2.1 INTRODUCTION

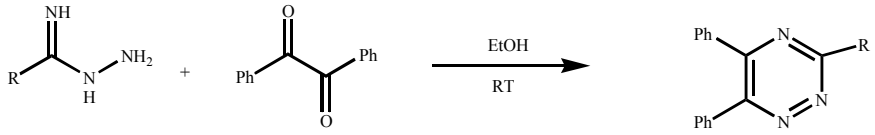
Substituted 1,2,4-triazines represent an important class of nitrogen-containing heterocycles. The 1,2,4-triazine core is a versatile synthetic platform to access a wide-range of condensed heterocyclic ring system *via* intramolecular Diels-Alder reactions with a vast array of dienophiles. Moreover, the triazines ring system is a key component of commercial dyes, herbicides, insecticides and more recently, pharmaceutical composition. While only a few of these heterocycles are found in nature, they have been prepared and treated as potentially active building blocks in agrochemical and medicinal field. In addition, 1,2,4-triazines have been extensively used as electron deficient dienes for the preparation of pyridine derivatives through their reactions with electron rich dienophiles by the application of Diels-Alder cycloaddition reactions with inverse electron demand.

2.1.1 Review of literatures

1,2,4-triazines are useful intermediates in the synthesis of several heterocyclic systems. They are well established as heterodienes in the inverse electron demand Diels-Alder reaction to form functionalized pyridine derivatives and undergo ring interconversions into five or six-membered aza hetero aromatics when reacted with nucleophile reagent.

The synthesis of 1,2,4-triazines and thier application to the synthesis of pyridine compounds *via* an inverse electron demand Diels-Alder reaction are summarized as follows:

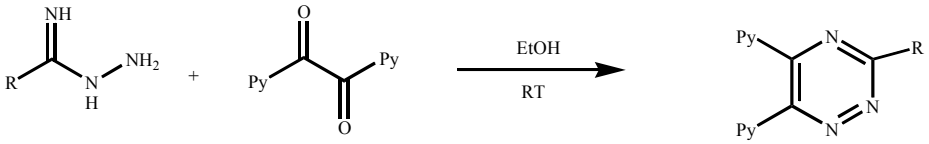
Case (Case, 1965) prepared a number of 1,2,4-triazine derivatives **17a-d**, **19a-g**, **21a-f** and **24** from hydrazidines and α,β-diketones. The synthetic route to 1,2,4-triazines **17a-d**, **19a-g**, **21a-f** and **24** is shown in **Schemes** 9-12, respectively.



15 **16** **17**

Compound	R
a	2-pyridyl
b	4-methyl-2-pyridyl
c	4-ethyl-2-pyridyl
d	2-quinolyl

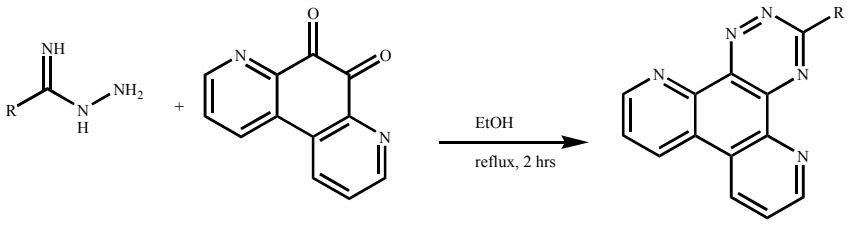
Scheme 9 The synthetic route to 3-substituted-5,6-diphenyl-1,2,4-triazines **17a-d**



15 **18** **19**

Compound	R
a	2-pyridyl
b	4-methyl-2-pyridyl
c	4-ethyl-2-pyridyl
d	2-quinolyl
e	2-thiazolyl
f	4-phenyl-2-pyridyl
g	2-(1-10-phenanthrolyl)

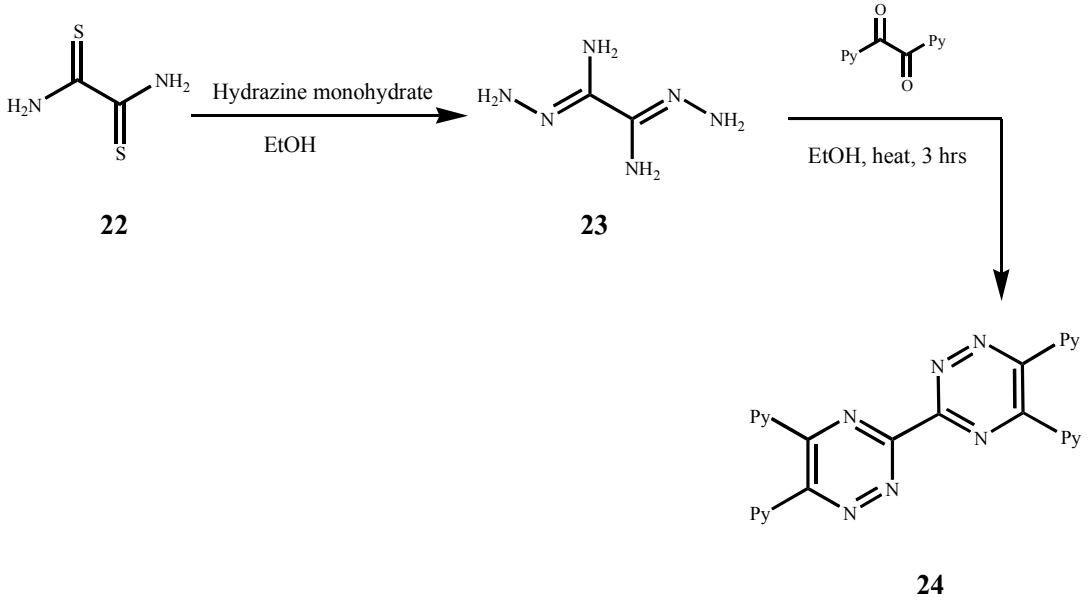
Scheme 10 The synthetic route to 3-substituted-5,6-di(2-pyridyl)-1,2,4-triazines, **19a-g**



20 **21**

Compound	R
a	2-pyridyl
b	4-methyl-2-pyridyl
e	2-thiazolyl
f	4-phenyl-2-pyridyl

Scheme 11 The synthetic route to 1,2,4-triazines **21a-f**

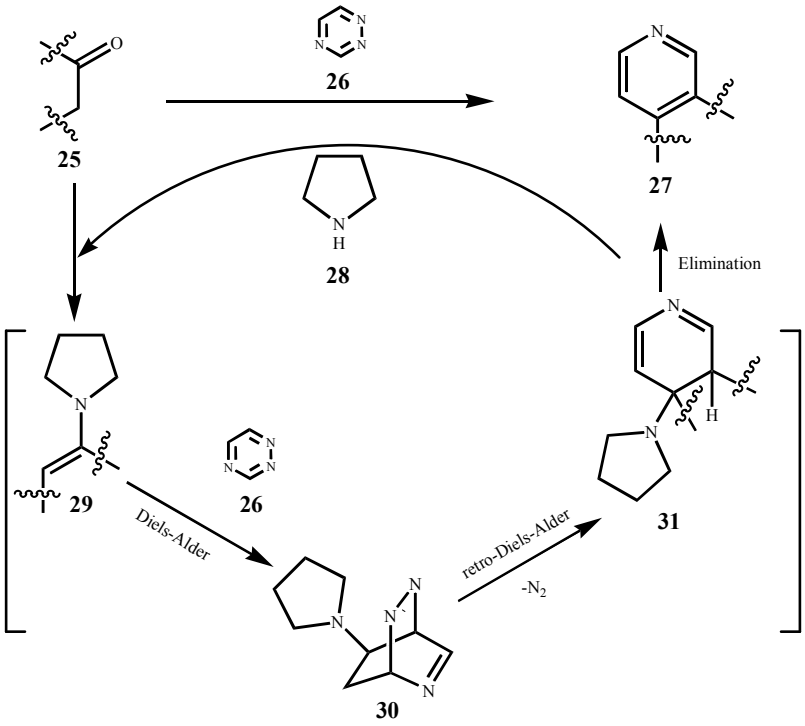


22 **23** **24**

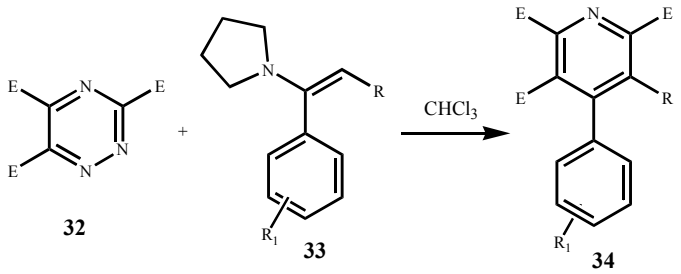
Scheme 12 The synthesis of bi-1,2,4-triazine **24**

Boger and Panek (Boger and Panek, 1981) reported the short synthetic route for the construction of substituted pyridines **27** as shown in **Scheme** 13. Although this studied led to the development of simple pyridine annulation based on the

regiospecific inverse electron demand Diels-Alder reaction of 1,2,4-triazine **26** with enamine **29**, it has two limitations. The first one is the requirement for a preformed the enamine and the other one is the unusual stability of the intermediate when using enamines derived from cyclohexanone. In 1982, they circumvented these difficulties for 1,2,4-triazine or 3-substituted-1,2,4-triazines: 4 Å molecular sieves allowed in situ enamine **29** formation and catalysed the elimination step forming pyridine **27** from dihydropyridine **31**, but yield was poor. In addition, they have also prepared the Biaryl CD ring of steptonigrin **36** *via* thermal cycloaddition of 1,2,4-triazine **32** with enamines **33** (**Scheme** 14).



Scheme 13 Inverse electron demand Diels-Alder reaction of 1,2,4-triazine **27**

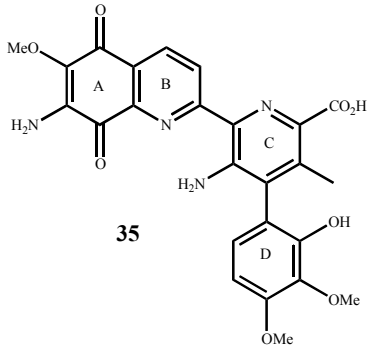


E = $CO_2CH_2CH_3$

a: R = R_1 = H

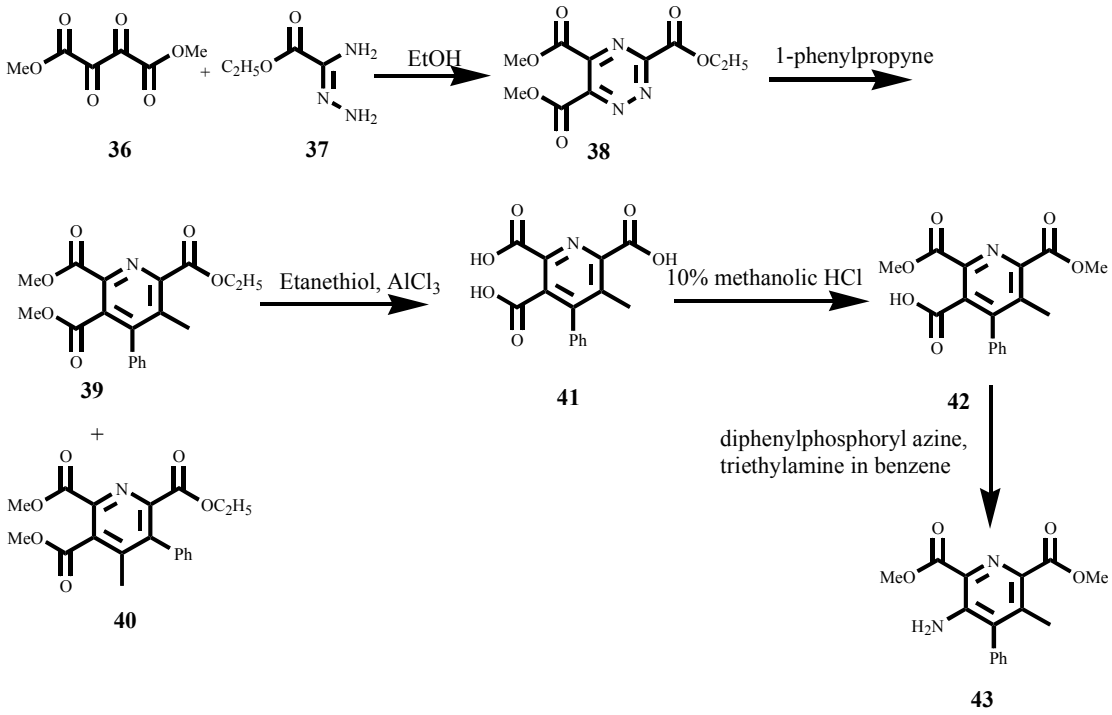
b: R = Me; R_1 = H

c: R = Me; R_1 = 2-$OCH_2C_6H_3$-3,4-$(OCH_3)_2$



Scheme 14 The synthesis of biaryl CD ring of steptonigrin **35** *via* thermal cycloaddition of 1,2,4-triazine **32** with enamines **33a-c**

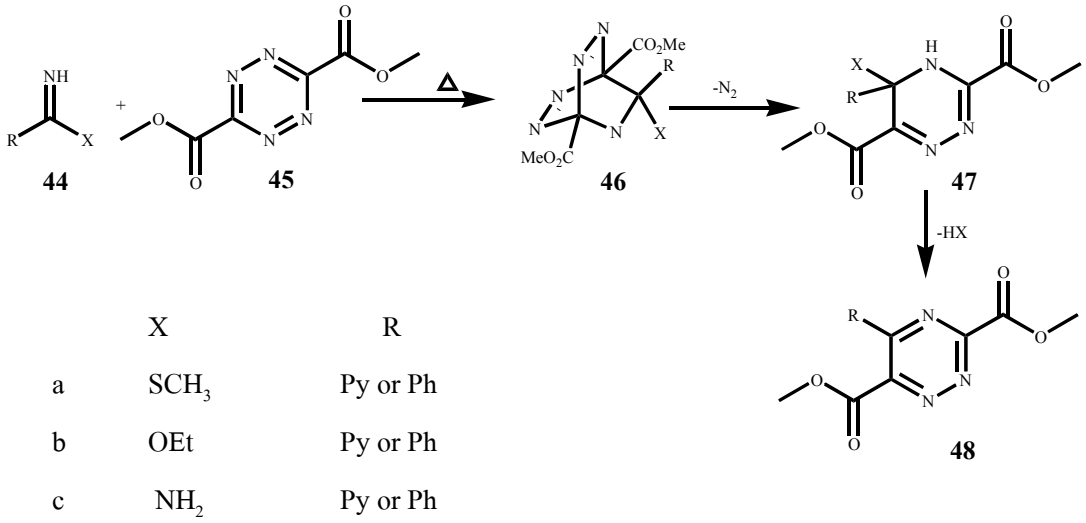
Martin (Martin, 1982) has prepared pyridine C ring of streptonigrin **35** by Diels-Alder reaction of 1,2,4-triazine **38** and aromatic alkyne. The synthetic route to pyridine C ring of streptonigrin was indicated in **Scheme** 15.



Scheme 15 Preparation of pyridine C ring of streptonigrin **35**

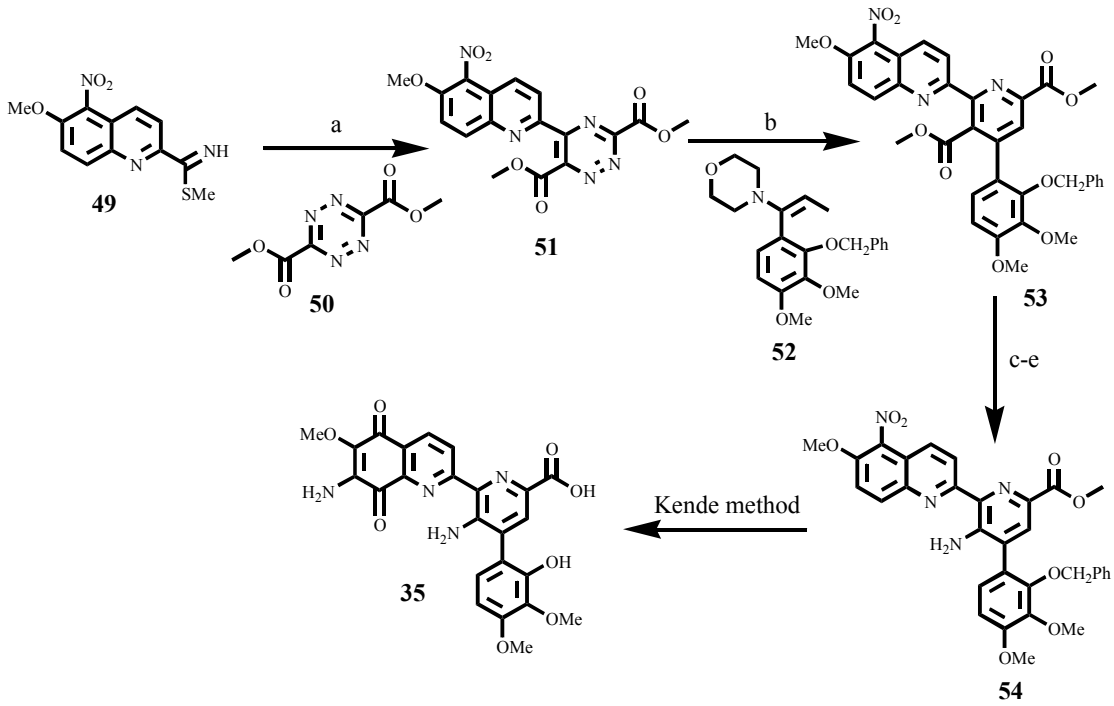
Boger and Panek (Boger and Panek, 1983) have prepared 1,2,4-triazines **48a-c** *via* thermal cycloaddition of dimethyl-1,2,4,5-tetrazine-3,6-dicarboxylate **45a-c** with thioimidate. The synthetic route to 1,2,4-triazines **48a-c** was indicated in **Scheme** 16.

Borwell and Hughes (Borwell and Hughes, 1983) have reported the total synthesis of streptonigrin **35** based on the implementation of two consecutive inverse electron demand Diels-Alder reactions: 1,2,4,5-tetrazine **50** + *S*-methyl thiomidate **49** (steptronigrin ABC ring construction) and 1,2,4-triazine **51** + morpholino enamine **52** (steptronigrin DE ring construction). The synthetic route to steptronigrin **35** was shown in **Scheme** 17.



	X	R
a	SCH_3	Py or Ph
b	OEt	Py or Ph
c	NH_2	Py or Ph

Scheme 16 The synthetic route to 1,2,4-triazines **48a-c**

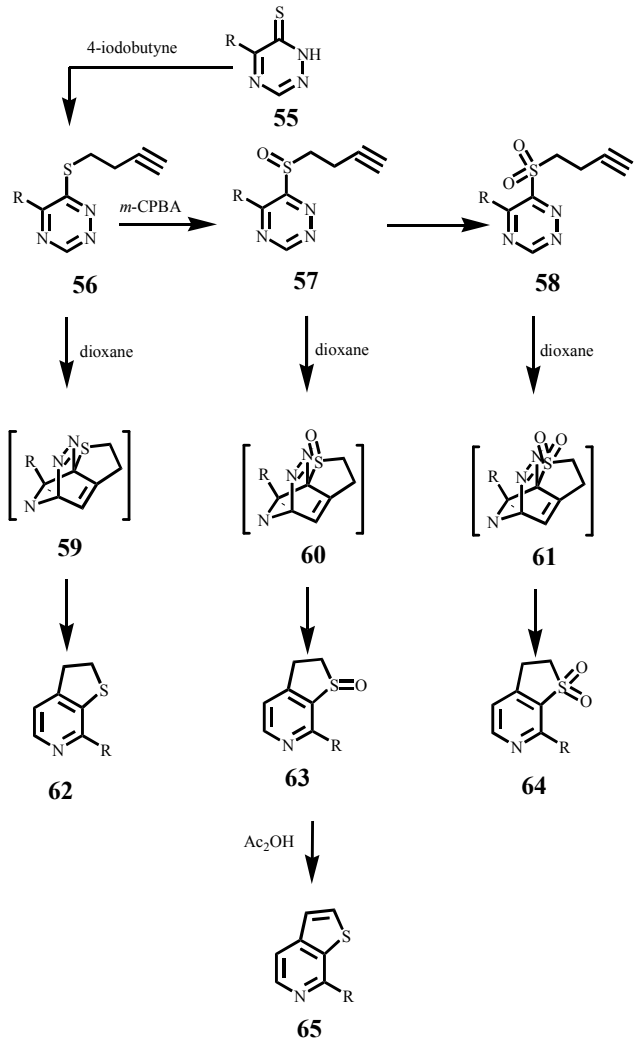


a) dioxane, tetrazine; b) 4 eq enamine, $CHCl_3$; c) 12 eq. of PhSeNa, THF-HMBA; MeOH, HCl cat;

d) 5 eq. of $(PhO)_2P(O)N_3$, benzene/reflux, 2.5 hrs, H_2O/reflux, 2.5 hrs; e) excess CH_3I, K_2CO_3, THF

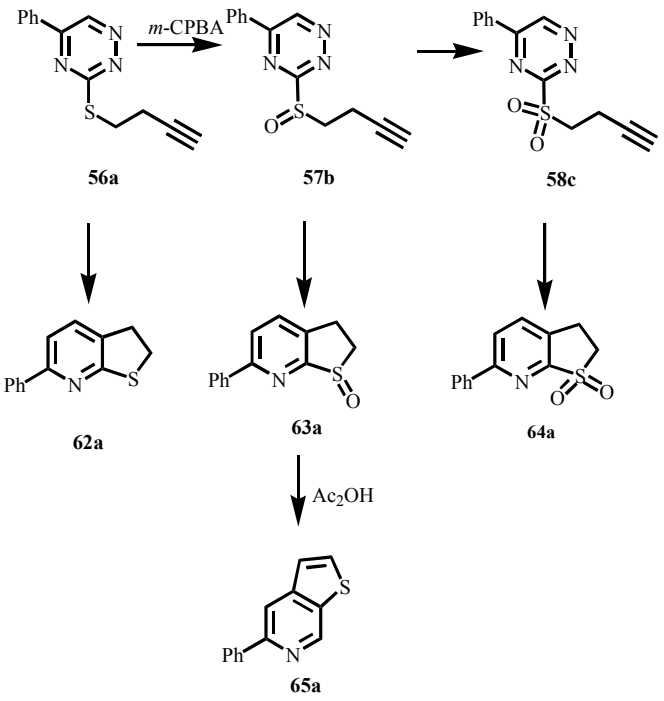
Scheme 17 The total synthetic route to steptronigrin **35**

Taylor and Macor (Taylor and Macor, 1985) have reported the novel synthesis of thieno[2,3-*b*]pyridines **62** and thieno[2,3-*c*]pyridines **65** by using the novel intramolecular Diels-Alder reaction of alkynithio derivative 1,2,4-triazines **56**- **58**. The synthetic route to thieno[2,3-*c*]pyridines **62**-**65** and thieno[2,3-*b*]pyridines **62a**- **65a** are shown in **Scheme** 18a and 18b, respectively. Further investigation of this methodology, in 1986, they have also reported the synthesis of highly substituted pyridine compounds **69a-f** and **75** as indicated in **Schemes** 19 and 20.

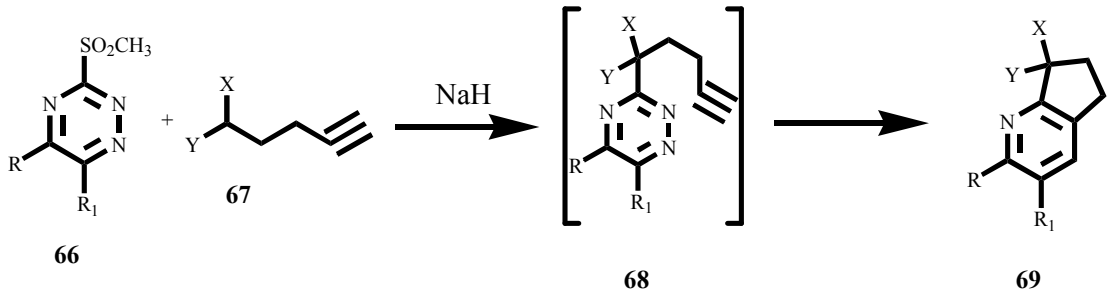


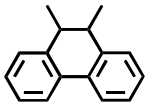
a: R = Me; b: R = $CH(CH_3)_2$; c: R = Ph

Schemes 18a The synthetic route to thieno[2,3-*c*] pyridines **62- 65**

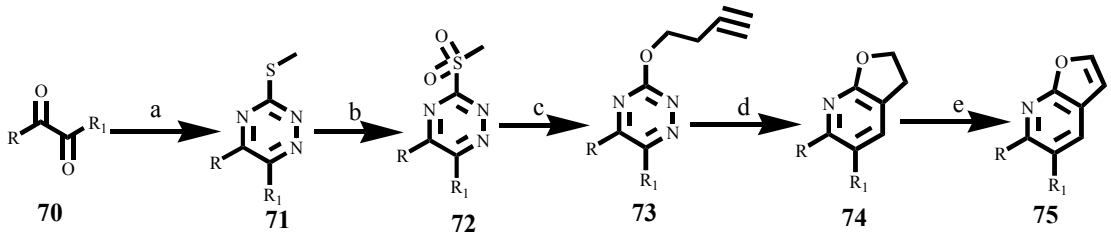


Schemes 18b The synthetic route to thieno[2,3-*b*]pyridines **62a**- **65a**

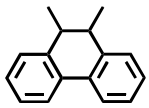


	R	R_1	X	Y
a	C_6H_5	H	COOMe	COOMe
b	p-ClC_6H_4	H	COOMe	COOMe
c			COOMe	COOMe
d	*p*-ClC_6H_4	H	COOEt	CN
e	*p*-ClC_6H_4	H	CN	CN
f	*p*-ClC_6H_4	H	COOEt	COOMe

Schemes 19 The synthesis of highly substituted pyridine compounds **69a-f**



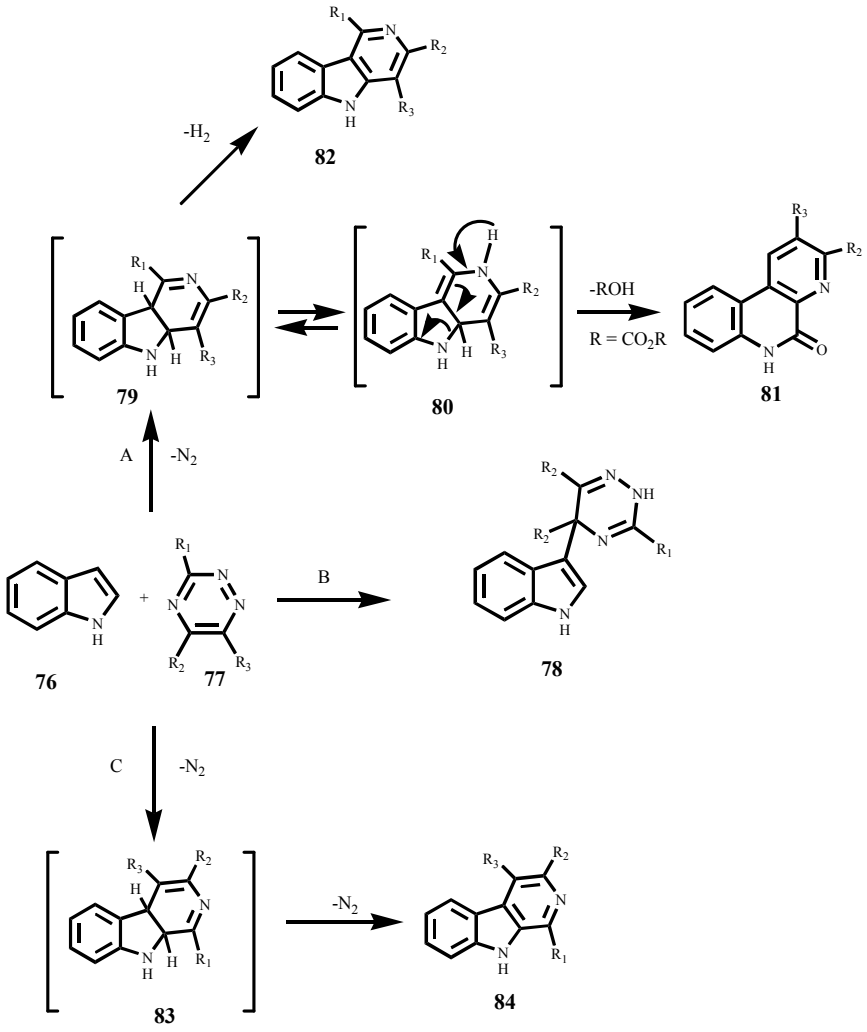
a) $H_2NNHC(SCH_3)=NH_2^+I^-$; b) *m*-CPBA; c) $Na^+OCH_2CH_2C\equiv CH$; d) reflux; e) DDQ

	R	R_1
a	H	H
b	CH_3	CH_3
c	C_6H_5	H
d	4-ClC_6H_4	H
e		

Schemes 20 The synthesis of highly substituted pyridine compounds **75a-e**

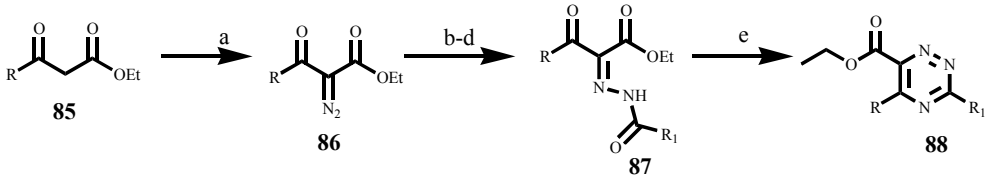
Benson and co-workers (Benson et al., 1990) have synthesized γ-carbolides **84a-k**, benzo[*f*][1,7]napthiridines **81a-k** and **82a-k**, or the noncyclized 3-[5-(1,2,4-triazinyl)]indole **78a-k** by the reaction of 1,2,4-triazines **77a-k** and indole **76**. The synthetic pathway was shown in **Scheme** 21.

Ohsumi and Neunhoeffer (Ohsumi and Neunhoeffer, 1992) have prepared the 1,2,4-triazines **88** and **92** with a functional group in the C-6 position. The synthetic route as shown in **Scheme** 22. In addition, in the same year, they have reported the regioselective synthesis of ethyl-1,2,4-triazine-5-carboxylate **100a-i** and the methodology was indicated in **Scheme** 23.

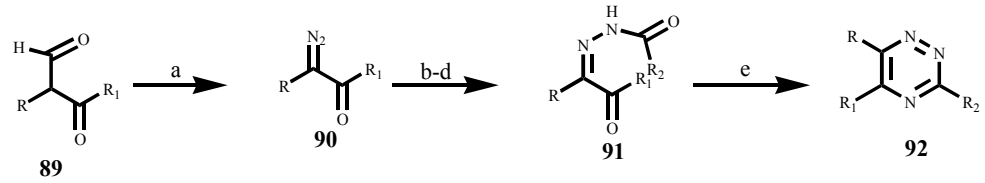


	R_1	R_2	R_3
a	CO_2Et	CO_2Et	CO_2Et
b	CO_2Et	CO_2Me	CO_2Me
c	CO_2Et	CH_3	CO_2Et
d	CO_2Et	C_6H_5	H
e	CO_2Et	H	H
f	CO_2Et	CO_2Et	CH_3
h	SCH_3	CO_2Me	CO_2Me
i	CO_2Et	CH_3	CH_3
j	SO_2CH_3	H	H
k	CH_3	H	C_6H_5

Scheme 21 Synthetic pathway to carbolides **84a-k**, benzo[*f*][1,7]napthiridines **81a-k** and **82a-k**, or the noncyclized 3-[5-(1,2,4-triazinyl)]ndole **78a-k**



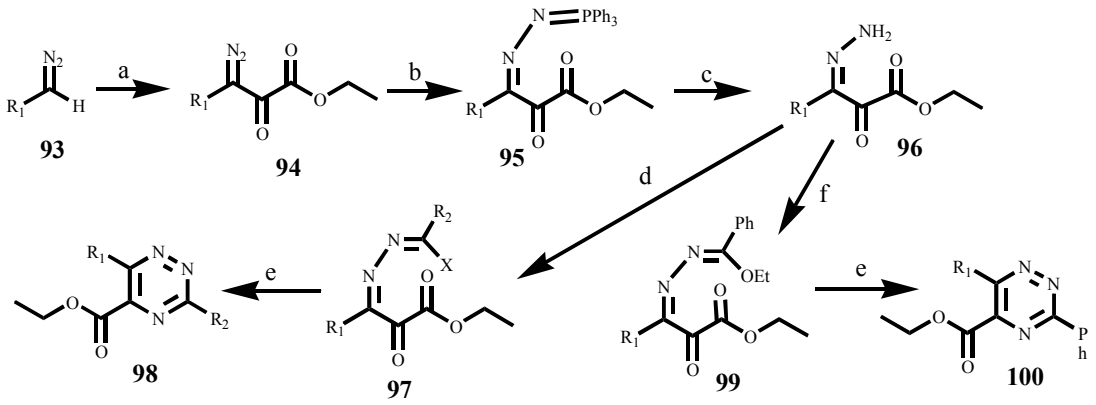
a) TsN_3, Et_3N; b) Ph_3P; c) EtOH, H_2O; d) $(R_1CO)_2O$; e) $AcO^-{}^+NH_4$



a) TsN_3, Et_3N; b) Ph_3P; c) EtOH, H_2O; d) $(R_2CO)_2O$; e) $AcO^-{}^+NH_4$

$R_1 = R_2$= alkyl or phenyl groups

Scheme 22 The synthetic route to 1,2,4-triazines **88** and **92** with a functional group in the C-6



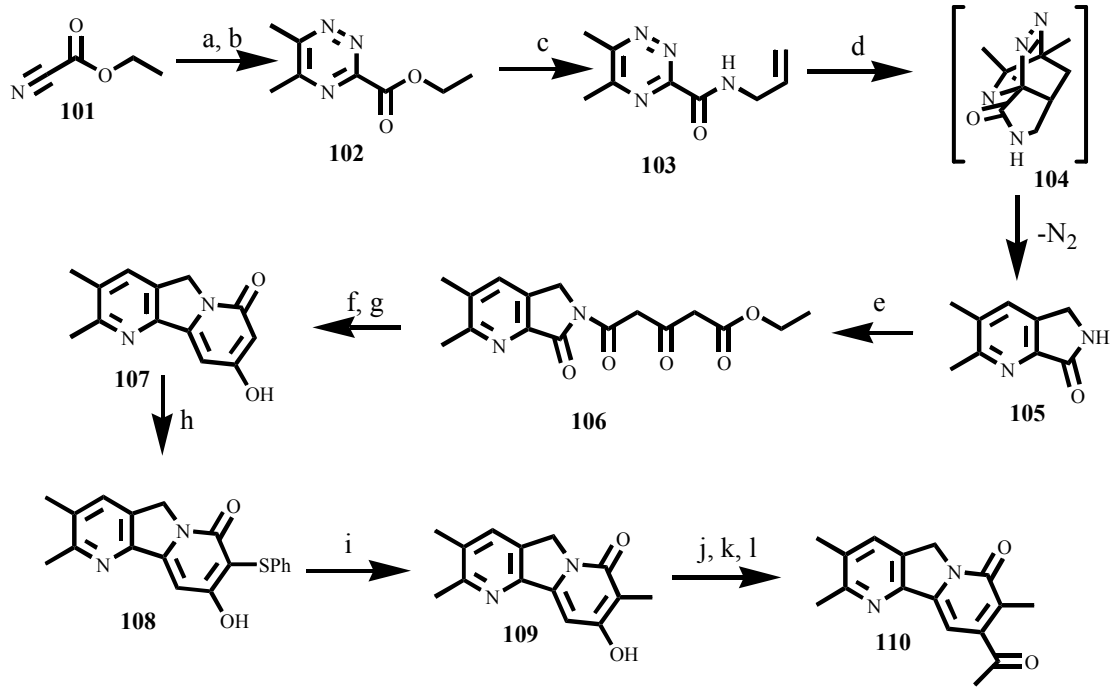
a) $ClCOCO_2Et$, Et_3N, Et_2OH; b) Ph_3P, Et_2OH; c) EtOH, H_2O; d) $R_2C(OMe)_2NMe_2$; e) $AcO^-{}^+NH_4$, AcOH;

f) $PhC(OEt)_3$, AcOH

	R_1	R_2	X		R_1	R_2	X		R_1	R_2	X
a	H	H	NMe_2	e	Me	Me	NMe_2	i	n-Pr	Ph	OEt
b	Me	H	NMe_2	f	*n*-Pr	Me	NMe_2				
c	*n*-Pr	H	NMe_2	g	H	Ph	OEt				
d	H	Me	NMe_2	h	Me	Ph	OEt				

Scheme 23 The regioselective synthesis of ethyl-1,2,4-triazine-5-carboxylate **100a-i**

Pendrak and co-workers (Pendrak et al., 1994) have published the synthesis of mappicine ketone **100** (MPK) analog. The Pyridine-lactam intermediate **104**, which contain the B and C rings of MPK, could be prepared from 1,2,4-triazine **103** *via* an inverse electron demand intramolecular Diels-Alder reaction. The synthetic route to MPK **100** is indicated in **Scheme** 24.

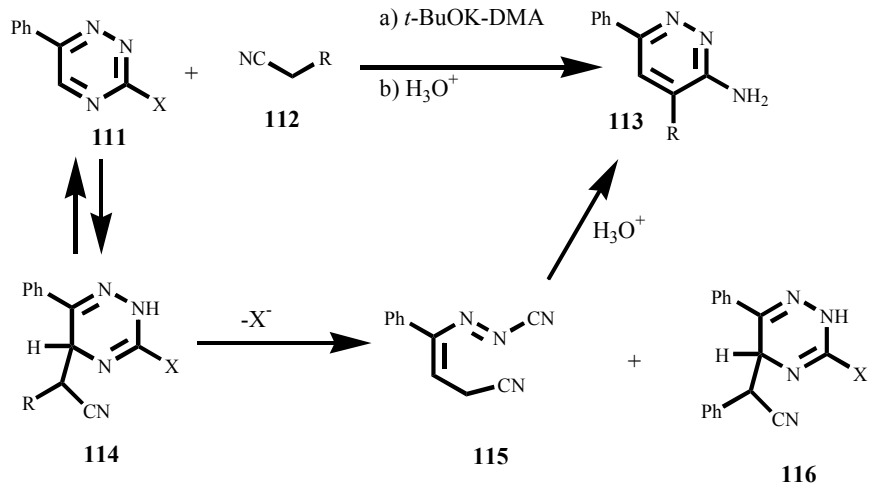


a) H_2S, Et_2NH, $PhCH_3$; b) H_2NNH_2, 2,3-butanedione, EtOH; c) yeast lipase, allyamine, Hexane/CCl_4; d) xylene; e) diethyl 1,3-acetonedicarboxylate, xylene; f) piperidine, DMF; g) conc. HCl; h) 37% aqueous formaldehyde, thiophenol, AcOH, piperidine, EtOH; i) Raney nikel, EtOH; j) Tf_2NPh, DMF; k) butyl vinyl ether, Et_3N, $Pd(OAc)_2$, dppd, CH_3CN; l) AcOH, HCl

Scheme 24 The synthetic route to MPK **110**

Rykowsky and Wolinsk (Rykowsky and Wolinsk, 1996) have described a novel route to functionalized 3-aminopyridazines **113** by ring opening and ring closure

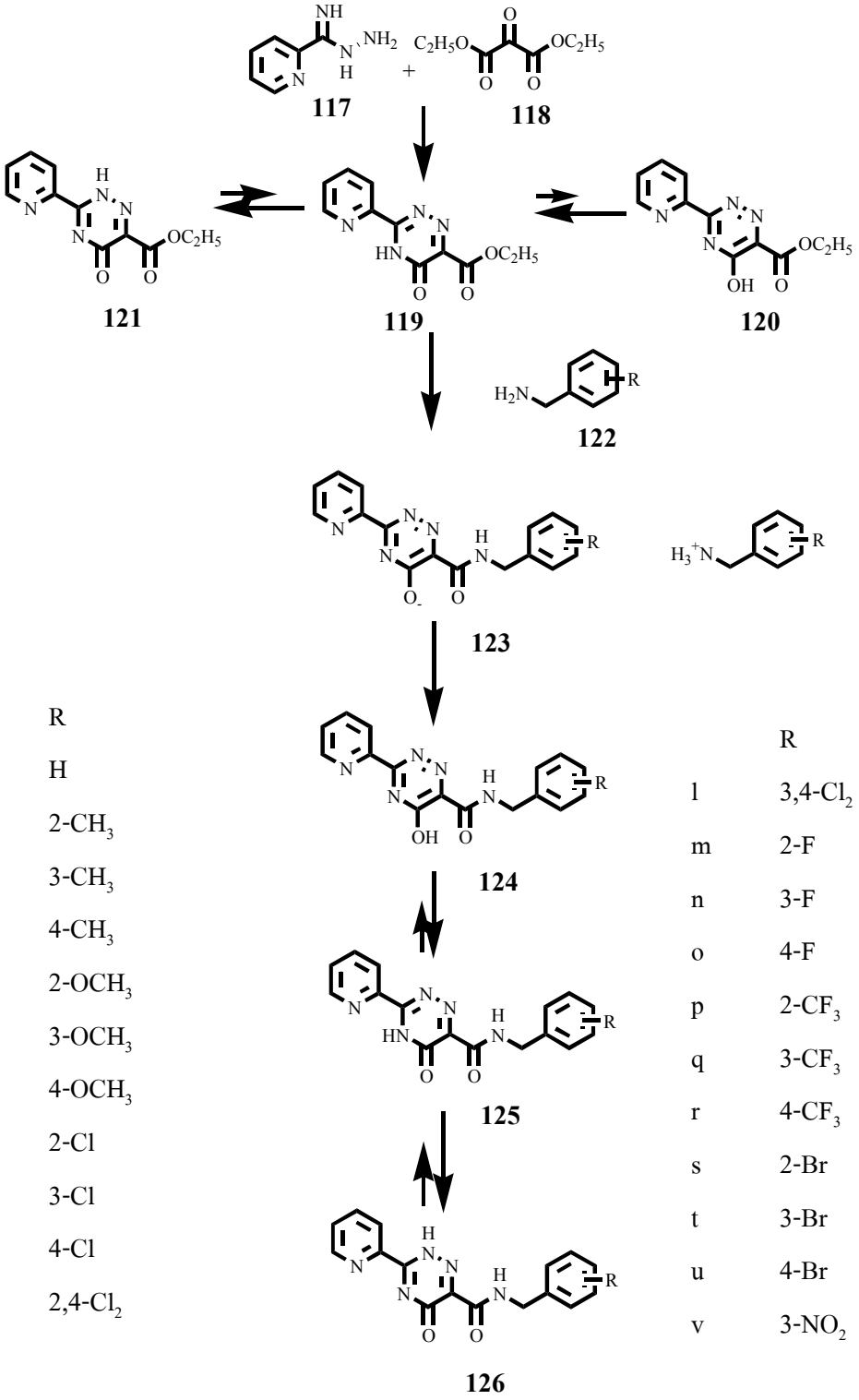
reaction of 1,2,4-triazines **111a-c** with carbon nucleophiles being a cyano substituent **112a-c** at a carbanionic center. A novel route to functionalized 3-aminopyridazines **113a-c** is shown in **Scheme** 25.



	R	X
a	Ph	Cl or SCH_3
b	CO_2Et	Cl or SCH_3
c	CN	Cl or SCH_3

Scheme 25 A novel route to functionalized 3-aminopyridazines **113a-c**

Mamolo and co-workers (Mamolo et al., 2000) have synthesized 4*H*-1,2,4-triazine-5-one derivatives **126** and tested for their in *vitro* antimycobaterial activity. Some triazines from their synthesis showed interesting activity against a strain of Mycobacterium tuberculosis. The synthetic route to 4*H*-1,2,4-triazine-5-one derivatives **126** was shown in **Scheme** 26.

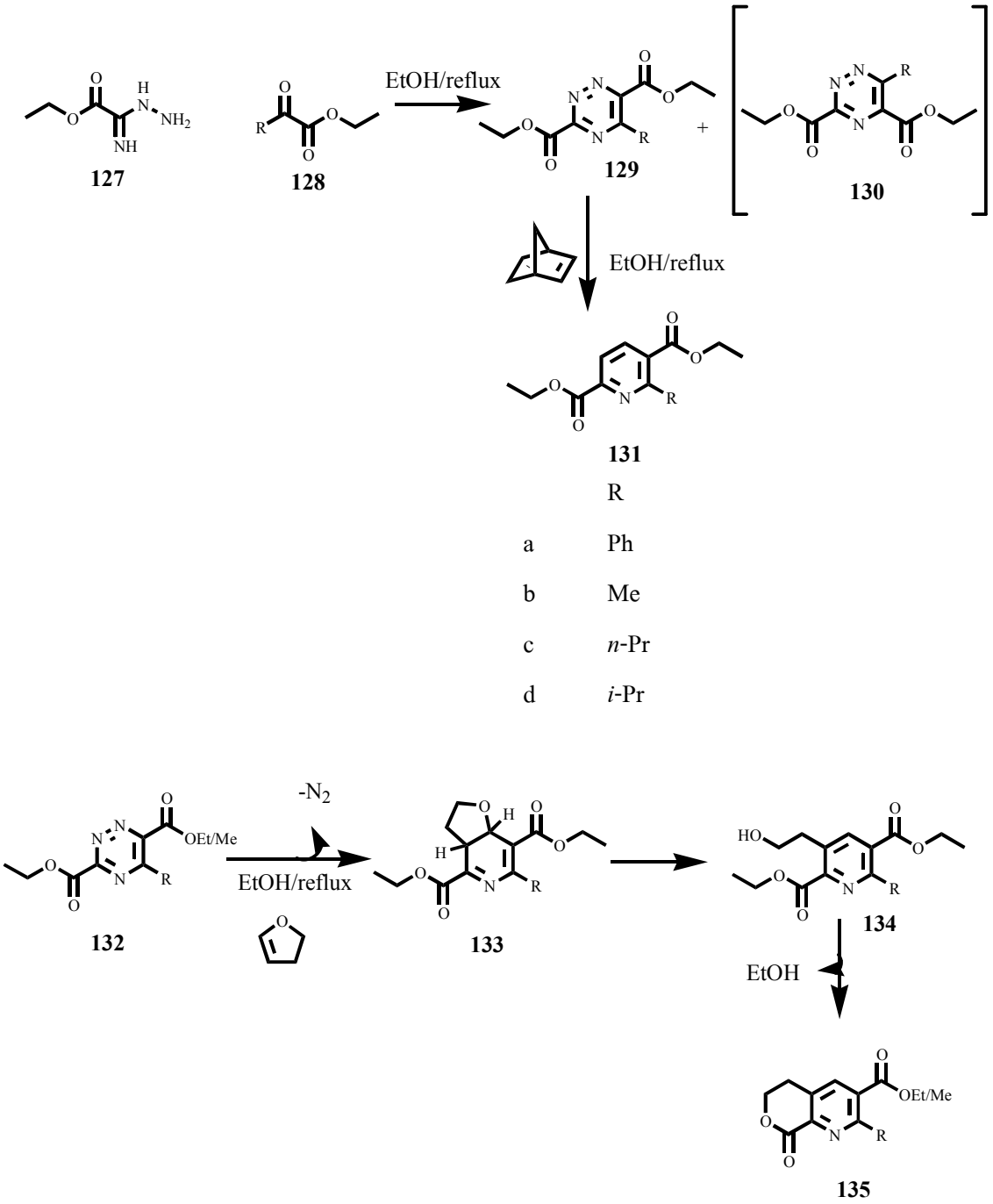


	R
a	H
b	2-CH_3
c	3-CH_3
d	4-CH_3
e	2-OCH_3
f	3-OCH_3
g	4-OCH_3
h	2-Cl
i	3-Cl
j	4-Cl
k	2,4-Cl_2

	R
l	3,4-Cl_2
m	2-F
n	3-F
o	4-F
p	2-CF_3
q	3-CF_3
r	4-CF_3
s	2-Br
t	3-Br
u	4-Br
v	3-NO_2

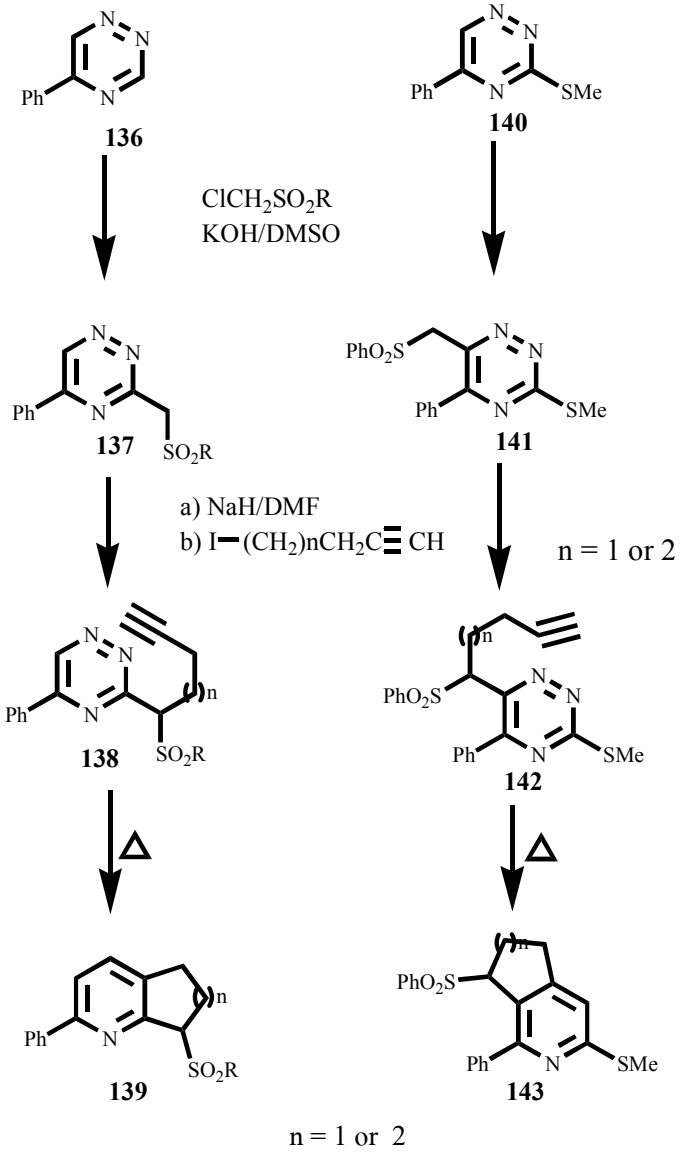
Scheme 26 The synthetic route to 4*H*-1,2,4-triazine-5-one derivatives **126a-v**

Stanforth and co-workers (Stanforth et al., 2002) reported the synthesis of pyridine compounds **131a-d** by using aza Diels-Alder reaction. As shown in **Schemes** 27, the triazines **129** and **132** were converted into their corresponding pyridines **131** and **135** in aza Diels-Alder reaction with 2,5-norbornadiene or with 2,3-dihydrofuran, respectively.



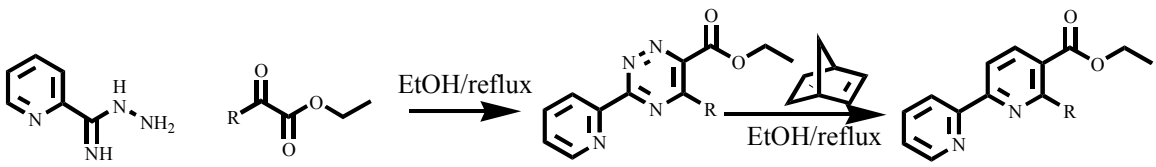
Scheme 27 The synthesis of pyridine compounds **131a-d** and **135** by using aza Diels-Alder methodology

Branosawa and co-workers (Branosawa et at., 2002) have synthesized cycloalkenopyridines **139** and **143** *via* the tandem vicarious nucleophilic substitution (VNS) and intramolecular inverse electron demand Diels-Alder reaction on 1,2,4-triazines **137** and **141**. Some of them are compound with significant importance. They processed potent antishock, tuberculostic and antimalarial properties. The synthetic route to cycloalkenopyridines **139** and **143** was indicated in **Scheme** 28.



Scheme 28 The synthetic route to cycloalkenopyridines **139** and **143**

Further investigation come from Stanforth and co-workers, in 2003 they have reported the preparation of a series of functionalized 2,2′-bipyridines **147a-c** from 1,2,4-triazine **146a-c** precursors by using the aza Diels-Alder methodology (Stanforth et al., 2003). The synthetic route to 2,2′-bipyridines **147a-c** was shown in **Scheme** 29.



144 **145** **146** **147**

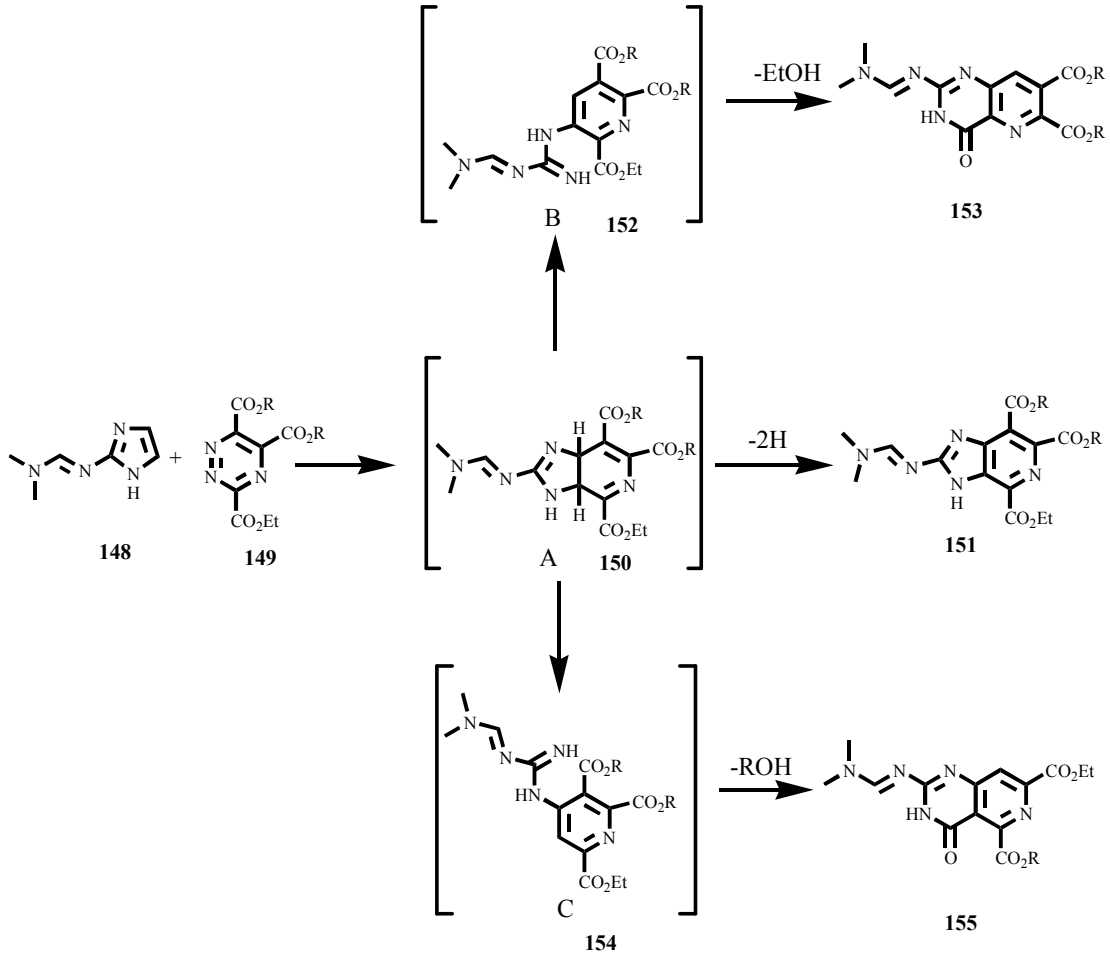
	R
a	Ph
b	*n*-Pr
c	*i*-Pr

Scheme 29 The synthetic route to 2,2′-bipyridines **147a-c**

Lahue and co-workers (Lahue et al., 2003) have published the intramolecular inverse electron demand cycloaddition of 2-substituted amidazoles **148** with various 1,2,4-triazines **149a-b** to produce both imidazo[4,5-c]pyridine (3-deazapurines) **153a-b** and pyrido[3,2-d]pyridine-4-ones(8-deazapurines) **155a-b** was shown in **Scheme** 30.

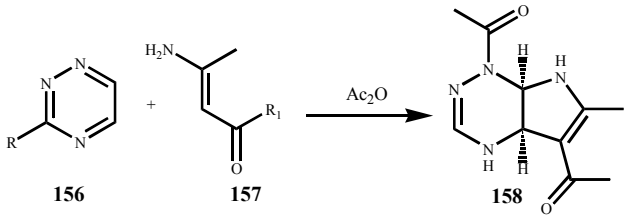
Charuchin and co-workers (Charushin et al., 2003) have decribed the reaction of 1,2,4-triazines **156a-g** with enamine **157a-g** in which the reactivity of C=C double bond was reduced by electron withdrawing substituents. From this reaction, they found that the reaction of 5,6-unsubstituted 3-aryl-1,2,4-triazines with amino vinyl ketones and aminovinyl esters in acetic anhydride proceeds regioselectively and smoothly at

room temperature resulting in the formation of pyrolo[3,2-e]1,2,4-triazines **158a-g**. The synthetic route to pyrolo[3,2-e]1,2,4-triazines **158a-g** was indicated in **Scheme** 31.



	R
a	Et
b	Me

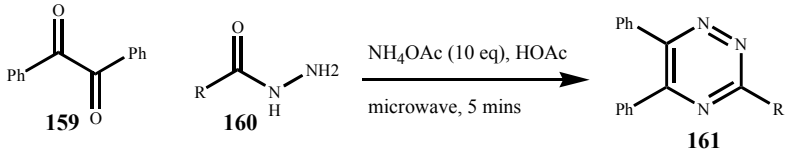
Scheme 30 The synthesis of 3-deazapurines **153a-b** and 8- deazapurines **155a-b**



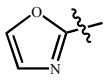
	R	R_1
a	Ph	OEt
b	*p*-MeO-C_6H_4	OEt
c	*p*-NO_2-C_6H_4	OEt
d	SCh_2Ph	OEt
e	Ph	Me
f	Ph	Ph
g	SC_2H_5	OEt

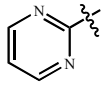
Scheme 31 The synthetic route to pyrolo[3,2-e]1,2,4-triazines **158a-g**

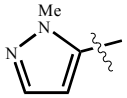
Zhao and co-worker (Zhao et al., 2003) have prepared 1,2,4-triazines **161a-h** by the application of microwave technology as indicated in **Scheme** 32. In the same year, they have also reported a one pot microwave-mediated synthesis of the basic cathine skeleton **163** (Lindsley et al., 2003). The synthetic route to access the cathine skeleton **163** utilized indole as a dienophile and 1,2,4-triazine **162** as a diene in an intramolecular inverse electron demand Diels-Alder reaction. The synthetic route to cathine **163** was indicated in **Scheme** 33.

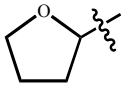


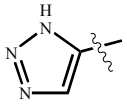
R

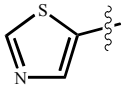
a 

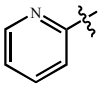
b 

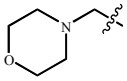
c 

d 

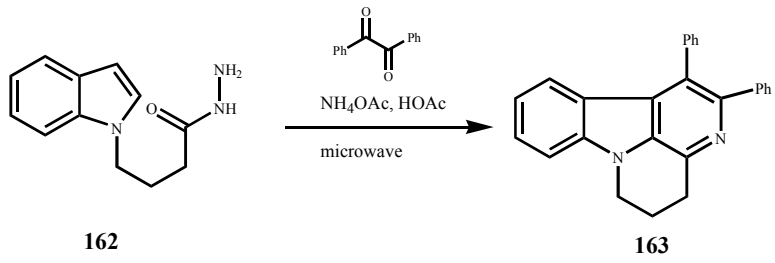
e 

f 

g 

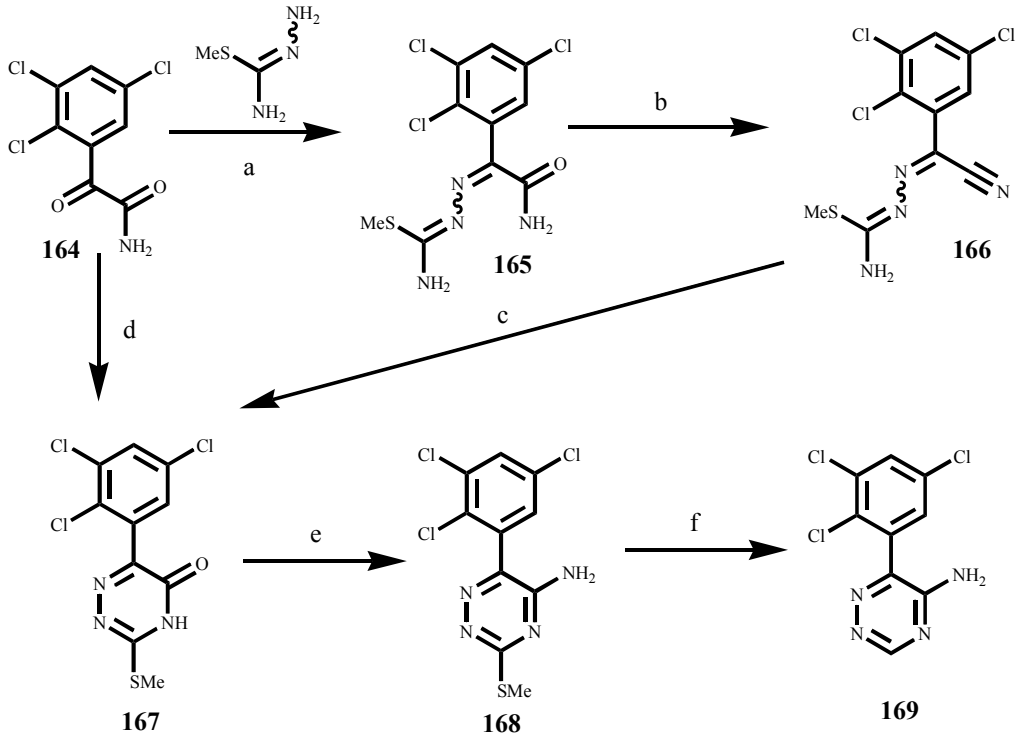
h 

Scheme 32 The synthesis of 1,2,4-triazines **161a-h** by the application of microwave technology



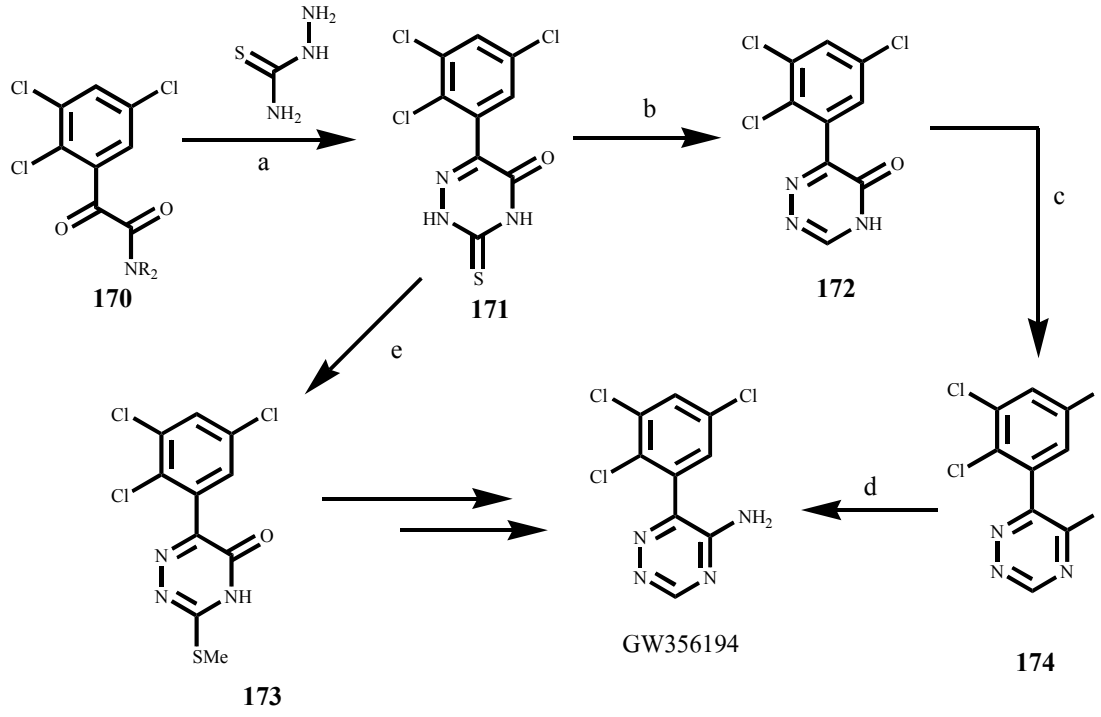
Scheme 33 One pot microwave-mediated synthesis of basic cathine skeleton **163**

Adam and co-workers (Adam et al., 2003) have reported several new approach to the amino 1,2,4-triazine, **169** (GW356194) and identified an efficient approach, based on the use of thiosemicarbazide **167** as a key building block for the synthesis of core heterocycle. The synthetic approaches to **169** (GW356194) were shown in **Schemes** 34 and 35.



a) EtOH/reflux; b) $(POCl_2)_2O$, 1,4-dioxane; c) propan-1-ol; d) EtOH/reflux; e) i. oxalyl chloride, 1,4-dioxane, ii. NH_3, propan-2-ol; f) i. *m*-CPBA, DMF, EtOAc, ii. $NaBH_4$, EtOH

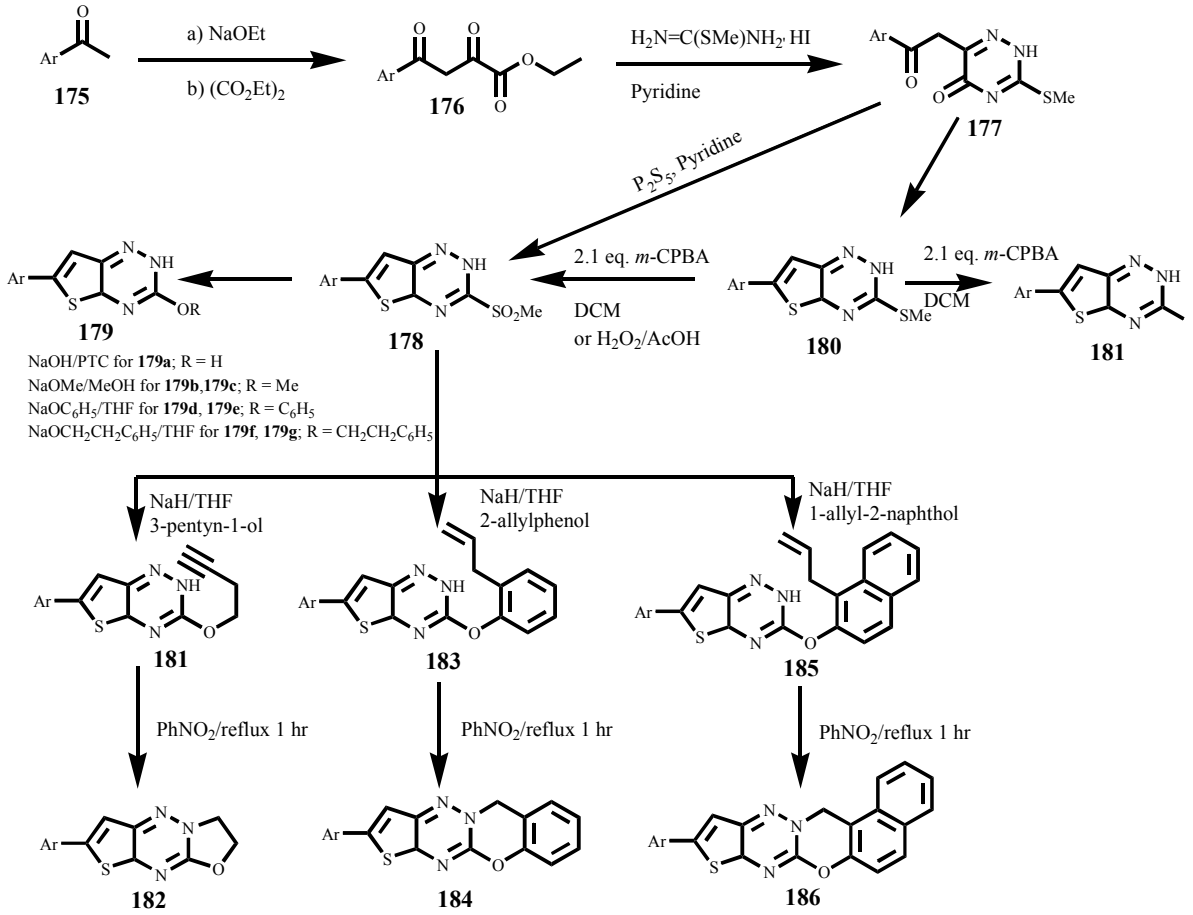
Schemes 34 The synthetic approaches to **169** (GW356194) (route A)



a) NaOH/reflux; b) i. NaOH, EtOH, H_2O_2, ii. conc.HCl; c) PCl_5, toluene; d) NH_3, THF, toluene; e) MeI, NaOH, EtOH

Schemes 35 The synthetic approaches to GW356194 **169** (route B)

Ibrahim and co-workers (Ibrahim et al., 2003) reported the synthetic approaches towards new condensed thienopyridine ring systems including furo[2,3-*b*]thieno[3,2-*e*]pyridines, bisthieno[2,3-*b*:3′,2′-*e*]pyridines, 5*H*-chromeno[2,3-*b*]thieno[3,2-*e*]pyridines, 5*H*-benzo(*f*)chromeno[2,3-*b*]thieno[3,2-*e*]pyridines by using the application of intramolecular [4+2] cycloaddition reactions of suitably designed thieno[2,3-*e*][1,2,4]triazines **181a-e**, **183a-e** and **185a-e** tethered with alkene or alkyne terminals. The synthetic route to triazine derivatives **182a-e**, **184a-e** and **186a-e** was shown in **Scheme** 36.

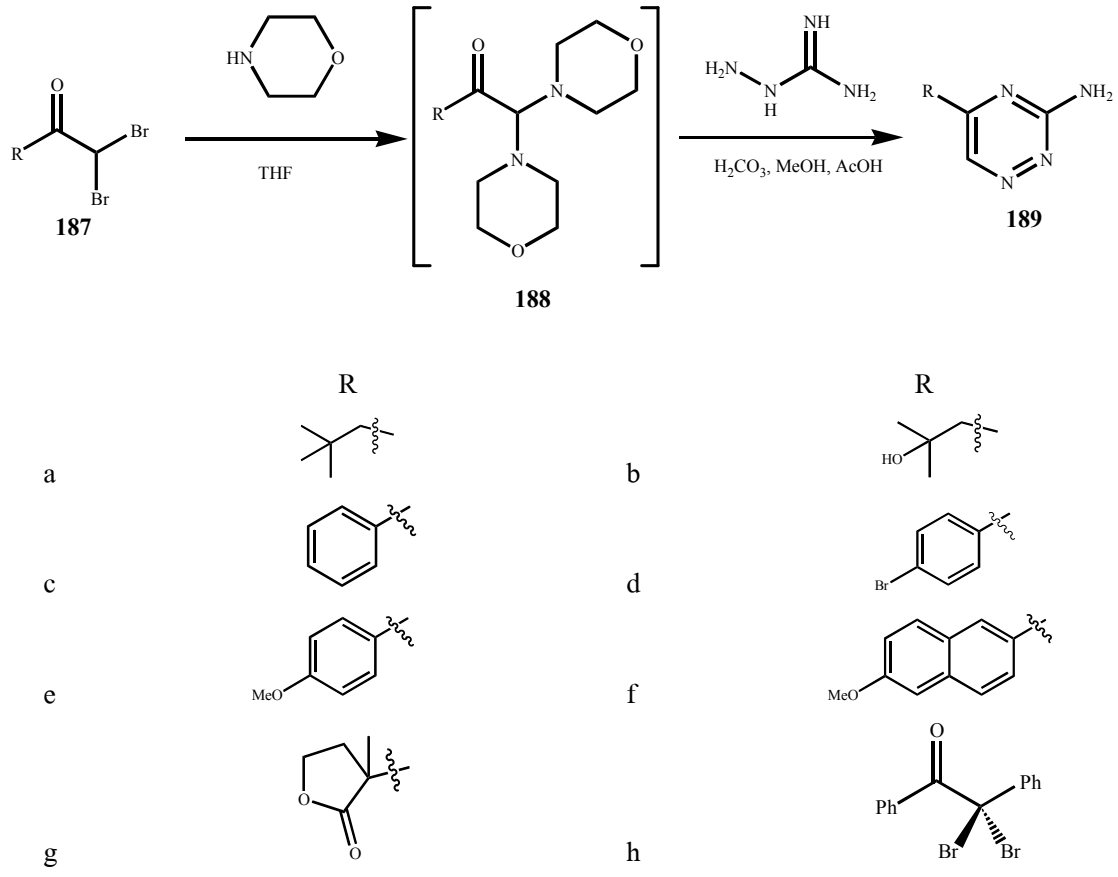


	Ar
a	C_6H_5
b	*p*-$CH_3OC_6H_4$
c	2-furyl
d	2-thienyl
e	2-pyridyl

Scheme 36 The synthetic route to 1,2,4-triazine derivatives **182a-e**, **184a-e** and **186a-e**

Limanto and co-workers (Limanto et al. 2003) described a successful regioselective synthetic approach to 5-substituted-3-amino-1,2,4-triazine **189**. The

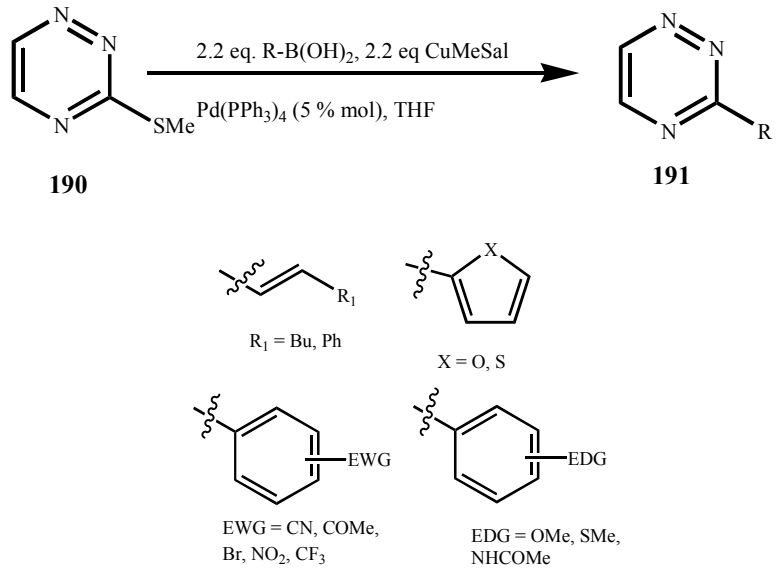
reaction involves a nucleophilic displacement of readily available α,α-dihalocarbonyl compounds **187a-h**, followed by a condensation of the resulting crude ketonaminals **188a-h** with aminoguanidine in the presence of AcOH in MeOH. The regioselective synthetic route to 5-substituted-3-amino-1,2,4-triazine **189a-h** is indicated in **Scheme** 37.

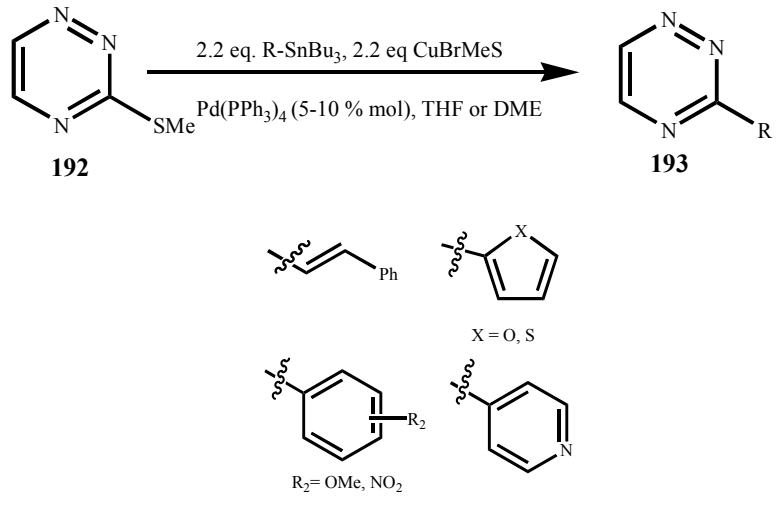


Scheme 37 The regioselective synthetic route to 5-substituted-3-amino-1,2,4-triazine **189a-h**

Alphonse and co-workers (Alphonse et al., 2004) reported a general approach to selective functionalization of 1,2,4-triazines **191** and **193** by using the combining

addition reaction and palladium catalyzed cross-coupling reaction of organometallics with 3-methyl sulfenyl-1,2,4-triazines **190** and **192** as shown in **Scheme** 38.

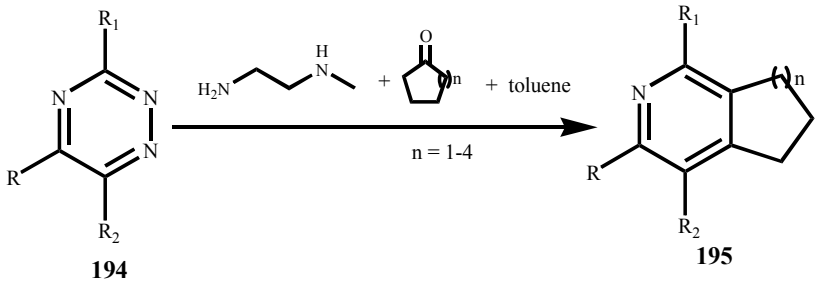




Scheme 38 Palladium catalyzed cross-coupling reaction of organometallics with 3-methyl sulfenyl-1,2,4-triazines **191** and **193**

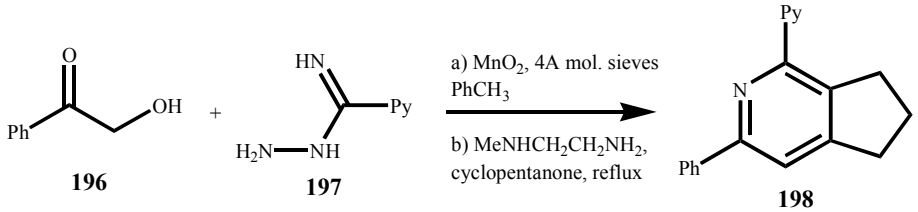
Raw and Taylor (Raw and Taylor 2004) have published the synthesis of highly substituted pyridines **195a-k** *via* tethered imine-enamine (TIE) methodology.

This methodology converted 1,2,4-triazines **194a-k** into highly substituted pyridines **195a-k** *via* the inverse electron demand Diels-Alder reaction which avoided the need for a discrete aromatization step (**Scheme** 39). The TIE methodology has also been applied in one pot reaction cascades involving 1,2,4-triazines **196** and utilizing MnO_2-mediate tandem oxidation processes (TOPs) (**Scheme** 40).



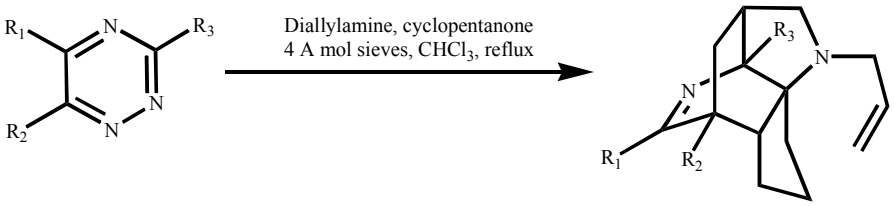
	R	R_1	R_2	n
a	Ph	Py	H	1
b	Ph	Py	H	2
c	Ph	Py	H	3
e	Ph	Py	H	4
f	Furyl	Py	Furyl	1
g	Furyl	Py	Furyl	2
h	Ph	CO_2Et	H	1
i	Ph	CO_2Et	H	2
j	H	CO_2Et	H	1
k	Ph	*n*-$C_{17}H_{36}$	H	1

Scheme 39 The TIE one pot cascades reaction of 1,2,4-triazines **195a-k**



Scheme 40 The TOP- TIE approaches to dihydropyridines and pyridines **198**

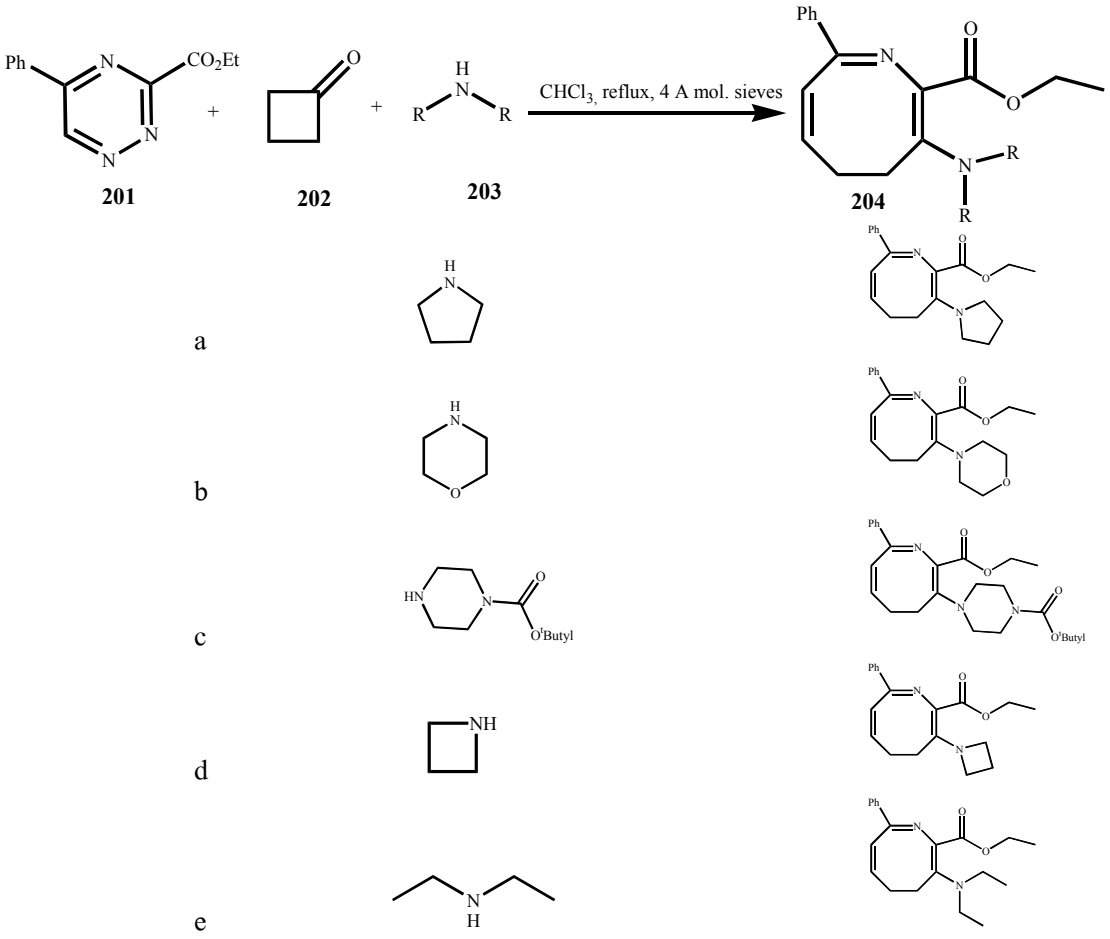
Further investigation of the chemistry of 1,2,4-triazines, they have also reported an operationally simple method for the construction of complex polycyclic system **200a-d** in a cycloaddition cascade sequence from 1,2,4-triazines **199a-d** (**Scheme** 41) and a one pot cascade reaction sequence from 1,2,4-triazines **201** which allowed formation of 4,5-dihydroazocins **204a-e** (**Scheme** 42).



199 **200**

	R_1	R_2	R_3
a	Ph	H	2-Pyridyl
b	2-Furyl	2-Furyl	2-Pyridyl
c	Ph	H	CO_2Et
d	H	H	CO_2Et

Scheme 41 Cascade cycloaddition reaction of 1,2,4-triazines to complex polycyclic system **200a-d**



Scheme 42 One pot cascade reaction sequence from 1,2,4-triazines to 4,5-dihydroazocins **204a-e**

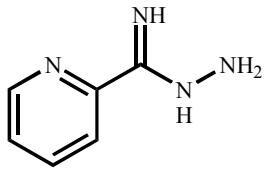
The objective of this project is optimizing synthetic methods to 1,2,4-triazines and the use of these compounds in a new route to prepare highly substituted pyridines.

2.2 EXPERIMENTAL

2.2.1 Instruments and Chemicals

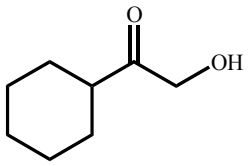
^{1}H and ^{13}C NMR spectra were recorded on Jeol EX-270 and EX-400 instruments running at 270 MHz and 400 MHz for proton and 68 MHz and 100 MHz carbon nuclei, respectively using residual solvent peaks as the internal standard. Coupling constants were given in Hertz and ^{13}C spectra were verified using DEPT experiments. Microwave reactions were carried out in a CEM Discover® Microwave Synthesizer. Melting points were recorded on an Electrothermal IA9100 digital melting point apparatus and were uncorrected. Infrared spectra were recorded on an ATI Mattson Genisis FT-IR spectrophotometer using NaCl plates. Low resolution electron impact (EI) mass spectra were recorded on a Kratos MS 25 spectrometer. Chemical ionization (CI) and high resolution mass spectra were recorded on a Micromass Autospec spectrometer. Flash column chromatography was performed using Matrex silica gel 60 (70-200 μm) and the eluent specified. PE is the fraction of petroleum ether boiling in the range 40-60 °C, EtOAc is ethyl acetate, DCM is dichloromethane and EtOH is ethanol which were stored over 4 Å molecular sieves. Except where specified, all reagents were purchased from commercial sources and were used without further purification.

2.2.2 Synthesis of 2-pyridylamidrazone 205



A mixture of 2-cyanopyridine (5.346 g, 51 mmol), EtOH (9 mL) and hydrazine monohydrate (15 mL) was stirred at room temperature for 3 hours, after which water (9 mL) was added and the reacting mixture was extracted with ether (3 x 20 mL). Upon extraction a white solid precipitated which was filtered and stored. The filtrate was dried over anhydrous $MgSO_4$, and the ether was removed under reduced pressure. The residue was combined with the white solid and recrystallized from hot toluene to give 2-pyridylamidrazone **205** as a white solid (3.091 g, 44%), mp 95.5-96.0 °C; R_f 0.20 (MeOH-EtOAc, 1:9); δ_H (400 MHz, $CDCl_3$) 8.15 (1H, *d*, *J* = 4.0 Hz, H-6), 7.93 (1H, *d*, *J* = 7.9 Hz, H-3), 7.61 (1H, *dd*, *J* = 1.2, 7.9 Hz, H-4), 7.20 (1H, *dd*, *J* = 1.2, 7.9 Hz, H-5), δ_C (100 MHz, $CDCl_3$) 150.1 (q), 148.0 (q), 147.9 (CH), 136.3 (CH), 123.7 (CH), 119.6 (CH).

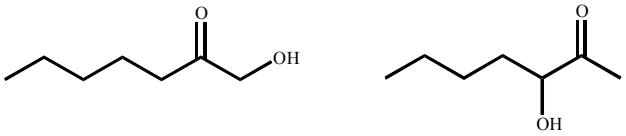
2.2.3 Synthesis of 1-cyclohexyl-2-hydroxyketone 206b



2-Cyclohexylmethylketone (0.4 mL, 3 mmol) was added to a stirred

solution of trifluoroacetic acid (0.4 mL, 5 mmol), water (5 mL) and CH_3CN (10 mL). Then [*bis*(trifluoroacetoxy)iodo]benzene (2.22 g, 5 mmol) was added and the solution was heated at reflux for 3 hours. The reaction was monitored by TLC. When the reaction was complete the reaction mixture was cooled and concentrated *in vacuo* to remove the CH_3CN. The residue was partitioned with DCM (50 mL) and water (10 mL) and the aqueous phase was extracted with DCM (3 x 20 mL). The combined organic extracts were then washed with a saturated $NaHCO_3$ (3 x 20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (100% DCM) to give the title compound **206b** as a colorless oil (0.299 g, 55%); R_f 0.40 (PE-EtOAc, 1:1); δ_H (400 MHz, $CDCl_3$) 4.23 (2H, s), 2.31 (1 H, *tt*, *J* = 3, 11.3 Hz), 1.78-1.64 (4H, m), 1.63-1.60 (1H, m), 1.49-1.13 (5H, m).

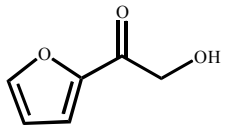
2.2.4 Synthesis of 1-hydroxy-2-heptanone 206c and 3-hydroxyl-2-heptanone 206d



2-Heptanone (0.7 mL, 5 mmol) was added to a stirred solution of trifluoroacetic acid (0.6 mL, 8 mmol), water (5 mL) and CH_3CN (15 mL). [*bis*(Trifluoroacetoxy)iodo]benzene (3.45 g, 8 mmol) was added and the solution heated at reflux for 3 hours. The reaction was monitored by TLC. When the reaction was complete the reaction mixture was cooled and concentrated *in vacuo* to remove the CH_3CN. The residue was partitioned with DCM (50 mL) and water (10 mL) and the aqueous phase was extracted with DCM (3 x 20 mL). The combined organic extracts were then washed with a saturated $NaHCO_3$ (3 x 20 mL), dried over

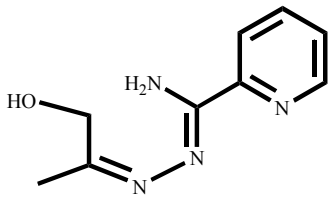
anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (100% DCM) to give the mixture of **206c** and **206d** as colorless oils (0.38 g, 58%, ratio 1.6:1 by ^{1}H NMR); R_f 0.50 (PE-EtOAc, 1:1); δ_H (400 MHz, $CDCl_3$) **206c**: 4.16 (2H, s), 2.32 (2H, *t*, *J* = 7.6 Hz), 1.55 (2H, *quin*, *J* = 7.6 Hz), 1.22 (4H, *m*), 0.81 (3 H, *t*, *J* = 7.6 Hz); **206d**: 4.10 (1H, *dd*, *J* = 3.7, 7.3 Hz), 2.11 (3H, *s*), 1.79-1.71 (1H, *m*), 1.49-1.16 (7H, *m*), 0.82 (3H, *t*, *J* = 7.0 Hz).

2.2.5 Synthesis of 1-(2-furyl)-2-hydroxyketone 206f



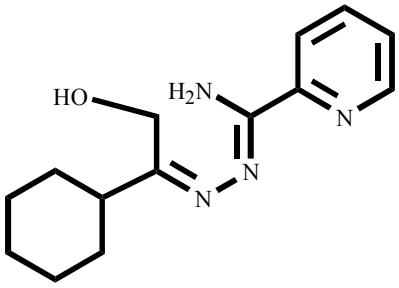
2-Furylmethylketone (0.566 g, 5.1 mmol) was added to a stirred solution of trifluoroacetic acid (0.4 mL, 5 mmol), water (5 mL) and CH_3CN (10 mL). [*bis*(Trifluoroacetoxy)iodo]benzene (2.35 g, 5.4 mmol) was added and the solution was refluxed for 3 hours. The reaction was monitored by TLC. When the reaction was complete the reaction mixture was cooled and concentrated *in vacuo* to remove the CH_3CN. The residue was partitioned with DCM (50 mL) and water (10 mL). The aqueous phase was extracted with DCM (3 x 20 mL). The combined organic extracts were then washed with a saturated $NaHCO_3$ (3 x 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (100% DCM) to give the title compound **206f** as a white solid (0.162 g, 25%), mp 79.8-80.4 °C; R_f 0.33 (PE-EtOAc, 1:1); δ_H (400 MHz $CDCl_3$) 7.56 (1H, *d*, *J* = 1.2 Hz), 7.23 (1H, *dd*, *J* = 1.2, 1.2 Hz), 6.53 (1H, *d*, *J* = 1.2 Hz), 4.67 (2 H, s).

2.2.6 Synthesis of amidrazone 207a



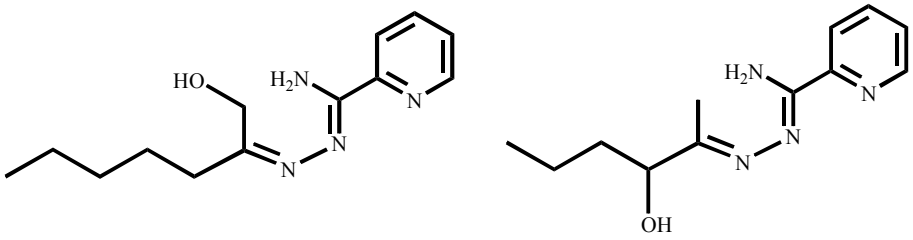
To a solution of 2-pyridylamidrazone **205** (0.457 g, 3.3 mmol) in EtOH (5 mL) was added hydroxy acetone (0.100 mL, 1.4 mmol) and the mixture stirred at room temperature for 4 hours. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (MeOH- EtOAc, 1:9) to give the title compound **207a** as a yellow solid (0.262 g, 93%), mp 94.5-95.6 °C; R_f 0.25 (MeOH- EtOAc, 1:9); ν_{max}(film/cm^{-1}) 3500, 3375, 1630, 1587, 1474, 1072 and 801; δ_H (400 MHz, $CDCl_3$) 8.43 (1H, *d*, *J* = 4.6 Hz, pyridyl), 8.18 (1H, *d*, *J* = 8.0 Hz, pyridyl), 7.61 (1 H, *dd*, *J* = 8.0, 8.0 Hz, pyridyl), 7.20 (1H, *dd*, *J* = 4.6, 8.0 Hz, pyridyl), 4.17 (2H, *s*), 1.95 (3H, *s*, CH_3); δ_C (100 MHz, $CDCl_3$) 163.0 (q), 154.1 (q), 150.4 (q), 148.2 (CH), 136.4 (CH), 124.9 (CH), 121.0 (CH), 65.3 (CH_2), 14.7 (CH_3); *m/z* (CI):193 ($[M+H]^+$, 100%) [HRMS (CI): calcd. for $C_9H_{13}N_4O$, 193.1089. Found: $[M+H]^+$, 193.1088.

2.2.7 Synthesis of amidrazone 207b



To a solution of 2-pyridylamidrazone **205** (0.316 g, 2.3 mmol) in EtOH (5 mL) was added 1-cyclohexyl-2-hydroxyketone **206b** (0.165 g, 1.1 mmol) and the mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (PE- EtOAc, 1:1) to give the title compound **207b** as a dark yellow viscous oil (0.265 g, 88%), R_f 0.43 (PE- EtOAc, 1:1); ν_{max} (film/cm^{-1}) 3471, 3381, 2956, 2930, 2863, 1630, 1586, 1563, 1470, 1266, 1047, 800 and 739; δ_H (400 MHz, $CDCl_3$) 8.50 (1 H, d, *J* 4.9, pyridyl), 8.05 (1 H, d, *J* 8.0, pyridyl), 7.71 (1H, ddd, *J* = 1.5, 8.0, 8.0 Hz, pyridyl), 7.28 (1H, *dd*, *J* = 4.9, 8.0, pyridyl), 4.49 (2H, s), 2.15 (1H, *tt*, *J* = 3.08, 11.3, cyclohexyl), 1.82-1.61 (5H, *m*, cyclohexyl), 1.36-1.09 (5H, *m*, cyclohexyl); δ_C (100 MHz, $CDCl_3$) 169.9 (q), 154.9 (q), 149.5 (q), 148.3 (q), 136.6 (CH), 125.1 (CH), 120.9 (CH), 63.6 (CH), 44.7 (CH), 30.3 (2 x CH_2), 26.1 (2 x CH_2), 25.9 (CH_2); *m/z* (CI): 261 ($[M+H]^+$, 100%) [HRMS (CI): calcd. for $C_{14}H_{21}N_4O$, 261.1715. Found: $[M+H]^+$, 261.1714.

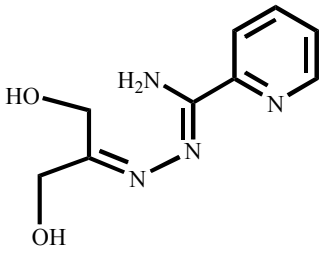
2.2.8 Synthesis of amidrazone 207c and 207d



To a solution of 2-pyridylamidrazone **205** (0.400 g, 2.9 mmol) in EtOH (3 mL) was added the mixture of 1-hydroxy-2-heptanone **206c** and 3-hydroxyl-2-heptanone **206d** (0.136 g, 1.0 mmol). The mixture was stirred at room temperature for 2 hours and the reaction mixture concentrated *in vacuo* and purified by flash column chromatography (PE-EtOAc, 1:1) to give the title compounds **207c** and **207d** as a

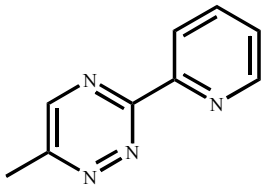
yellow viscous oil which were inseparable by column chromatography (0.207 g, 80%), R_f 0.5 (PE-EtOAc, 1:1).

2.2.9 Synthesis of amidrazone 207e



To a solution of 2-pyridylamidrazone **205** (0.250 g, 1.8 mmol) in EtOH (3 mL) and DCM (3 mL) was added 1,3-dihydroxyketone (dimer) **206e** (0.225 g, 1.2 mmol) and the mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (MeOH- EtOAc, 1:9) to give the title compound **207e** as a yellow solid (0.413 g, 80%), mp 117.8-118.7 °C; R_f 0.46 (MeOH- EtOAc, 1:9); ν_{max} (film/cm^{-1}) 3374, 1627, 1586, 1564, 1470, 1057 and 742; δ_H (400 MHz, methanol-d_3) 8.59 (1H, *d*, *J* = 4.3 Hz, pyridyl), 8.12 (1H, *d*, *J* = 8.0 Hz, pyridyl), 7.84 (1H, *ddd*, *J* = 1.8, 8.0, 8.0 Hz, pyridyl), 7.44 (1H, dd, *J* = 4.3, 8.0 Hz, pyridyl), 4.63 (2H, *s*), 4.44 (2H, *s*); δ_C (100 MHz, methanol-d_3) 166.3 (q), 157.0 (q), 151.8 (q), 149.6 (CH), 137.9 (CH), 126.4 (CH), 122.3 (CH), 63.2 (CH_2), 60.5 (CH_2); *m/z* (CI) 209 ($[M+H]^+$, 76%), 122 (100) [HRMS (CI): calcd for $C_9H_{13}N_4O_2$, 209.1038. Found: $[M+H]^+$, 209.1035.

2.2.10 Synthesis of 3-(2-pyridyl)-6-methyl-1,2,4-triazine 208a

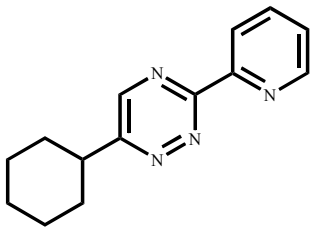


Microwave heating: To a 10 mL CEM Discover® reaction vial with a stir bar was placed amidrazone **207a** (0.096 g, 0.5 mmol), toluene (0.5 mL) and MnO_2 (0.228 g, 2.6 mmol). The reaction vessel was irradiated for 5 minutes at 120 °C (power 200 W, pressure up to 300 psi). After 5 minutes, the vessel was cooled down to 50 °C. The crude mixture was then filtered through Celite®, washed well with DCM and concentrated *in vacuo* giving the pale yellow solid. In the second step, the yellow solid, along with toluene (1 mL) and glacial AcOH (0.02 mL) were placed in a 10 mL microwave vessel and irradiated at 150 °C for 10 minutes (power 300 W, pressure up to 300 psi) followed by cooling to 50 °C. The homogenous solution was concentrated *in vacuo* to give the title compound **208a** as a red solid (0.084g, 98% without purifying), mp 68.2-69.0 °C; R_f 0.20 (MeOH- EtOAc, 1:9); ν_{max} (film/cm^{-1}) 3413, 2960, 1641, 1560, 1408, 1280, 1048 and 769; δ_H (400 MHz, $CDCl_3$) 8.81 (1H, *d*, *J* = 3.7 Hz, pyridyl), 8.63 (1H, *s*, H-5, triazine), 8.60 (1H, *d*, *J* = 7.9 Hz, pyridyl), 7.86 (1H, *ddd*, *J* = 1.8, 7.9, 7.9 Hz, pyridyl), 7.40 (1H, *ddd*, *J* = 1.8, 3.7, 7.9 Hz, pyridyl), 2.75 (3H, *s*, CH_3); δ_C (100 MHz, $CDCl_3$) 161.5 (q), 157.6 (q), 152.6 (q), 150.4 (CH), 149.9 (CH), 137.2 (CH), 125.5 (CH), 123.7 (CH), 19.6 (CH_3); m/z (EI) 172 ($[M]^+$, 40%), 144 (47), 105 (100), 78 (32), 51 (24), 39 (28) [HRMS (EI): calcd. for $C_9H_8N_4$, 172.0748. Found: $[M]^+$, 172.0752 (1.9 ppm error)].

Conventional heating: To a solution of aldehyde amidrazone **210a** (0.070 g, 0.36 mmol) in DCM (2 mL) was added glacial AcOH (0.01 mL). The reaction mixture

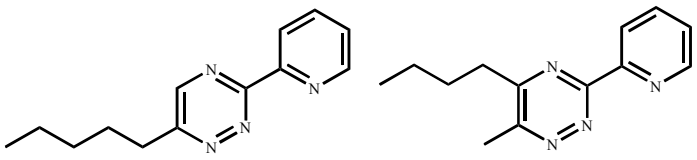
was heated at reflux for 48 hours followed by TLC. The reaction mixture was then concentration *in vacuo* to give the title compound **208a** (0.056 g, 89%).

2.2.11 Synthesis of 3-(2-pyridyl)-6-cyclohexyl-1,2,4-triazine 208b



To a 10 mL CME Discover® reaction vial with a stir bar was placed amidrazone **207b** (0.157 g, 0.6 mmol), toluene (0.8 mL) and MnO_2 (0.192 g, 2.2 mmol). The reaction vessel was irradiated for 15 minutes at 150 °C (power 300 W, pressure up to 300 psi). After 15 minutes, the vessel was cooled down to 50 °C and the crude mixture filtered through Celite® and the residue washed well with DCM and concentrated *in vacuo* giving the title compound **208b** as a dark yellow solid (0.138 g, 97%, without further purification), mp 108.7-109.0 °C; R_f 0.40 (MeOH-EtOAc, 1:9); ν_{max} (film/cm^{-1}) 2927, 2851, 1624, 1564, 1498, 1470, 1443, 1046, 989, 773 and 743; δ_H (400 MHz, $CDCl_3$) 8.82 (1H, *d*, *J* = 4.9 Hz, pyridyl), 8.64 (1H, *s*, H-5, triazine), 8.63 (1H, *d*, *J* = 8.0 Hz, pyridyl), 7.88 (1H, *ddd*, *J* = 1.5, 8.0, 8.0 Hz, pyridyl), 7.43 (1H, *dd*, *J* = 4.9, 8.0 Hz, pyridyl), 2.99 (1H, *t*, *J* = 8.0 Hz, cyclohexyl), 2.03-1.87 (4H, *m*, cyclohexyl), 1.78-1.61 (3H, *m*, cyclohexyl), 1.48-1.20 (3H, *m*, cyclohexyl); δ_C (100 MHz, $CDCl_3$) 163.7 (q), 161.0 (q), 151.9 (q), 149.6 (CH), 148.1 (CH), 136.5 (CH), 124.7 (CH), 122.9 (CH), 41.7 (CH), 31.4 (2 x CH_2), 25.4 (2 x CH_2), 24.9 (CH_2); *m/z* (EI) 240 ([M]$^+$, 76%), 105 (100) [HRMS (EI): calcd. for $C_{14}H_{16}N_4$, 240.1374. Found: [M]$^+$, 240.1380 (2.2 ppm error)].

2.2.12 Synthesis of 3-(2-pyridyl)-6-pentyl-1,2,4-triazine 208c and 3-(2-pyridyl)-5-butyl-6-methyl-1,2,4-triazine 208d



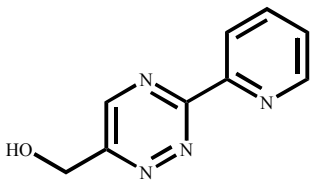
To a 10 mL CEM Discover® reaction vial with a stir bar was placed the mixture of amidrazone **207c** and **207d** (0.069 g, 0.27 mmol, ratio 1.6:1), toluene (1.0 mL) and MnO_2 (0.117 g, 1.3 mmol). The reaction vessel was irradiated for 30 minutes at 120 °C (power 200 W, pressure up to 300 psi). After 30 minutes, the vessel was cooled down to 50 °C and the crude mixture then filtered through Celite®, washed well with DCM and concentrated *in vacuo* to give the dark yellow viscous oil. In the second step, the dark yellow oil, toluene (1 mL) and glacial AcOH (0.2 mL) were placed in a 10 mL microwave vessel and irradiated at 150 °C for 10 minutes (power 300 W, pressure up to 300 psi). The mixture was then cooled down to 50 °C and the homogenous solution concentrated *in vacuo* to give the crude mixture of **208c** and **208d**. Purification by flash column chromatography (MeOH-EtOAc, 5:95) gave the title compounds **208c** (0.021 g, 55%, calculated from the ratio of **207c**: **207d**) and **208d** (0.015 g, 63%, calculated from the ratio of **207c**: **207d** (1.6:1)) as dark brown viscous oils.

Data for compound **208c,** R_f 0.28 (MeOH- EtOAc, 0.5:9.5); ν_{max} (film/cm^{-1}) 2956, 2929, 2860, 1674, 1586, 1507, 1270, 1118, 771 and 735; δ_H (400 MHz, $CDCl_3$) 8.77 (1H, *d*, *J* = 4.6 Hz, pyridyl), 8.76 (1H, *s*, H-5, triazine), 8.57 (1H, *d*, *J* = 7.9 Hz, pyridyl), 7.82 (1H, *ddd*, *J* = 1.8, 7.9, 7.9 Hz, pyridyl), 7.37 (1H, *dd*, *J* = 4.6, 7.9 Hz, pyridyl), 2.97 (2H, *t*, *J* = 7.6 Hz, CH_2), 1.76 (2H, *quin*, *J* = 7.6 Hz), 1.30-1.29 (4H, *m*),

0.81 (3H, *t*, *J* = 7.0 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 161.6 (q), 161.2 (q), 152.6 (q), 150.4 (CH), 149.7 (CH), 137.2 (CH), 125.5 (CH), 123.7 (CH), 33.5 (CH_2), 31.3 (CH_2), 28.9 (CH_2), 22.4 (CH_2), 14.0 (CH_3); *m/z* (EI) 228 ($[M]^+$, 35%), 172 (88), 105 (100) [HRMS (EI): calcd. for $C_{13}H_{16}N_4$, 228.1374 Found: $[M]^+$, 228.1375.

Data for compound **208d**, R_f 0.23 (MeOH-EtOAc, 0.5:9.5); ν_{max} (film/cm^{-1}) 2958, 2931, 1669, 1624, 1587, 1523, 1394, 1049 and 997; δ_H (400 MHz, $CDCl_3$) 8.81 (1H, *d*, *J* = 4.6 Hz, pyridyl), 8.53 (1H, *d*, *J* = 7.9 Hz, pyridyl), 7.83 (1H, *ddd*, *J* = 1.2, 7.9, 7.9 Hz, pyridyl), 7.38 (1H, *dd*, *J* = 4.6, 7.92 Hz, pyridyl), 2.86 (2H, *t*, *J* = 7.6 Hz), 2.73 (3H, *s*, CH_3), 1.72 (2H, *m*), 1.42 (2H, *sextet*, *J* = 7.64 Hz), 0.91 (3H, *t*, *J* = 7.64 Hz); δ_C (100 MHz, $CDCl_3$) 163.4 (q), 162.3 (q), 157.4 (q),154.0 (q), 151.1 (CH), 137.9 (CH), 126.0 (CH), 124.6 (CH), 35.4 (CH_2), 30.4 (CH_2), 23.6 (CH_2), 20.2 (CH_3), 14.7 (CH_3); *m/z* (EI) 228 ($[M]^+$, 16%), 105 (100) [HRMS (EI): calcd. for $C_{13}H_{16}N_4$, 228.1374 Found: $[M]^+$, 228.1376.

2.2.13 Synthesis of 3-(2-pyridyl)-6-methylenehydroxyl-1,2,4-triazine 208e

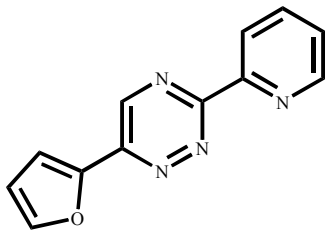


Microwave heating: Aldehyde amidrazone **210e** (0.030 g, 0.14 mmol) and toluene (1.0 mL) were placed in a 10 mL microwave reaction tube and irradiated at 150 °C for 15 minutes (power 300 W, pressure up to 300 psi). After 15 minutes, the vessel was cooled to 50 °C and checked by TLC. which showed the reaction to be complete. The homogenous solution was concentrated *in vacuo* to give the title compound **208e** as a red solid (0.034 g, 95%, without further purification), mp 246 °C (decomposed); R_f 0.27 (MeOH-EtOAc, 2:1); ν_{max} (film/cm^{-1}) 3404, 1634, 1587, 1402,

1073, 1026 and 772; δ_H (400 MHz, methanol-d_3) 9.01 (1H, *s*, H-5, triazine), 8.75 (1H, *d*, *J* = 4.8 Hz, pyridyl), 8.57 (1H, *d*, *J* = 7.8 Hz, pyridyl), 8.04 (1H, *ddd*, *J* = 1.5, 7.8, 7.8 Hz, pyridyl), 7.6 (1H, *ddd*, *J* = 1.5, 4.83, 7.9 Hz, pyridyl), 5.00 (2H, *s*, CH_2); δ_C (100 MHz, methanol-d_3) 162.8 (q), 161.7 (q), 153.2 (q), 150.7 (CH), 150.2 (CH), 138.9 (CH), 127.1 (CH), 124.8 (CH), 62.4 (CH_2); *m/z* (EI) 188 ($[M]^+$, 6%), 105 (100) [HRMS (EI): calcd. for $C_9H_8ON_4$, 188.0698. Found: $[M]^+$, 188.0702.

Conventional heating: To a solution of aldehyde amidrazone **210e** (0.021 g, 0.1 mmol) in $CHCl_3$ (2 mL). The reaction mixture was heated to reflux for 24 hours monitored by TLC. which showed the reaction to be complete. The mixture was then concentration *in vacuo* to give the title compound **208e** (0.017g, 89%).

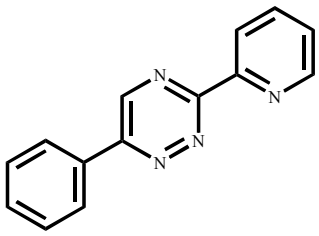
2.2.14 Synthesis of 3-(2-pyridyl)-6-(2-furyl)-1,2,4-triazine 208f



To a 10 mL CEM Discover® reaction vial was placed 1-(2-furyl)-2-hydroxyketone **206f** (0.035, 0.3 mmol), amidrazone **205** (0.040 g, 0.3 mmol) and EtOH (0.2 mL). The reaction vessel was irradiated for 40 minutes at 90 °C (power = 200 W, pressure up to 300 psi). After 40 minutes, the vessel was cooled to 50 °C and monitored by TLC. which showed the reaction to be complete. The homogenous solution was concentrated *in vacuo* to give dark yellow viscous oil. In the second step, the dark yellow oil, toluene (1 mL) and MnO_2 (0.052 g, 0.6 mmol) were placed in a 10 mL microwave vessel and irradiated at 120 °C for 30 minutes (power 200 W, pressure up to 300 psi). After 30 minutes, the vessel was cooled to 50 °C and monitored by

TLC. which showed the remaining starting material so a second portion of MnO_2 (0.052 g, 0.6 mmol) was added and irradiated at 150 °C for 5 minutes (power = 200 W, pressure up to 300 psi). After cooling down to 50 °C, the reaction mixture was filter through Celite®, washed with DCM, concentrated *in vacuo* and purified by flash column chromatography (EtOAc) to give the title compound **208f** as a red solid (0.015 g, 22%), mp 157.8-159.2 °C; R_f 0.19 (EtOAc); ν_{max} (film/cm^{-1}) 3054, 2986, 2305, 1639, 1422, 1265, 896, 737 and 706; δ_H (400 MHz, $CDCl_3$) 9.08 (1H, *s*, H-5, triazine), 8.81 (1H, *d*, *J* = 4.0 Hz, pyridyl), 8.64 (1H, *d*, *J* = 7.9 Hz, pyridyl), 7.87 (1H, *ddd*, *J* = 1.5, 7.9, 7.9 Hz, pyridyl), 7.65 (1H, *brs* , furyl), 7.44 (1H, *d*, *J* = 3.4 Hz, furyl), 7.44-7.40 (1H, *m*, pyridyl), 6.62-6.61 (1H, *m*, furyl); δ_C (100 MHz, $CDCl_3$) 160.9 (q), 152.2 (q), 150.3 (CH), 149.0 (C), 148.2 (q) 145.5 (CH), 145.2 (CH), 137.1 (CH), 125.5 (CH), 123.7 (CH), 112.9 (CH), 112.8 (CH); m/z (CI) 225 ([M+H]$^+$, 100%) [HRMS (EI): calcd. for $C_{12}H_9N_4O$, 225.0776 Found: [M+H]$^+$, 225.0775.

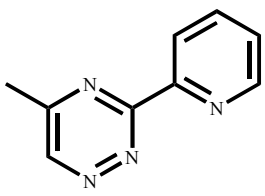
2.2.15 Synthesis of 3-(2-pyridyl)-6-cyclohexyl-1,2,4-triazine 208g



To a 10 mL CEM Discover® reaction vial with a stir bar was placed hydroxy acetophenone **206g** (0.040, 0.3 mmol), amidrazone **205** (0.040 g, 0.3 mmol) and EtOH (0.2 mL). The reaction vessel was irradiated for 10 minutes at 90 °C (power 100 W, pressure up to 300 psi). After 10 minutes, the vessel was cooled to 50 °C and the homogenous solution was concentrated *in vacuo* to give dark yellow viscous oil. In the

second step, the dark yellow oil, toluene (1 mL) and MnO_2 (0.026 g, 0.3 mmol) were placed in a 10 mL microwave vessel and irradiated at 120 °C for 15 minutes (power 200 W, pressure up to 300 psi). After 15 minutes, the vessel was cooled to 50 °C and monitored by TLC. which showed that the starting material remained so a second portion of MnO_2 (0.026 g, 0.3 mmol) was added and the mixture irradiated at 120 °C for 15 minutes (power 200 W, pressure up to 300 psi). After cooling to 50 °C, the reaction mixture was filter through Celite®, washed well with DCM, concentrated *in vacuo* and purified by flash column chromatography (EtOAc) to give the title compound **208g** as a yellow solid (0.034 g, 50%), mp 164.5-165.5 °C; R_f 0.20 (EtOAc); ν_{max} (film/cm^{-1}) 1583, 1444, 1400, 1115, 1075, 1043, 987, 775, 740, 729 and 688; δ_H (400 MHz, $CDCl_3$) 9.14 (1H, *s*, H-5, triazine), 8.84 (1H, *d*, *J* = 4.0 Hz, pyridyl), 8.68 (1H, *d*, *J* = 8.2 Hz, pyridyl), 8.14 (2H, *m*, pyridyl and aromatic), 7.89 (1H, *ddd*, *J* = 1.8, 8.2, 8.2 Hz, pyridyl), 7.55-7.54 (3H, *m*, aromatic), 7.40 (1H, *ddd*, *J* = 1.8, 4.0, 8.2 Hz, pyridyl); δ_C (100 MHz, $CDCl_3$) 161.5 (q), 155.9 (q), 152.2 (q), 150.3 (CH), 146.9 (CH), 137.1 (CH), 132.8 (q), 131.1 (q), 129.3 (2 x CH), 126.8 (2 x CH), 125.5 (CH), 123.7 (CH); *m/z* (EI) 234 ($[M]^+$, 20%), 206 (60) 102 (100) [HRMS (EI): calcd. for $C_{14}H_{16}N_4$, 234.0905. Found: $[M]^+$, 234.0901.

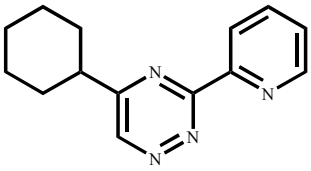
2.2.16 Synthesis of 3-(2-pyridyl)-5-methyl-1,2,4-triazine 209a



To a 10 mL CEM Discover® reaction vial was placed amidrazone **205** (0.040 g, 0.3 mmol), hydroxy acetone **206a** (0.022 mL, 0.3 mmol), MnO_2 (0.026 g, 0.3

mmol), powder 4Å molecular sieves (0.100 g) and DCM (0.5 mL). The reaction vessel was irradiated for 80 minutes at 55 °C (power 100 W, pressure up to 300 psi). After 80 minutes, the vessel was cooled to 50 °C and the mixture filtered through Celite® and the residue washed well with DCM and concentrated *in vacuo* to give dark yellow viscous oil. In the second step, the dark yellow viscous oil and toluene (1 mL) were placed in a 10 mL microwave vessel and irradiated at 120 °C for 50 minutes and cooled down to 50 °C. The homogenous solution was concentrated *in vacuo* and purified by flash column chromatography (MeOH-EtOAc, 5:95) to give title compound **209a** (0.023, 45%) as a red solid, mp 86.5-87.6 °C; R_f 0.19 (MeOH-EtOAc, 5: 95); ν_{max} (film/cm^{-1}) 1633, 1353, 1279, 1252, 1150, 987, 767 and 739; δ_H (270 MHz, $CDCl_3$) 9.05 (1H, *s*, H-6, triazine), 8.79 (1H, *dd*, *J* = 2.2, 4.8 Hz, pyridyl), 8.55 (1H, *d*, *J* = 8.2 Hz, pyridyl), 7.81 (1H, *ddd*, *J* = 2.2, 8.2, 8.2 Hz, pyridyl), 7.37 (1H, *dd*, *J* = 4.8, 8.2 Hz, pyridyl), 2.61 (3H, *s*, CH); δ_C (100 MHz, $CDCl_3$) 161.8 (q), 157.9 (q), 152.3 (q), 150.3 (CH), 149.8 (CH), 137.1 (CH), 125.4 (CH), 123.6 (CH), 19.5 (CH_3); *m/z* (EI) 172 ($[M]^+$, 17%), 144 (45), 105 (100), 78 (37), 51 (28), 39 (33) [HRMS (EI): calcd. for $C_9H_8N_4$, 172.0748. Found: $[M]^+$, 172.0749.

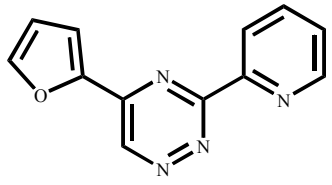
2.2.17 Synthesis of 3-(2-pyridyl)-5-cyclohexyl-1,2,4-triazine 209b



To a 10 mL CEM Discover® reaction vial was placed amidrazone **205** (0.050 g, 0.37 mmol), 1-cyclohexyl-2-hydroxyketone **206b** (0.053 g, 0.37 mmol), MnO_2 (0.032 g, 0.37 mmol) and DCM (0.5 mL). The reaction vessel was irradiated for 30

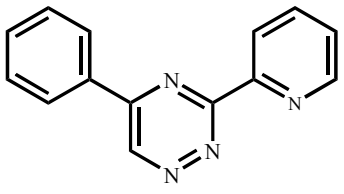
minutes at 55 °C (power 100 W, pressure up to 300 psi). After 30 minutes, the vessel was cooled to 50 °C and second portion of MnO_2 (0.037 g, 0.38 mmol) and powder 4Å molecular sieves (0.100 g) added. The reaction vessel was irradiated for 50 minutes at 55 °C (power 100 W, pressure up to 300 psi). After 55 minutes, the vessel was cooled to 50 °C, the residue was then filtered through Celite®, washed with DCM, concentrated *in vacuo* and purified by flash column chromatography (MeOH-EtOAc, 5:95) to give the title compound **209b** as a yellow solid (0.033 g, 38%), mp 117.4-118.5 °C; R_f 0.30 (MeOH- EtOAc, 5:95); ν_{max} (film/cm^{-1}) 3026, 2924, 1855, 1630, 1546, 1520, 1254, 799 and 780; δ_H (400 MHz, $CDCl_3$) 9.09 (1H, *s*, H-6, triazine), 8.80-8.79 (1H, *m*, pyridyl), 8.52 (1H, *d*, *J* = 8.0 Hz, pyridyl), 7.81 (1H, *ddd*, *J* = 1.8, 8.0, 8.0 Hz, pyridyl), 7.36 (1H, *dd*, *J* = 4.9, 8.0 Hz, pyridyl), 2.83 (1H, *tt*, *J* = 3.1, 11.9 Hz, cyclohexyl), 1.96 (2H, *br d*, *J* = 12.5 Hz, cyclohexyl), 1.82 (2H, *td*, *J* = 3.1, 13.2 Hz, cyclohexyl), 1.69 (1H, *br d*, *J* = 12.5 Hz, cyclohexyl), 1.54 (4H, *dq*, *J* = 3.1, 12.5 Hz, cyclohexyl), 1.39-1.12 (3H, *m*, cyclohexyl); δ_C (100 MHz, $CDCl_3$) 166.4 (q), 162.1.9 (q), 152.7 (q), 150.1 (CH), 147.3 (CH), 136.7 (CH), 125.1 (CH), 123.8 (CH), 43.9 (CH), 31.1 (2 x CH_2), 25.5 (2 x CH_2), 25.2 (CH_2); *m/z* (CI) 241 ($[M+H]^+$, 100%) [HRMS (CI): calcd. for $C_{14}H_{16}N_4$, 241.1453. Found: $[M+H]^+$, 241.1453 (0.0 ppm error)].

2.2.18 Synthesis of 3-(2-pyridyl)-5-(2-furyl)-1,2,4-triazine 209c



To a 10 mL CEM Discover® reaction vial with a stir bar was placed amidrazone **205** (0.040 g, 0.3 mmol), 1-(2-furyl)-2-hydroxyketone **206f** (0.037 mL, 0.3 mmol), MnO_2 (0.026 g, 0.3 mmol) and DCM (0.5 mL). The reaction vessel was irradiated for 60 minutes at 55 °C (power 100 W, pressure up to 300 psi). After 60 minutes, the vessel was cooled to 50 °C and the residue filtered through Celite®, washed with DCM, concentrated *in vacuo* and purified by flash column chromatography (MeOH-EtOAc, 5:95) to give the title compound **209c** as a dark yellow solid (0.037 g, 56%), mp 93.0-94.0 °C; R_f 0.35 (MeOH-EtOAc, 5:95); ν_{max} (film/cm^{-1}) 1588, 1534, 1440, 1405, 1136, 1048, 1015 and 771; δ_H (400 MHz, $CDCl_3$) 9.47 (1H, *s*, H-6, triazine), 8.80 (1H, *d*, *J* = 4.0 Hz, pyridyl), 8.53 (1H, *d*, *J* = 7.9 Hz, pyridyl), 7.83 (1H, *ddd*, *J* = 1.5, 7.9, 7.9 Hz, pyridyl), 7.66 (1H, *brs*, furyl), 7.59 (1H, *d*, *J* = 3.4 Hz, furyl), 7.39 (1H, *dd*, *J* = 4, 7.9 Hz, pyridyl), 6.60-6.59 (1H, *m*, furyl); δ_C (100 MHz, $CDCl_3$) 162.4 (q), 152.7 (q), 150.3 (CH), 148.8 (q), 147.3, (q), 147.1 (CH), 143.3 (CH), 137.0 (CH), 125.5 (CH), 124.0 (CH), 116.9 (CH), 113.3 (CH); *m/z* (CI) 225 ($[M+H]^+$, 100%) [HRMS (CI): calcd. for $C_{12}H_9N_4O$, 225.0776. Found: $[M+H]^+$, 225.0771.

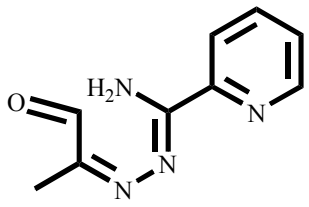
2.2.19 Synthesis of 3-(2-pyridyl)-5-cyclohexyl-1,2,4-triazine 209d



To a 10 mL CEM Discover® reaction vial with a stir bar was placed amidrazone **205** (0.040 g, 0.3 mmol), hydroxyacetophenone **206g** (0.040 mL, 0.3

mmol), MnO_2 (0.026 g, 0.3 mmol) and DCM (0.5 mL). The reaction vessel was irradiated for 95 minutes at 55 °C (power 100 W, pressure up to 300 psi). After 95 minutes, the vessel was cooled to 50 °C and the residue filtered through Celite®, washed with DCM, concentrated *in vacuo* and purified by flash column chromatography (MeOH-EtOAc, 5:95) to give the title compound **209d** as a yellow solid (0.027 g, 40%), mp 136.3-137.0 °C; R_f 0.40 (MeOH-EtOAc, 1:9); δ_H (400 MHz, $CDCl_3$) 9.68 (1H, *s*, H-6, triazine), 8.89 (1H, *d*, *J* = 4 Hz, pyridyl), 8.64 (1H, *d*, *J* = 7.9 Hz, pyridyl), 8.26 (1H, *d*, *J* = 8.0 Hz, aromatic), 7.92 (1H, *ddd*, *J* = 1.8, 7.9, 7.9 Hz, pyridyl), 7.57-7.45 (3H, *m*, aromatic), 7.46 (1H, *dd*, *J* = 4.0, 7.9 Hz, pyridyl); δ_C (100 MHz, $CDCl_3$) 162.6 (q), 155.6 (q), 152.8 (q), 150.3 (CH), 145.2 (CH), 137.0 (CH), 133.2 (q), 132.5 (CH), 129.3 (2 x CH), 127.7 (2 x CH) 125.5 (CH), 124.0 (CH).

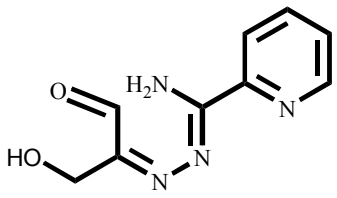
2.2.20 Synthesis of aldehyde amidrazone 210a



To a solution of 2-pyridylamidrazone **205** (0.137 g, 1.0 mmol) in EtOH (5 mL) was added hydroxy acetone **206a** (0.1 mL, 1.4 mmol) and the mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo*. The second step, the crude condensation product was added powdered 4 Å molecular sieves (0.300 g), MnO_2 (0.106 g, 1.2 mmol) in DCM (6 mL) and the mixture heated at reflux for 1 hour and monitored by TLC. which showed that the starting material remained so a second portion of MnO_2 (0.273 g, 3.1 mmol) was added and continue heating at reflux for 1 hour followed by addition of a third portion of MnO_2 (0.454 g,

5.0 mmol) with heating at reflux for 2 hours. The reaction mixture was refluxed for a further 16 hours, cooled, filtered through Celite® and washed well with DCM. The combined organics were concentrated *in vacuo*. The crude product was purified by flash column chromatography (DCM) to give the title compound **210a** as a yellow solid (0.137 g, 79%), mp 147.8-148.9 °C; R_f 0.40 (PE-EtOAc, 1:1); ν_{max} (film/cm^{-1}) 3416, 3280, 1677, 1513, 1264, 171, 1029, 855, 800 and 737; δ_H (400 MHz, $CDCl_3$) 9.61 (1H, *s*, aldehyde), 8.62 (1H, *d*, *J* = 4.0 Hz, pyridyl), 8.45 (1H, *d*, *J* = 7.9 Hz, pyridyl), 7.82 (1H, *ddd*, *J* = 1.8, 7.9, 7.9 Hz, pyridyl), 7.44 (1H, *dd*, *J* = 4.0, 7.9 Hz, pyridyl), 2.18 (3H, *s*, pyridyl); δ_C (100 MHz, $CDCl_3$) 194.6 (CH), 161.3 (q), 158.4 (q), 149.8 (q), 148.9 (CH), 137.1 (CH), 126.2 (CH), 122.6 (CH), 10.6 (CH_3), *m/z*: (CI) 191 ($[M+H]^+$, 100 %) [HRMS (CI): calcd. for $C_9H_{11}N_4O$, 191.0932. Found: $[M+H]^+$, 191.0934.

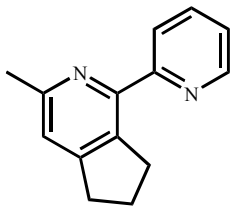
2.2.21 Synthesis of aldehyde amidrazone 210c



To a solution of 2-pyridylamidrazone **205** (0.155 g, 1.1 mmol) in EtOH (5 mL) was added 1,3-dihydroxyketone (dimer) **206e** (0.112 g, 0.6 mmol) and the mixture was stirred at room temperature for 1 hour and the reaction mixture concentrated *in vacuo*. The second step, to the crude condensation product was added powdered 4 Å molecular sieves (0.307 g), MnO_2 (0.166 g, 1.9 mmol) and DCM (10 mL) and the mixture was heated to reflux for 1 hour and monitored by TLC. which showed that the starting material remained so a second portion of MnO_2 (0.179 g, 2.0

mmol) was added, heated at reflux for 1 hour followed by addition of a third portion of MnO_2 (0.319 g, 3.6 mmol) with heating at reflux for 3 hours. A fourth portion of MnO_2 (0.200 g, 2.3 mmol) was added and the reaction mixture was refluxed for a further 24 hours, cooled, filtered through Celite® and washed well with DCM. The combined organics were concentrated *in vacuo*. The crude product was purified by flash column chromatography (MeOH-EtOAc, 5:95) to give the title compound **210c** (0.102 g, 52%), mp 125.4-127.1 °C; *Rf* 0.34 (PE-EtOAc, 1:1); ν_{max} (film/cm^{-1}) 3405, 3283, 1677, 1640, 1513, 1407, 1275, 1177, 1083, 802 and 738; δ_H (400 MHz, $CDCl_3$) 9.51 (1H, *s*, aldehyde), 8.6 (1H, *d*, *J* = 4.0 Hz, pyridyl), 8.18 (1H, *d*, *J* = 7.9 Hz, pyridyl), 7.79 (1H, *ddd*, *J* = 1.8, 7.9, 7.9 Hz, pyridyl), 7.42 (1H, *dd*, *J* = 4.0, 7.9 Hz, pyridyl), 4.71 (3H, *s*); δ_C (100 MHz, $CDCl_3$) 192.3 (CH), 159.9 (q), 159.4 (q), 148.9 (CH), 148.1 (q), 137.14 (CH), 126.6 (CH), 122.3 (CH), 57.9 (CH_2, C-7'); *m/z* (CI) 207 ($[M+H]^+$, 100 %) [HRMS (CI): calcd for: $C_9H_{11}N_4O_2$, 207.0882. Found: $[M+H]^+$ 207.0877.

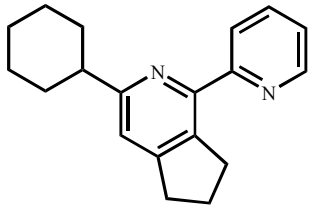
2.2.22 Synthesis of 3-methyl-1-(2-pyrydyl)-6,7-drihydro-5*H*-[2]pyrindine 211b



Triazine **209a** (0.017 g, 0.1 mmol), cyclopentanone (10 μL, 0.11 mmol), *N*-methylethylenediamine (10 μL, 0.12 mmol) and toluene (0.1 mL) were placed in a 10 mL CEM Discover® reaction vial and irradiated at 150 °C for 60 minutes (power 300 W, pressure up to 300 psi). After 60 minutes, the vessel was cooled down to 50 °C and diluted with DCM followed by concentration *in vacuo* and purification by flash

column chromatography (EtOAc) to give the title compound **211b** as a yellow viscous oil (0.008 g, 41%), R_f 0.33 (EtOAc); ν_{max} (film/cm^{-1}) 2955, 1587, 1564, 1471, 1418 and 744; δ_H (400 MHz, $CDCl_3$) 8.61 (1H, *d*, *J* = 4.9 Hz, pyridyl), 8.07 (1H, *d*, *J* = 7.9, pyridyl), 7.72 (1H, *dd*, *J* = 7.9, 7.9 Hz, pyridyl), 7.19 (1H, *dd*, *J* = 4.9, 7.9 Hz, pyridyl), 7.03 (1H, *s*, H-3), 3.22 (2H, *t*, *J* = 7.6 Hz), 2.85 (2H, *t*, *J* = 7.6), 2.55 (3H, *s*), 2.01 (2H, *quin*, *J* = 7.3); *m/z* (CI): 211 ([M+H]$^+$, 100%) [HRMS (CI): calcd. for $C_{14}H_{15}N_2$, 221.1235. Found: [M+H]$^+$, 221.1237.

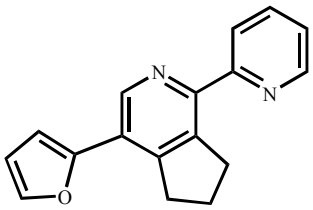
2.2.23 Synthesis of 3-cyclohexyl-1-(2-pyrydyl)- 6,7-drihydro-5*H*-[2]pyrindine 211d



Triazine **209b** (0.025 g, 0.1 mmol), cyclopentanone (10 μL, 0.11 mmol), *N*-methylethylenediamine (10 μL, 0.12 mmol) and toluene (0.1 mL) were placed in a 10 mL CEM Discover® reaction vial and irradiated at 150 °C for 90 minutes (power 300 W, pressure up to 300 psi). After 90 minutes, the vessel was cooled down to 50 °C and diluted with DCM followed by concentration *in vacuo* and purification by flash column chromatography (PE-EtOAc, 1:1) to give the title compound **211d** as a yellow viscous oil (0.010 g, 33%); R_f 0.45 (PE-EtOAc, 4:1); ν_{max} (film/cm^{-1}) 2925, 2851, 1586, 1563, 1470, 1449, 1417, 1255, 1096, 802 and 744; δ_H (400 MHz, $CDCl_3$) 8.58 (1H, *d*, *J* = 4.0 Hz, pyridyl), 8.16 (1H, *d*, *J* = 7.9 Hz, pyridyl), 7.71 (1H, *dd*, *J* = 7.9, 7.9 Hz, pyridyl), 7.19 (1H, *s*, H-3), 7.16 (1H, *dd*, *J* = 4.0, 7.9 Hz, pyridyl), 3.25 (2H, *t*, 7.6 Hz), 2.84 (2H, *t*, *J* = 7.6 Hz), 2.71 (1H, *tt*, *J* = 3.1, 8.6 Hz), 2.00 (2H, *quin*, *J* = 7.6 Hz), 1.95-1.18 (10H, *m*); δ_C (100 MHz, $CDCl_3$) 163.7 (q), 158.7 (q), 156.1 (q),150.7

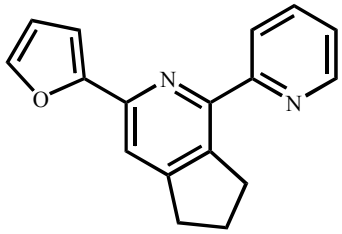
(q), 148.4 (CH), 136. (q), 136.3 (CH), 123.1 (CH), 122.4 (CH), 116.9 (CH), 46.2 (CH) 33.2 (2 x CH_2), 32.6 (CH_2), 32.5 (CH_2), 26.6 (2 x CH_2), 26.1 (CH_2), 25.0 (CH_2); *m/z* (CI): 279 ($[M+H]^+$, 100%) [HRMS (CI): calcd. for $C_{19}H_{23}N_2$, 279.1861. Found: $[M+H]^+$, 279.1862.

2.2.24 Synthesis of 4-furyl-1-(2-pyridyl)- 6,7-drihydro-5*H*-[2]pyrindine 211h



Triazine **208f** (0.012 g, 0.05 mmol), cyclopentanone (4 μL, 0.05 mmol), *N*-methylethylenediamine (4 μL, 0.05 mmol) and toluene (0.05 mL) were placed in a 10 mL CEM Discover® reaction vial and irradiated at 170 °C for 15 minutes (power 300 W, pressure up to 300 psi). After 15 minutes, the vessel was cooled down to 50 °C. It was then diluted with DCM, followed by concentration *in vacuo* and purification by flash column chromatography (EtOAc) to give the title compound **211h** as a yellow solid (0.010 g, 71%), mp 96.5-97.8 °C; R_f 0.20 (EtOAc); ν_{max} (film/cm^{-1}) 1638, 1429, 1091 and 744; δ_H (400 MHz, $CDCl_3$) 8.84 (1H, *s*, H-3), 8.62 (1H, *d*, *J* = 3.4 Hz, pyridyl), 8.15 (1H, *d*, *J* = 8.0 Hz, pyridyl), 7.75 (1H, *t*, *J* = 8.0 Hz, pyridyl), 7.51 (1H, *s*, furyl), 7.21 (1H, *m*, pyridyl), 6.65 (1H, *d*, *J* = 3.4 Hz, furyl), 6.48 (1H, *m*, furyl), 3.38 (2H, *t*, *J* = 7.6 Hz), 3.11 (2H, *t*, *J* = 7.6 Hz), 2.10 (2H, *quin*, *J* = 7.6 Hz); *m/z* (CI): 263 ($[M+H]^+$, 100%) [HRMS (CI): calcd. for $C_{17}H_{15}N_2O$, 263.1184. Found: $[M+H]^+$, 263.1187.

2.2.25 Synthesis of 3-furyl-1-(2-pyridyl)- 6,7-drihydro-5*H*-[2]pyrindine 211i

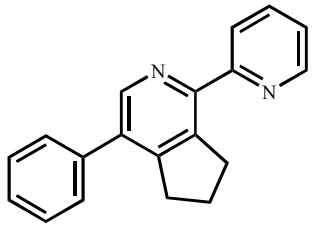


Triazine **209d** (0.022 g, 0.1 mmol), cyclopentanone (8 μL, 0.1 mmol), *N*-methylethylenediamine (8 μL, 0.1 mmol) and toluene (50 μL) were placed in a 10 mL CEM Discover® reaction vial and irradiated at 170 °C for 15 minutes (power 300 W, pressure up to 300 psi). After 15 minutes, the vessel was cooled down to 50 °C, diluted with DCM and then concentrated *in vacuo* and purified by flash column chromatography (PE-EtOAc, 1:1) to give the title compound **211i** as a yellow solid (0.015 g, 60%), mp79.5-81.6 °C; R_f 0.42 (PE-EtOAc, 1:4); ν_{max} (film/cm^{-1}) 2954, 1605, 1585, 1564, 1494, 1472, 1417, 1391, 1006 and 738; δ_H (400 MHz, $CDCl_3$) 8.60 (1H, *d*, *J* = 4.0 Hz, pyridyl), 8.26 (1H, *d*, *J* = 7.9 Hz, pyridyl), 7.74 (1H, *ddd*, *J* = 1.8, 7.9, 7.9 Hz, pyridyl), 7.55 (1H, *s*, H-4), 7.45 (1H, *d*, *J* = 0.9 Hz, furyl), 7.22-7.20 (1H, *m*, pyridyl), 7.01 (1H, *d*, *J* = 3.4 Hz, furyl), 6.45 (1H, *dd*, *J* = 0.9, 3.4 Hz, furyl), 3.33 (2H, *t*, *J* = 7.6 Hz), 2.91 (2H, *t*, *J* = 7.6 Hz), 2.04 (2H, *quin*, *J* = 7.6 Hz); δ_C (100 MHz, $CDCl_3$) 158.2 (q), 156.5 (q), 154.3 (q), 151.4 (q), 148.3 (CH), 146.8 (q), 142.6 (CH), 137.7 (q), 136.4 (CH), 123.1 (CH), 122.7 (CH), 114.7 (CH), 111.8 (CH), 107.7 (CH), 32.9 (CH_2), 32.7 (CH_2), 24.9 (CH_2); *m/z* (CI): 263 ($[M+H]^+$, 100%) [HRMS (CI): calcd. for $C_{17}H_{15}N_2O$, 263.1184. Found: $[M+H]^+$, 263.1187..

One pot reaction: 1-(2-Furyl)-2-hydroxy ketone **206f** (0.037 g, 0.3 mmol), 2-pyridylamidrazone **205** (0.040 g, 0.3 mmol), cyclopentanone (26 μL, 0.3 mmol), *N*-methylethylenediamine (26 μL, 0.3 mmol), MnO_2 (0.026 g, 0.3 mmol) and toluene (50

μL) were placed in a 10 mL CEM Discover® reaction vial and irradiated at 170 °C for 15 minutes (power 300 W, pressure up to 300 psi). After 15 minutes, the vessel was cooled down to 50 °C, diluted with DCM and then concentrated *in vacuo* and purified by flash column chromatography (PE-EtOAc, 1:1) to give the title compound **211i** as a yellow solid (0.011 g, 15%).

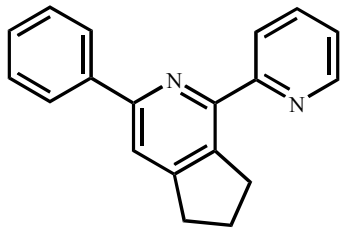
2.2.26 Synthesis of 4-phenyl-1-(2-pyrydyl)- 6,7-drihydro-5*H*-[2]pyrindine 211j



Triazine **208g** (0.023 g, 0.1 mmol), cyclopentanone (8 μL, 0.1 mmol), *N*-methylethylenediamine (8 μL, 0.1 mmol) and toluene (0.1 mL) were placed in a 10 mL CEM Discover® reaction vial and irradiated at 170 °C for 15 minutes (power 300 W, pressure up to 300 psi). After 15 minutes, the vessel was cooled down to 50 °C, diluted with DCM and then concentrated *in vacuo* and purified by flash column chromatography (EtOAc) to give the title compound **211j** (0.015 g, 55%) as a yellow solid, mp 121.3-122.8 °C; R_f 0.25 (PE- EtOAc, 4:1); ν_{max} (film/cm^{-1}) 3056, 2956, 1583, 1552, 1445, 1428, 1375, 1088, 766, 745, 723 and 700; δ_H (400 MHz, $CDCl_3$) 8.63 (1H, *d*, *J* = 4.3 Hz, pyridyl), 8.48 (1H, *s*, H-3), 8.12 (1H, *d*, *J* = 8.2 Hz, pyridyl), 7.75 (1H, *ddd*, *J* = 1.2, 8.2, 8.2 Hz, pyridyl), 7.45-7.31 (5H, *m*, aromatic), 7.22 (1H, *ddd*, *J* = 1.2, 4.28, 8.2 Hz, pyridyl), 3.38 (2H, *t*, *J* = 7.3 Hz), 2.97 (2H, *t*, *J* = 7.3 Hz), 2.01 (2H, *quin*, *J* = 7.3 Hz); δ_C (100 MHz, $CDCl_3$) 157.9 (q), 153.3 (q), 150.6 (q), 148.6 (2 x CH), 146.4 (CH), 139.3 (q), 137.6 (q), 136.3 (2 x CH), 133.6 (q), 128.5 (2 x

CH), 127.6 (CH), 122.9 (CH), 122.6 (CH), 33.3 (CH_2), 32.5 (CH_2), 25.4 (CH_2); *m/z* (CI): 273 ($[M+H]^+$, 100%) [HRMS (CI): calcd. for $C_{19}H_{17}N_2$, 273.1391. Found: $[M+H]^+$, 273.1393.

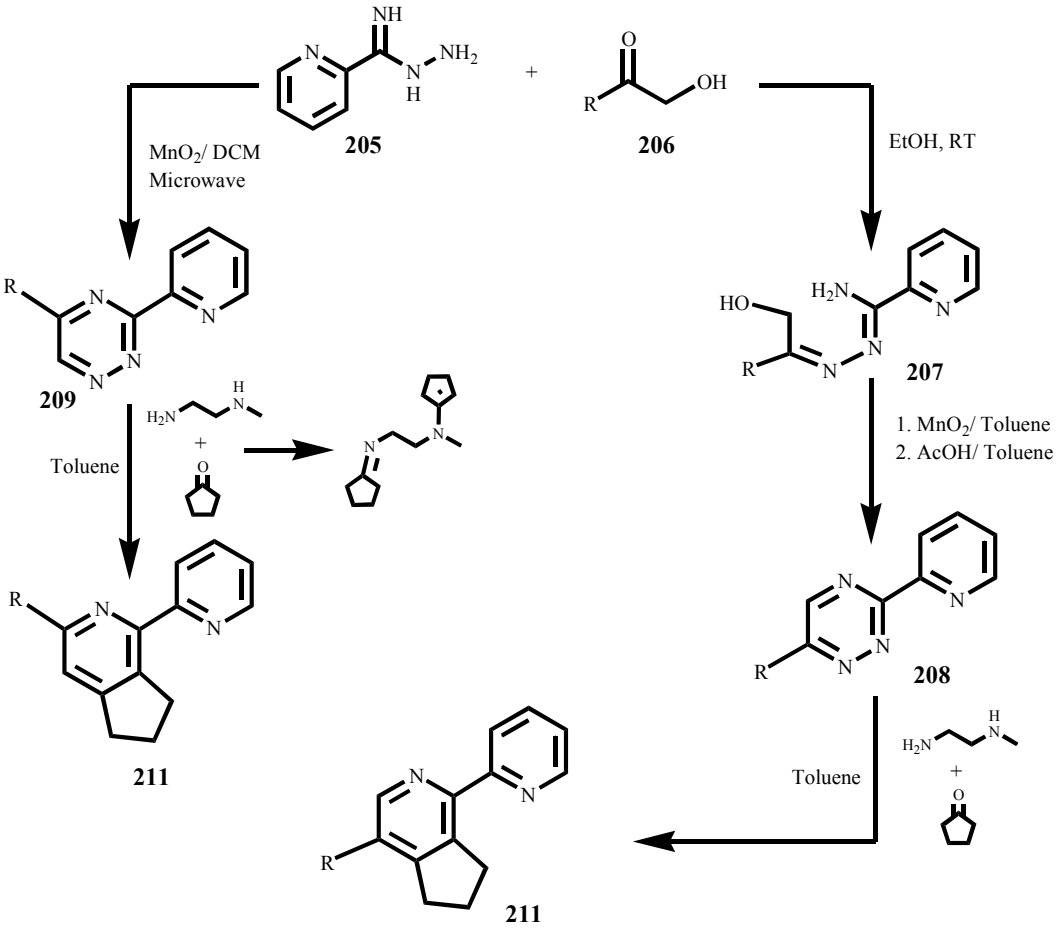
2.2.27 Synthesis of 3-phenyl-1-(2-pyrydyl)- 6,7-drihydro-5*H*-[2]pyrindine 211k



Triazine **209e** (0.023 g, 0.1 mmol), cyclopentanone (8 μL, 0.1 mmol), *N*-methylethylenediamine (8 μL, 0.1 mmol) and toluene (0.1 mL) were placed in a 10 mL CEM Discover reaction vial and irradiated at 150 °C for 60 minutes (power 300 W, pressure up to 300 psi). After 15 minutes, the vessel was cooled down to 50 °C, diluted with DCM and then concentrated *in vacuo* and purified by flash column chromatography (PE-EtOAc, 4:1) to give the title compound **211k** (0.018 g, 67%) as a white solid, mp 106.3-107.0 °C; R_f 0.37 (PE- EtOAc, 4:1); δ_H (400 MHz, $CDCl_3$) 8.62 (1H, *d*, *J* = 4.0 Hz, pyridyl), 8.37 (1H, *d*, *J* = 7.9 Hz, pyridyl), 8.04 (2H, *d*, *J* = 7.0 Hz, aromatic), 7.76 (1H, *ddd*, *J* = 1.5, 7.9, 7.9 Hz, pyridyl), 7.60 (1H, *s*, H-4), 7.40 (2H, *t*, *J* = 7.0 Hz, aromatic and pyridyl), 7.32 (2H, *t*, *J* = 7.0 Hz, aromatic), 3.38 (2H, *t*, *J* = 6.7 Hz), 2.94 (2H, *t*, *J* = 6.7 Hz), 2.07 (2H, *quin*, *J* = 6.7 Hz); δ_C (100 MHz, $CDCl_3$) 158.5 (q), 156.8 (q), 154.4 (q), 151.1 (q), 148.3 (CH), 139.8 (q), 137.9 (q), 136.4 (CH), 128.5 (2 x CH), 128.4 (CH), 126.8 (2 x CH), 123.1 (CH), 122.6 (CH), 116.5 (CH), 32.9 (CH_2), 32.7 (CH_2), 25.0 (CH_2).

2.3 RESULTS AND DISCUSSION

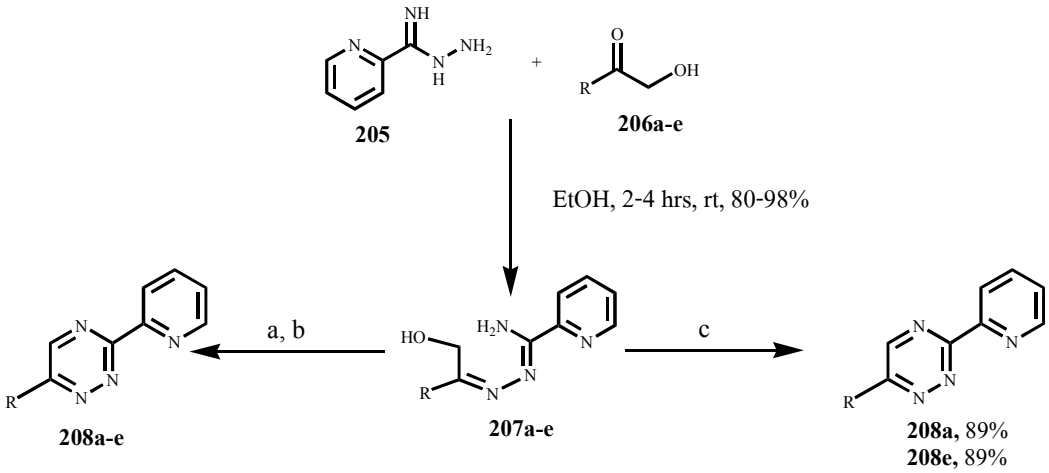
The tethered imine-enamine methodology has been developed for the direct conversion of 1,2,4-triazines into highly substituted pyridine **211** *via* the inverse electron demand Diels-Alder reaction. The synthetic route to highly substituted pyridines **211** was outline in **Scheme** 43. This methodology employed the condensation reaction of precursor amidrazone **205** and alcohol ketones **206** as a key step, to give the corresponding 1,2,4-triazines **208** and **209** which were directly converted into highly substituted pyridines **211**.



Scheme 43 Microwave assisted synthesis of highly substituted pyridines **211**

2.3.1 Microwave assisted regioselective synthesis of 6-substituted 1,2,4-triazines 208a-e

6-Substituted 1,2,4-triazines **208a-e** could be obtained via the amidrazone **207a-e** which were prepared from amidrazone **205** (Case, 1965), and hydroxyl alcohols **207a-e** (Moriarty et al., 1992). Compounds **207a-e** were obtained from direct reaction between amidrazone **205** and alcohols **206a-e** in EtOH at room temperature for 2-4 hours, to give the corresponding compounds **207a-e** in excellent yield (80-93%, **Table** 28, **Scheme** 44). The next step was oxidation of the 1°-alcohol of compound **207a-e** to the aldehyde (without isolation) which could be achieved by the reaction of **207a-e** with MnO_2 in toluene and irradiated at 120 °C for 10-30 minutes. After cooling, filtering and concentration, the crude product was further irradiated at 150 °C for 10 minutes in toluene and in the presence of AcOH to give the 1,2,4-triazines **208a-e** in moderate to excellent yield (55-98%, **Table** 28, **Scheme** 44)

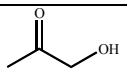
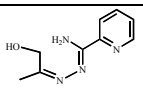
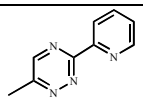
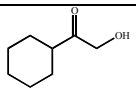
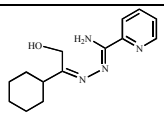
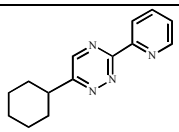
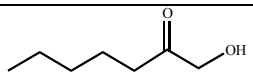
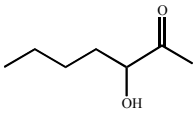
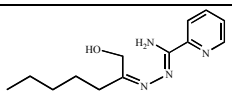
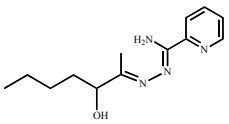
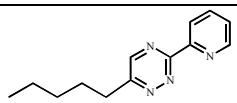
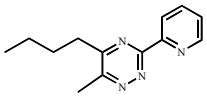
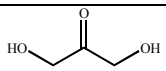
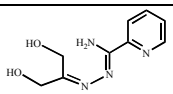
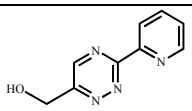


a: R = methyl; b: R = cyclohexyl; c: R= pentyl; e: R = methylene hydroxy

a) MnO_2, $PhCH_3$, MW, 120 °C, 5-30 mins, b) $PhCH_3$, AcOH, MW, 150 °C, 10 mins, c)DCM 2 mL/ AcOH 10 μL for **207a**, 48 hrs $CHCl_3$ 2mL for **5c**, 24 hrs

Scheme 44 Microwave assisted synthesis of 6-substituted 1,2,4-triazines **208a-e** (route A) and conventional heating synthesis of **208a** and **208c** (route B)

Table 28 Microwave assisted synthesis of 6-substituted 1,2,4-triazines **208a-e**

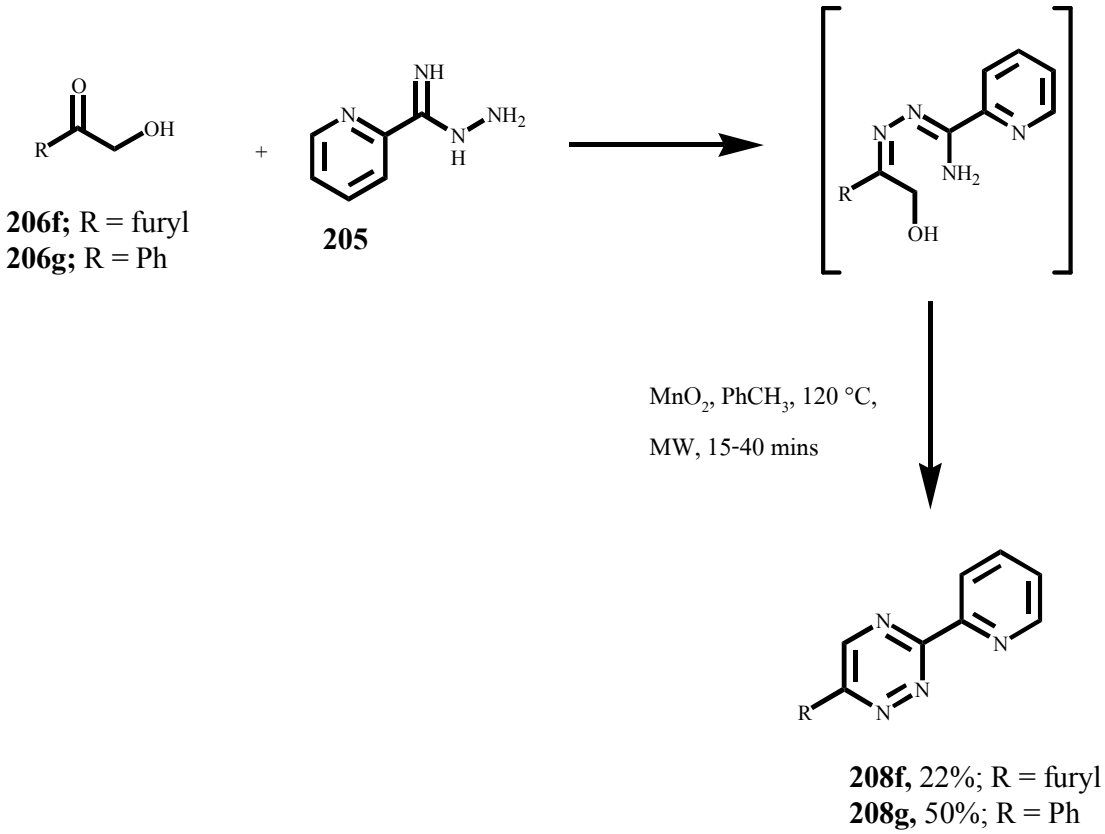
Entry	Compound	**5** (% yield)	**6** (% yield)
1	 **206a**	 **207a** (93)	 **208a** (98)[a]
2	 **206b**	 **207b** (88)	 **208b** (97)[a]
3	 **206c** +  **206d**	 **207c** +  **207d** (80, mixtures)	 **208c** (55)[b]  **208d** (63)[b]
4	 **206e**	 **207e** (80)	 **208e** (95)[c]

[a]The yield without isolation. [b]Isolated yield and calculation from the ratio of the alcohol **206c** and **206d** (1.6:1). [c]The product was derived from the aldehyde **210b** and irradiated at 150 °C in toluene (less trizine **208e** was observed when compound **207e** used as starting material)

The reaction of **207a** and **207e** *via* conventional heating needed reaction time more than those of microwave heating and the yields were slightly less than the reaction *via* microwave heating.

The condensation reaction of hydroxyl alcohols **206f** and **206g** with amidrazone **205** were not successful *via* conventional heating. This may be due to the

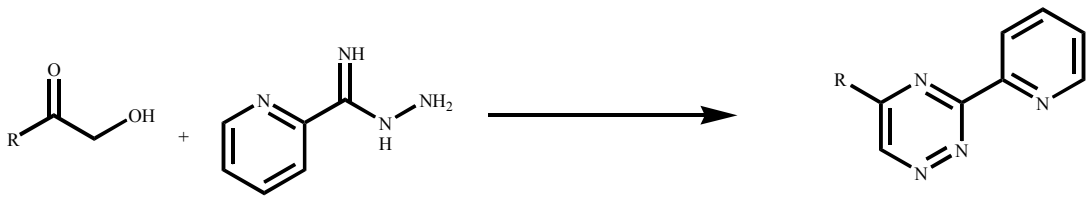
less reactivity of carbonyl functionality which were stabilized by the aromatic ring system of both of phenyl and 2-furyl moieties and probably this reaction needed higher temperature than those of hydroxyl alcohols **206a-e**. Fortunately, these reactions were successful *via* microwave heating. The irradiation at 90 ºC for 10-40 minutes of hydroxyl alcohols **206f** or **206g** and amidrazone **205** in EtOH gave the corresponding intermediates **207f** and **207g** (detected from TLC checked and without isolation). After cooling down to 50 °C and concentration, the crude products were immediately oxidized with MnO_2 in toluene and irradiated at 120 °C for 15-40 minutes to yield the 1,2,4-triazines **208f** (22 %) and **208g** (50%) (**Scheme** 45).



Scheme 45 Microwave assisted synthesis of 6-substituted triazine derivatives **208f** and **208g**

2.3.2 Microwave assisted regioselective synthesis of 5-substituted 1,2,4-triazines 209a-e

The synthesis of regioselective of 5-substituted 1,2,4-triazine would be derived from one pot reaction of amidrazone, hydroxyl ketones and MnO_2. The reaction mixture of amidrazone, hydroxyl ketones and MnO_2 in DCM was irradiated at 55 °C for 55-95 minutes to give the triazine **209a-d**. As can be seen that the one pot reaction was obtained in moderate yield for these cascade reactions; the long sequence being condensation, oxidation and cyclization to the triazines **209a-d** in overall yields of 45%, 38%, 56% and 40%, respectively (**Scheme** 46).



206a; R = Me **205** **209a**; R = Me; 45%

206b; R = Cyclohexyl **209b**; R = Cyclohexyl; 38%

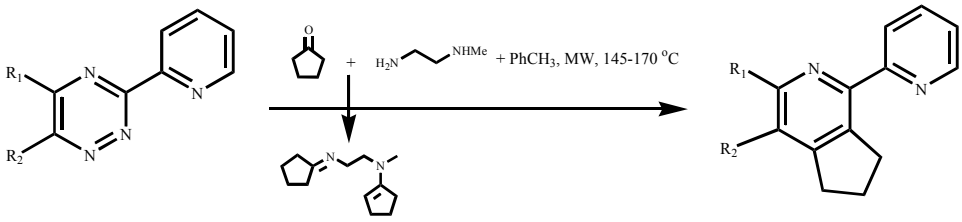
206f; R = 2-Furyl **209c**; R = 2-Furyl; 56%

206g; R = Ph **209d**; R = Ph; 40%

Scheme 46 Microwave assisted synthesis of 5-substituted triazine derivatives **209a-d**

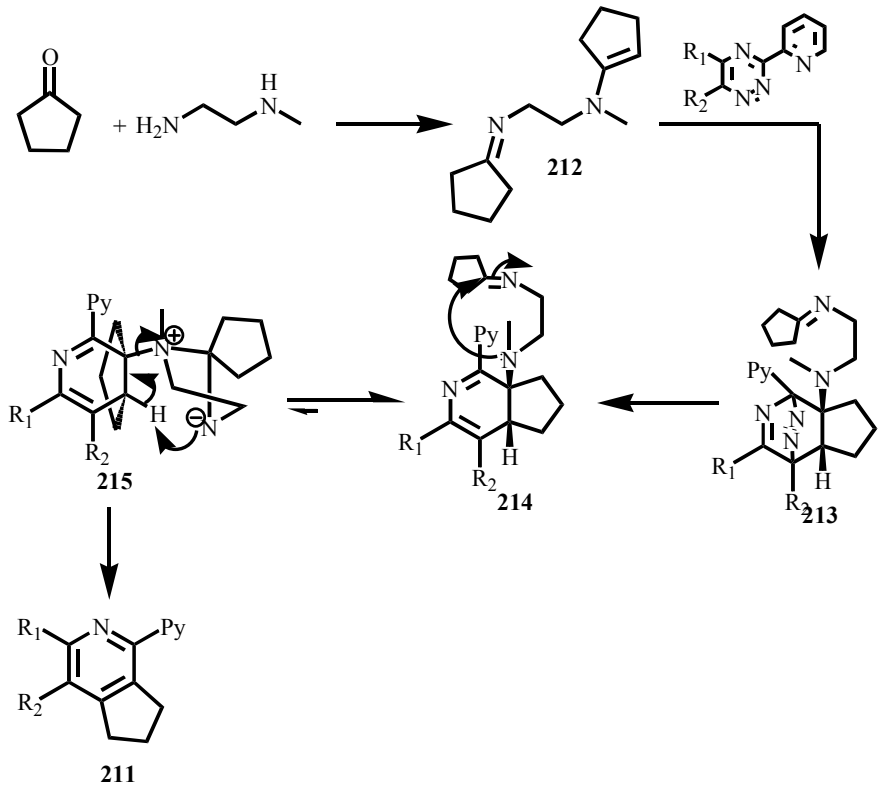
2.3.3 Microwave assisted synthesis of 3 and 4-substituted of 6,7-Dihydro-5*H*-[2]pyrindines 211a-h

The conversion of 1,2,4-triazine into [2]pyrindine compounds used the Boger's methodology. This chemistry exploits the inverse electron demand Diels-Alder reaction of triazines and enamine. [2]Pyrindins **211a-h** would be obtained from triazines **208a-g** and **209a-d**. The reactions of triazines **208a-g** or **209a-d** and cyclopentanone in toluene in the presence of *N,N*-methylethyldiamine were irradiated at 145-170 °C for 30-60 minutes which led to the formation of [2]pyrindins **211a-h** in moderate to good yields (**Scheme** 47, **Table** 29). The mechanism of this reaction was shown in **Scheme** 48. In the first step, the cyclopentanone was reacted with *N,N*-methylethyldiamine to give the intermediate emine-enamine (**212**) which was immediately treated with 1,2,4-triazine yielding the intermediate (**213**). The intramolecular cyclization of the intermediate afforded dihydropyridine **211** which could exist as a zwitterion **215**. Finally, the zwitterion would undergo elimination *in situ*, leading directly to [2]pyrindines.



208a-g or 209a-d **211a-j**

Scheme 47 Microwave assisted synthesis of 3 and 4-substituted of 6,7-Dihydro-5*H*-[2]pyrindines **211a-h**



Scheme 48 The mechanism of the formation of 3- and 4-substituted of 6,7-Dihydro-5*H*-[2]pyrindines **211a-h**

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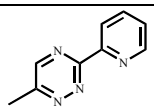
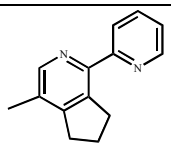
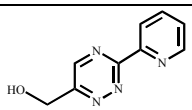
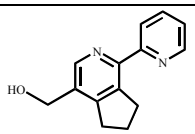
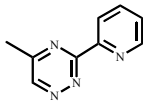
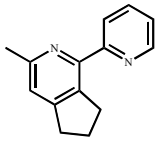
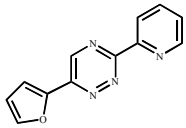
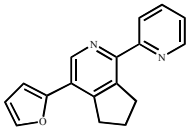
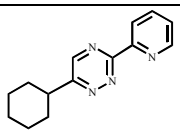
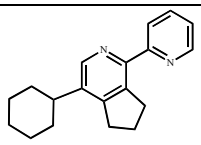
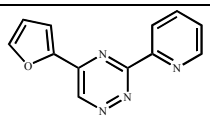
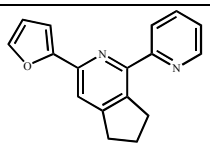
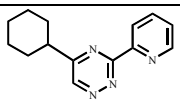
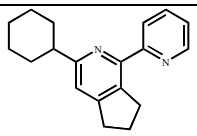
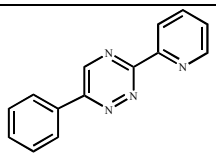
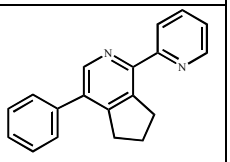
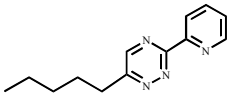
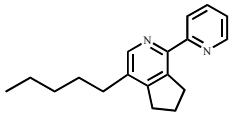
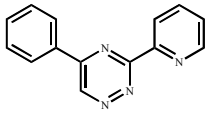
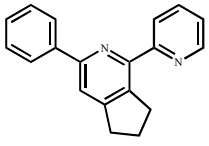
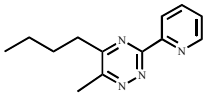
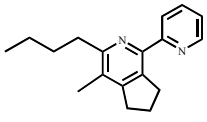
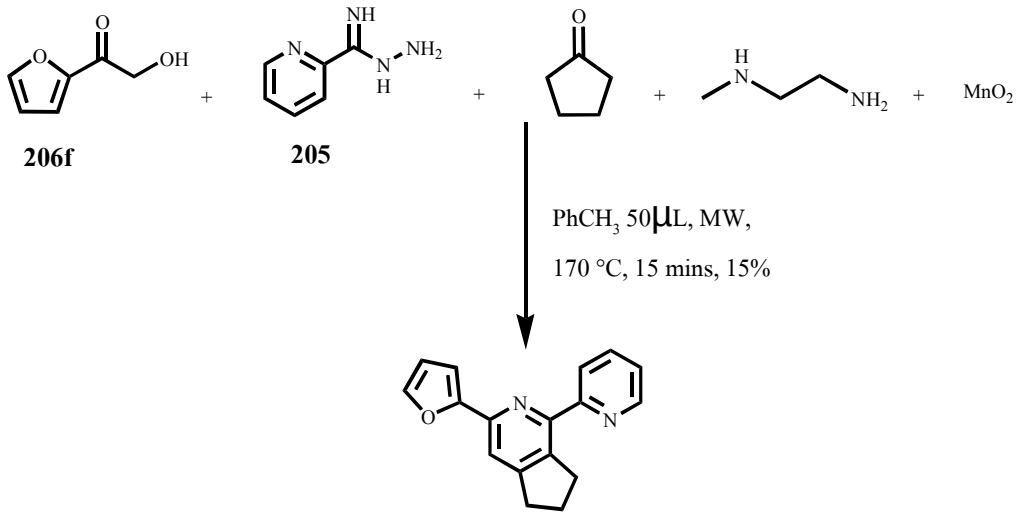
The substitutents at C-5 or C-6 of 1,2,4-triazines showed an effect in the inverse electron demand Diels-Alder reaction. For example, if the substituted groups were phenyl or 2-furyl moieties (both position C-5 and C-6), the reaction gave the best results, moderate to good yield with the yield 71%, 60%, 65% and 67% for [2]pyrindin **211h**, **211i**, **211j** and **211k**, respectively. While the alkyl groups at C-5 or C-6 of 1,2,4-triazines exhibited less reactive than those of phenyl or 2-furyl groups at the same position (**Table** 29). It is interesting to note that the C-5 alkyl substituted 1,2,4-triazines showed the better reactivity than those of C-6 alkyl substituted 1,2,4-triazines with 41% and 33% isolated yield for **211b** and **211c**, respectively. No reaction was observed when using C-6 alkyl substituted 1,2,4-triazines as starting material (**Table** 29). Finally, the one pot reaction of 1-(2-furyl)-2-hydroxy ketone, amidrazone, cyclopentanone, *N,N*-methylethyldiamine, MnO_2 in toluene was irradiated at 170 °C

for 15 minutes to give the corresponding [2]pyrindine **211g**. The reaction was obtained in low yield for these cascade reactions, the long sequence being oxidation, double condensations, Diels-Alder, retro-Diels-Alder and aromatization to **211g** in overall yield of 15% from **206f** (**Scheme** 49). The ^{1}H NMR spectra of **208**, **209** and **211** were summarized in appendix.

Table 29 Microwave assisted synthesis of 3- and 4-substituted of pyridines **211a-h**

Entry	Triazine	**211** yield (%)	Entry	Triazine	**211** yield (%)
1	 **208a**	 **a** (0)	7	 **208e**	 **g** (0)
2	 **209a**	 **b** (41)	8	 **208f**	 **h** (71)
3	 **208b**	 **c** (0)	9	 **209c**	 **i** (60)
4	 **209b**	 **d** (33)	10	 **208g**	 **j** (55)
5	 **208c**	 **e** (less)	11	 **209d**	 **k** (67)
6	 **208d**	 **f** (0)			



Scheme 49 Microwave assisted synthesis of 3-(2-furyl)-1-(2-pyridyl)-6,7-dihydro-5*H*-[2]pyrindine **211i**

In conclusion, the direct conversion of 1,2,4-triazines **208** or **209** into highly substituted pyridines **211** was developed which eliminated the need for a second, discrete aromatization step. The methodology was operationally simple and afforded pyridines **211** in moderate to good yields.