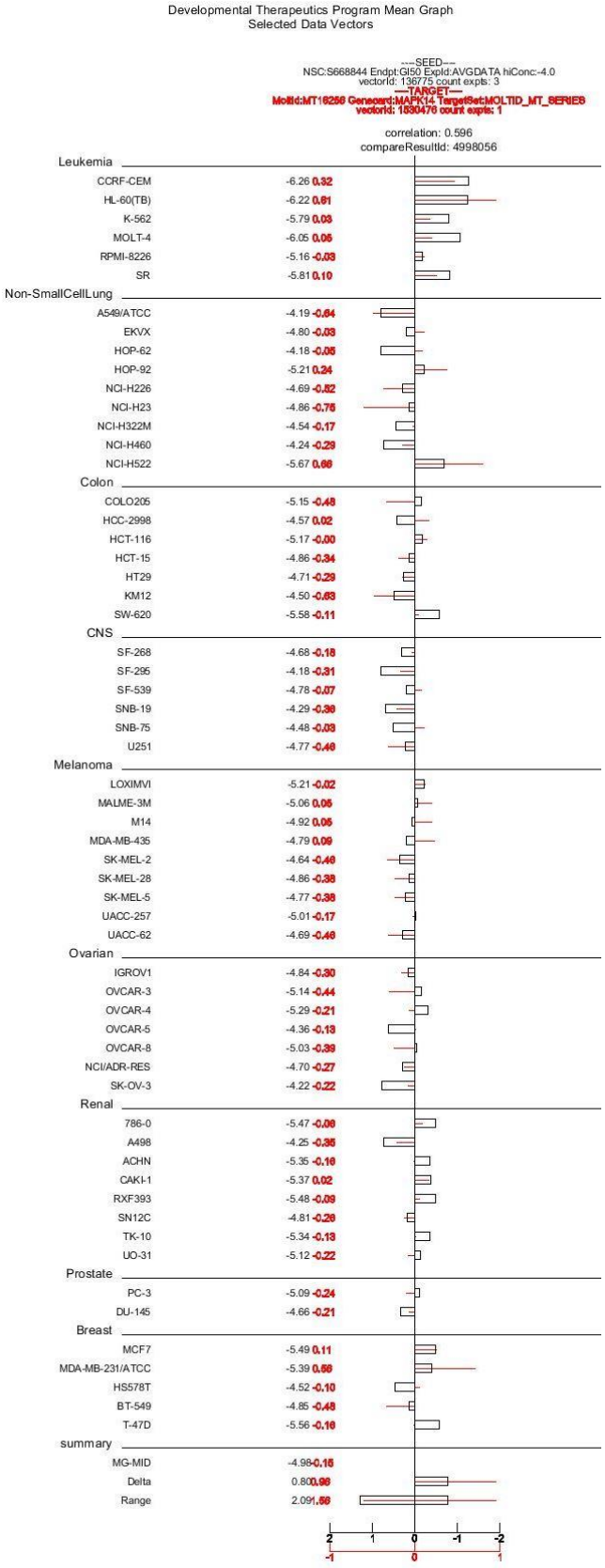
Correlation of pleurotin to MAPK14



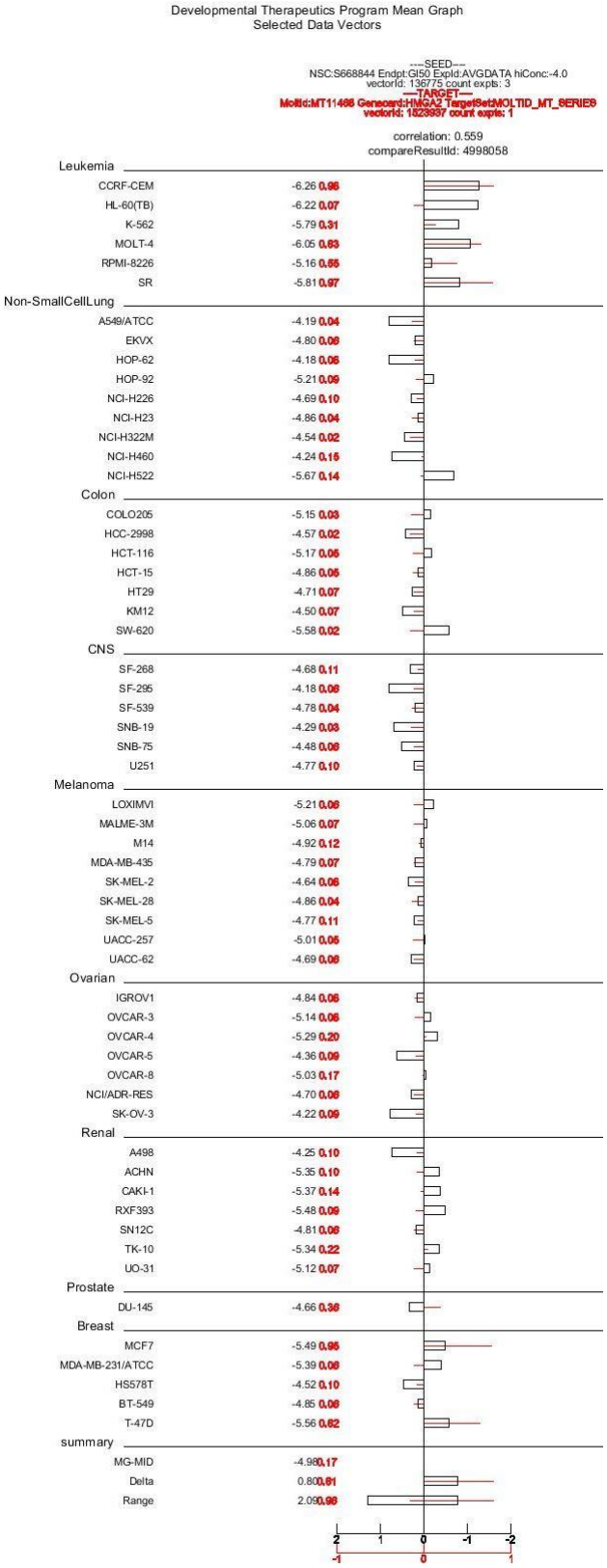
Correlation of pleurotin to HMGA2



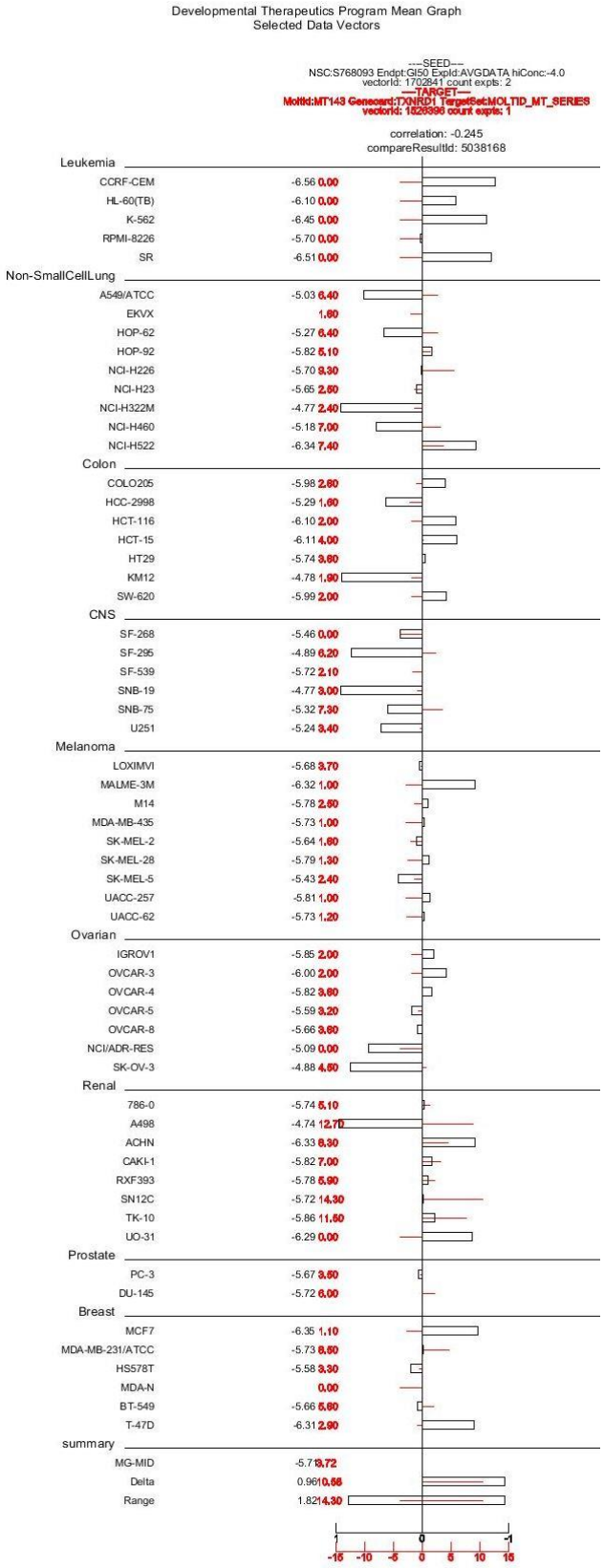
Correlation of NSC S668844 to MAPK14



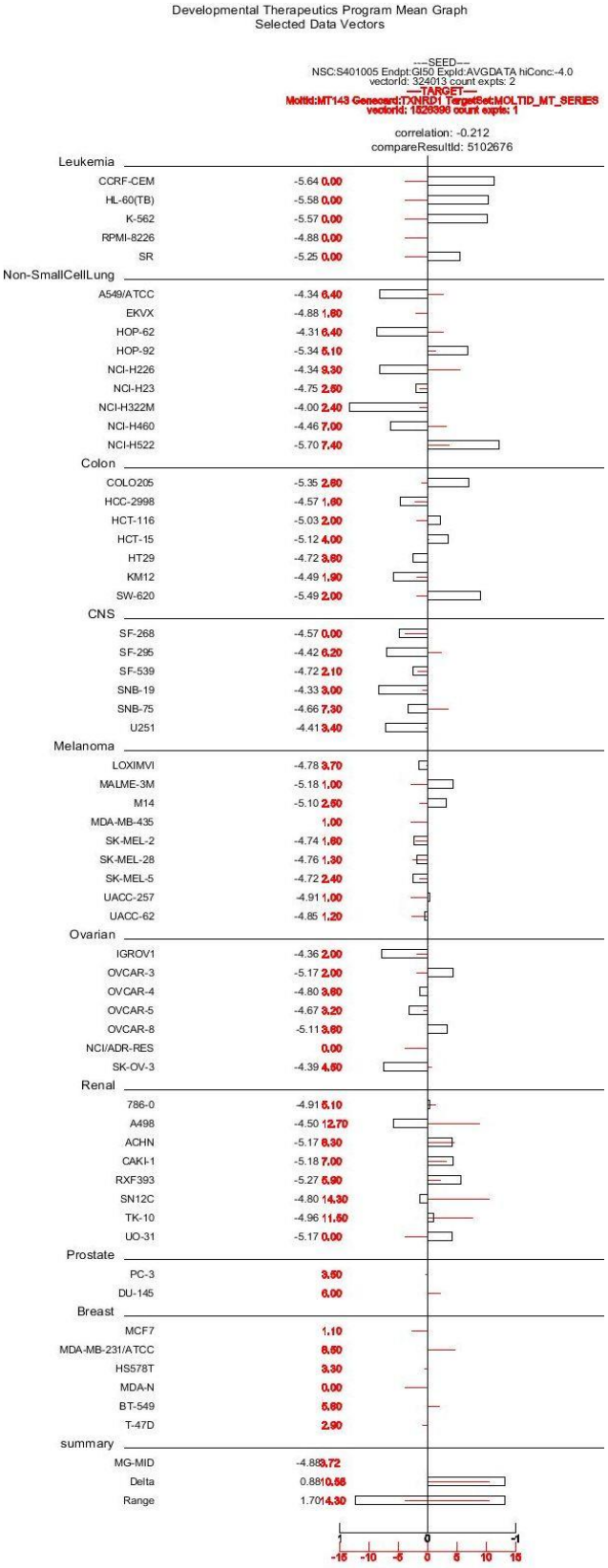
Correlation of NSC S668844 to HMGA2



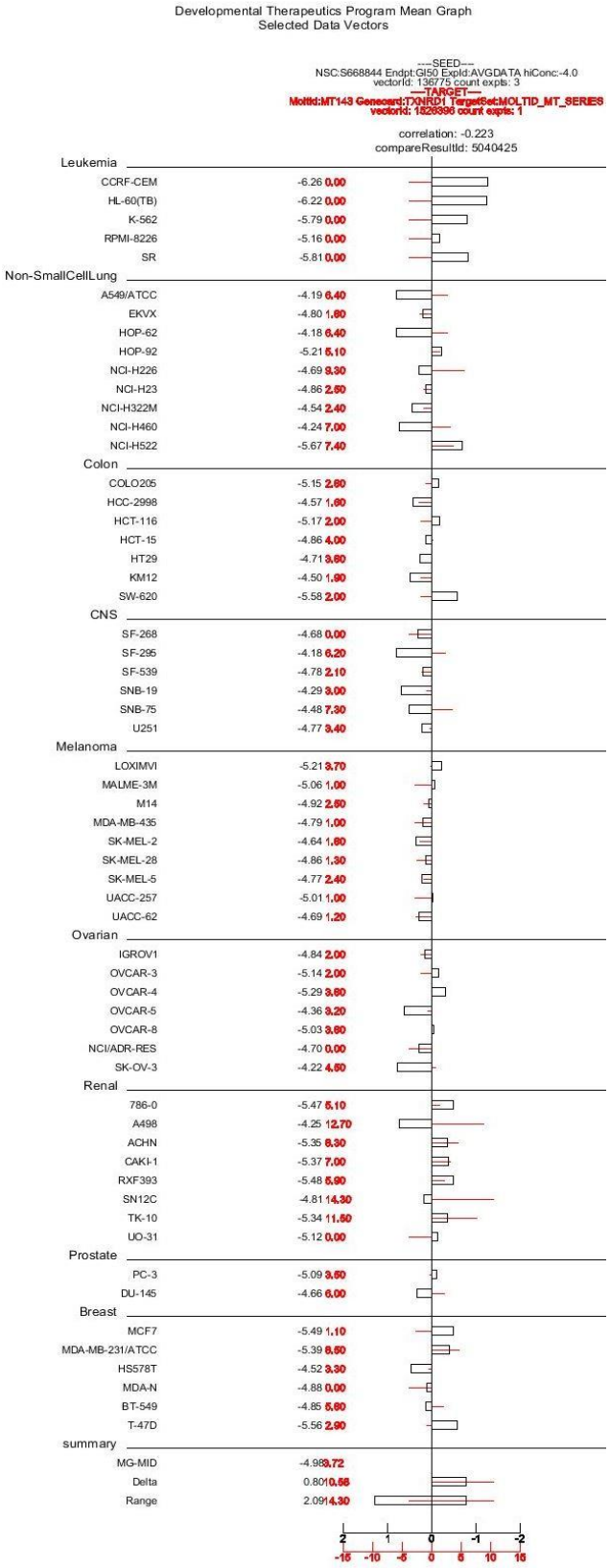
Correlation of compound 19a to TXNRD1



Correlation of pleurotin to TXNRD1



Correlation of NSC S668844 to TXNRD1



Conference Proceedings and Peer Reviewed Publications

Conference Proceedings

"Intramolecular Aromatic Substitution of Cyclopropyl Radicals Generated using Barton Esters" R. Coyle. 2011 Eli Lilly Postgraduate Chemistry Symposium National University of Ireland, Galway, September 2011. ***Oral Communication***.

2011 Eli Lilly Postgraduate Chemistry Symposium

"Barton Esters for Initiator-Free Radical Cyclisation with Heteroaromatic Substitution" R. Coyle, K. Fahey, P. McArdle and F. Aldabbagh. 21st Grasmere Heterocyclic Symposium, May 2013. ***Poster Communication***.

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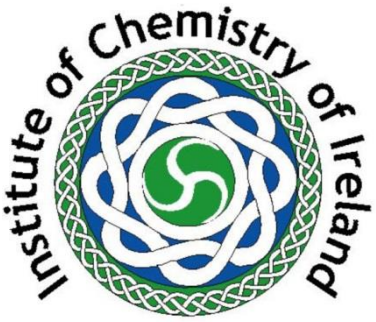
"Barton Esters for Initiator-Free Radical Cyclisation with Heteroaromatic Substitution" R. Coyle. 65th Irish Universities Chemistry Research Colloquium, June 2013. ***Oral Communication***.

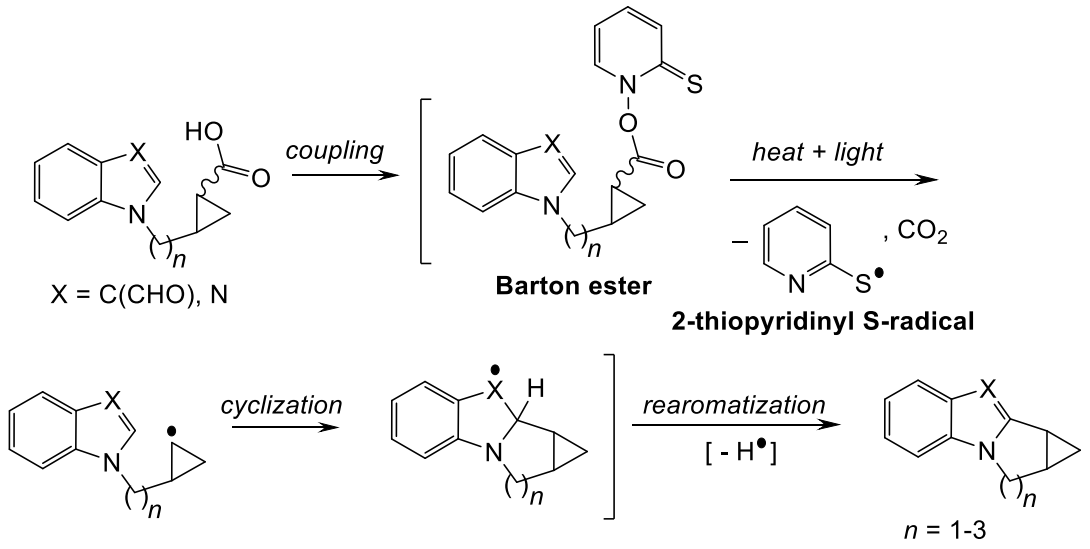


2011 Eli Lilly Postgraduate Prize in Chemistry Symposium, NUI Galway, Ireland

Presenter: **Robert Coyle** Supervisor: **Dr. Fawaz Aldabbagh**

Title of Presentation: **Intramolecular Aromatic Substitution of Cyclopropyl Radicals Generated using Barton Esters: Access to Potent Anti-Tumour Agents**

Abstract: There are scant reports of three-membered ring radicals undergoing aromatic substitution, and reported yields of aromatic substitution products are low.[1,2] Cyclopropane fused onto pyrrolo[1,2-*a*]indole, and pyrrolo[1,2-*a*]benzimidazole form the skeleton of highly potent bioreductive anti-tumour agents.[3,4] Their reported syntheses follow well-established cycloaddition protocols. In this presentation an alternative radical route is described, involving 1,2-conjugate additions of cyclopropyl radicals onto the 2-position of indole-3-carbaldehyde and benzimidazole with subsequent rearomatisation of the adduct radical to give cyclopropane fused onto five-to-seven membered rings in moderate to high yields. The synthesis involves an efficient formation of Barton esters, and a new annulation protocol.



Relevance to Irish Chemical and Biopharamceutical Industry: Many synthetic radical transformations in academia and industry rely on the use of Bu_3SnH and azo-initiator, which are toxic, give waste disposal issues and can be hazardous. Further it is a challenge to get "oxidized" aromatic product in the presence of the "reductant" Bu_3SnH.[5,6] This new protocol avoids the use of chemical initiators to establish an efficient homolytic aromatic substitution. The heterocyclic products are potent bioreductive anti-tumour agents of great pharmaceutical interest.

References: [1]Ziegler, F. E.; Belema, M. *J. Org. Chem.* **1994**, *59*, 7962-7967; [2]Ziegler, F. E.; Belema, M. *J. Org. Chem.* **1997**, *62*, 1083-1094; [3]Cotterill, A. S.; Moody, C. J. Mortimer, R. J.; Norton, C. L.; O'Sullivan, N.; Stephens, M. A.; Stradiotto, N. R.; Swann, E.; Stratford, I. J. *J. Med. Chem.* **1994**, *37*, 3834-3843; [4]Lynch, M.; Hehir, S.; Kavanagh, P.; Leech, D.; O'Shaughnessy, J.; Carty, M. P.; Aldabbagh, F. *Chem. Eur. J.* **2007**, *13*, 3218-3226. [5]Bowman, W. R.; Storey, J. M. D. *Chem. Soc. Rev.* **2007**, *36*, 1803-1822; [6]Fagan, V.; Bonham, S.; Carty, M. P.; Aldabbagh, F. *Org. Biomol. Chem.* **2010**, *8*, 3149-3156.

Barton Esters for Initiator-Free Radical Cyclisation with Heteroaromatic Substitution†

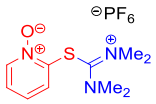
Robert Coyle, Karen Fahey, Patrick McArdle and Fawaz Aldabbagh*

School of Chemistry, National University of Ireland Galway, Ireland

Introduction

Trialkylmetal hydrides such as Bu_3SnH with an azo-initiator are now routinely used in organic synthesis to perform intramolecular homolytic aromatic substitutions. Since effectively a hydrogen atom ($H^{\bullet}$) is lost, it is well documented that difficulties exist in forming ''oxidised'' aromatic substitution product in the presence of the ''reductant'' Bu_3SnH. We now present initiator-free alkyl and cyclopropyl radical intramolecular aromatic substitutions onto the 2-position of indoles and benzimidazoles formed *via* the decomposition of Barton esters. The Barton esters were formed using HOTT; S-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium hexafluorophosphate.

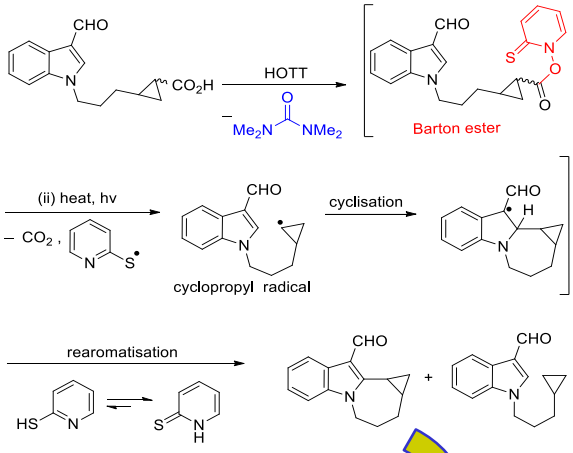
HOTT



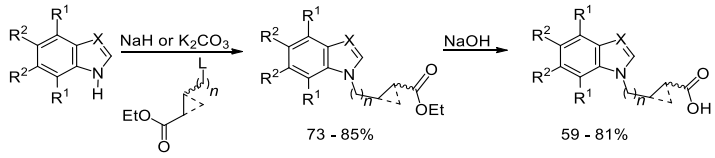
Used for the formation of Barton esters from hindered carboxylic acids.

P. Garner et al, *J. Org. Chem*. **1998**; *63*, 5732-5733

Barton Ester Formation & Cyclopropyl Radical Cyclisation

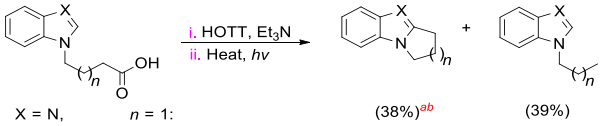


Radical Precursors



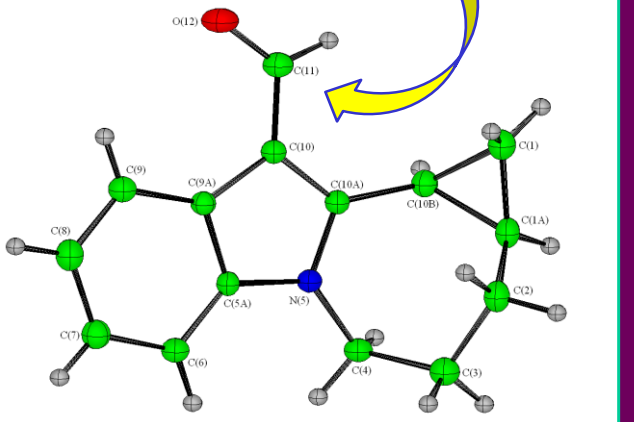
Radical precursors were readily accessed using a straight forward two-step synthesis involving *N*-alkylation and saponification of resultant ester. The use of carboxylic acids is advantageous due to their robustness, unlike many conventional more labile radical cyclisation precursors.

Alkyl Radical Cyclisations

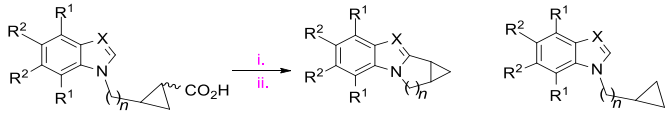


X = N, *n* = 1:	(38%)[ab]	(39%)
X = C(CN), *n* = 1:	(78%)	(00%)
X = CH, *n* = 2:	(00%)	(76%)
X = C(CHO), *n* = 2:	(79%)	(00%)
X = N, *n* = 2:	(77%)[a]	(00%)
X = C(CN), *n* = 2:	(82%)	(00%)
X = N, *n* = 3:	(37%)[ab]	(39%)
X = C(CN), *n* = 3:	(61%)	(21%)

[a] DMAP required, [b] CSA required



Cyclopropyl Radical Cyclisations



R^1	R^2	X	*n*	%	%
H	H	C(CHO)	1	(38)	(43)
H	H	C(CN)	1	(75)	(00)
H	H	C(CHO)	2	(78)	(00)
H	H	N	2	(81)	(00)
H	H	C(CN)	2	(77)	(00)
H	Me	N	2	(76)[a]	(00)
OMe	H	N	2	(80)[ab]	(00)
H	H	C(CN)	3	(37)	(41)

i. HOTT (1.5 equiv), Et_3N (3 equiv),THF-MeCN (3:1) 0.1 M, rt, dark, 40 min
ii. MeCN (0.01 M), reflux, 2 X 100 W, 6 h

Due to Barton ester sensitivity, their formation is carried out under aphotic conditions.
Cyclisation of nucleophilic radicals requires activation at the heterocyclic 3-position. In the case of indoles an EWG (CN, CHO) is required and for benzimidazoles quaternisation using camphorsulfonic acid (CSA) is required for more difficult cyclisations. Five and seven membered cyclisations onto indole-3-carbonitrile were more facile than onto indole-3-carbaldehyde or benzimidazole.
The skeleton of the anti-cancer agent cyclopropamitosene, expanded and diazole analogues is thus readily accessed directly from carboxylic acids.

Conclusions

- First reported examples of homolytic aromatic substitution leading to fusion of the cyclopropane ring.
- First synthetically useful radical cyclisation onto aromatics using Barton esters.

† R. Coyle, K. Fahey and F. Aldabbagh, *Org. Biomol. Chem.* **2013**; *11*, 1672-1682.

Acknowledgements

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Barton Esters for Initiator-Free Radical Cyclisation with Heteroaromatic Substitution

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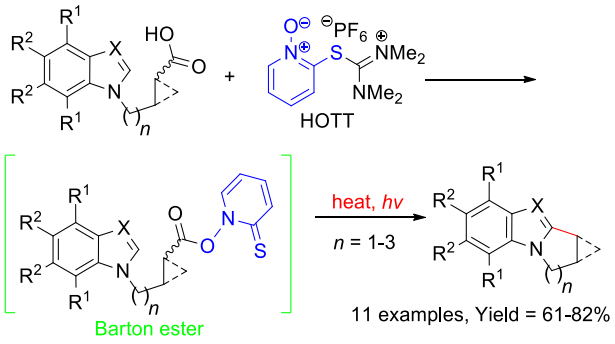
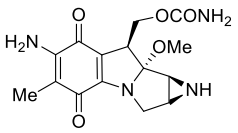
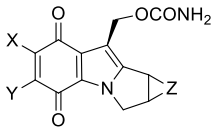
***Email**: R.coyle2@nuigalway.ie, *fawaz.aldabbagh@nuigalway.ie*

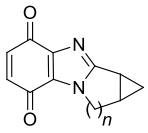
LECTURE - Bu_3SnH with an azo-initiator is now a commonly used protocol for intramolecular homolytic aromatic substitution.[1,2,3] It is now accepted that the reaction proceeds via a non-chain reaction, requiring excess amounts of initiator in order to optimise yields of substitution product. Two inherent disadvantages of using Bu_3SnH are the toxicity of tin-waste generated, and the requirement for slow syringe addition to minimise premature reduction of the cyclising radical. The first synthetically useful radical cyclisations onto aromatics via Barton esters are now presented.[4] Initiator-free alkyl and cyclopropyl radical cyclisations allow access to five, six and seven-membered [1,2-*a*] alicyclic-ring fused heterocycles with and without an additional fused cyclopropane using robust carboxylic acids as precursors.



This is part of our broad objectives to discover heterocycles with improved efficacy in comparison to the archetypical bioreductive anti-cancer agent, mitomycin C, its bioactivated form aziridinomitosene and the cyclopropane analogue cyclopropamitosene.[5,6,7] The lecture ends by describing progress towards initiator free domino radical approaches to ring-expanded aziridinomitosenes via Barton esters.


Mitomycin C


Aziridinomitosene:
X = NH_2, Y = Me, Z = NH,
Cyclopropamitosene:
X = OMe, Y = H, Z = CH_2


Benzimidazolequinones
n = 1, 2

[1] W. R. Bowman, J. M. D. Storey, *Chem. Soc. Rev.*, **2007**, 36, 1803-1822.

[2] M. Lynch, S. Hehir, P. Kavanagh, D. Leech, J. O'Shaughnessy, M. P. Carty, F. Aldabbagh, *Chem. Eur. J.*, **2007**, 13, 3218-3226.

[3] V. Fagan, S. Bonham, M. P. Carty, F. Aldabbagh, *Org. Biomol. Chem.*, **2010**, *8*, 3149-3156.

[4] R. Coyle, K. Fahey, F. Aldabbagh, *Org. Biomol. Chem.*, **2013**, *11*, 1672-1682.

[5] S. Bonham, L. O'Donovan, M. P. Carty, F. Aldabbagh, *Org. Biomol. Chem.*, **2011**, *9*, 6700-6706.

[6] V. Fagan, S. Bonham, M. P. Carty, P. Saenz-Méndez, L. A. Eriksson, F. Aldabbagh, *Bioorg. Med. Chem.*, **2012**, 20, 3223-3232.

[7] A. S. Cotterill, C. J. Moody, R. J. Mortimer, C. L. Norton, N. O'Sullivan, M. A. Stephens, N. R. Stradiotto, E. Swann, I. J. Stratford, *J. Med. Chem.*, **1994**, 37, 3834-3843.