1.1 INTRODUCTION

Heterocyclic rings are present as fundamental components in the skeleton of more than half of the biologically active compounds produced by nature.[1] One of the reason for the widespread use of heterocyclic compounds in nature as well as in the pharmaceutical industry is their implication in a wide range of reaction types allowing subtle structural modification.[2-5]

Nitrogen-containing heterocycles like indolozine, quinolines, isoquinolines are recognized pharmacophores which have received great attention due to their reactivity and biological properties.

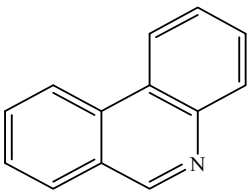


Figure 1.1. Phenanthridine

Similarly, phenanthridines (Figure 1.1) also constitute an important class of *N*-containing heterocycles having a 6-6-6 tricyclic skeleton fashioned by replacing a CH moiety by a nitrogen atom in the central ring of this π- framwork. Polycyclic phenanthridine derivatives (Figure 1.2) have attracted momentous attention in medicinal chemistry due to their existence in several important alkaloids.[6,7]

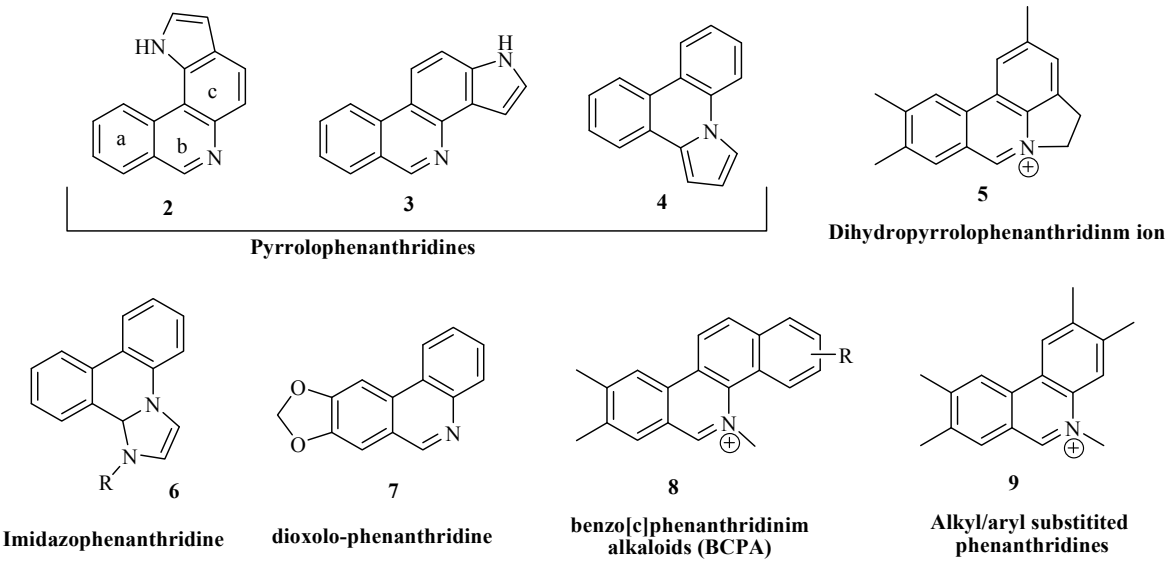


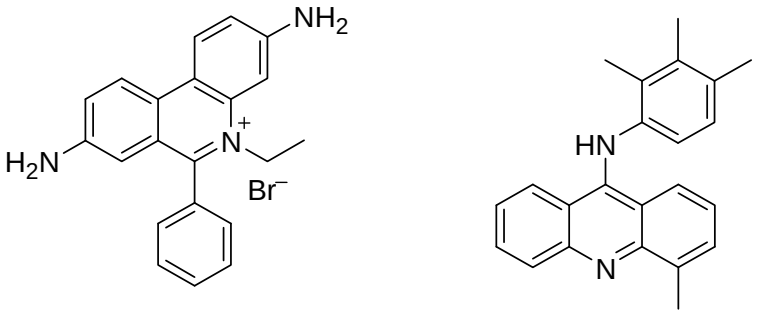
Figure 1.2. Polycyclic phenanthridine derivatives

The search of phenanthridine moiety containing therapeutic agents get increased after the trypanocidal activity of some phenanthridinium compounds became noticeable.[8] Furthermore, phenanthridine derivatives exhibit interesting biological activities and reactivity in annelation reactions.[9-11]

Phenanthridine moiety containing substrates are important in pharmaceuticals due to its implication in the scaffold of a number of DNA intercalating agents with antitumor properties,[12,13] antibacterial, antiprotozoal, and anticancer agents,[14-17] DNA drug targeting applications,[18] DNA binding agents with cytotoxic properties.[19]

One of the most used and explored phenanthridine derivative is 3,8-diamino-5-ethyl-6-phenylphenanthridinium moiety (**10**) known as ethidium bromide (EB) which is employed as DNA or RNA- intercalator and fluorescent maker for ds-DNA and ds-RNA.[20] Besides, antiparasitic activity, EB also possesses significant antitumor activity.[19,21-23]

Several pyrrolophenanthridines (PPHs) have shown remarkable antiproliferative activity against Friend erythroleukemia cells (FLC) and multi-drug resistant cell lines (DRTL).[24]



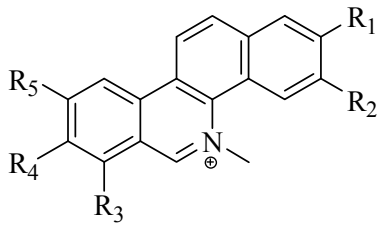
10 **11**

Figure 1.3. Ethidium Bromide and AMSA derivative.

Some PPHs which are structurally related to ethidium bromide (**10**) and to 9-acridinyl methane sulfonanilide derivatives (AMSA) (**11**), have ability to diminish virus induced cytopethogenicity and stimulate the multiplication of MT cells that is a crucial factor in anti AIDS therapy.[25]

Benzophenanthridine alkaloids (**12**), more suitably referred as benzo[*c*]phenanthridines (BCPA), constitute an important class of alkaloids in the isoquinoline family which show antibacterial activity against several pathogens.[7,14,26,27] Around thirty naturally occurring benzophenanthridinium alkaloids have already been isolated from plant sources. It includes (+)-chelidonine, corynoline, corynoloxine, corynolamine, 5- hydroxycorynoline, 6-epicorynoline, (+)-14-epicorynoline, acetylcorynoline, (+)-acetylisocorynoline, dihydrosanguinarine, oxysanguinarine, 8-methoxydihydronitidine, bocconoline,

(+)sanguinarine, chelerylthrine, avicine, chelirubin, macarpine, bucconine, nitidine, fagaronine, 1,3- bis(8-hydrosanguinarinyl)-acetone, etc. (Figure 1.4).



12

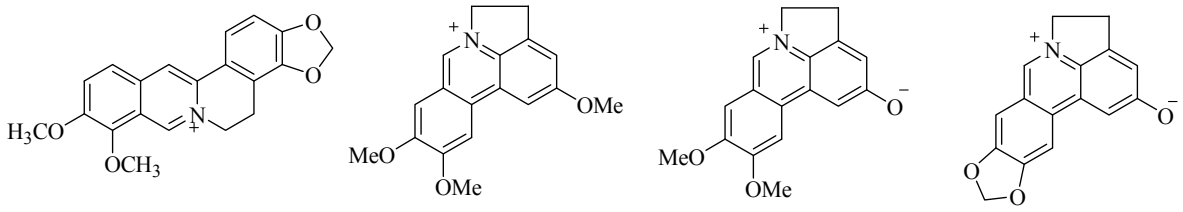
Compound	R^1	R^2	R^3	R^4	R^5
Nitidine	-OCH_2O-		H	OCH_3	OCH_3
Fagaronine	OH	OCH_3	H	OCH_3	OCH_3
Fagaridine	-OCH_2O-		OCH_3	OH	H
Chelerythrine	-OCH_2O-		OCH_3	OCH_3	H
Sanguinarine	-OCH_2O-		-OCH_2O-		H
NK 109	-OCH_2O-		OH	OCH_3	H

Figure 1.4. Benzophenanthridine alkaloids.

Nitidine (Figure 1.4) and its derivatives isolated from *Fagara macrophyla* and Fagaronine isolated from *Fagara zanthoxyloides*, are studied for their higher toxicity and antileukemic activity.

Sanguinarin (Figure 1.4) has been reported for its antibacterial activity which works by altering bacterial FtsZ Z-ring formation.[28a] FtsZ is a key protein that plays essential role in bacterial cell devision and it can be used a promising therapeutic target.[28b,c] Berberine (**13**) is also a structurally related alkaloid which affects the cytokinesis in bacteria in similar manner.[29,30]

Tortuosine (**14**) and its structural relative alkaloids such as Criasbetaine (**15**) and Ungeremine (**16**) are some pyrrolo fused phenanthridine alkaloids which were synthesized for antitumor screening.[31]



13 **14** **15** **16**

Figure 1.5. Some benzo- and pyrrolo- fused phenanthridine alkaloids.

Apart from these, phenanthridine derivatives have great utility in the physical domain including photo conducting and photovoltaic properties,[32,33] production of optical materials such as lithographic and holographic plates used in printing and electric equipments.[34]

The unique polycyclic structure and potentially useful pharmacological actions of PPHs have promoted to chemists to develop efficient synthetic routes for these annelated compounds.[35,36] Substituted benzophenanthridines and anellation of rings **a** and **c** of phenanthridinium framework have been extensively investigated while the heteroaromatic middle ring **b** has been explored barely (Figure 1.2).

1.2 SYNTHESIS :

For a systematic study, the synthetic procedures followed in literature can be divided into two classes:

1.2.1 Six- membered ring- fused phenanthridines

1.2.1.1 Benzo-fused phenanthridines

1.2.1.2 Oxazine-fused phenanthridines

1.2.2 Five- membered ring- fused phenanthridines

1.2.2.1 Pyrrolo-fused phenanthridines

1.2.2.2 Imidazo- and pyrazolo-fused phenanthridines

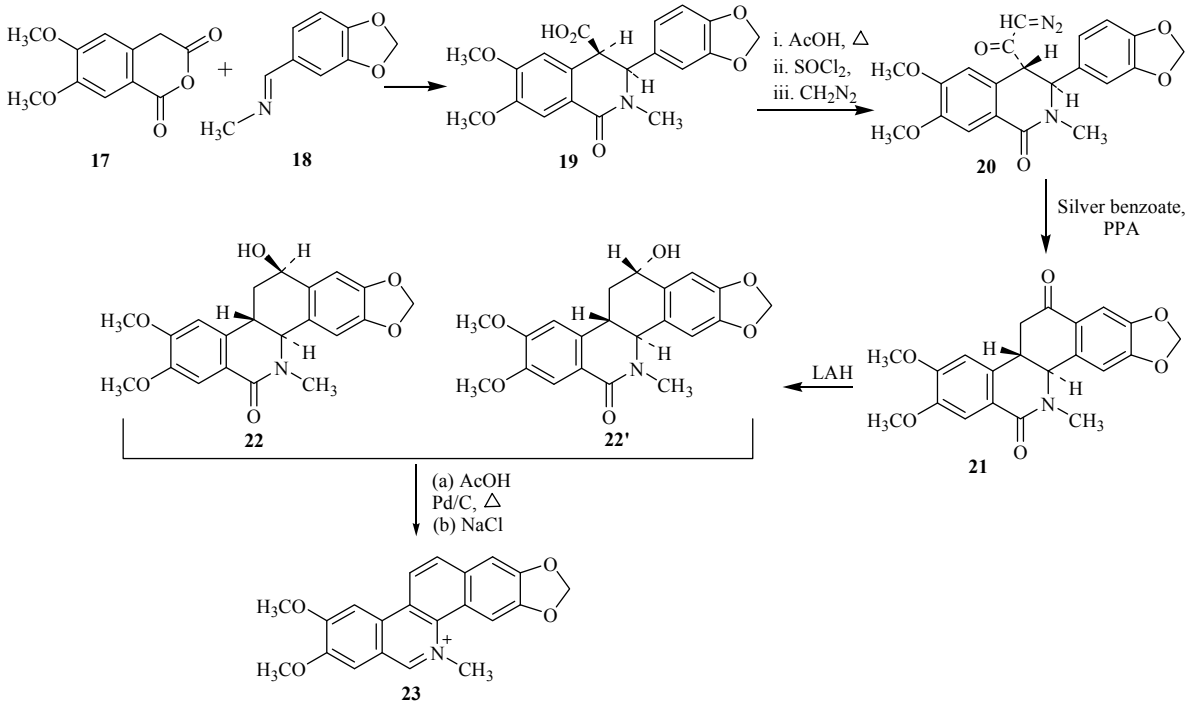
1.2.2.3 Oxazole-fused phenanthridine

1.2.1.1 Benzo-fused phenanthridines:

The benzophenanthridine alkaloids incorporate nitrogen containing 6-6-6-6 tetracyclic skeleton and are highly studied (Figure 1.4). Some of the benzophenanthridine alkaloids were isolated from plants, whereas others were synthesized by several chemical procedures to increase the pharmaceutical library.

1.2.1.1.1 Metal catalyzed synthesis:

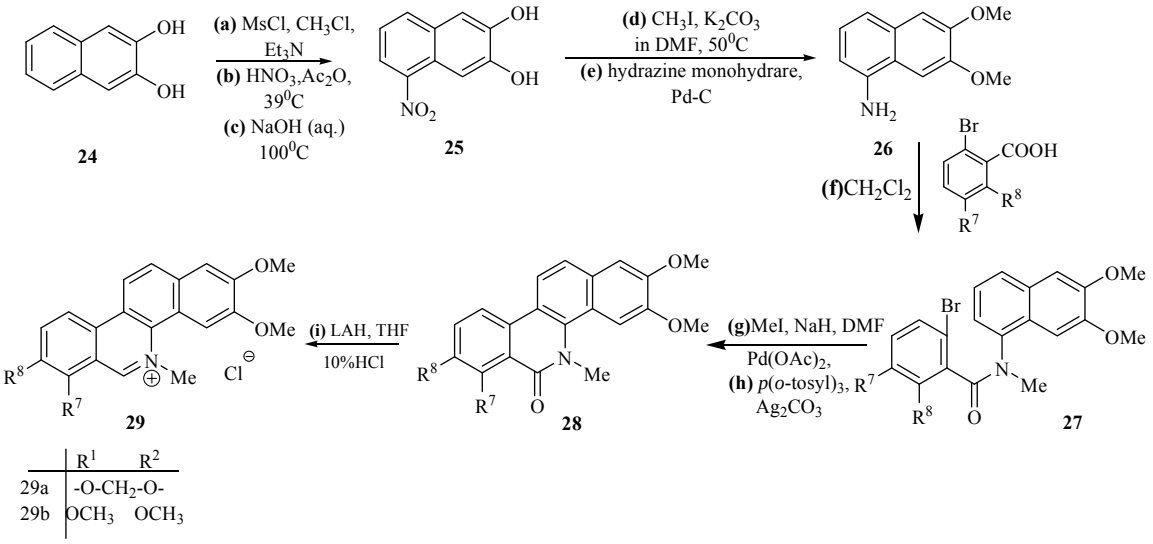
The synthesis of nitidine was firstly reported by two research groups in 1973, viz. Cheng and Cheng and Kametani et al., simultaneously and independently. Both of these synthetic strategies are based on an intermediate, 3,4-dihydro-6,7-methylenedioxy-1-(*2H*)napthalenone.[12a,b] Further, Cushman and Chang reported a unique synthetic route, using, 4,5-dimethoxyhomophthalic anhydride (**17**) and Schiff base-3,4-methylenedioxybenzylidenemethylamine (**18**) (Scheme 1.1).[12c]



Scheme 1.1. Metal catalyzed synthesis of Nitidine.

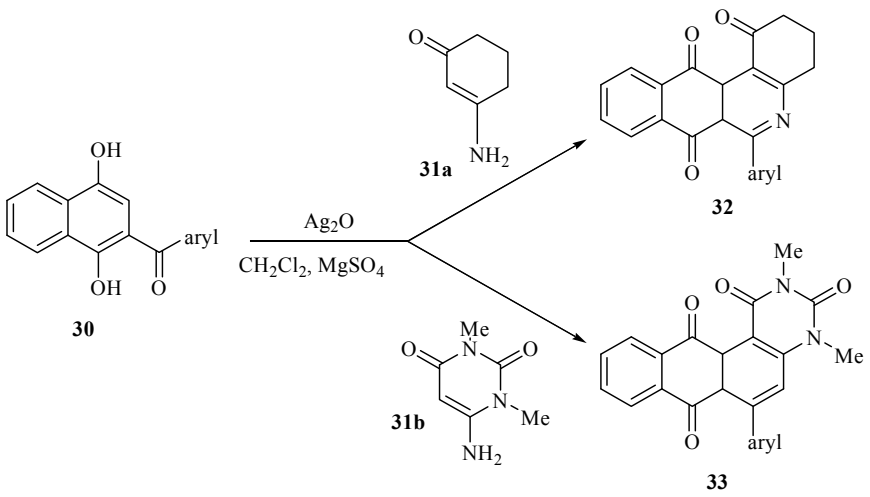
Likewise, unsubstituted or phenyl substituted- 2,3,8,9-tetramethoxy-5-methylbenzo[*c*]phenanthridinium chlorides were synthesized by Parhi et al. and it was confirmed that substituents at 1- or 12- positions significantly enhanced antibacterial activity related to the former parent compound.[27] Synthesis of 2,3,7,8-tetramethoxy-5-methylbenzo[c]phenanthridiniumchloride (**29b**) and 2,3-dimethoxy-7,8-methylenedioxy-5-methylbenzo[c]phenanthridinium chloride (**29a**) (Scheme 1.2) was initiated by conversion of 2,3-dihydroxynaphthalene (**24**) to its dimesylate, which provided the 5- nitro derivative **25** on treating with nitric acid. Firstly, the hydrolysis of the mesylates followed by treatment with methyl iodide generated 1-nitro-5,6-dimethoxynaphthylamine (**25**), which changed to benzamide derivative on treatment with acid chloride of bromosubstituted benzoic acid. This benzamide was treated with NaH and after that methyl iodide to afford their tertiary amide intermediates, which were converted to their relevant 5-

methylbenzo[*c*]phenanthridine-6-one (**28**) following the Heck cyclization. successive treatment of **28** with LAH and further acidification with HCl provided the desired compound **29**(Scheme 1.2).



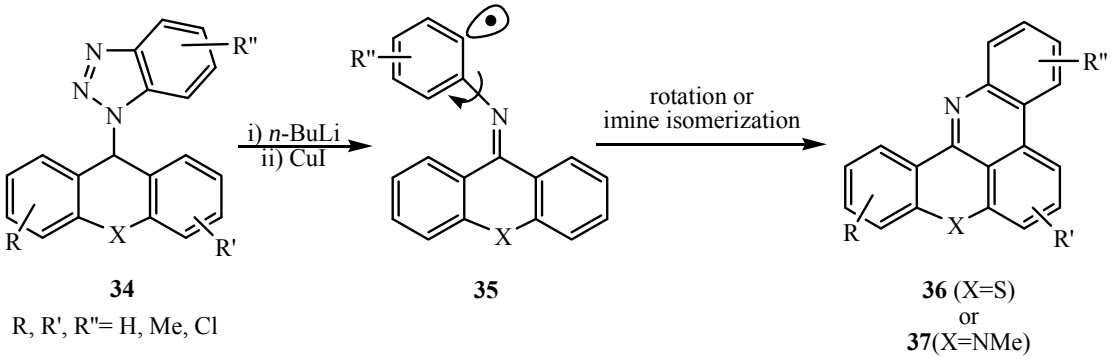
Scheme 1.2. Metal-catalyzed Synthesis of substituted methylbenzo[*c*]phenanthridinium chloride.

A range of novel arylsubstituted benzo[*j*]phenanthridine (**32**) and benzo[*g*]-pyrimido[4,5-*c*]isoquinolinequinones (**33)** have been synthesized from 1,4-naphthoquinone, arylaldehydes and enaminones using one-pot synthetic approach.[37] As shown in Scheme 1.3, acylnaphthohydroquinone (**30**) reacted with 3-aminocyclohex-2-ene-1-one (**31a**) or 5-amino-1,3-dimethyluracil (**31b)** in the presence of silver(I)oxide in dichloromethane to afford the compounds **32** and **33** respectively. These compounds were tested *in vitro* for their anticancer activity against normal human cell lung fibroblasts MRC-5 and three other human cell lines: SK-MES-1 lung, AGS gastric adenocarcinoma, and J82 bladder carcinoma.



Scheme 1.3. Silver(I)oxide catalyzed reaction of acylnaphthohydroquinone with cyclic amine or 5-amino-1,3-dimethyluracil.

An altetrnative approach for the synthesis of temperature or radiation sensitive polycyclic phenanthridines such as thiochromenophenanthridines (**36**) and quinoacridines (**37**) has been developed by Katritzky and co-workers.[38] This procedure involved formation of deep blue colored stabilized carbanion from substituted 9-(benzotriazol-1-yl)acridine(**34**), which turned to a radical intermediate (**35**) on oxidation with copper iodide. Elimination of nitrogen followed by ring closure gave product **36**and **37** (Scheme 1.4).



34
R, R', R"= H, Me, Cl

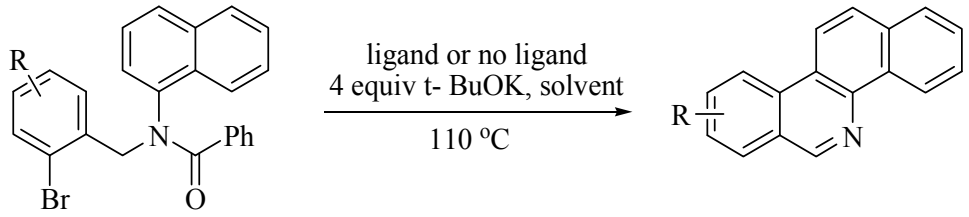
35

36 (X=S)
or
37(X=NMe)

Scheme 1.4. Cu-catalyzed cyclization of aromatic imines for the synthesis of polycyclic phenanthridines.

1.2.1.1.2 Direct C-H bond Arylation:

Several successful alternative approaches of a transition metal-free method are reported for the synthesis of phenanthridine annelated compound to avoid the use of expensive metal catalysts. For example, use of simple diol united with potassium tertiary-butoxide, resulted in to respective fused-phenanthridine derivatives by intramolecular C-H arylation.[39] Recently, a similar procedure, intramolecular homolytic aromatic substitution (HAS) has been reported to afford bezo[*c*]phenanthridine derivatives without using organic molecule (diol) as legand (Scheme 1.5).[40]

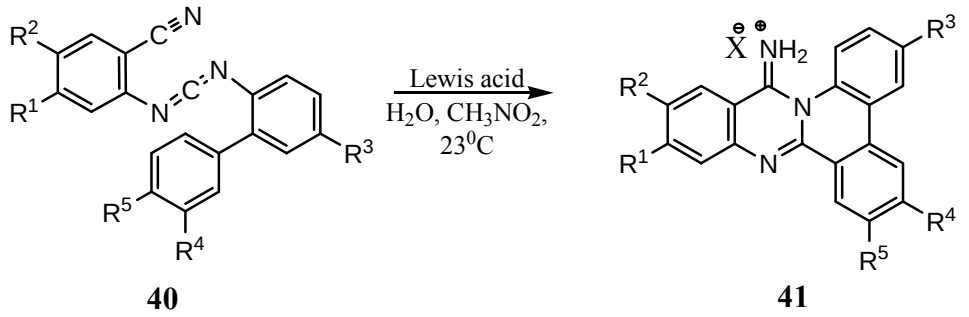


38 **39**

up to 79 % yield

Scheme 1.5. Metal-free direct C-H arylation for the synthesis of BCPA derivative.

A one-pot Lewis acid catalyzed tandem cyclization of 2-((([1,1'-biphenyl]-2-ylimino)methylene)amino)bezotriazole (**40**) was introduced to form phenanthridine fused quinolizinium salts (**41**).[41] It involved C-N and C-C bond formation *via* nucleophilic addition and Friedel-Crafts reaction, respectively (Scheme 1.6).

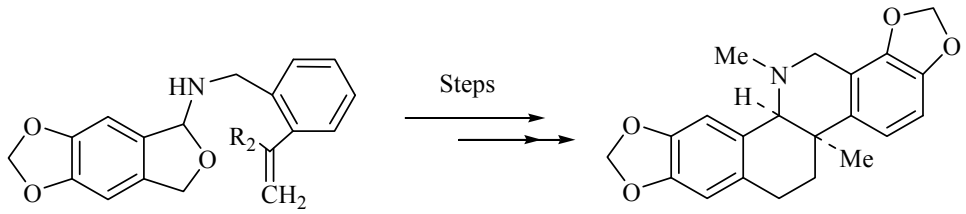


40 **41**

Scheme 1.6. Lewis acid catalyzed Synthesis of phenanthridine-fused quinolizinium salt.

1.2.1.1.3 Cycloaddition:

A new strategy for the synthesis of the core skeleton of the bezophenanthridine alkaloid, Corynoline has been developed by Padwa and Eidell, which is based on intramolecular [4+2] cycloaddition of an amino substituted isobenzofuran derivative (Scheme 1.7).[42]



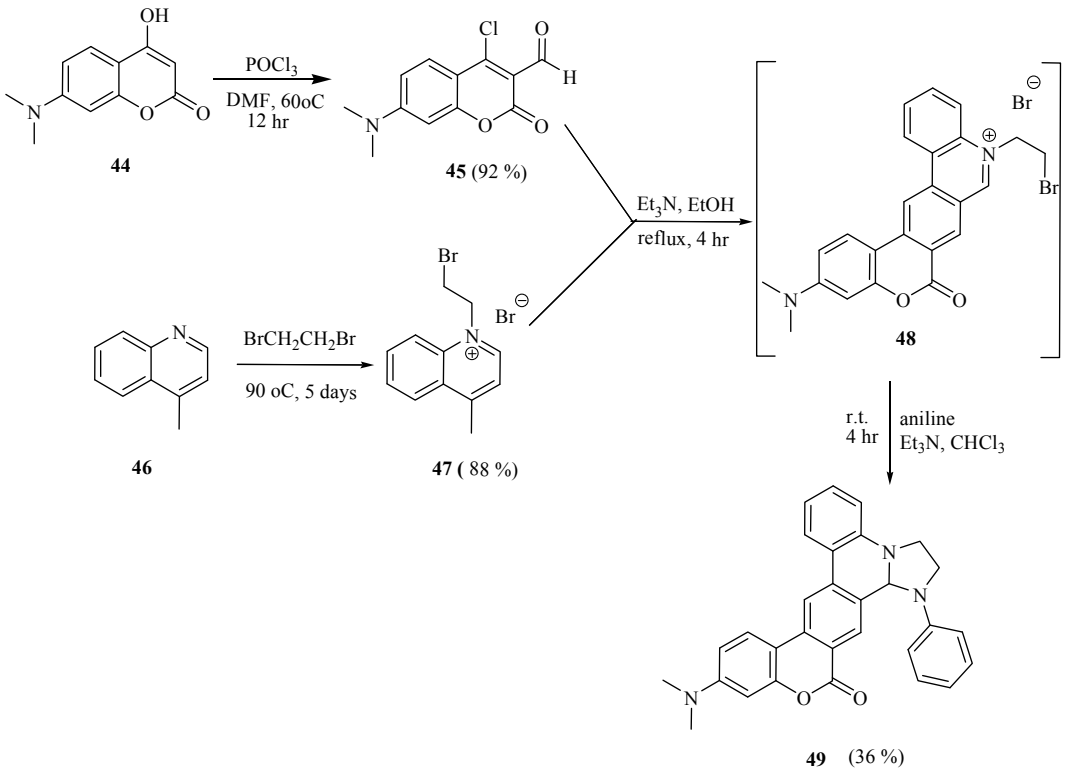
42 **43**

Scheme 1.7. Intramolecular [4+2] cycloaddition of amino substituted isobenzofuran to form Corynoline.

1.2.1.1.4 Cyclocondensation:

Annulation of *N*-isoquinolium salt and coumarin has also been reported for the synthesis of coumarin/phenanthridine fused heterocycles using basic medium (Scheme 1.8).[43] Initially, 7-dimethylamino-4-hydroxycoumarin (**44**) was converted

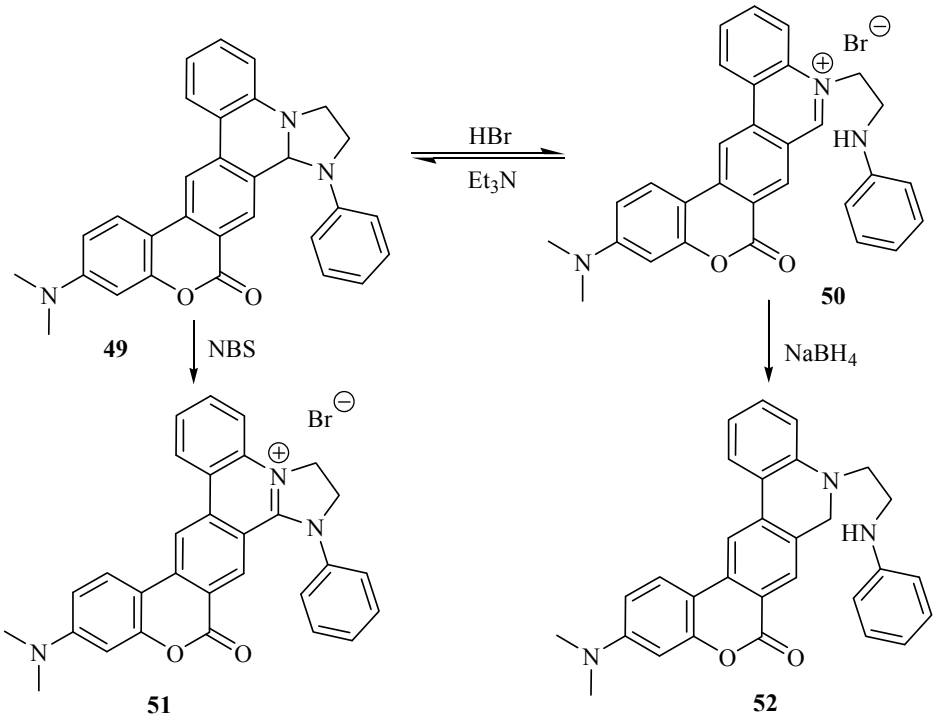
to 4-chloro-7-dimethylamino-2-oxo-2*H*-chromene-3-carbaldehyde (**45**) on treatment with phosphorus oxychloride. The successive condensation of **45** and *N*-(2-bromoethyl)-4-methylquinolinium bromide (**47**) in the presence of triethylamine, under reflux conditions, gave the intermediate iminium bromide **48**. This intermediate get reacted with aniline at room temperature to give the target compound **49**. Compound **47** was synthesized from refluxing of 4-methylquinoline (**46**) with 1,2-dibromoethane as described in literature.



Scheme 1.8. Base mediated annulations of *N*-isoquinolium salt.

The acidichromic properties of compound **49** were also explored. The light yellow, fluorescent ring-closed compound **49** was transformed to the corresponding red, non-emissive ring-opened iminium salt **50** on treatment with an acid (HBr), (Scheme 1.9). This ring-opening process can be reverted by addition of a base

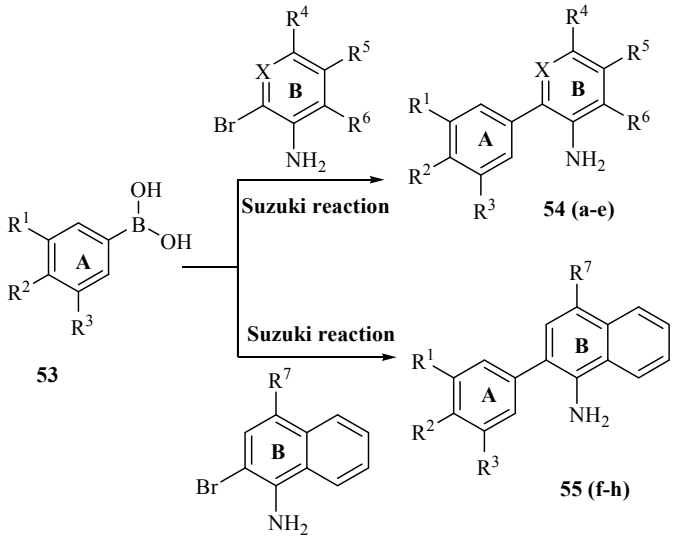
(Et_3N). in the same manner, the acid-sensitive **49** could be oxidized with NBS and base-sensitive **50** could be reduced with $NaBH_4$ to the iminium bromide **51** and amine **52**, both being pH- inert. (Scheme 1.9)[43]



Scheme 1.9. A lockable colorimetric fluorescence molecular switch.

1.2.1.1.5. Pictet-Spengler strategy:

An efficient and versatile two step synthesis including Suzuki and the modified Pictet-Spengler strategy has been developed for the synthesis of phenanthridine ring systems.[44] The key step in this synthetic strategy involves synthesis of the substrates **54** and **55,** which was accomplished in single step by the condensation of 3,4-dimethoxyphenylboronic acid **53** with 2-bromo-arylamines involiving Suzuki reaction. The reaction was carried out without protecting the amino functionality (Scheme 1.10).

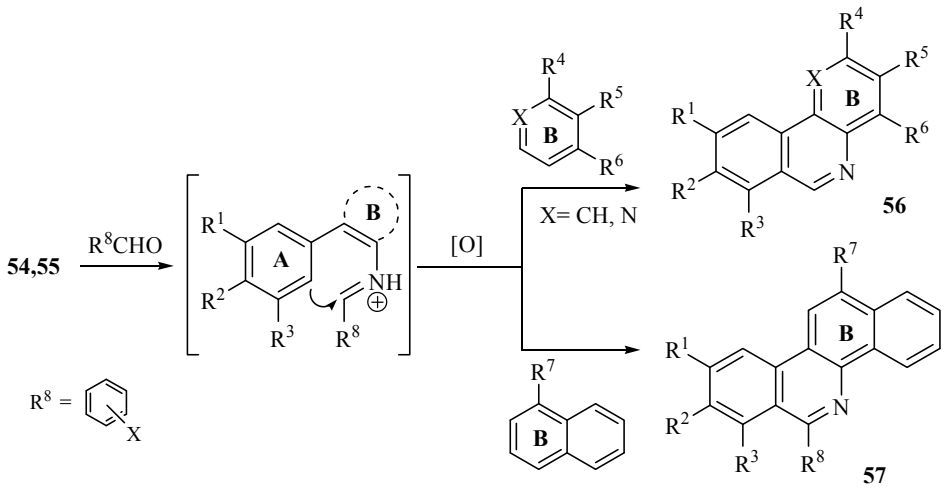


	R^1	R^2	R^3	R^4	R^5	R^6
a	OCH_3	OCH_3	H	H	H	H
b	OCH_3	OCH_3	H	CH_3	H	H
c	OCH_3	OCH_3	H	H	CF_3	H
d	CH_3	H	CH_3	H	H	H
e	OCH_3	OCH_3	H	H	H	H

	R^1	R^2	R^3	R^7
f	OCH_3	OCH_3	H	H
g	OCH_3	OCH_3	H	3,4- dimethoxyphenyl
h	CH_3	CH_3	CH_3	3,4,5- trimethylphenyl

Scheme 1.10. Condensation of 3,4-dimethoxyphenylboronic acid with 2-bromo-arylamines via Suzuki reaction.

For the Pictet–Spengler cyclization (Scheme 1.11), the substrate **54** was initially treated with 4-chlorobenzaldehyde involving 2% TFA in dichloromethane at both, 0^oC and at room temperature. However, the reaction gave a cyclized product in >20% yield, which necessitated the use of different solvents. the use of toluene medium in presence of 2% TFA effected the complete conversion of **54** and resulted compound **56** in >85% purity based on HPLC. This protocol was extended to the synthesis of benzophenanthridine **57** by condensing substrate **55** with 4-chlorobenzadehyde in 2% TFA in toluene, under reflux conditions.[44]

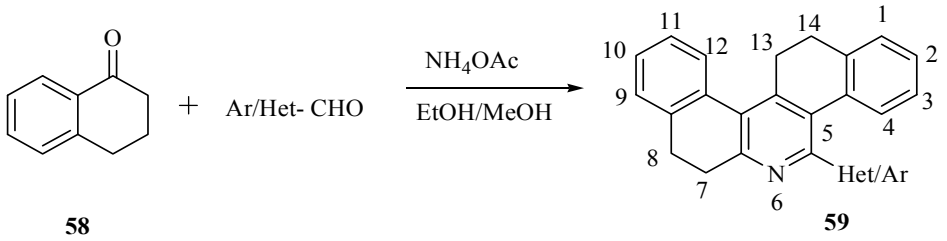


Scheme 1.11. Pictet–Spengler cyclization for the synthesis of benzophenanthridine.

1.2.1.1.6. Multi-component reaction:

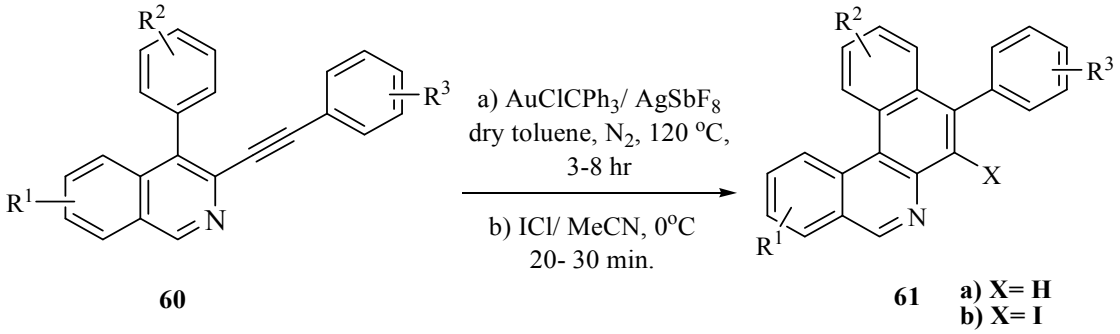
One-pot, multi-component reactions are promising as a new area of interest for organic synthesis as these have incredible advantages over conventional multistep synthesis, besides their potential applications in medicinal chemistry for the generation of varied scaffolds.[45]

A series of 5-aryl or heteryl-7,8,13,14-tetrahydrodibenzo[*a,i*]phenanthridines(**58**) have been obtained from the reaction of α-tetralone (2mmol) (**59**), the concerned araldehyde/heteraldehyde (1mmol) and ammonium acetate (1.5 mmol) in anhydrous ethanol (Scheme 1.12).[46]



Scheme. 1.12. One-pot synthesis of tetrahydrodibenzo[*a,i*]phenanthridines from α-tetralone.

Recently, Mandadapu et al.[47] reported a multi-component tandem reaction or carbocyclization of 4-aryl-3-arylethynylisoquinoline. The ring closure takes place either via iodo-catalysed regioselective electrophilic cyclization or via Au/Ag-catalysed intramolecular hydroarylation.

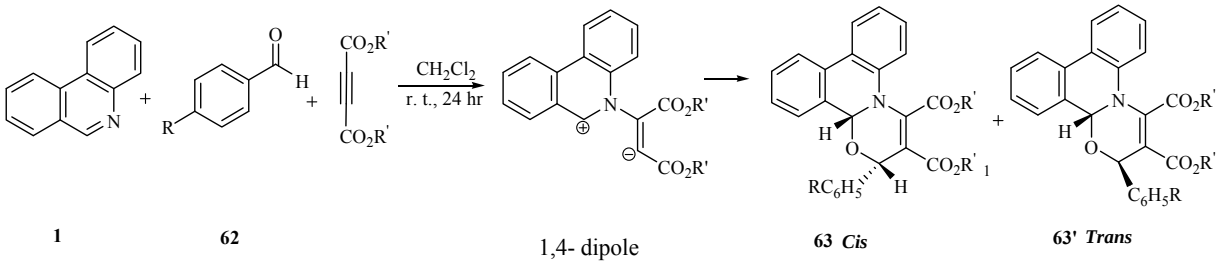


Scheme 1.13. Au/Ag-catalyzed multi-component carbocyclization of 4-aryl-3-arylethynylisoquinoline.

1.2.1.2 Oxazine-fused phenanthridines:

A facile, one-pot, three-components reaction of phenanthridine, dialkyl acetylenedicarboxylate and aromatic aldehyde following by 1,4- dipolar cycloaddition has been reported leading to the synthesis of new annelated phenanthridine derivatives.[48] The reaction involves initial addition of phenanthridine to the activated alkyne to form zwitterionic intermediate which

undergoes 1,4-dipolar cycloaddition with aromatic aldehyde to afford oxazine-fused phenanthridines **63** and **63'** (Scheme 1.12).



Scheme 1.14. 1,4-Dipolar cycloaddition reaction of phenanthridine with aromatic aldehyde and dialkyl acetylenedicarboxylate.

1.2.2.1Pyrrolo-fused phenanthridines:

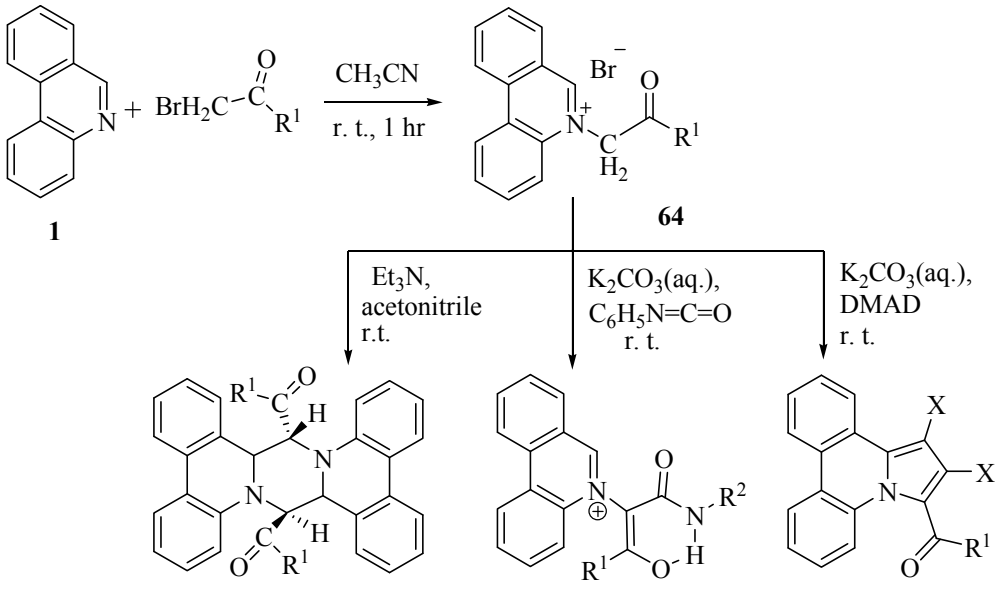
Several facile methods have been developed for the synthesis of pyrrolo- and dihydropyrrolophenanthridines (PPH/DPP), imidazo- and dihydroimidazophenanthridines (IP/DIP). These methods are based on earlier described strategies, such as 1,3-dipolar cycloadditions , multicomponent synthesis, metal catalyzed C-H bond activation or direct arylation, etc. Among all these strategies, dipolar cycloaddition of phenanthridinium based azomethine ylides[49] has been highly studied for the synthesis of pyrrolo- and imidazophenanthridines.

1.2.2.1.1 1, 3-Dipolar cycloaddition:

Carbonyl stabilized azomethine ylides including phenanthridinium ylides are known to undergo versatile 1,3- dipolar cycloaddition reaction with a series of dipolarophiles.[50] In this way, five-membered ring fused phenanthridines can be

produced easily. Phenanthridinium derivatives[51] have higher tendency to generate cycloadduct due to its low aromaticity.

Several 5-phenacylphenanthridinium salts (**64**) were reacted with dipolarophiles, such as DMAD, phenyl isocynate, isothiocynate and benzoyl isocynate using two phase method in the presence of potassium carbonate as a base to generate pyrrolophenanthridines (**67**). Pyrrolo[1,2-*f*]phenanthridine derivatives were obtained by reacting 50% aqueous K_2CO_3 as the polar phase, and DMAD as organic phase. In the absence of dipolarophile, dimers (**65**) were obtained in high yield in the presence of a base like Et_3N (Scheme 1.15).[49]



1 **64** **65** **66** **67**

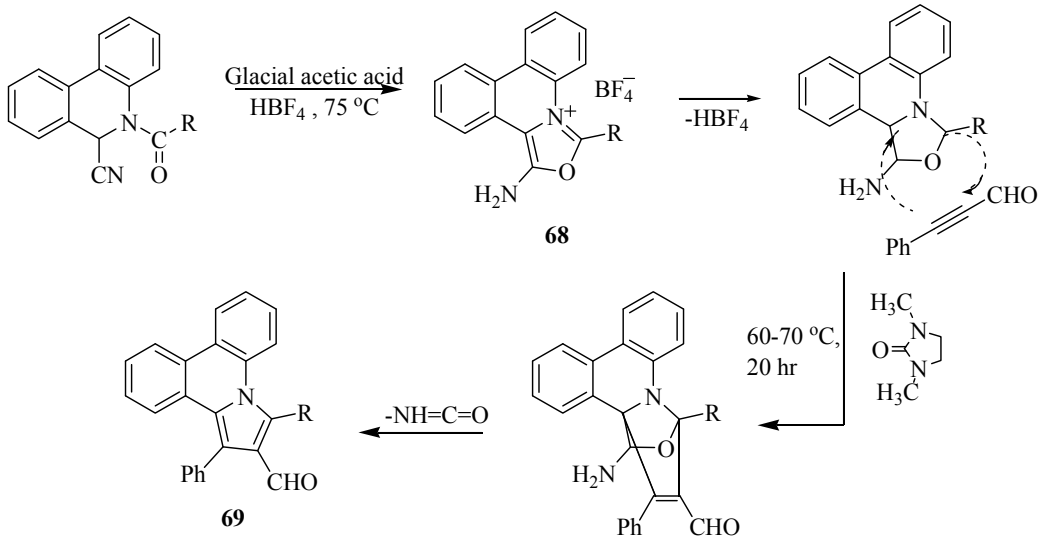
	R
a	C_6H_5
b	*p*-ClC_6H_4
c	*p*-BrC_6H_4
d	*p*-$NO_2C_6H_4$

	R^1	R^2
a	C_6H_5	C_6H_5
b	*p*-ClC_6H_4	C_6H_5
c	C_6H_5	COC_6H_5
c	*p*-BrC_6H_4	COC_6H_5
d	*p*-$NO_2C_6H_4$	COC_6H_5

R = H, NO_2
X = $COOCH_3$

Scheme 1.15. Synthesis of PPHs by 1,3-Dipolar cycloaddition of 5-phenacylphenanthridinium bromide salt.

A synthetic method for producing pyrrolo[2,1-*a*]phenanthridines from phenanthridinium reissert salt has been reported.[52] For example, 1,3- dipolar cycloaddition of reissert salt **68**[53] in the presence of a base *N*,*N*-dimethylimidazolidinone reacted with 3-phenyl-2-propynal followed by heating afforded **69** which was found to be useful in the synthesis of novel HMG CoA reductase inhibitor.[54]

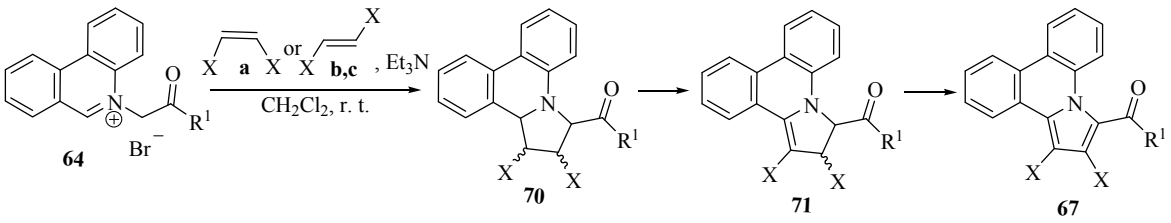


Scheme 1.16. Synthesis of pyrrolo[2,1-*a*]phenanthridines from phenanthridinium reissert salt.

A series of pyrrolidino[1,2-*f*]phenanthridines has been synthesized by Potacek et al. from the reaction of phenanthridinium based azomethine ylides with dipolarophiles like DMAD, dimethyl maleate, dimethyl fumerate, fumeronitrile, etc. in presence of a base with more or less stereoselectivity.[55--59]

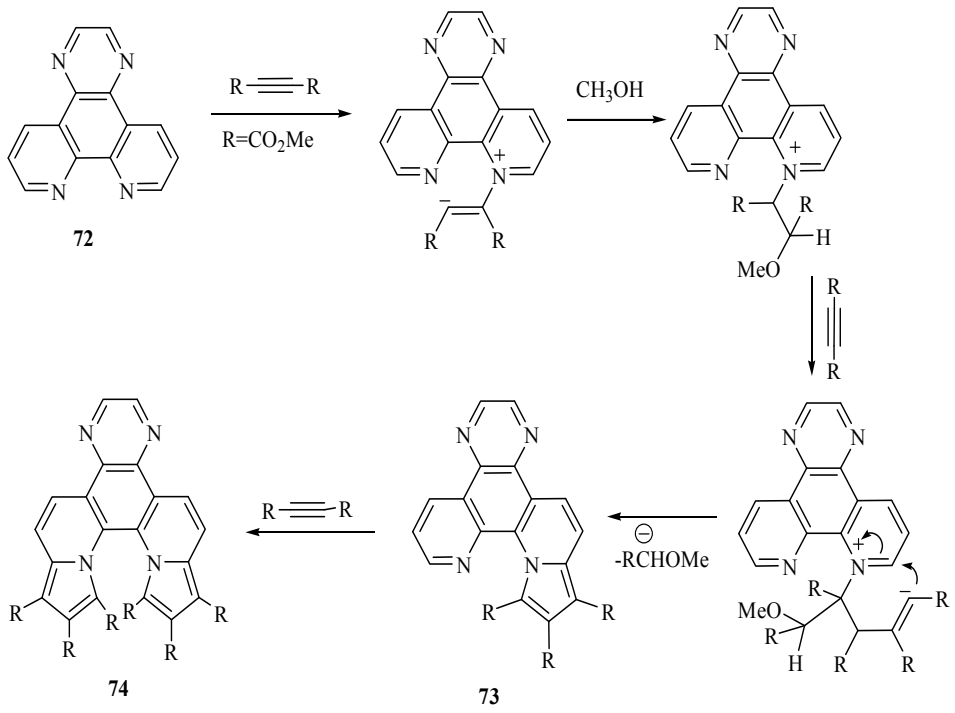
Phenanthridinium salt, generated from *N*-alkyl or *N,N'*-dialkylbromoacetamide and phenanthridine in presence of a base, such as triethylamine produce azomethine ylide *in situ*, which undergo 1,3-dipolar cycloaddition with

dipolarophiles to afford (*N*-alkylcarbamoyl)-1,2,3,12b-tetrahydropyrrolidino[1,2-*f*]phenanthridines.[57] Dehydrogenation of the latter in open air yields completely unsaturated products, namely*N*-(alkylcarbamoyl)-pyrrolo[1,2-*f*]phenanthridine. Diastereoselectivity and regioselectivity is observed in these reactions in case of unsymmetrically substituted dipolarophiles like fumeronitrile (Scheme 1.15).[56-59]



Scheme 1.17. 1,3-Dipolar cycloaddition of phenanthridium bromide with dipolarophiles.

Some helical compounds have also been synthesized from 1,3-dipolar cycloaddition of pyrazino[2,3-*f*][1,10]phenanthroline derivatives (ppl) with acetylenic esters in methanol. The initial treatment of *N*- heterocycles with dimethyl acetylenedicarboxylate produced a cycloadduct. This cycloadduct protonated by a protic solvent to generate vinyl phenanthrolinium cation which underwent further dipoar cyclization with DMAD to produce dipyrrolo[1,2-*a*:2'1'-*o*]pyrazino[1,10]phenanthroline-9,10,11,14,15,16-hexacarboxylate derivatives as new helical compounds (Scheme 1.16).[60]



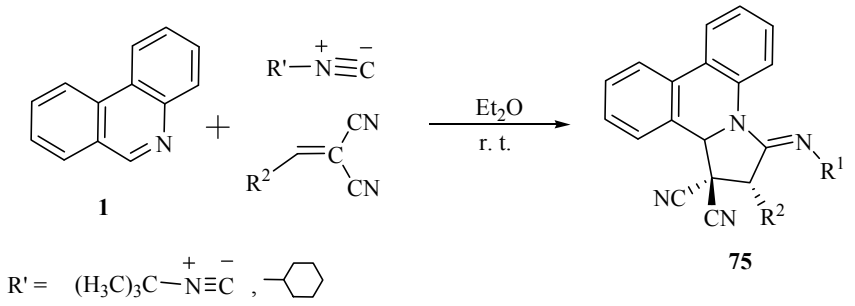
Scheme 1.18. Synthesis of pyrrolofused-phenanthroline compound from 1,3-dipolar cycloaddition of ppl derivatives.

Similar strategy was followed on dipyrido[3,2-a:2',3'-c]phenazine (dppz) derivatives for the synthesis of hexaalkyl diindolizino[6,5-a:5',6'-c]phenazine-11,12,13,16,17,18- hexacarbolylate derivatives using DMAD or DEAD as dipolarophiles.[60] Here, the crowding of the pyrrole rings enforces nonplanrity in the helical compound .

1.2.2.1.2. Multi-component reactions:

As discussed earlier, multi-component reactions have emerged very useful for the synthesis of annelated phenanthridines also.[61-63] A novel displacement strategy involving 1,3-dipolar cycloaddition reaction of phenanthridine with zwitterions, generated *in situ* from the reaction of 2-aylidenemalononitriles with isocynides, for the rapid construction of dihydropyrrolo[1,2-*f*]phenanthridine (**75**) has been

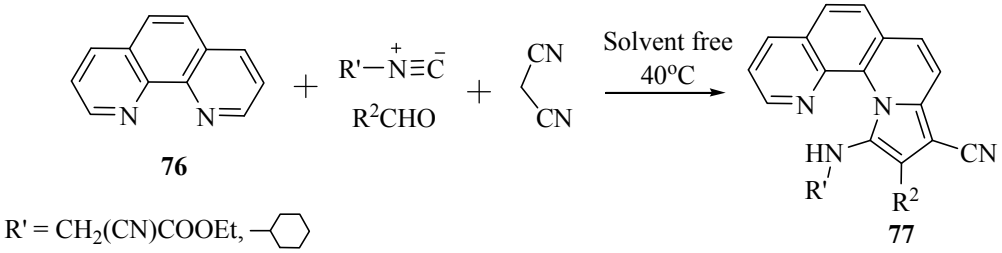
reported (Scheme 1.19).[64] Although the target compounds have two chiral centres, only single diastereo isomer was obtained indicating high regio- and distereoselectivity of the reaction.



R^2 = (*p*-F)C_6H_4, (*p*-Cl)C_6H_4, (*p*-Br)C_6H_4, (*p*-NO_2)C_6H_4, (*m*-Br)C_6H_4, (*o*-F)C_6H_4, (*o*-Br)C_6H_4, (*o*-NO_2)C_6H_4, Ph, (*p*-Me)C_6H_4, (*p*-OMe)C_6H_4, (*p*-OH)C_6H_4,

Scheme 1.19. Synthesis of DPP from the reaction of phenanthridine, 2-aylidenemalononitriles and isocynides.

A similar strategy was followed for the synthesis of pyrrolo[1,2-*a*][1,10] phenanthroline including cyclization of 1,10-phenanthroline with zwitterions generated *in situ* from isocynide,malononitrile and aldehyde. This is an one-pot Knovenagel condensation-1,3-dipolar cycloaddition reaction or Domino cyclocondensation (Scheme 1.20).[65]

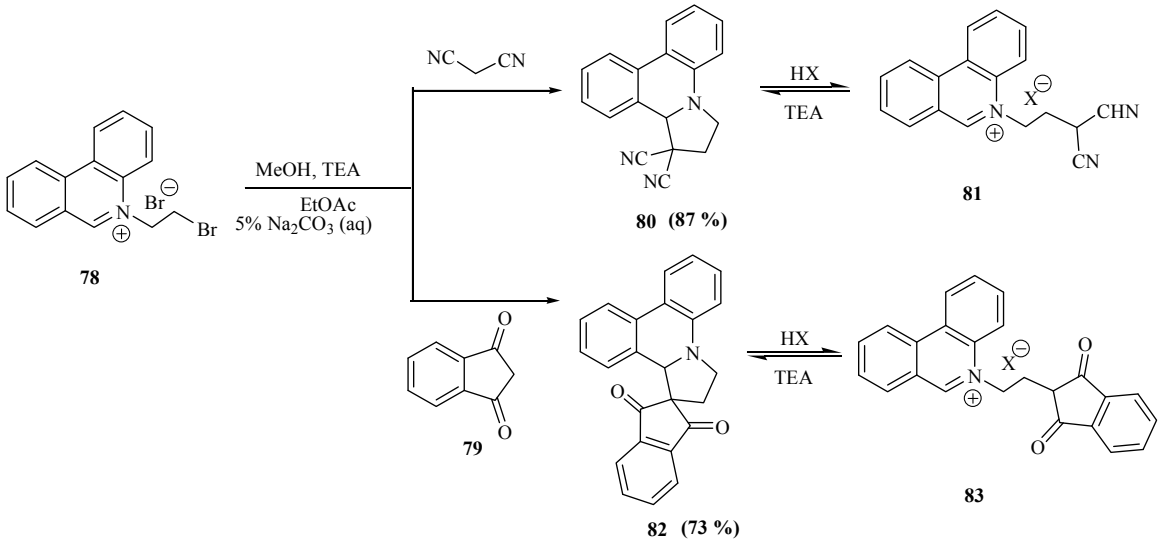


R^2 = (*p*-F)C_6H_4, (*p*-Cl)C_6H_4, (*p*-Br)C_6H_4, (*p*-NO_2)C_6H_4, (*m*-Br)C_6H_4, (*o*-F)C_6H_4, (*o*-Br)C_6H_4, (*o*-NO_2)C_6H_4, Ph, (*p*-Me)C_6H_4, (*p*-OMe)C_6H_4, (*p*-OH)C_6H_4,

Scheme 1.20. Solvent free One-pot Domino reaction for the formation of pyrrolophenanthroline.

It has also been observed that, some of these compounds showed a selective fluorescence and colorimetric change upon addition of Cu^{+} ion over a wide range of explored metal ions in H_2O or acetonitrile, signifying that these compounds could be used as impending sensor for the naked-eye detection of Cu^{+}.

A new class of 2,3-dihydro-12*H*-pyrrolo[1,2-*f*]phenanthridine derivatives were synthesized from malononitrile and 1,3- indandione (**79**).These compounds were initial nucleophiles, which reacted with N-bromoethylphenanthridinium bromide(**78**) to produce DPP-dicarbonitrile (**80**) and DPP-indandione (**82**) respectively (Scheme 1.21).[66]

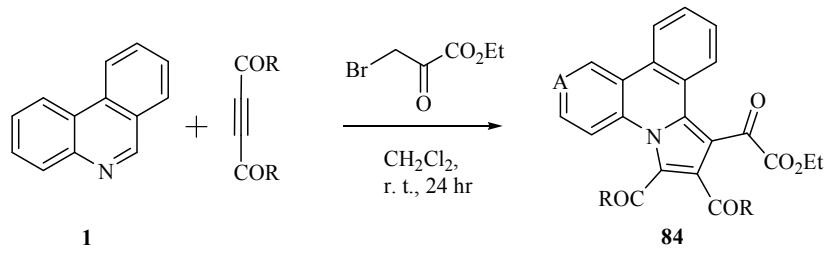


Scheme 1.21. Synthetic route for DPP and their pH controlled ring-opening-cyclization process.

The interesting feature of these DPP products is the reversible and pH controlled ring-opening-cyclization process. DPP undergoes rearomatization of the

phenanthridinium ring system under acidic conditions, which switches back to the initial DPP structure under basic conditions (Scheme 1.21).

Recently, a novel one-pot, three component synthesis of pyrrolo[1,2-*f*]phenanthridines has been developed by Mehrabi et al., following a dipolar cycloaddition mechanism of phenanthridine with ethyl bromopyruvate and dialkyl acetylenedicarboxylate. The interesting results were obtained by changing order of addition of the starting material.[67] On adding dialkyl acetylenedicarboxiate over 10 min followed by ethyl bromopyruvate over 1 hour, the reaction afforded the products (**84**) in good yield (Scheme 1.22).

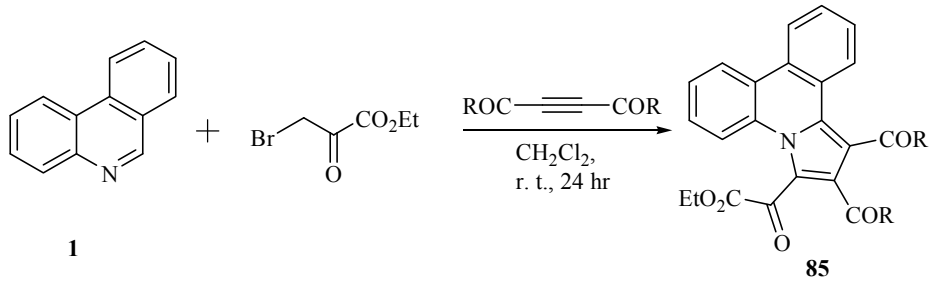


1 **84**

	a	**b**	**c**	**d**
R	OMe	OEt	*i*-Pro	*t*-BuO
yield	79%	86%	88%	85%

Scheme 1.22. One-pot cyclization of phenanthridine, ethyl bromopyruvate and dialkyl acetylenedicarboxylate

On the other hand, on adding ethyl bromopyruvate over 10 minutes to a magnetically stirred solution of precursor **1** followed by addition of dialkyl acetylenedicarboxylate over 1 hour, products (**85**) were obtained in good yield (Scheme 1.23).

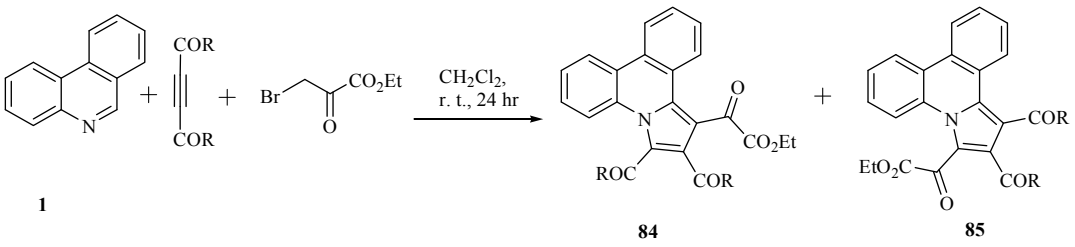


1 **85**

	a	b	c	d
R	OMe	OEt	*i*-Pro	*t*-BuO
yield	72%	80%	85%	89%

Scheme 1.23. One-pot cyclization reaction of phenanthridine with ethyl bromopyruvate and dialkyl acetylenedicarboxylate

Encouraged by these results, they performed the reaction by adding all these reagents (phenanthridine, activated acetylene and ethyl bromopyruvate) concurrently and found two regioisomers in reaction mixture after completion of the reaction. The progress of the reaction was observed by TLC, and later confirmed by NMR data (Scheme1.24). Unfortunately, separation of the regioisomers through column chromatography was not successfully done because of the similarity in their resolution factors.[67]



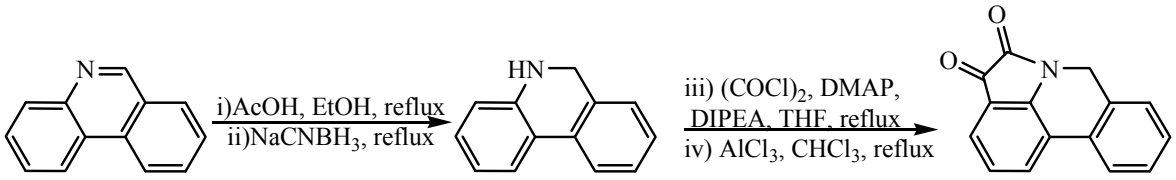
1 **84** **85**

	a	b	c	d
R	OMe	OEt	i-Pro	t-BuO
yield	72%	80%	85%	89%
ratio	2:1	2:1	1.5:1	1:1

Scheme 1.24. Regioselective synthesis of PPHs from phenanthridine, ethyl bromopyruvate and dialkyl acetylenedicarboxylate.

As bulkier alkoxy groups were introduced in dialkyl acetylenedicarboxylate, regioselectivity was decreased; these results revealed that acetylenic carbon in acetylene derivative is more electrophilic in nature than the α- carbon in ethyl bromopyruvate. Furthrmore, it was indicated that steric hindrance for the bulky group was a key factor in determining the ratio of the regioisomers.

pyrrolophenanthridine based derivative isatine (**86**) was synthesized from phenanthridine in attempt to increase the biological activity and cytotoxicity and assessed against U937 cells *in vitro*.[68]



1 **86**

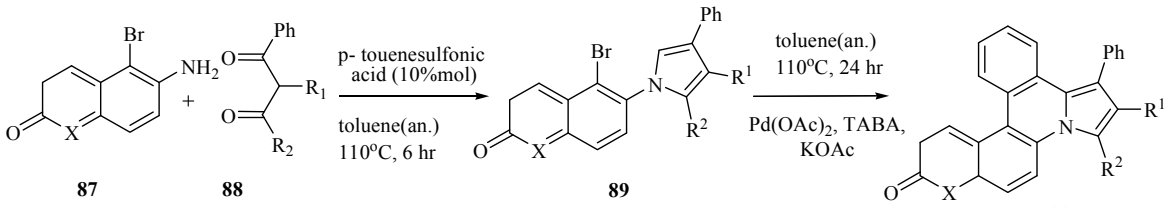
Scheme 1.25. Synthesis of pyrrolophenanthridine based derivative isatine.

1.2.2.1.3 Metal mediated C-H bond activation or Direct arylation reaction: Various metal catalyzed C-H bond activation methods have been developed for the synthesis of heterocyclic compounds,[35,36] especially using Pd, Ru, and Rh as catalyst. In particular, the ability of C-H bond activation by palladium has extensively been used in organic synthesis.[69]

A succinct synthesis of pyrrolo[1,2-*f*]phenanthridine- annelated polycyclic heterocycles was achieved by pd-catalyzed intramolecular direct arylation.[70] First, *N*-acyl pyrrole is prepared by the Paal- knorr condensation reaction of 1,4-diketones with either 6-amino-5-bromocoumarine, 6-amino-5-bromoquinolones or

2-amino-1-bromonaphthalene. Formed arylated pyrroles are refluxed in anhydroud toluene at 110°C with $Pd(OAc)_2$ in the presence of a base to trap HBr formed during the reaction.

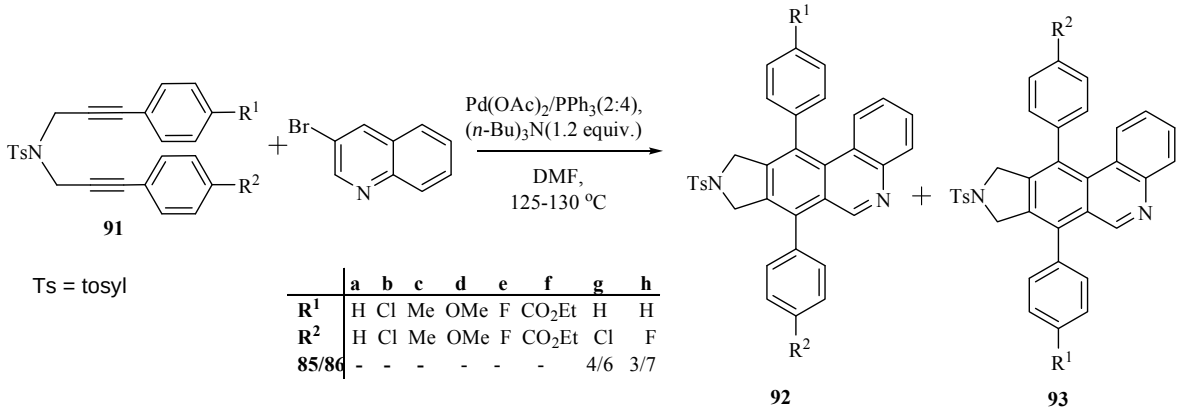
After optimization of the reaction conditions with different palladium catalysts, base and solvent conditions, it was found that $Pd(OAc)_2$ gave better results using TBAB as co-catalyst in the presence of base KOAc, in toluene (Scheme 1.26).



	X	R^1	R^2
a	O	CH_3	COOEt
b	O	Ph	H
c	O	$-(CH_2)_4-$	
d	NMe	CH_3	COMe
e	NMe	CH_3	COOEt
f	NEt	CH_3	COMe

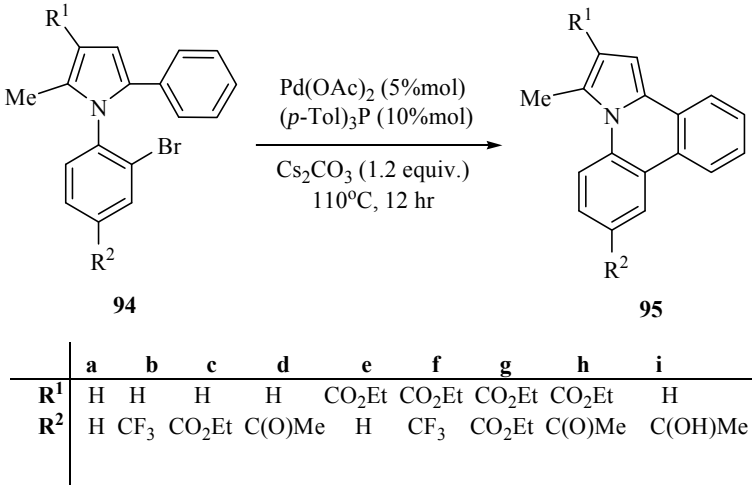
Scheme 1.26. Pd-catalyzed direct arylation to form phenanthridine- annelated polycyclic compound.

Yimin et al.[71] reported regioselective palladium catalyzed Domino reaction for the synthesis of fused pyrrolo[3,4-*j*]phenanthridines. Reaction of precursor **84** with 3-bromoquinoline (1.2 equiv.) in presence of $Pd(OAc)_2$ and PPh_3 as catalyst and $(n\text{-}Bu)_3N$ as a base in DMF provided an efficient and economic methodology for the construction of pyrrolo-annelated phenanthridines through multistep C-C bond formation and C-H bond activation of isoquinoline ring. It was observed that symmetrical substitution on the precursor **91** resulted in the formation of a single diastereomer **92/93,** while unsymmetric substitution gave two diasteromers **92** and **93** (Scheme 1.27).



Scheme 1.27. Pd-catalyzed Domino reaction for the formation of fused phenanthridine.

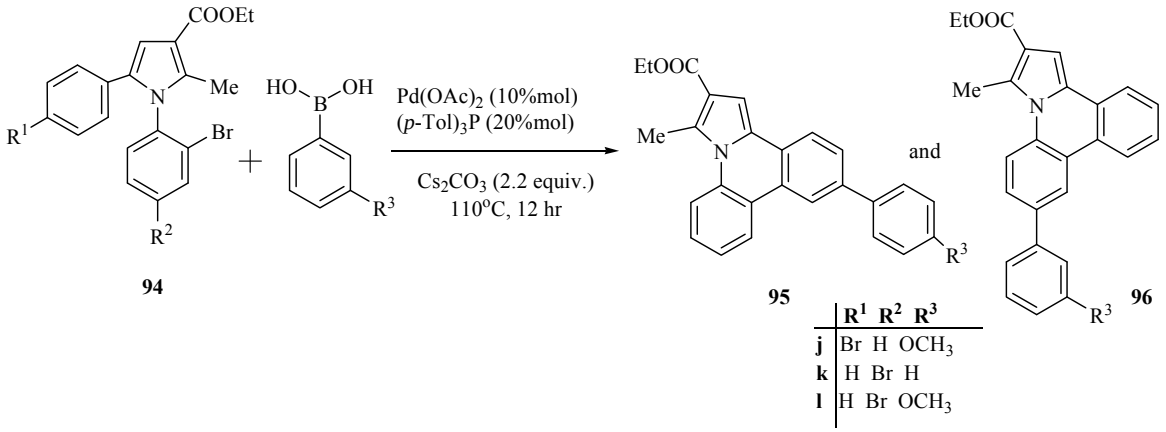
A chemoselective activation of the phenyl ring over methyl substituents in case of 2-phenyl-5-methylarylpyrrole derivatives also leads the formation of pyrrolo[1,2-*f*]phenanthridines in excellent yield ~ 93% (Scheme 1.28).[72]



Scheme 1.28. Pd-catalyzed cyclization of substituted arylpyrrole for the synthesis of PPHs.

In contrast with these results, product **96** was obtained in case of dibromoarylpyrroles, being treated with $Pd(OAc)_2$ in toluene, instead of giving the desired C-H activation product **95**. However, reaction of **94j,k,l** with

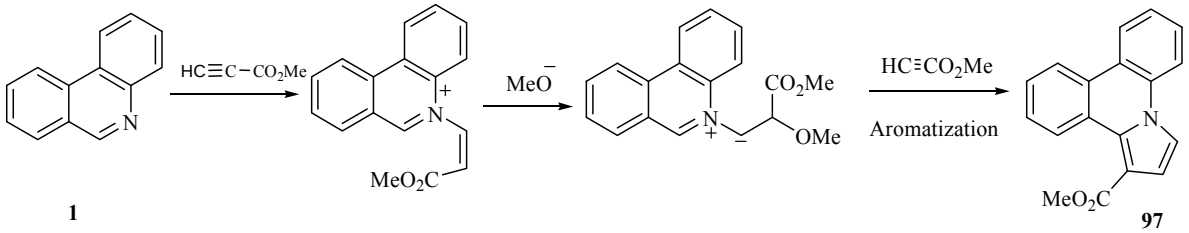
phenylboronic acid (1 equiv.) in presence of $Pd(OAc)_2$ (10% mol) and $(p\text{-Tol})_3P$ (20 mol) resulted in successive Suzuki cross-coupling and C-H activation leading to the formation of product **96** in good yield ~60-90 % (Scheme 1.29).[72]



Scheme 1.29. Pd-catalyzed intermolecular cyclization of N-aryl pyrroles with phenylboronic acid.

1.2.2.1.4 Michael addition:

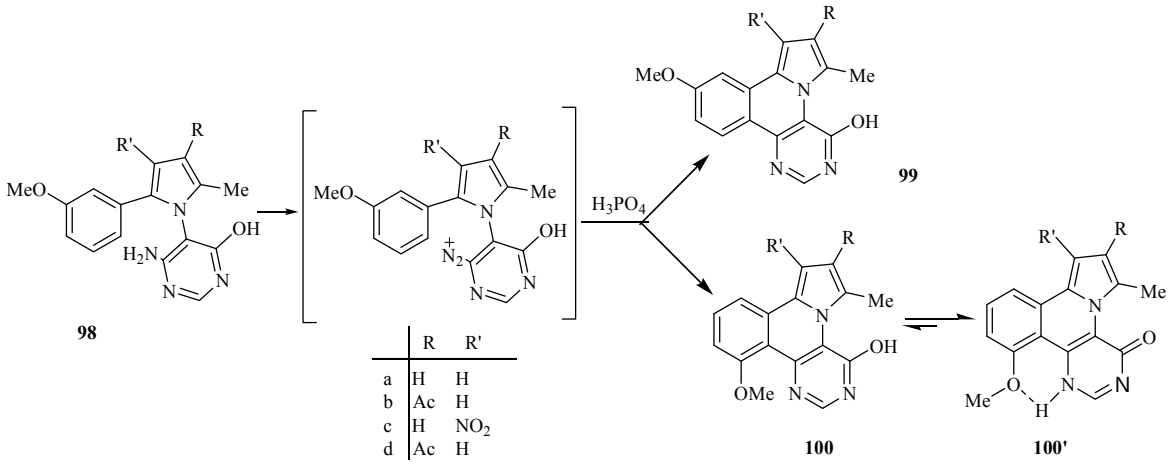
Acheson et al. reported the synthesis of pyrrolo[1,2-*f*]phenanthridines via Michael addition reaction of phenanthridine with methyl propiolate (Scheme 1.27).[73]



Scheme 1.30. Michael addition reaction of phenanthridine with methyl propiolate.

1.2.2.1.5 Pschorr-type Synthesis:

A Pschorr- type cyclization has been reported[74] for the synthesis of tri-aza-phenanthridines from the reaction of 1-(6-aminopyrimidin-5-yl-)pyrroles using sulfuric acid with the treatment of excessive sodium nitrite and hypophosphorous acid. Here diazotization of the compounds **98a,b** was carried out in methanol. The compound **100** was available in its tautomeric form **100′** which was stabilized by intramolecular hydrogen bonding. It was the only form present in the solution (Scheme 1.28).

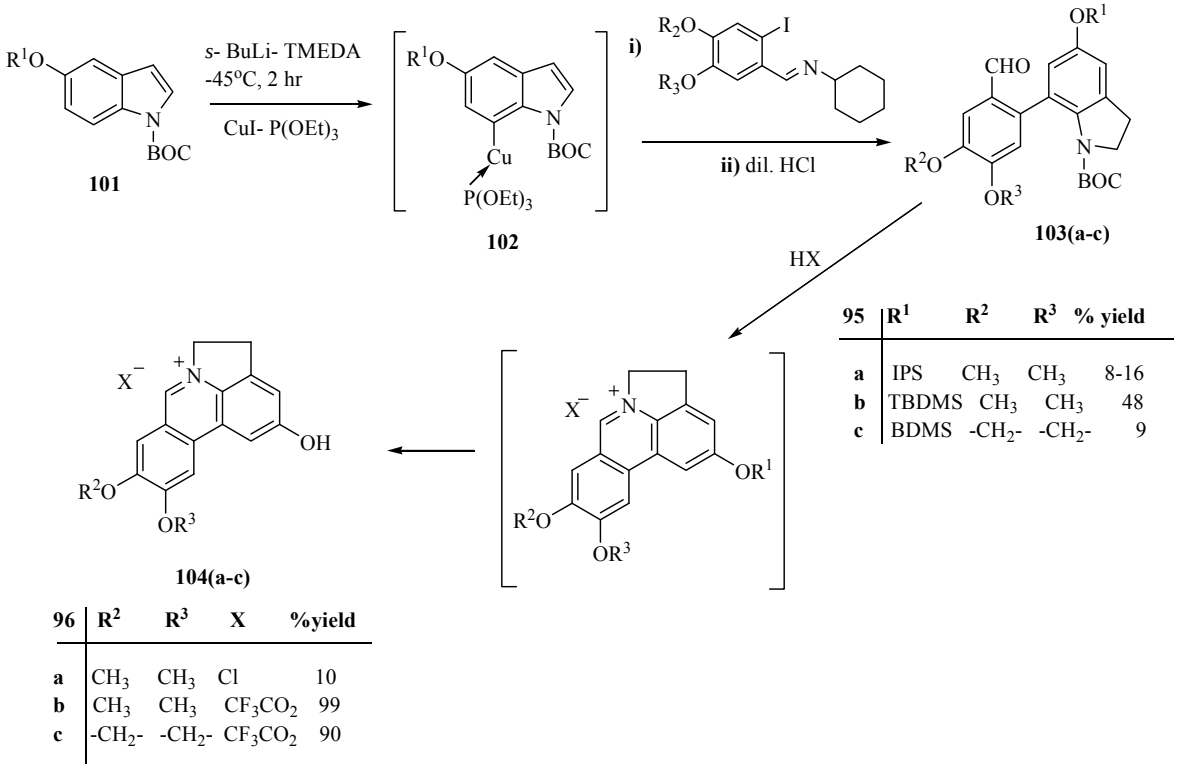


	R	R'
a	H	H
b	Ac	H
c	H	NO_2
d	Ac	H

Scheme 1.31. Pschorr- type cyclization for the formation of tri-aza-phenanthridines.

1.2.2.1.6 Ziegler-Ullmann Reaction:

Reaction is initiated by transmetalation of the synthon **101** with CuI-$P(OEt)_3$, followed by Ziegler- Ulmann coupling of the complex **102** with 2-iodoarylimine to give the product **103**. Concomitant cyclization and dehydration of the latter affords the desired product **104** (Scheme 1.32).[31]



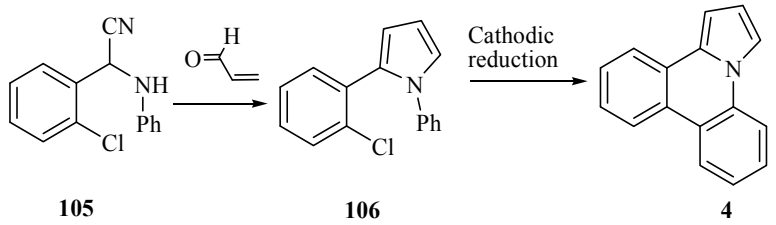
95	R^1	R^2	R^3	% yield
a	IPS	CH_3	CH_3	8-16
b	TBDMS	CH_3	CH_3	48
c	BDMS	$-CH_2-$	$-CH_2-$	9

96	R^2	R^3	X	%yield
a	CH_3	CH_3	Cl	10
b	CH_3	CH_3	CF_3CO_2	99
c	$-CH_2-$	$-CH_2-$	CF_3CO_2	90

Scheme 1.32. Synthetic route for PPHs involving Ziegler- Ulmann coupling.

1.2.2.1.7. Electrochemical cyclization:

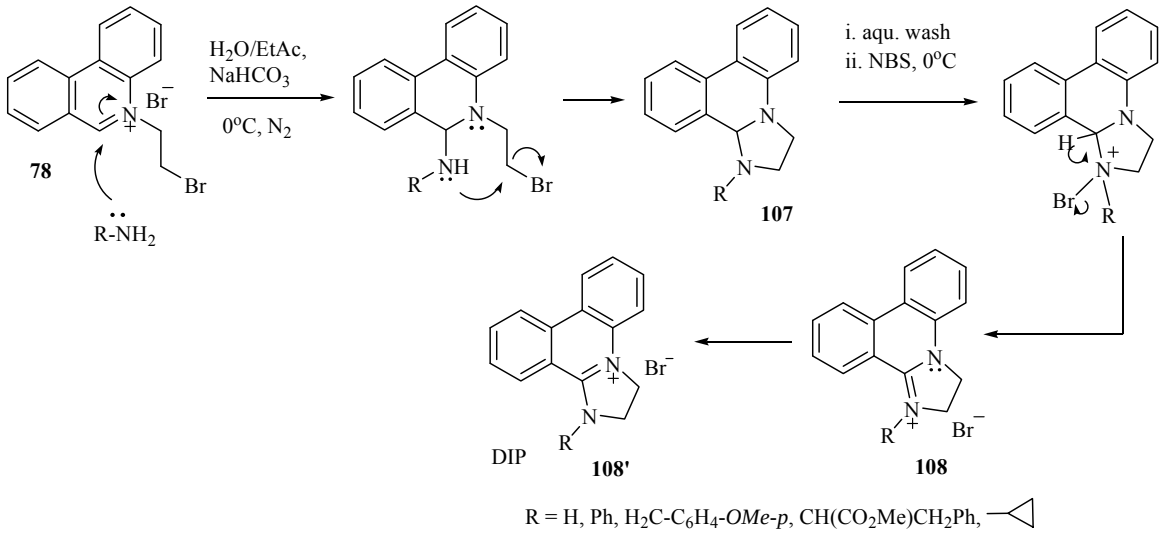
Grimshaw et al.[75] synthesized pyrrolo[1,2-*f*]phenanthridines using electrochemical cyclization procedure. Reaction involved electrochemical reduction of pyrrole **106** prepared from the condensation of anilinonitrile **105** with acrolein (Scheme 1.33).



Scheme 1.33. Electrochemical cyclization of aryl-substituted pyrrole.

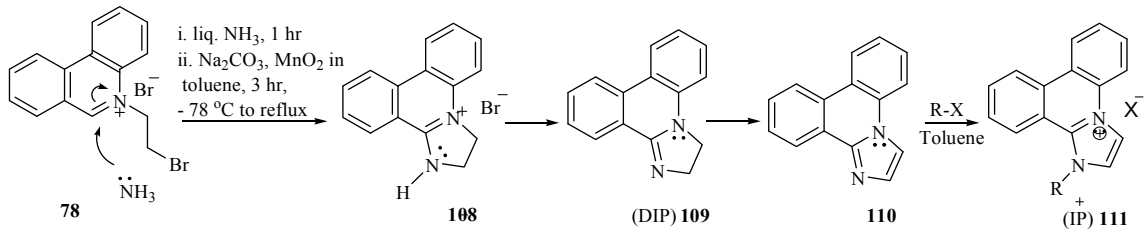
1.2.2.2Imidazolo- and pyrazolo-fused phenanthridines:

Parenty et al. reported two procedures involving one- pot, multi-component reaction leading to dihydroimidazo- and imidazo-phenanthridinium derivatives ($DIPs^+$/ IPs^+).[11,19] The first method involves nucleophilic addition of a primary amine with 2-bromoethylphenanthridinium bromide followed by five-membered ring cyclization and subsequent oxidation step (Scheme 1.34).



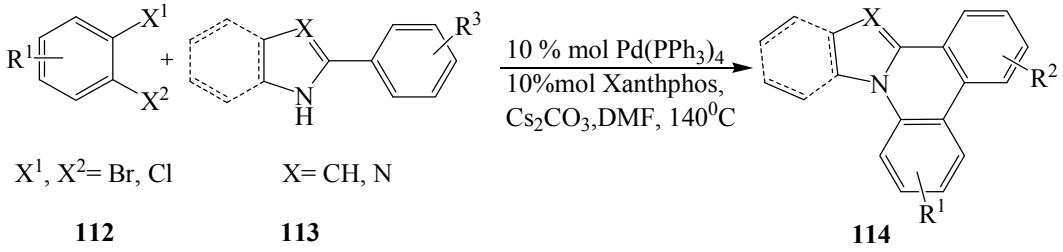
Scheme 1.34. One-pot multicomponent reaction of 2-bromoethylphenanthridinium bromide with amines to form $DIPs^+$/ IPs^+.

The second reaction of 2-bromoethylphenanthridinium bromide with ammonia (Scheme 1.32).[19,76-78] It was a five-step one-pot synthetic route for the synthesis of a new cationic DNA intercalacting platform, imidazo[1,2-*f*]phenanthridinium compound (**111**).



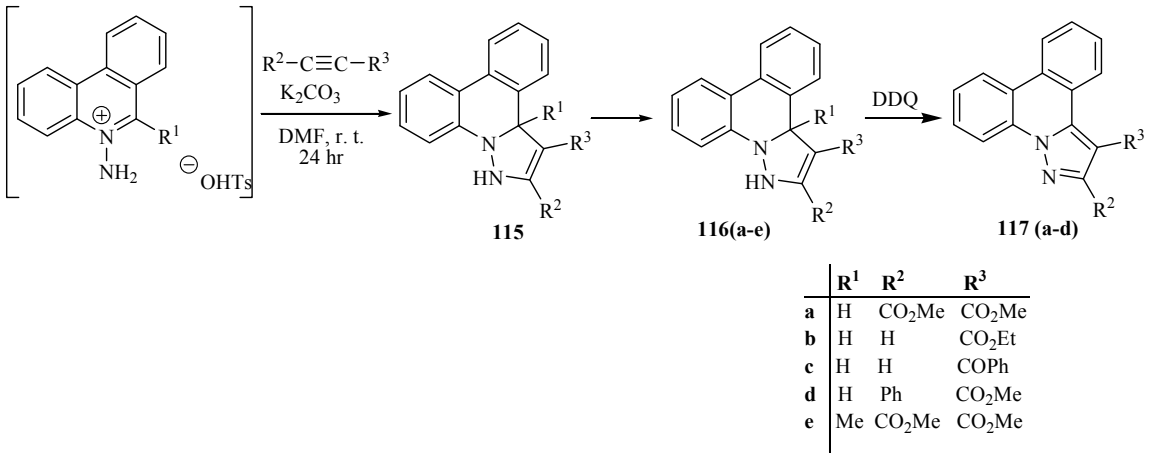
Scheme 1.35. One-pot synthetic route for the synthesis of DIP^+/ IP^+.

A variety of pyrrolo, imidazole, bezimidazole- fused phenanthridines were obtained by a modular and high regioselective approach which involved pd-catalyzed tandem N-H/C-H bond arylation. These structurally diverse fused phenanthridines exhibited interesting photophysical and electrochemical properties, thermal stability, long flurescence lifetimes, excellent blue- emitting performance.[79-82]



Scheme 1.36. Pd-catalyzed C-H bond arylation to form fused phenanthridine.

Tamuara et al.[83] reported the synthesis of pyrazolo[1,5-*f*]phenanthridines. The reaction of *N*-amino or *N*-benzoylaminophenanthridinum salts with dipolarophiles, such as ethyl propiolate and benzoylacetylene or DMAD in the presence of K_2CO_3 at room temperature or at 50 °C yielded only dimer of **115**, but at 80°C with concominant oxidation, it afforded aromatized pyrazolo[1,5-*f*]phenanthridine **(117)** (Scheme 1.37).

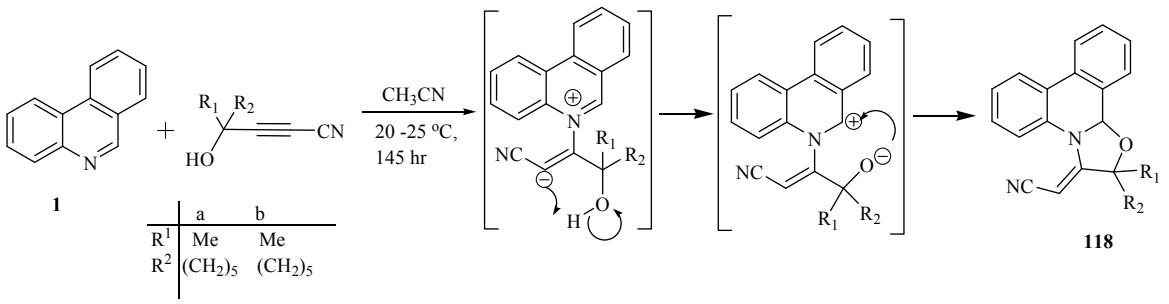


	R1	R2	R3
a	H	CO_2Me	CO_2Me
b	H	H	CO_2Et
c	H	H	COPh
d	H	Ph	CO_2Me
e	Me	CO_2Me	CO_2Me

Scheme 1.37. Dipolar cycloaddition of *N*-aminophenanthridinum salts with dipolarophiles to afford pyrazolophenanthridine.

1.2.2.3Oxazolo-fused phenanthridines:

The reaction of phenanthridines with cynoacetylenes affords 1,3-oxazolidinodihydrophenanthridines possessing an active *N*-2-cynovinyl (acrylic) functional group which provides broad opportunities for further modifications of the compounds synthesized (Scheme 1.38).[84]

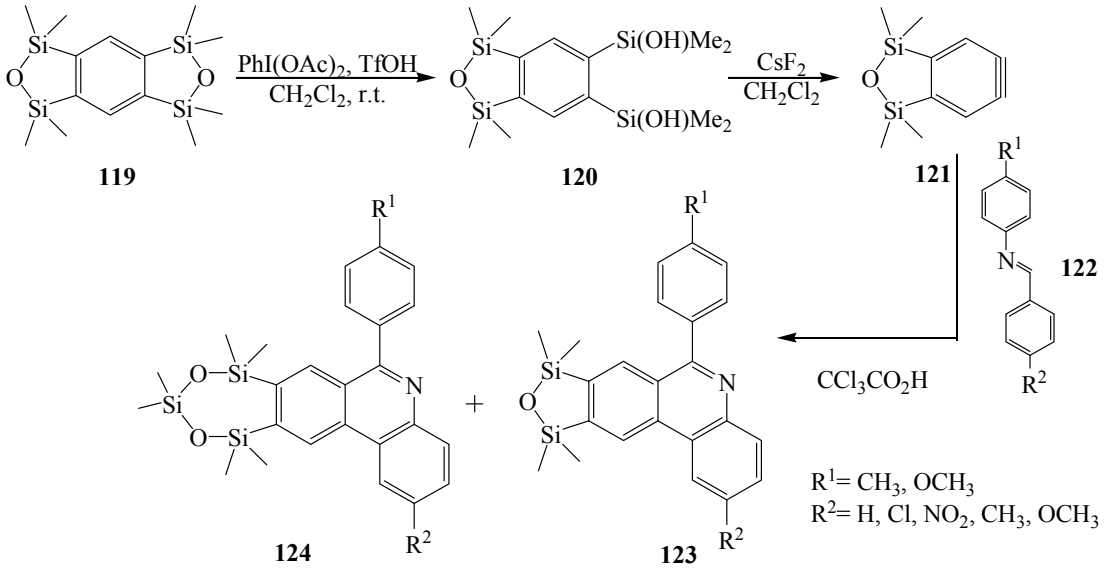


	a	b
R1	Me	Me
R2	$(CH_2)_5$	$(CH_2)_5$

Scheme 1.38. A dipolar cycloaddition of phenanthridines with cynoacetylenes to form oxazolo-fused phenanthridine.

An efficient protocol for the synthesis of oxadisilole-fused (**123**) and dioxadisilole-fused (**124**) phenanthridines by Aza DA reaction and dehydrogenation aromatization reaction of benzyne (**121**) with N-benzylideaniline derivatives (**122**)

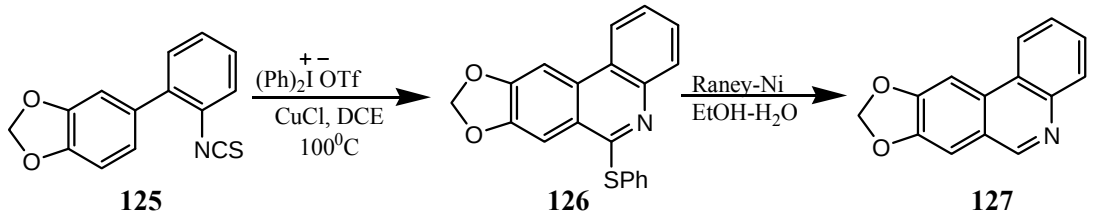
has been reported and their photophysical, redox, thermal and fluorescent properties were determined.[85]



Scheme 1.39. Aza DA reaction and aromatization reaction of benzyne with N-benzylideaniline derivatives.

Physiochemical studies revealed that these fused phenanthridines can be used as blue emitters for OLED due to their high fluorescence quantum yield and thermal stability.

Dioxolo-phenanthiridine termed as Trisphaeridine (**7**) has been synthesized by reduction of 6-(arylthio)-phenanthridine and analogues obtained from metal catalyzed cyclization of 2- biaryl isothyocinates with diaryliodonium salt.[86]



Scheme 1.40. Ni-catalyzed cyclization of 2- biaryl isothyocinates with diaryliodonium salt to afford Dioxolo-phenanthiridine.

1.3 STRUCTURAL STUDIES:

1.3.1 UV Spectroscopic studies:

The electronic spectra of dioxo-compounds of pyrrolo[2,1-*a*]isoquinoline and pyrrolo[1,2-*f*]phenanthridines and their condensed products with *o*-phenylenediamine have been studied by Mikhailovaskii and Shklyaev in 1990s.[87] The UV-absorption spectra of the compounds **128-131** were scanned in methanol, beginning with the wavelength 200 nm. The compounds were characterized by the presence of β-band of π-π* (λ_{max} = 200-234nm, logε = 3.55-4.62), aromatic ρ-band (λ_{max} = 245-294nm, logε = 3.60-4.62) and *K*-band (λ_{max} 315-413nm, logε = 3.89-4.47) of the total π-π* transitions. Spectra of **130** and **131** were more intense and showed bathochromic shift in comparison to **128** and **129**. The effect of substituents was also studied and it was observed that position of the *K*-band was directly affected by the substituent R^2. In the presence of an electron rich group (auxochrome) like amide group, hyperchromic shift was observed, whereas the presence of an electronegative group like $-CO_2C_2H_5$ caused an hypochromatic shift (λ_{max} = 351nm, logε = 4.08) in compound **131,** in comparison to the unsubstituted compound (λ_{max} = 374 nm, logε = 4.21).

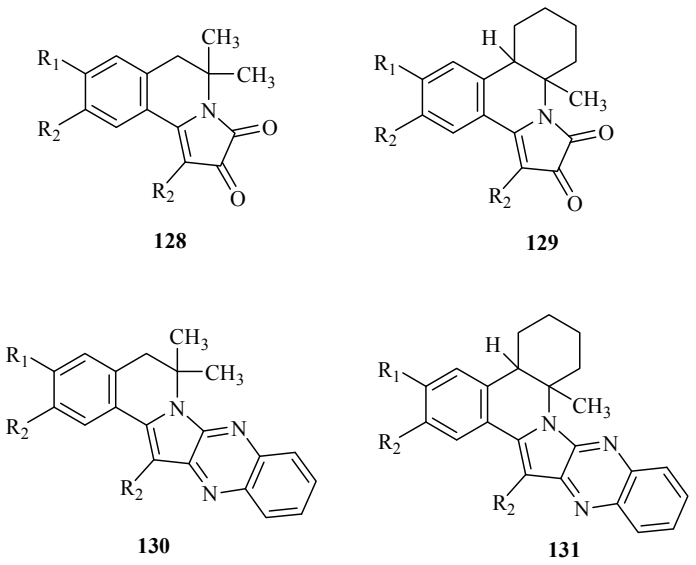


Figure 1.6. Dioxo-compounds of pyrrolo[2,1-*a*]isoquinoline(**128,129**) and pyrrolo[1,2-*f*]phenanthridines (**130,131**).

A halochromic phenomenon was detected for the compound **130**, as when dissolved in 70% $HClO_4$ solution or 95% H_2SO_4 solution, it acquired dark blue tinge thatturned to crimson on dilution (1:3).

Table 1.1: UV Spectra of the compound 131 in different solvents.

Solvent	**Absorption band, λ_{max}, nm (logε)**		
	B	**P**	***K***
CH_3OH	207 (4.34), 210 (4.38), 224(4.46), 234 (4.47)	268 (4.53), 274 (4.62)	362 (4.39), 376 (4.43), 408 (4.11), 427 (3.94)
H_2SO_4	220 (4.38)	260 (4.12), 269 (4.17), 287 (4.03), 299 (3.98)	327 (3.38), 435 (4.18),465 (4.29), 515 (4.15), 547 (4.20), 588 (4.00)

The fluorescence spectra of the quinoxalines **130** and **131** consist of broad structural bands (half width 70-80 nm, in visible region). The fluorescence maxima and quantum yield relative to rhodamine 6Zh are 482 nm (80 %) for the compound

131. Presence of fluorescent property confirms the coplanarity of the heteroaromatic fragment in the molecule.

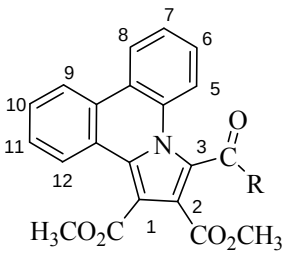
1.3.2. IR studies:

IR spectra of a number of pyrrolo, pyrrolidino, imidazo and dihydroimidazophenathridines have been studied.[41-60,67-80]

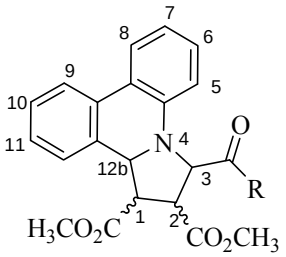
For example, in dihydropyrrolo[1,2-*f*]phenanthridines **76**, a strong band at 1660 cm^{-1} of the conjugated C=C bond is found in addition to C=C aromatic vibrations near 1600, 1500 and 1450 cm-1.[56] Strong band in the carbonyl region at 1730 cm^{-1} confirms the presence of the C=O group. In case of compound **75**, C-N bond shows strong absorption at 1666 cm^{-1} and cyno group also shows its characteristic peak at 2254 cm^{-1}.[64]

1.3.3. ^{1}H NMR studies:

^{1}H NMR spectroscopy has been employed extensively for characterizing annelated phenanthridines.[48,67,75-78]



67



70

Figure 1.7. Pyrrolo- and Pyrrolidinophenanthridine representative.

For example, in the ^{1}H NMR spectrum of the compound of type **70,** most deshielded proton is H-12b absorbing in the range of δ 7.80- 9.24 ppm.[56-59] The assignment of the relative configurations at the C-1, C-2, C-3 and C-12b atoms is based on the coupling constants, where vicinal coupling constants $^{3}J_{1,12b}$ and $^{3}J_{2,3}$ are found in range of: $^{3}J_{cis}$ = 8.5- 11.5 Hz and $^{3}J_{trans}$ = 2.5- 5.5 Hz. In the product like **67,** H-5 is found as most deshielded proton resonating in the range of δ 8.12- 8.40 ppm.[51,60,61] All other protons of the aromatic ring of phenanthridine are found in the aromatic region, δ 7-9 ppm.

1.3.4. ^{13}C NMR studies:

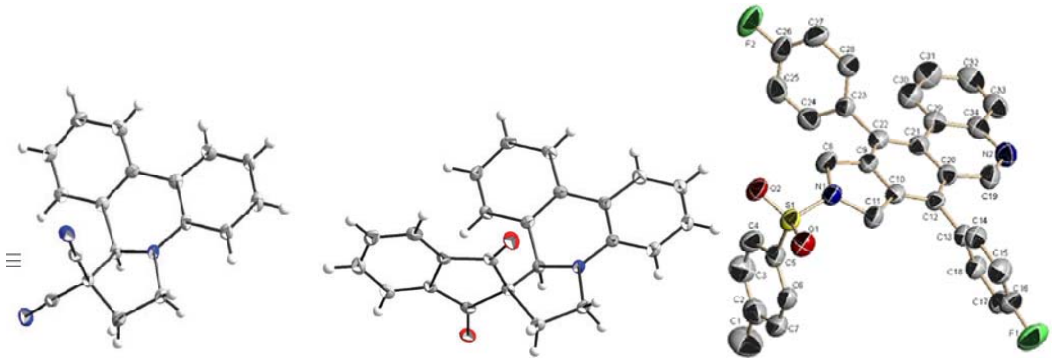
Like ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy has also been used extensively for the characterization of annelated phenthridines.[49,52,55-67,75-78]

For example in ^{13}C NMR spectrum of compound **67** and **70** carbonyl carbon is highly deshilded and appeared at ~ δ 172 ppm. Other two carbonyls of ester group are found in the range of δ 160- 168 ppm and all other protons are found in range of δ 110- 140 ppm, a well defined region for aromatic carbons. In contrast of ^{13}C NMR spectrum of compound **67**, appearance of four different signals in range of δ 48.7-52.4 ppm (C-1, C-2) and δ 62.2- 64.4 ppm (C-3, C-12b) in ^{13}C NMR spectrum of compound **70** indicated the structural differences in aromaticity.

1.3.5. X- ray studies:

The structures of a good number of annelated phenanthridines have been confirmed unambiguously by X-ray crystal structure analysis.[66,75,88]

As discussed earlier, two products **80** and **82** were obtained from N-bromoethylphenanthridinium bromide (**72**) (Scheme 1.21). The crystals formed by slow evaporation of the saturated methanolic solutions of the pure materials were examined by X- ray crystallography for confirmation of the structures (Figure 1.9).[64] Single X- ray crystallographic data of the compound **92 e** (Scheme 1.24) are also available (Figure 1.7).[68]



80 **82** **92e**

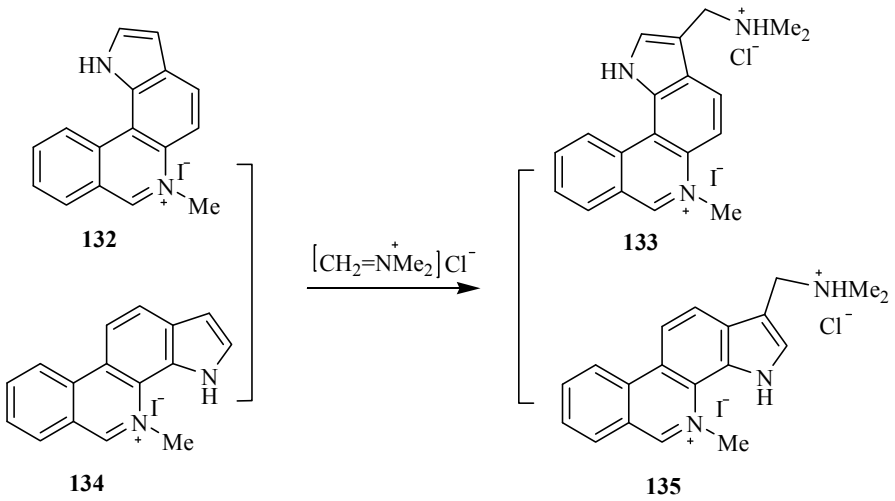
Figure 1.8. X-ray crystallographic structure of compounds **80**, **82** and **92e**.

1.4 REACTIONS:

Phenanthridine fused heterocycles are mostly synthesized for the study of their biological activity, DNA binding capacity and their uses in drug industry against several pathogens, as we discussed earlier. Rare annelation reactions were further performed from these fused heterocycles.

Aminomethylation:-2-*N*,*N*-Dimethylaminomethyl-1*H*-pyrrolo[2,3-*a]*-6-phenanthridinium chloride/iodide has been obtained in high yield from aminomethylation of 6-methyl-1*H*-pyrrolo[2,3-*a]*-6-phenanthridinium iodide with crystalline Mannich reagent in a mixture of dry DMF and absolute ethanol (5:2)

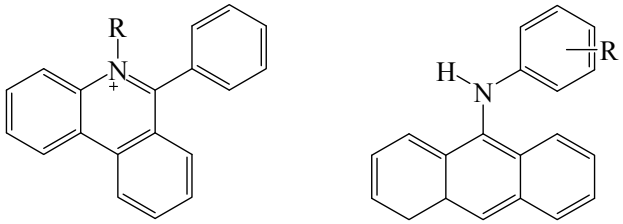
(Scheme 1.35).[9] 1-*N*,*N*-Dimethylaminomethyl-4*H*-pyrrolo[3,2-*c*]-4-phenanthridinium chloride-iodide has also been synthesized analogously from 4-methyl-3*H*-pyrrolo[3,2-*c*]-4-phenanthridinium iodide.



Scheme 1.41. Aminomethylation of pyrrolophenanthridine iodide.

1.4 APPLICATIONS

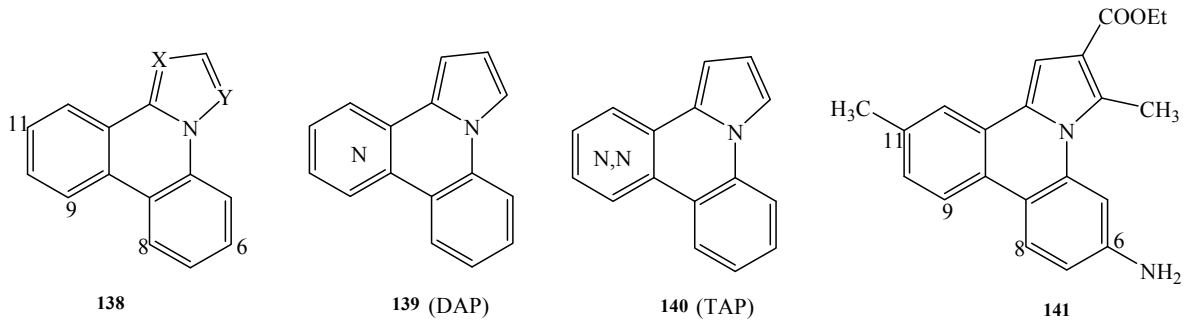
Phenanthridine derivativesof type **136** and acridine derivatives of type **137** are well known compounds owning property of stacking and charge transfer, hydrogen bonding, and electrostatic forces, so that; they can intercalate in to ds- DNA and can be effective pharmacophore units of drugs having antitumor activity.[6b88,89]



136 **137**

Figure 1.9. Phenanthridine and acridine derivatives.

Inspiring from progressive study of above frameworks, phenanthridine annelated heterocycles were studied as potential DNA-interactive agents. Several azolo, diazolo or triazolo- phenanthridines of type **138**, **139** and **140** have been synthesized and some of them exhibited cytotoxicity, antimicrobial activity and anti-proliferative activitiy in *in vitro* tests.[19,24,25,90]



138 **139** (DAP) **140** (TAP) **141**

Figure 1.10. Some fused heterocycles with phenanthridine framework.

Some pyrrolo[1,2-*f*]phenanthridines synthesized either from acid catalyzed decomposition or from pschorr-type cyclization of substituted pyrroles allow the functionalization of phenanthridine ring for interaction with DNA, particularly compound **141** showed unique property to reduce the HIV-induced cytopethogenicity and in stimulation of growth of MT cells at lower concentration.[24,,25,92] Here presence of amino or methoxy group on 6- and/or 11-

position is significant for the emergence of the biological activity.[24,25,77] These studies also enhanced the knowledge of molecular modeling and interactive studies with different cell lines and drug targeting applications.

Besides propitious biological features in drug industry, synthetic procedures of annelated pyrrolophenanthridines also provided convenient approaches for synthesis of new annelated heterocycles. For example metal catalized or direct arylation[35-39,69-72], one-pot multi-component reactions, [45-47,61-67] are not only time-saving, user- friendly procedures, but also, provide the convenient way to obtain some new azapolycyclic or helical compounds, which are difficult to prepare in normal conditions.[46,57]

Physical and fluorescent properties having *N*-heteroaryl-fused phenanthridines are potential candidate for several applications in optoelectronic devices, such as blue-emitting luminiphores in OLEDs, or an model for further developing heterocycles.[79-82]