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IMIDAZOQUINOLINES AS DIVERSE AND INTERESTING BUILDING BLOCKS: REVIEW OF SYNTHETIC METHODOLOGIES

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Abstract – Imidazoquinolines are interesting heterocyclic systems that depending on the position of fusion and the type of substituents display diverse biological and pharmaceutical properties. From the chemistry point of view, imidazoquinolines are heterocylic scaffolds resulting from the fusion between the 5-membered ring imidazole and the benzopyridine ring, quinoline. At least eight different combinations can be identified for these significant scaffolds. From the retrosynthetic point of view, imidazoquinolines can be prepared using one of two general approaches: imidazole-ring formation or pyridine-ring one. According to the type of imidazoquinoline and the position of the substituents either one of these two plans can be adopted. Pertinent to the specific plan to be used, different starting materials can be implanted as well. The most general starting materials are the diaminoquinolines and the aminobenzimidazoles. The main objective of this review article is to shed light on the reported synthetic pathways for each imidazoquinoline system.

INTRODUCTION

Imidazoquinolines are classified as diverse and interesting heterocyclic systems that represent *benzene*-fused deazapurine scaffolds (**Figure 1**).[1] These fused heterobicyclic scaffolds have shown significant biological and pharmaceutical properties depending on the position of the fusion and the nature of the substituents. A survey through the literature has revealed that different imidazoquinolines have been claimed to display contraceptive,[2] antihypertensive,[3] antiallergic,[4] antiasthmatic,[5] and antiplatelets aggregation[6] activities. They have also been reported to act as immunomodifying,[7] chelating,[8] antibacterial,[9] anticancer[10] agents and non-xanthine adenosine antagonists.[11]

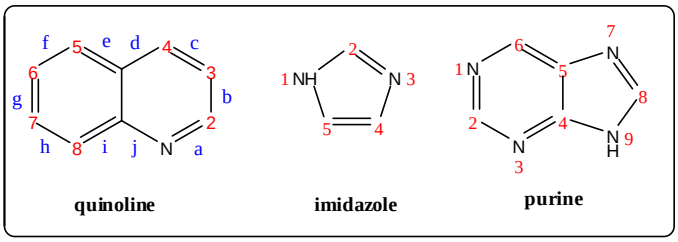


Figure 1. The IUPAC numbering for quinoline, imidazole and purine ring systems

Consequently, imidazoquinolines can be classified into two main subgroups:

1) Angular imidazoquinolines (**Figure 2**)

2) Linear imidazoquinolines (**Figure 3**)

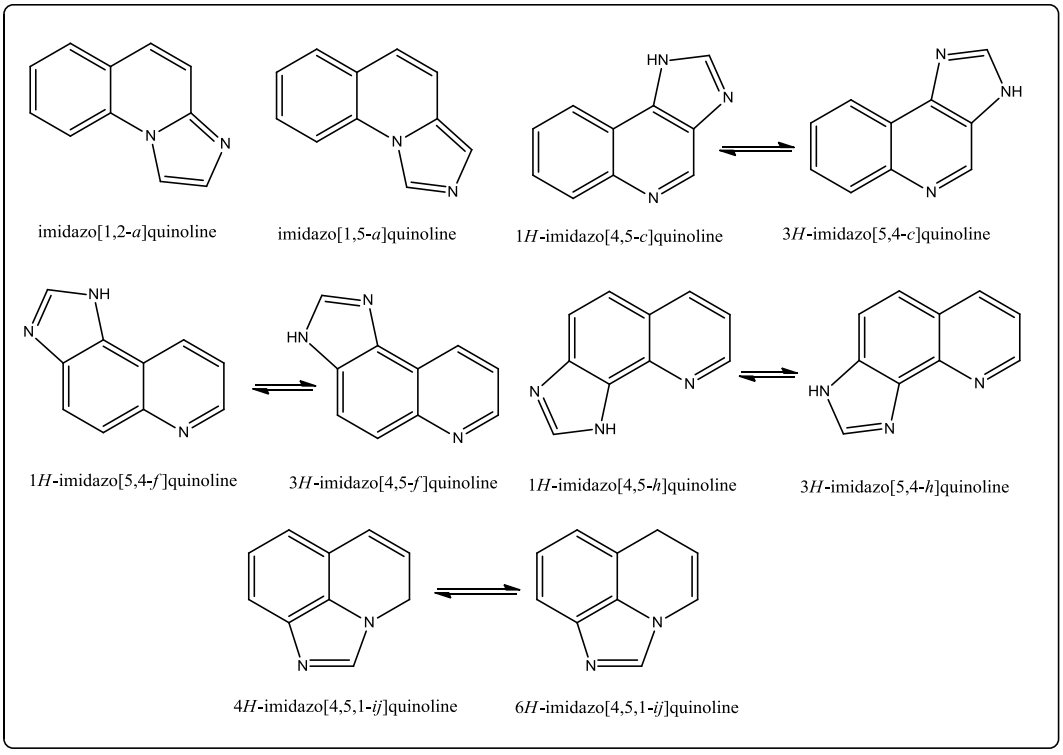


Figure 2. Structures of angular imidazoquinolines

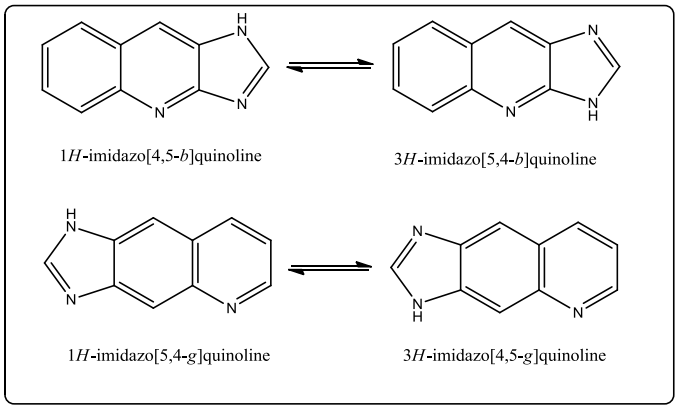


Figure 3. Structures of linear imidazoquinolines

Hitherto, no comprehensive survey has been published to outline the different synthetic methods for the preparation of imidazoquinolines as fused heterocyclic systems. In this review article, we would like to comprehensively outline different methodologies for the syntheses of these structurally diverse scaffolds.

1. SYNTHETIC APPROACHES

1.1. ANGULAR IMIDAZOQUINOLINES

1.1.1. IMIDAZO[1,2-*a*]QUINOLINES

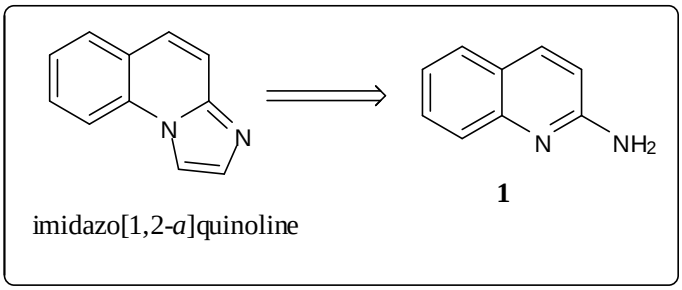
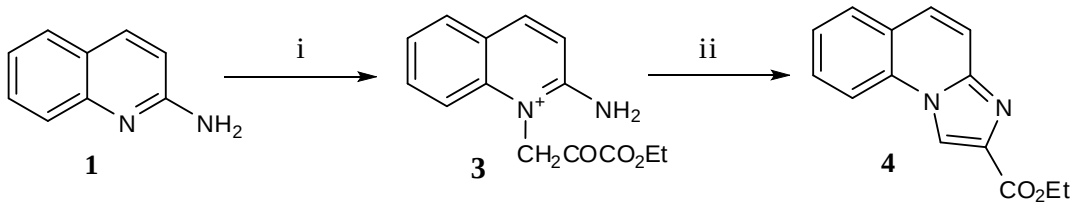


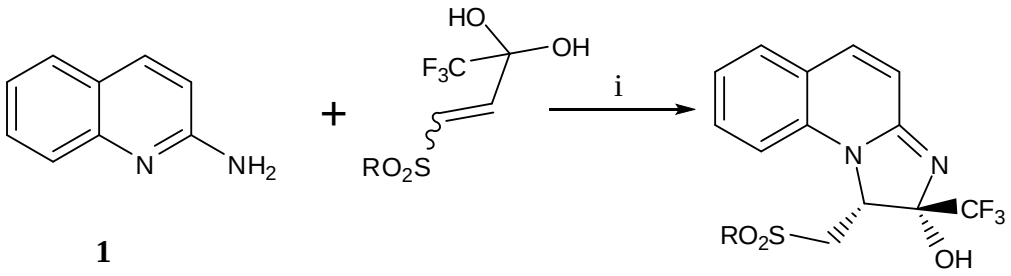
Figure 4. Retrosynthetic pathways for imidazo[1,2-*a*]quinolines

In accordance with the retrosynthetic possible pathways, the 2-aminoquinoline (**1**) is considered as the most common precursor for the preparation of imidazo[1,2-*a*]quinolines (**Figure 4**).[12-16] Consequently, its reaction with α–halocarbonyl compounds such as ethyl 3-bromopyruvate yielded the desired nucleus in 63-96% yields (**Scheme 1**).[12,13] The mechanism of the reaction can be summarized as the quinolinium quaternary salt **3** is first formed through the reaction of 2-aminoquinoline (**1**) with the pyruvate ester **2**. Heating **3** in ethanol followed by basification with sodium carbonate furnishes the way to the desired derivative **4**.[12,13]



Scheme 1. Reagents and conditions; i) $BrCH_2COCO_2Et$ (**2**), DME; ii) EtOH, Na_2CO_3, heating.

The reaction of 1,1,1-trifluoro-4-(phenyl/methylsulfonyl)but-3-ene-2,2-diols, **5a,b,** as 1,2-bielectrophilic reagents, with 2-aminoquinoline (**1**) is reported to afford the stable 2,3-dihydroimidazo[1,2-*a*]quinolin-2-ol derivatives **6a,b** in 80-96% yields, respectively. (**Scheme2**). This straightforward one-step cyclization reaction possesses the advantages of being simple, environmentally safe, and having reasonable reaction times.[14]



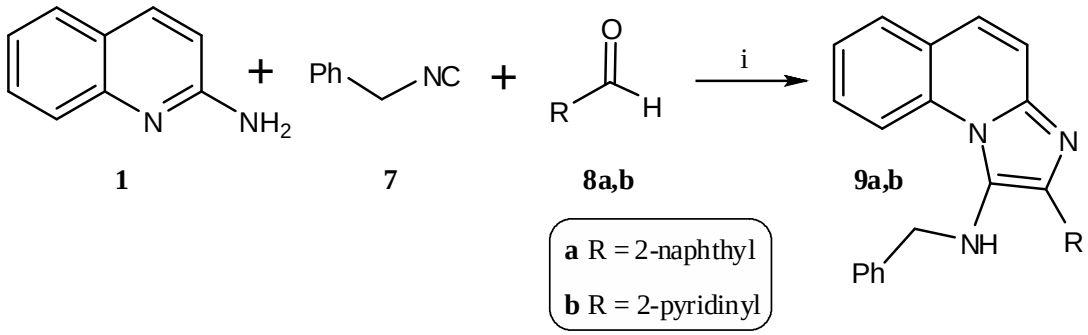
1 **5a,b** **6a,b**

5a; R = Ph
5b; R =Me

6a; R = Ph
6b; R =Me

Scheme 2. Reagents and conditions; i) stirring, 12 h, rt.

The use of a Ugi three-component coupling (3cc) reaction strategy in combination with microwave-assisted heating has been reported by Ireland *et al.* for the preparation of **9a,b** (**Scheme 3**).[15] This multi-component synthetic procedure afforded **9a,b** *via* the reaction of **1** with benzylisocyanide (**7**) and the appropriate aldehydes **8**. The target compounds, 1-(benzylamino)-2-arylimidazo[1,2-*a*]quinolines **9a,b** were formed through an iminium species followed by a [4+1] cycloaddition with the isocyanide. It is worth mentioning that the use of scandium triflate catalyst increased the conversion reaction rate to a notable extent.[15]

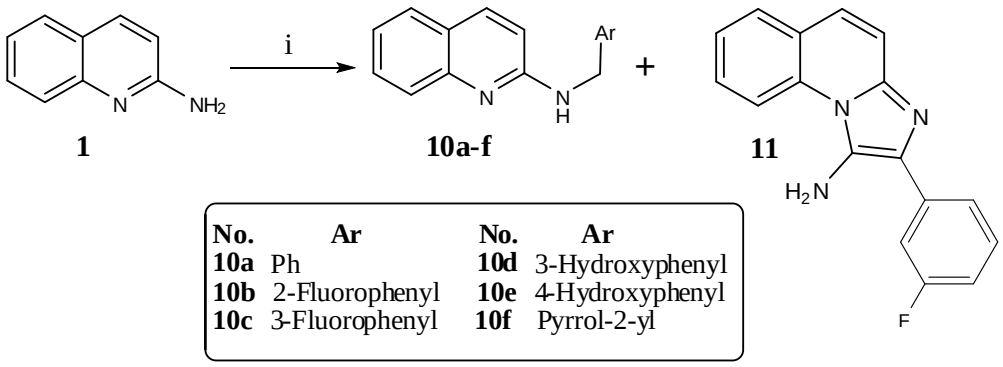


1 **7** **8a,b** **9a,b**

a R = 2-naphthyl
b R = 2-pyridinyl

Scheme 3. Reagents and conditions; i) Sc $(OTF)_3$ / MeOH, MW (200W), 160 °C, 10 min.

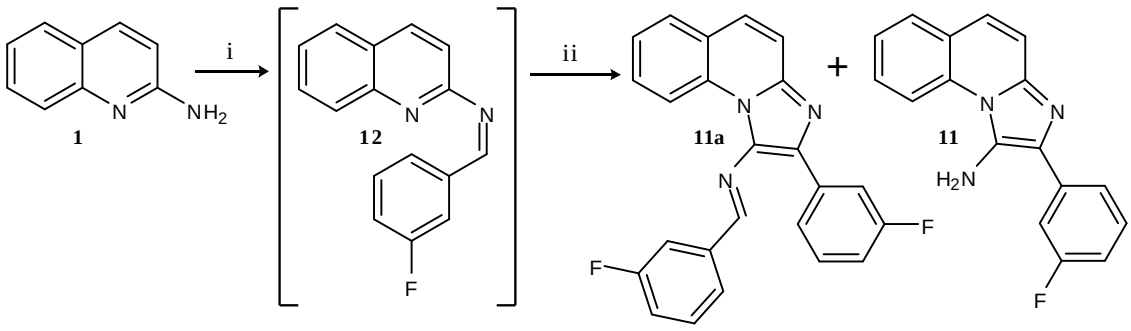
In the course of investigating the effect of 2-(arylmethylamino)quinolines **10a-f**, as ligands for the Tec SH3 domain, Inglis and his co-workers[16] reported the formation of the 3-fluorophenylimidazo[1,2-*a*]quinoline derivative **11**. This unexpected product, **11**, was separated in 10% yield under the reductive alkylation conditions of the amino group (**Scheme 4**).[16]



No.	Ar	No.	Ar
10a	Ph	**10d**	3-Hydroxyphenyl
10b	2-Fluorophenyl	**10e**	4-Hydroxyphenyl
10c	3-Fluorophenyl	**10f**	Pyrrol-2-yl

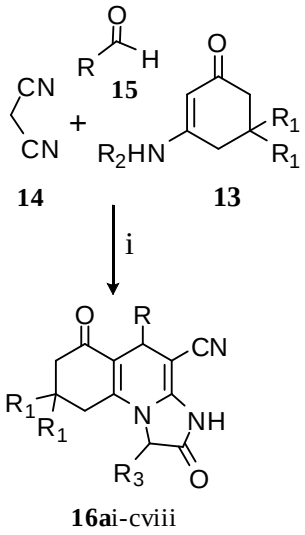
Scheme 4. Reagents and conditions; i) (1) ArCHO, Ti(*i*-pro)$_4$, THF, rt; (2) $NaBH_3CN$, EtOH.

The same compound was further verified *via* an independent synthetic pathway. In this case, 2-aminoquinoline (**1**) was reacted with an aldehyde to afford the imine intermediate **12**, which upon treatment with sodium cyanide in methanol at ca. 50 ^{o}C afforded **11** in 33% yield, along with a small percentage (4%) of **11a** as a result of condensation of **11** with another molecule of aldehyde (**Scheme 5**).[16]



Scheme 5. Reagents and conditions; i) 3-fluorobenzaldehyde / toluene / heating; ii) NaCN / MeOH / ca 50 °C

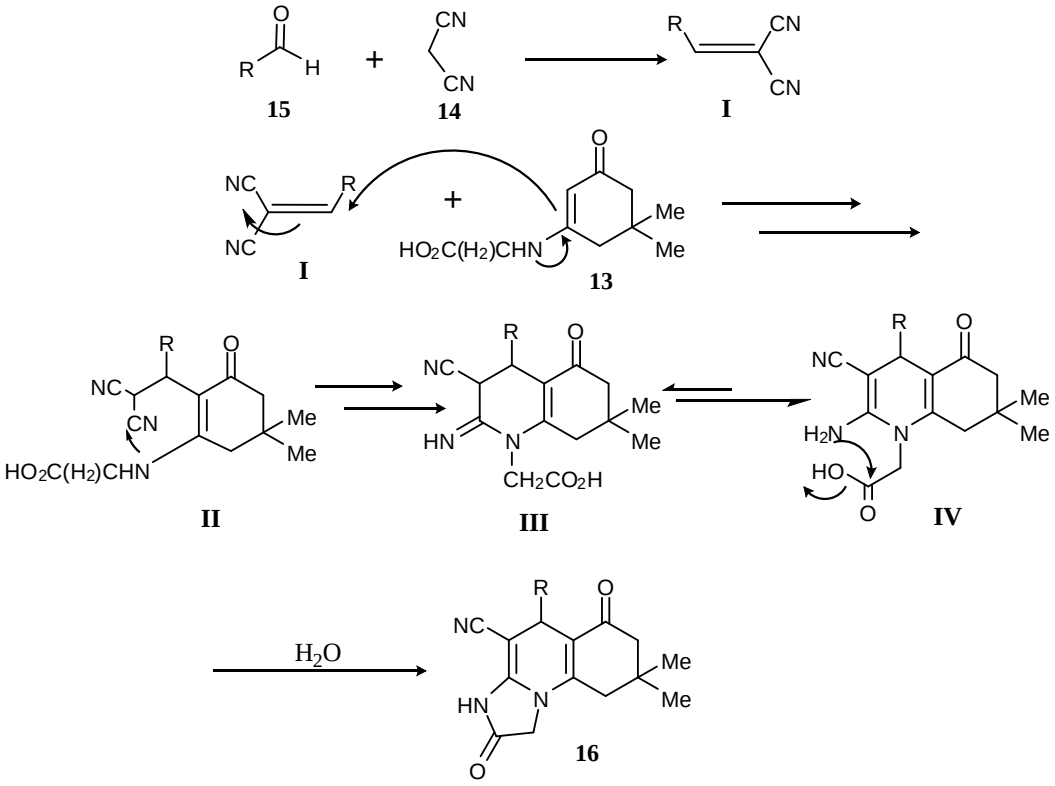
Although 2-aminoquinoline (**1**) is considered the most common precursor for the imidazo[1,2-*a*]quinolines, nevertheless, some other less-common approaches were also attempted. The polysubstituted imidazo[1,2-*a*]quinolines **16ai-cviii** were successfully prepared in a facile manner using both microwave-assisted heating and 3cc domino reaction protocol.[17] The above series of compounds were synthesized using the one-pot multicomponent strategy between the enaminones **13**, malononitrile **14**, and the appropriate aldehydes **15**. The yields range between 81-89% with a significant reduction in the reaction time (**Scheme 6**).



16	R_1	R_2	R_3	R (in **15** and **16**)
a	Me	CH_2CO_2H	H	i: 4-$NO_2C_6H_4$
				ii: 4-FC_6H_4
				iii: 4-ClC_6H_4
				iv: C_6H_5
				v: 4-$MeOC_6H_4$
				vi: 4-MeC_6H_4
				vii: 4-BrC_6H_4
				viii: thiophen-2-yl
				ix: $Me(CH_2)_3$
b	Me	$MeCHCO_2H$	Me	i-vii: the same substituents as in **16a**
				viii: 3-$NO_2C_6H_4$
				ix: 2-ClC_6H_4
				x: 4-OH-3-$NO_2C_6H_3$
c	H	CH_2CO_2H	H	i-vi: the same substituents as in **16a**
				vii: the same substituents as in **16b**-viii
				viii: the same substituents as in **16b**-ix

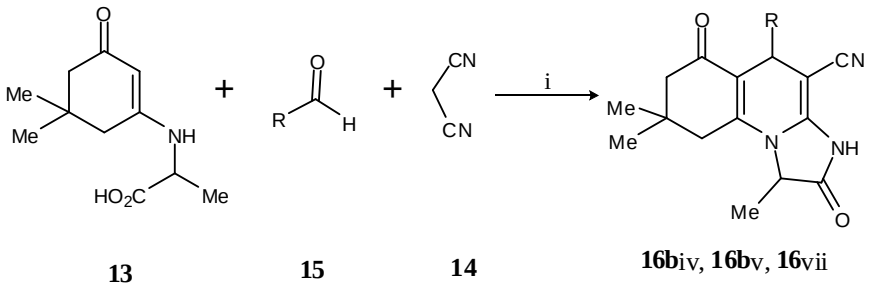
Scheme 6. Reagents and conditions; i) ethylene glycol, MW, 120 °C, 4-8 min.

The formation of the above compounds can be explained according to the following plausible mechanism (**Scheme 7**).[17] The first step is the condensation of malononitrile **14** with aldehyde **15** to yield the intermediate 2-arylidenemalononitrile **I**. The Michael addition of **I** to the enaminone **13** affords the intermediate **II**. This intermediate **II** undergoes further intramolecular cyclization and dehydration to afford **16ai-cviii**.[17]



Scheme 7. Reaction mechanism for the formation of **16a**i-cviii

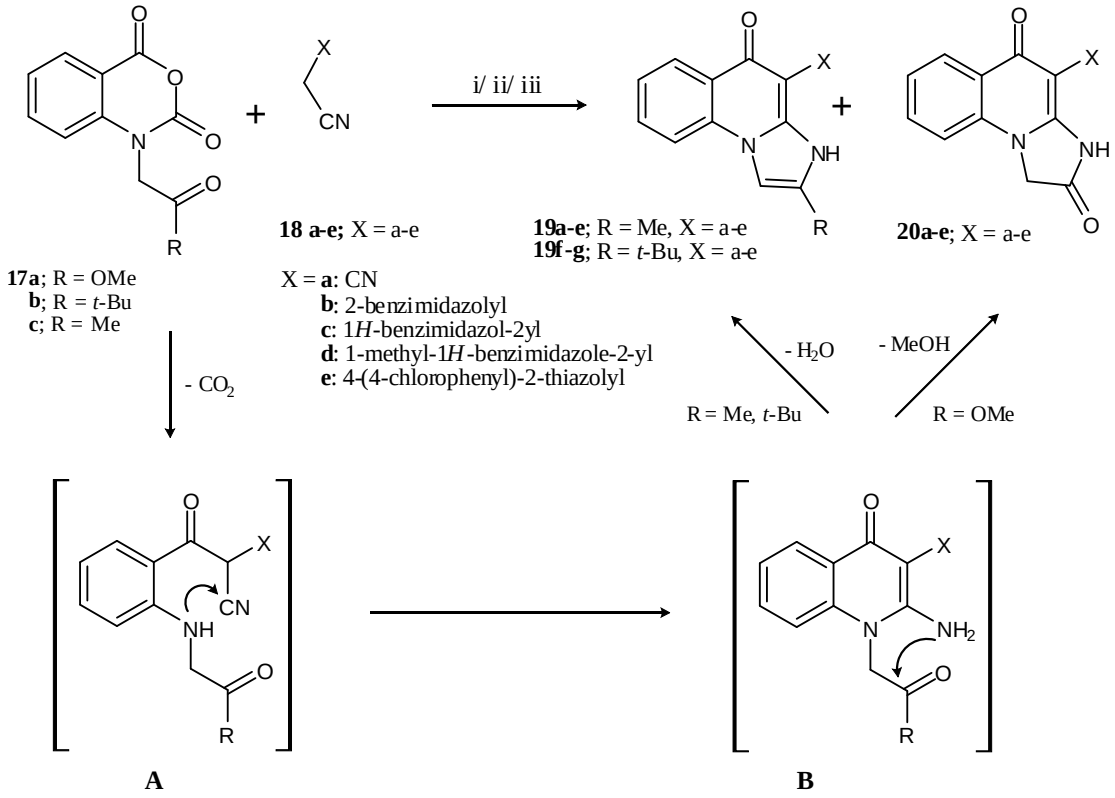
Some of the same polysubstituted imidazo[1,2-*a*]quinoline series **16ai-cviii** were recently prepared by a novel approach. The novelty of this protocol is in the use of the nanocrystalline CuO as an efficient catalyst for the following one-pot three-component synthesis (**Scheme 8**). The advantages of this method can be summarized in being environmentally friendly, run in aqueous medium, and cost efficient. The catalyst is easily recovered and maintains its catalytic activity for several runs.[18]



Scheme 8. Reagents and conditions; i) CuO nano particles, H_2O / 50 °C / 30 - 40 min.

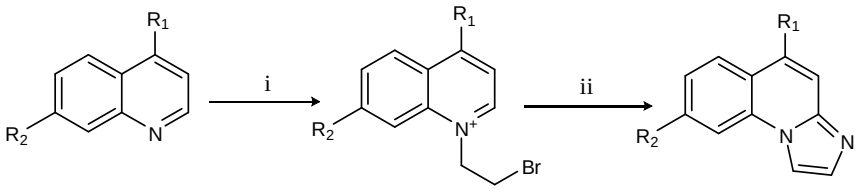
A minor route for the synthesis of imidazo[1,2-*a*]quinolines is the use of *N*-alkylisatoic anhydrides **17a-c**.[19] It is well-known that these anhydrides react with active methylene compounds such as **18a-e,** to yield the target imidazoquinoline derivatives.[19] The reaction proceeds in either acidic (acetic acid -

sodium acetate) or basic (DMF/dioxane – TEA) conditions to yield **19a-j** and **20a-e** (**Scheme 9**).[20] In this approach,[20] the synthesis of the above-mentioned imidazo[1,2-*a*]quinolines is based on the so-called "domino reaction".[21] The utilization of a domino reaction protocol allowed efficiently preparing complex molecules from simple precursors in an economic and ecologically sensitive manner.[21] This cascade tandem reaction can simply be defined as a consecutive series of intramolecular organic reactions proceeding *via* highly reactive intermediates **A** and **B**, in which the subsequent transformation takes place at the functionalities obtained in the former transformation.



Scheme 9. Reagents and conditions; i) AcOH, NaOAc, reflux; ii) DMF, Et_3N (cat.), 110 -120 °C; iii) dioxane, Et_3N (cat.), reflux.

Recently, a general, simple and effective method was reported for the preparation of the imidazo[1,2-*a*]quinolines. Compounds **23a-c** were prepared in a five-step one-pot protocol method starting from **21a-c**, respectively.[22] This method can be outlined as having two main parts; an activation step, and a five-step cascade annulation reaction. The activation step is achieved *via* the reaction of the quinoline derivatives with 1,2-dibromoethane to enhance the electrophilicity of the pyridine ring. The resulting 2-bromoethylquinolinium bromide derivatives **22a-c** undergo a five-step reaction to yield compounds **23a-c** in 65-100% yields (**Scheme 10**).[22]



21a; $R_1 = R_2 = H$ **22a**; $R_1 = R_2 = H$ **23a**; $R_1 = R_2 = H$
21b; R_1 = Me, $R_2 = H$ **22b**; R_1 = Me, $R_2 = H$ **23b**; R_1 = Me, $R_2 = H$
21c; $R_1 = H$, R_2 = NHCOMe **22c**; $R_1 = H$, R_2 = NHCOMe **23c**; $R_1 = H$, R_2 = NHCOMe

Scheme 10. Reagents and conditions; i) 1,2-dibromoethane, 90 °C, 5 days; ii) NH_3/ toluene, MnO_2, Na_2CO_3, 4 h.

1.1.2. IMIDAZO[1,5-*a*]QUINOLINES

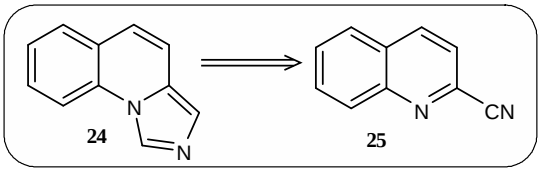
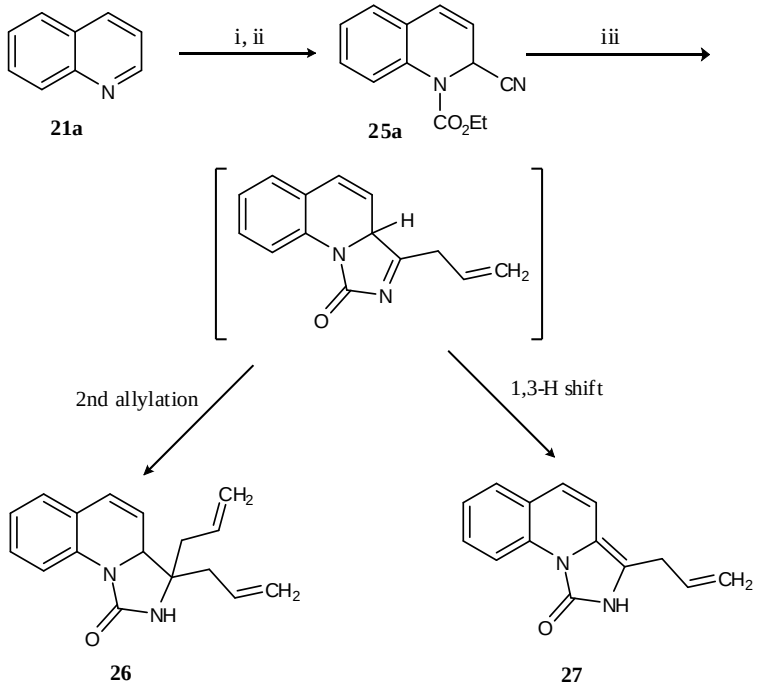


Figure 5. Retrosynthetic pathways for imidazo[1,5-*a*]quinolines

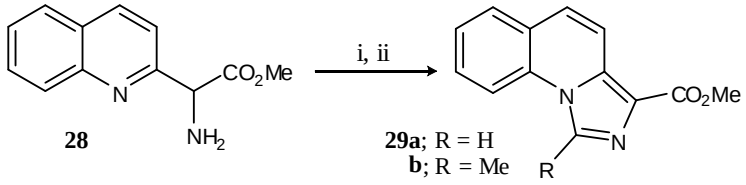
The chemistry of imidazo[1,5-*a*]quinoline **24** is not extensively studied. Through a few reported synthetic procedures, the quinoline-2-carbonitrile (**25**) was considered as the most common precursor.

Kim *et al.*[23] reported the preparation of substituted imidazo[1,5-*a*]quinolines. In this process, Reissert compound, such as 1-acyl-1,2-dihydroquinoline-2-carbonitrile **25a**,[24] has been developed for the preparation of allyl-substituted imidazo[1,5-*a*]quinolines **26** and **27** *via* the indium-mediated Barbier type allylation and dehydrative cyclization protocol (**Scheme 11**).[23]



Scheme 11. Reagents and conditions; i) $ClCO_2Et$, ii) KCN, iii) allyl bromide, In, THF, reflux.

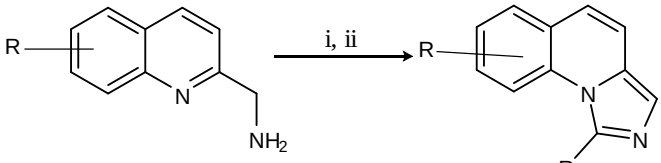
The quinolinylglycinate esters have also been introduced as a novel synthetic building blocks for the preparation of imidazo[1,5-*a*]quinolines.[25] In this regard, the methyl (quinolin-2-yl)glycinate (**28)** was heated at reflux with dimethylformamide dimethyl acetal (DMFDMA) or dimethylacetamide dimethyl acetal (DMADMA) mixtures to afford this fused system or its 1-methyl analog **29a**,**b**, respectively, as shown in **Scheme 12**.



28 **29a**; R = H
b; R = Me

Scheme 12. Reagents and conditions; i) DMFDMA, reflux; ii) DMADMA, reflux.

In the course of preparing novel fused tetracyclic imidazoquinoline derivatives, the benz[*f*]imidazo[1,5-*a*]quinolines **32** and the benz[*h*]imidazo[1,5-*a*]quinolines **33** were prepared from the corresponding 1-aminomethylbenzo-fused quinolines **30** and **31**, respectively, using a similar synthetic route (**Scheme 13**).[26]



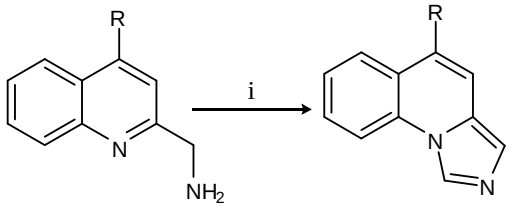
30; R = benz[*f*]
31; R = benz[*h*]

32; R = benz[*f*]
33; R = benz[*h*]

R_1 = H, Me, Ph, 3,4,5-$(MeO)_3C_6H_2$, adamantyl, $C_6H_2I_3$
X = Cl, OMe, R_1CO_2

Scheme 13. Reagents and condtions; i) R_1COX; ii) $POCl_3$.

With the aim of establishing a low-cost, *in situ*, analytical method for monitoring the levels of contamination of groundwater with chloroform, compounds **21** and **36** were prepared. In this related approach, the 2-(aminomethyl)quinoline **34** and its 4-methoxy derivatives **35** were reacted with chloroform, adopting a basic phase-transfer catalysis technique, to yield the highly fluorescent products **21** and **36**, respectively (**Scheme14**).[27]

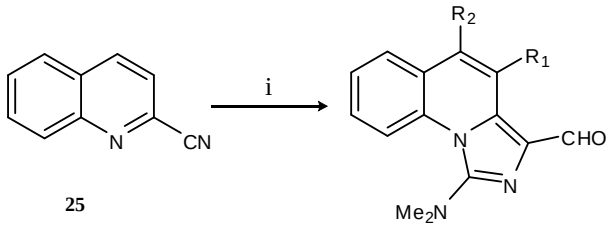


34; R = H
35; R = OMe

21; R = H
36; R = OMe

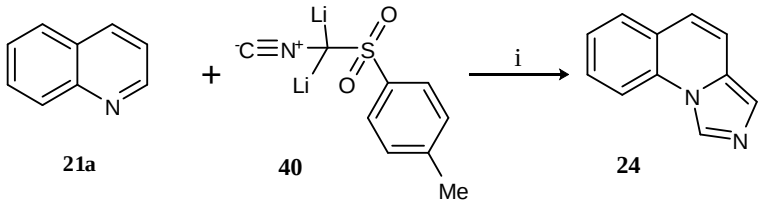
Scheme 14. Reagents and conditions; i) tetramethylammonium bromide, DME, NaOH, $CHCl_3$, 50 °C.

Sasaki and his co-workers reported the preparation of imidazo[1,5-*a*]quinolines **38** and **39** in a one-step reaction, adopting the Vilsmeier reaction conditions (**Scheme 15**).[28] In this context, the Vilsmeier reagent acts as a one-carbon unit donor.



Scheme 15. Reagents and conditions, i) DMF / $POCl_3$ / heating

It is worth mentioning that **21a** was reported to form **24** in 25% yield *via* the reaction with dilithiotosylmethyl isocyanide (**40**) in a single step reaction[29] (**Scheme 16**).



Scheme 16. Reagents and conditions; i) THF, - 70 °C.

1.1.3. 1*H*-IMIDAZO[4,5-*c*]QUINOLINES

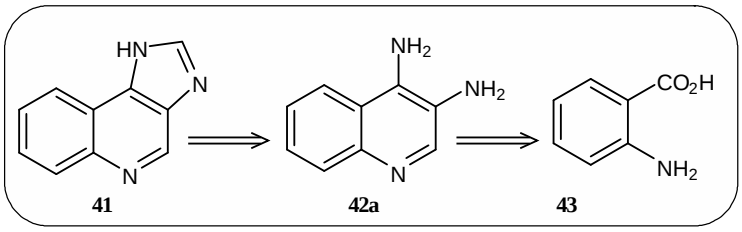
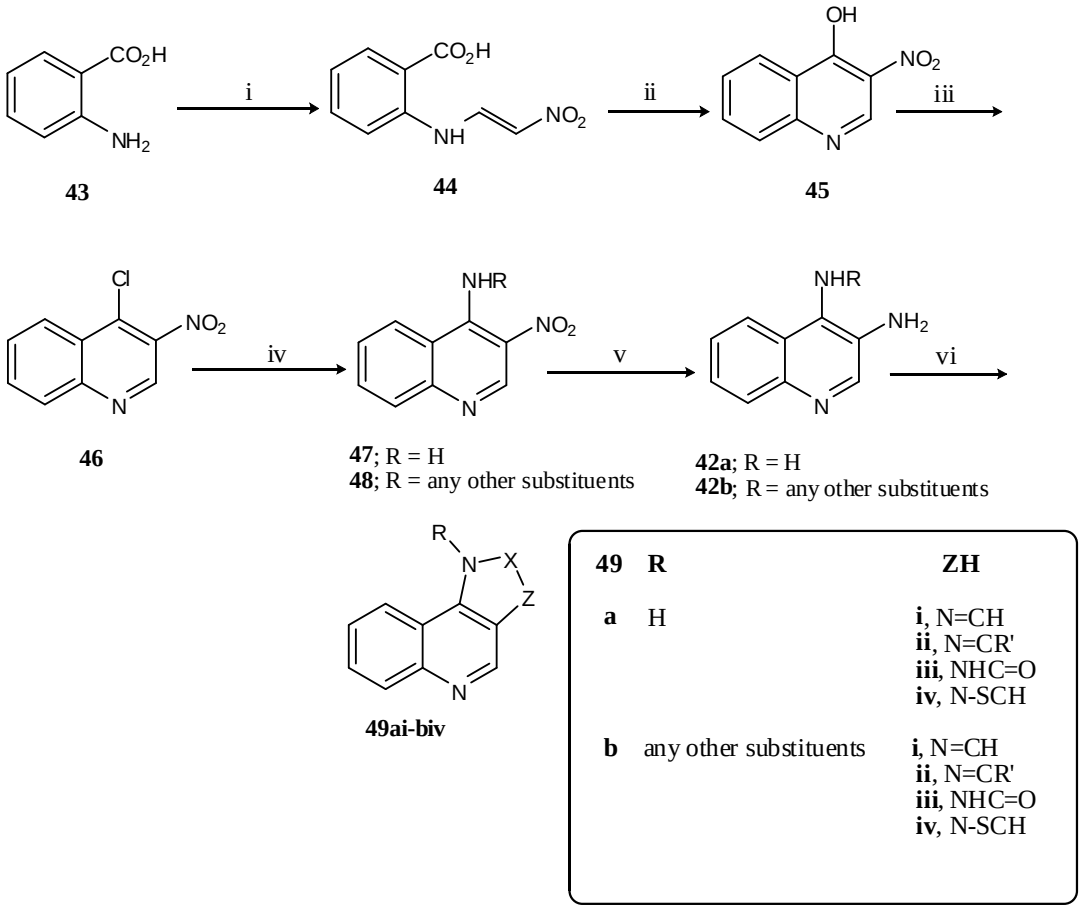


Figure 6. Retrosynthetic pathways for 1*H*-imidazo[4,5-*c*]quinolines

Derivatives of 1*H*-imidazo[4,5-*c*]quinolines **41** have proven to possess diverse biological activities. Subsequently, the syntheses of various substituted-1*H*-imidazo[4,5-*c*]quinolines have been reported since the 1950's.[30] A perusal of the literature has revealed that anthranilic acid (**43)** is the most common precursor for the synthesis of imidazo[4,5-*c*]quinolines. Other less common approaches have also been reported. Such precursors, besides anthranilic acid, have been introduced with the aim of either exploring

different methodologies[31] or introducing different fuctionalilities at different positions on the nucleus.[32] Consequently, the following general scheme for the synthesis of compound **49**, starting from anthranilic acid**,** is suggested as depicted in **Scheme 17**.



Scheme 17. Reagents and conditions; i) 2 $MeNO_2$ / NaOH ($O_2NCH_2CH=NOH$); ii) Ac_2O, AcONa; iii) $POCl_3$ or $SOCl_2$; iv) RNH_2; v) NO_2 reduction; vi) imidazole ring formation.

The nitromethane reacts with a strong base, e.g. NaOH, to form methazonic acid or 2-nitroacetaldehyde oxime *in situ*.[33] This oxime when reacted with anthranilic acid affords the 2-(2-nitroethylideneamino)benzoic acid (**44**).[33,34] It is worth mentioning that this reaction is conducted completely under ice cooling to avoid the potential hazards of heating nitromethane.[34] This is considered as an essential modification from the originally reported procedure where the reaction was to be completed by heating up to 55 °C.[33] The cyclization of compound **44** using acetic anhydride / sodium acetate mixture leads to the formation of 3-nitro-4-hydroxyquinoline (**45**).[33] Compound **45** is converted to the corresponding halo derivative **46** upon heating at reflux with $POCl_3$,[35-39] or with $SOCl_2$.[32a] The nucleophilic substitution reaction of this compound with ammonia[35-37] or other secondary amines[32a,38,39] affords compounds **47** and **48**, respectively. The reduction of the nitro group was reported *via* different

techniques; catalytic hydrogenation with 5% Pd/C,[35,36,38,40] Pt/C,[32a] nickel(II) chloride hexahydrate ($NiCl_2.6H_2O$) and sodium borohydride ($NaBH_4$)[32b] or Raney nickel.[38] Having the diaminoquinoline derivatives **42a-b** in hand enables the imidazole ring cyclization in the proceeding step to obtain the desired products **49ai-biv**. According to the type of the ring formed, a diverse variety of reagents can be used, e.g. aliphatic carboxylic acids,[35] aromatic carboxylic acids/HMPA,[36] different carboxylic acids/PPA[37] or HATU,[39,41] different ortho esters,[32a-b,37,38] or the respective aldehydes/sodium pyrosulphate ($Na_2S_2O_7$)[32c] to afford the imidazole ring either with or without substitution on the 2-position (**ZX** = N=CH, N=CR'). The 2-oxoimidazole ring (**ZX** = NHC=O) can be formed through reaction with CDI[34] or diphosgene.[38] Also, the 2-mercaptoimidazole derivatives (**ZX** = N=CSH) can be prepared *via* the reaction with CS_2.[34,42]

1.1.4. 3*H*-IMIDAZO[4,5-*f*]QUINOLINES

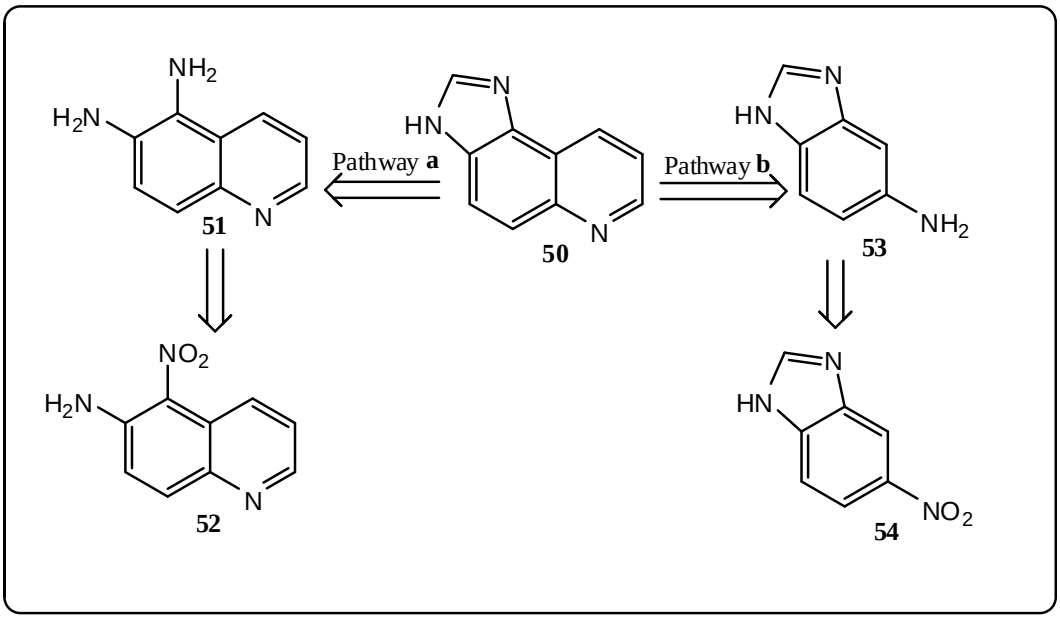


Figure 7. Retrosynthetic pathways for 3*H*-imidazo[4,5-*f*]quinolines

Studying the possible retrosynthetic pathways for the 3*H*-imidazo[4,5-*f*]quinoline **50**, in relation to the reported synthetic approaches, revealed two major pathways (**Figure 7**). Those pathways are classified according to the type of ring to be formed;

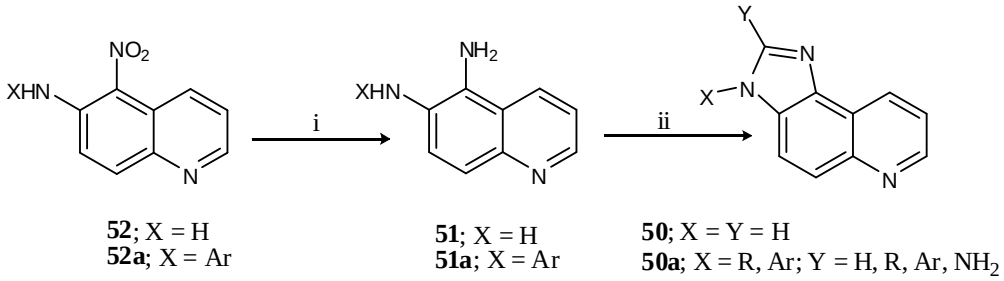
i) Pathway a: *Imidazole-ring* formation

ii) Pathway b: *Pyridine-ring* formation

1.1.4.1. Pathway **a**: *Imidazole-ring* formation

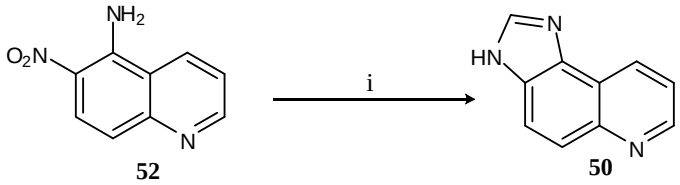
The precursor for this pathway is 5,6-diaminoquinoline (**51**), which can be obtained through the reduction

of the nitro group of compound **52** *via* different approaches.[43-48] As a general protocol, compound **51** can be reacted with different reagents, e.g. carboxylic acids,[49-51] aldehydes[43] or different cyclizing agents, e.g. cyanogen bromide,[44,45] or carbon disulfide,[45] under varying conditions to afford the 3*H*-imidazo[4,5-*f*]quinoline ring system **50** and other related derivatives **50a** (**Scheme 18**).



Scheme 18. Reagents and conditions; i) NO_2 reduction; ii) ring cyclization

It is worth mentioning that compound **50** was reported to be synthesized directly from **52** in a *two-in-one*, one-pot protocol using iron powder and formic acid (**Scheme 19**).[46]



Scheme 19. Reagents and conditions; i) Fe powder, NH_4Cl, 2-PrOH, HCO_2H, 80 °C.

In 1980, 2-amino-3-methylimidazo[4,5-*f*]quinoline (**IQ**), its 2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline analogue (**Me-IQ**) (**Figure 8**) and other structurally-related compounds were isolated as carcinogenic pyrolysate products from protienaceous foods.[52] Pertinent to such findings, several studies have been carried out.

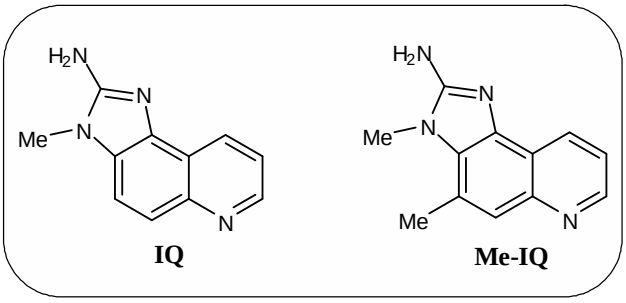
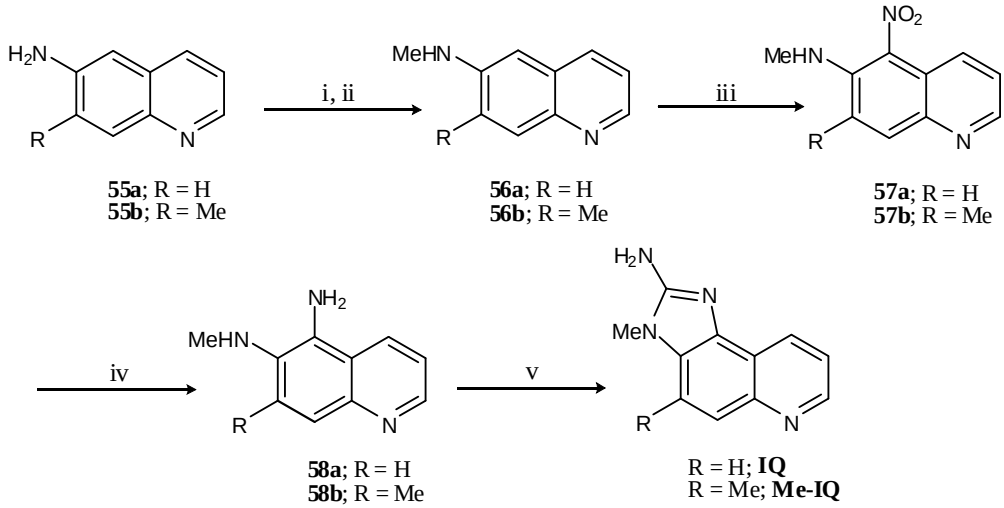


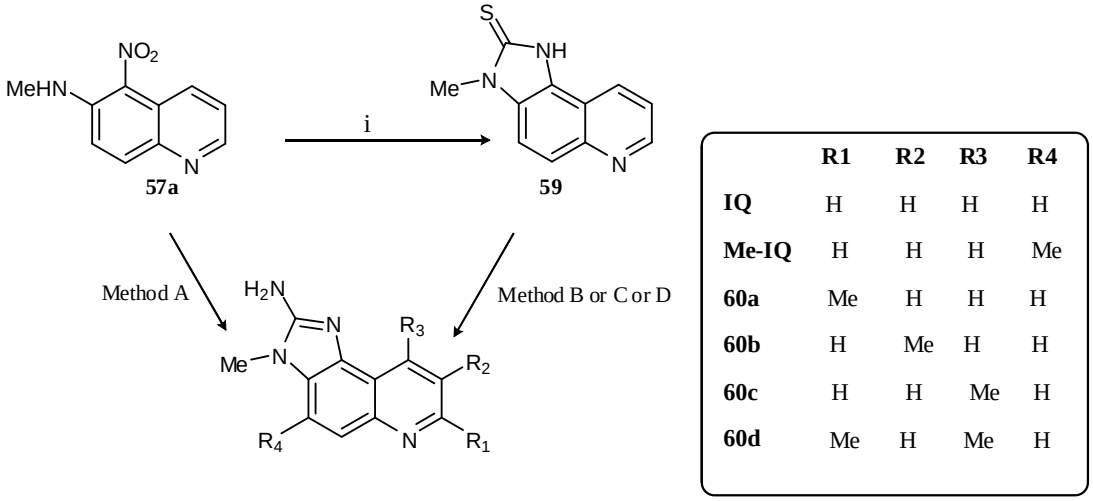
Figure 8. Structures of 2-aminoimidazo[4,5-*f*]quinoline derivatives **IQ** and **Me-IQ**

In order to verify the final structure and establish a detailed biological profile for such group of compounds, many synthetic trials have been reported.[44,45,53-56] In this context, Lee *et al.* were able to synthesize azaaromatic mutagenic ring systems in a simple high-yielding procedure.[54] Starting with 6-aminoquinoline (**55a**) or its 7-methyl analogue **55b**, the *N*-methylated derivatives **56a,b** were prepared. In this context, formylation of compounds **55a,b** followed by reduction with $LiAlH_4$ afforded the target 6-(methylamino)quinoline derivatives **56a,b**. The selective mononitration of **56a,b** at position 5 was achieved using conc. H_2SO_4 – conc. HNO_3 mixture. The diaminoquinoline derivatives **58a,b**, produced from the reduction of the nitro group, were reacted with cyanogen bromide to yield **IQ** and **Me-IQ** in 35% and 30% yields, respectively (**Scheme 20**).



Scheme 20. Reagents and conditions; i) Ac_2O - HCO_2H / rt / stirring; ii) $LiAlH_4$ / THF / 0 °C; iii) conc HNO_3 - conc H_2SO_4 / 0 °C; iv) H_2-Pd/C / AcOH/ rt; v) BrCN / MeOH / rt.

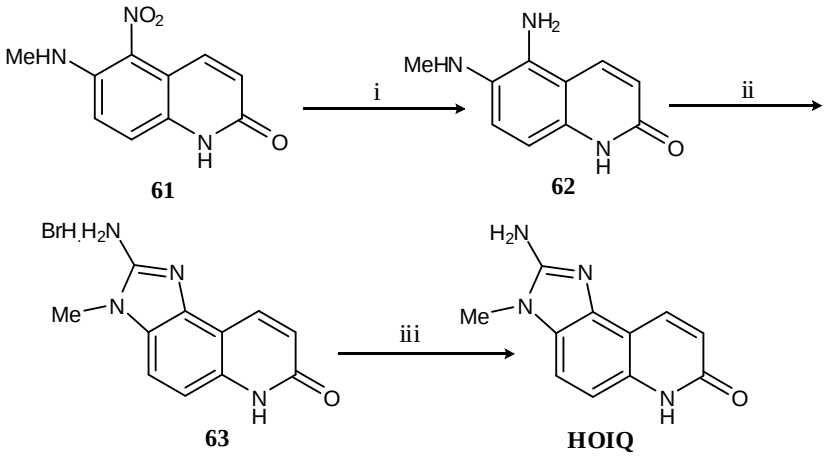
Furthermore, in 1994, Ronne and his co-workers synthesized **IQ**, **Me-IQ** and many structurally-related compounds **60a-d** with the aim of establishing a detailed structure-activity relationships study for such health hazardous products.[45] The small-scale synthesis of the compounds were achieved *via* two pathways starting from the same precursor, **57a**. The first approach was to react the *in situ*-formed diaminoquinoline derivative directly with cyanogen bromide to afford **IQ**. The reaction of **IQ** with *tert*-butyl hydroperoxide afforded its methylated derivatives, **Me-IQ,** and **60a-d** in 27–47% yields, respectively (**Scheme 21, Method A**). The second approach was introduced to avoid the use of the highly toxic, hazardous reagent cyanogen bromide according to the method of Ziv *et al.*,[56] but with certain modifications. This multi-step synthetic pathway was to prepare the 2-mercaptoimidazo[4,5-*f*]quinoline **59** as a center for amination through varying routes (**Scheme 21, Methods B, C, & D**).[45]



	R1	R2	R3	R4
IQ	H	H	H	H
Me-IQ	H	H	H	Me
60a	Me	H	H	H
60b	H	Me	H	H
60c	H	H	Me	H
60d	Me	H	Me	H

Scheme 21. Reagents and conditions; i) $Na_2S_2O_4$ / MeOH / 25% aq. NH_3 / reflux / CS_2 / MeOH / reflux; Method A. 1) H_2 - Raney Ni / EtOH / rt / BrCN, 2) 70% aq. *t*-butyl hydroperoxide / $FeSO_4$ /1 *M* H_2SO_4 / rt; Method B. 1) MeI / reflux, 2) $KMnO_4$ - AcOH / rt, 3) $NaNH_2$- liq. NH_3/ reflux or NH_3 - EtOH / 150 °C; Method C. 1) $SOCl_2$ - $POCl_3$ / reflux, 2) $NaNH_2$ - liq. NH_3 / reflux or NH_3 - EtOH / 150 °C; Method D. 1) H_2O_2 / rt, 2) $NaNH_2$ - liq. NH_3 / reflux or NH_3 - EtOH /150 °C.

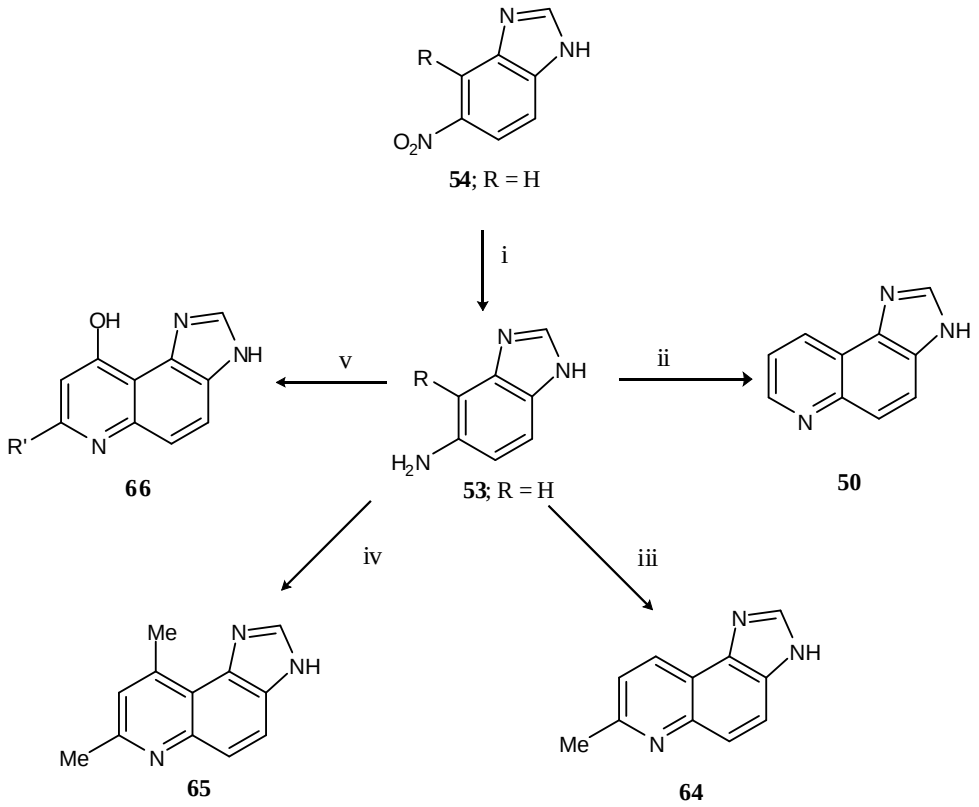
In continuation of the detailed studies on the mutagenicity and carcinogenicity of **IQ** and **Me-IQ**, the 2-amino-3,6-dihydro-3-methyl-7*H*-imidazo[4,5-*f*]quinolin-7-one (**HOIQ**) was identified as a metabolite of **IQ**. In contrast to **IQ**, **HOIQ** is an active, potent, direct-acting mutagenic metabolite produced by the action of human intestinal flora on **IQ**. The preparation of **HOIQ** is outlined in **Scheme 22**.[44]



Scheme 22. Reagents and condiions; i) H_2Pd/C, rt; ii) MeOH, rt; iii) 1*N* NaOH.

1.1.4.2. Pathway **b**: *Pyridine-ring* formation

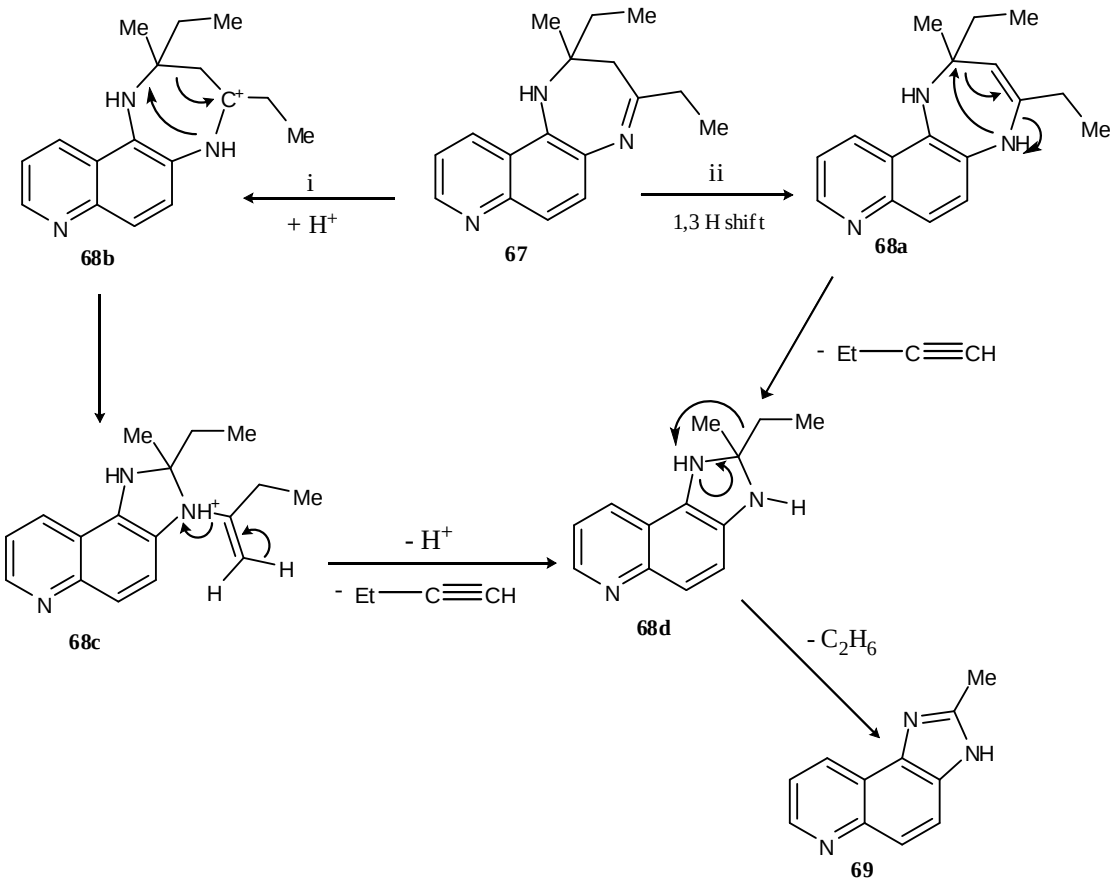
The cornerstone precursor for this pathway is the 5-aminobenzimidazole (**53**). The general pathway for the quinoline ring formation can start with the catalytic reduction of 5-nitrobenzimidaole **54** to afford the corresponding amino derivative **53**. The pyridine-ring cyclization is achieved through the adaptation of Skraup's/Doebner–von Miller[57] or Conrad – Limpach[57] methods for quinoline synthesis. The condensation of the resulting amino group with different unsaturated carbonyl derivatives, e.g. acrolein,[58,59] crotonaldehyde,[47,48,60] methyl propenyl ketone,[48] or different β-ketoesters[48, 61, 62] followed by cyclization, yields the imidazo[4,5-*f*]quinolines **50** or the substituted analogues **64**-**66**, respectively (**Scheme 23**). It is worth mentioning that if the 4(7)-position of the benzimidazole ring -where cyclization occurs - is occupied (i.e. R ≠ H), the linear imidazo[4,5-*g*]quinolines will be formed instead.[47]



Scheme 23. Reagents and conditions; i) Pd-C or Ra-Ni/ H_2, or Sn /HCl, or Fe / NH_4Cl; ii) glycerol / conc H_2SO_4; iii) crotonaldehyde / conc HCl; iv) methyl propenyl ketone / conc HCl; iv) (a) $R'COCH_2CO_2Et$, (b) reflux.

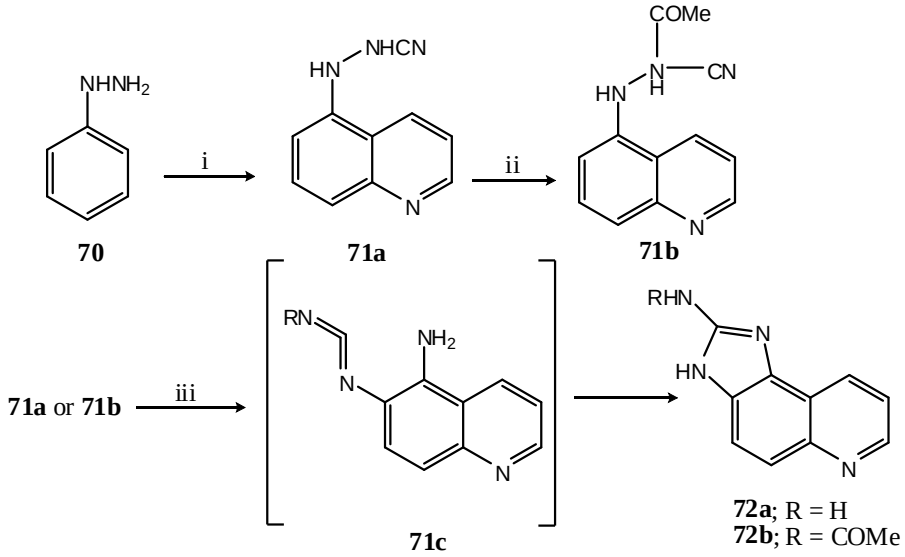
As a minor synthetic pathway, the imidazo[4,5-*f*]quinoline **69** was also reported to be prepared through a ring-transformation strategy.[63] The imidazo[4,5-*f*]quinoline **69** was formed through the course of studying the stability of 2,2,4-trialkyl-2,3-dihydro-1*H*-[1,4]diazepino[2,3-*f*]quinolines (**67**) after treatment with acidic or at elevated-temperature conditions.[63] A plausible mechanism for this reaction is outlined in

Scheme 24. Under thermal conditions, the ring transformation takes place through a 1,3-hydrogen shift followed by an alkyne group and a bulky alkane elimination to afford compound **69**. On the other hand, under acidic conditions, the diazepine **67** is first protonated and then undergoes a stepwise loss of alkyne, proton and finally a bulky alkane. Such ring contraction accompanied by a bulky group loss has been previously reported.[64]



Scheme 24. Reagents and conditions: i) 180-200 °C; ii) methanolic HCl, reflux.

Another minor pathway is to begin with 5-hydrazinoquinoline (**70**) as a starting material. In this approach, the heterocyclic cyanamide **71a** or its acetyl derivative **71b** undergo a smooth rearrangement under thermal conditions to afford the 2-aminoimidazo[4,5-*f*]quinolines **72a,b** (**Scheme 25**).[65] This reaction is suggested to happen *via* a [3.3] sigmatropic rearrangement of either compound **71a** or **71b** to form the intermediate **71c**, followed by an intramolecular cyclization, aromatization, and a hydrogen shift.



Scheme 25. Reagents and conditions; i) BrCN / Et_2O; ii) MeCOCl / TEA; iii) diphenyl ether / 90 °C.

1.1.5. 3*H*-IMIDAZO[4,5-*h*]QUINOLINES

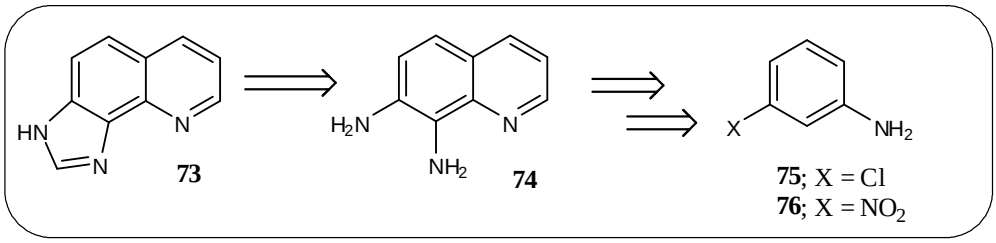
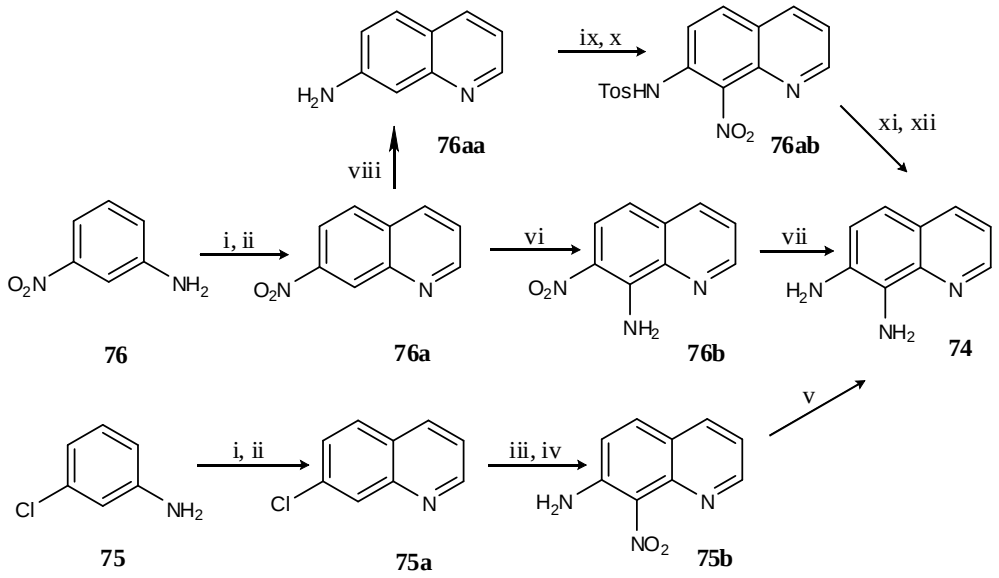


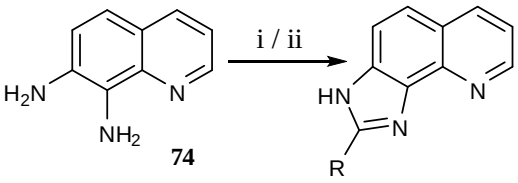
Figure 9. Retrosynthetic plan for 3*H*-imidazo[4,5-*h*]quinolines

In general, 3*H*-imidazo[4,5-*h*]quinoline (**73**) can be prepared through two successive ring-closure procedures; the closure of the quinoline ring, followed by the imidazole ring. Consequently, the quinoline ring was reported to be synthesized *via* Skraup's reaction protocol from either 3-chloroaniline (**75**)[59] or the 3-nitro analogue **76**[66,67] to afford **75a** and **76a**, respectively. Accordingly, different procedures for introduction of the 7,8-diamino functionalities to the quinoline nucleus were investigated, to afford **74**. The nitration of **75a** followed by aminolysis afforded compound **75b**.[59] This aminonitroquinoline derivative **75b** was reduced using catalytic hydrogenation to yield compound **74**.[59] On the other hand, the 7-nitroquinoline **76a** was reacted with hydroxylamine to introduce the 8-amino functionality and afford the 8-amino-7-nitroquinoline analogue **76b**.[67,68] Alternatively, the protection of **76aa**[66] with toluenesulfonyl chloride followed by nitration afforded **76ab**.[66] The deprotection of **76ab** proceeded by reduction of the nitro group yielded compound **74** in an improved procedure[66] (**Scheme 26**).



Scheme 26. Reagents and conditions; i) Skraup's reaction; ii) isomer separation; iii) conc H_2SO_4, KNO_3, - 10 °C; iv) NH_3, 180 atm., 160 °C; v) 5% Pd / C, H_2; vi) $NH_2OH.HCl$ / KOH; vii) Ni, N_2H_4 or $SnCl_2$, HCl; viii) Fe, 50% AcOH; ix) toluenesulfonyl chloride, pyridine, reflux; x) conc HNO_3, 60-70 °C; xi) conc H_2SO_4; xii) $SnCl_2$, HCl.

This 7,8-diaminoquinoline derivative **74** is considered as the building block for the imidazole ring-closure step. The reaction of **74** either with nitriles in the presence of polyphosphoric acid at 250 °C[59,69,70] or formic acid / HCl yielded the desired ring system **73a-g** or **73**, respectively (**Scheme 27**).



No.	R	No.	R
73	H	**73d**	4-Ph-2-pyridyl
73a	2-pyridyl	**73e**	2,2'-biphenyl-6-yl
73b	4-Me-2-pyridyl	**73f**	2-phenanthroyl
73c	4-Et-2-pyridyl	**73g**	2-isoquinidin-3-yl

Scheme 27. Reagents and conditions; i) RCN, PPA; ii) HCO_2H, HCl.

1.1.6. 4*H*-and 6*H*-IMIDAZO[4,5,1-*ij*]QUINOLINES

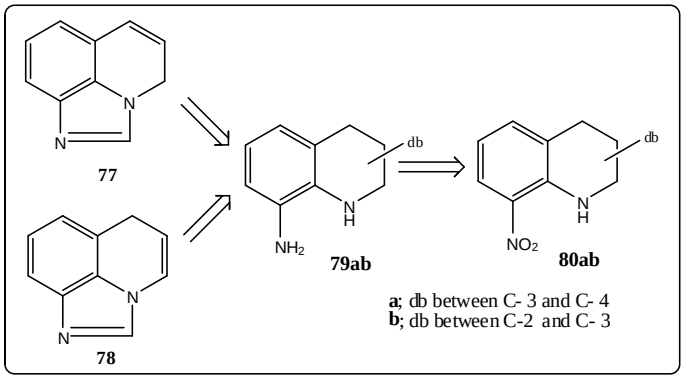
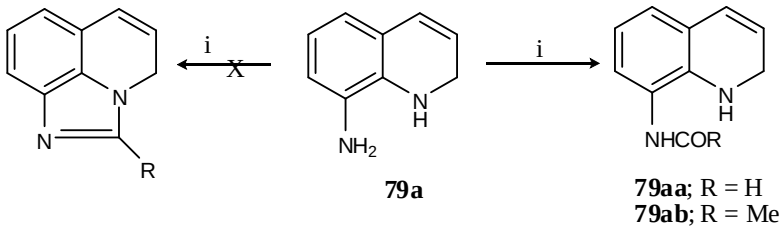


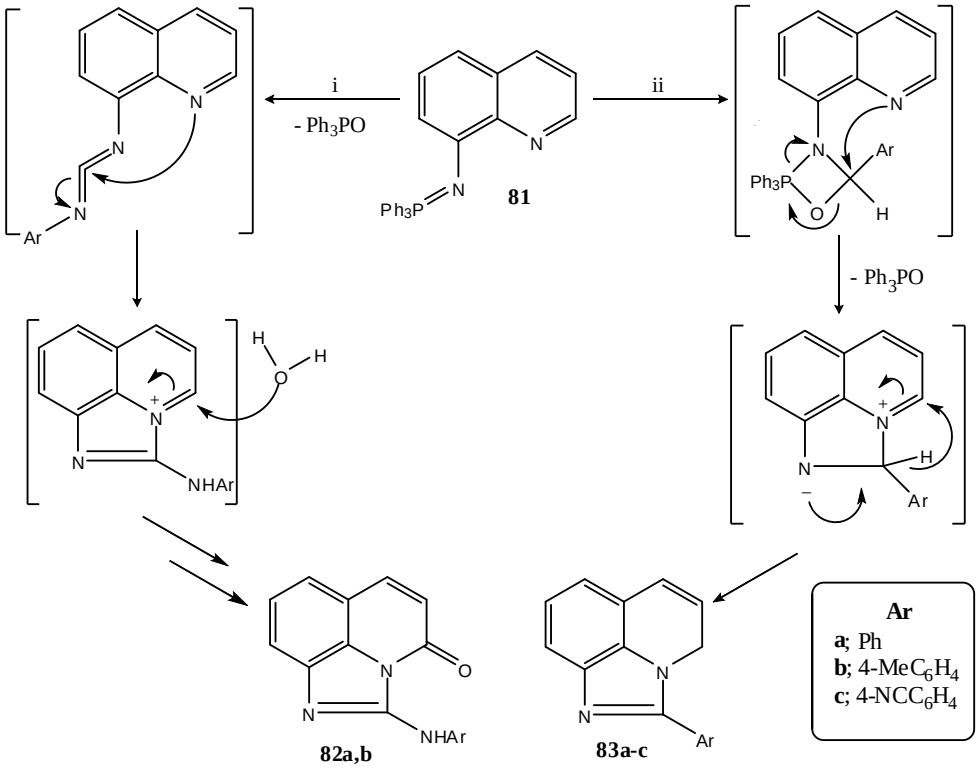
Figure 10. Retrosynthetic plan for 4*H*- and 6*H*-imidazo[4,5,1-*ij*]quinolines

Theoretically, from a retrosynthetic point of view, 8-aminoquinoline nuclei **79a,b** should be the most common precursors for the synthesis of this class of compounds, as shown in **Figure 10**. On the contrary, the reaction of 8-amino-1,2-dihydroquinoline (**79a**) with formic or acetic acid was reported to afford only the formylated and the acetylated derivatives **79aa** and **79ab**, respectively (**Scheme 28**).[71]



Scheme 28. Reagents and conditions; i) RCO_2H, reflux.

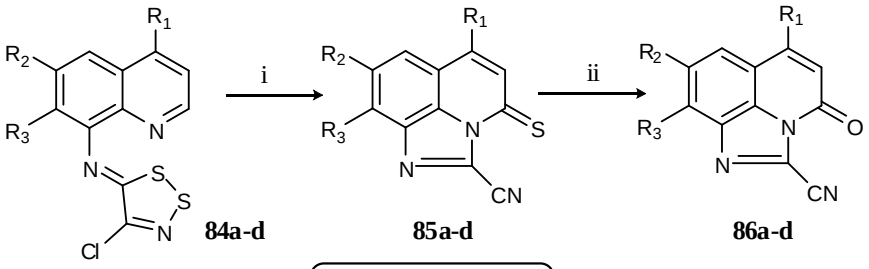
An alternative approach for the preparation of compounds possessing the 4*H*-imidazo[4,5,1-*ij*] quinoline skeleton **77** was reported through the reaction of 8-triphenylphosphoiminoquinoline **81** with aryl isocyanates and aryl aldehydes to yield the series **82a,b** and **83a-c**, respectively (**Scheme 29**).[72]



Scheme 29. Reagents and conditions; i) ArNCO, anhydrous benzene, 80 °C, sealed tube; ii) ArCHO, anhydrous xylene, 125 °C, sealed tube.

Besson *et al.* have reported a novel approach for the preparation of the 2-cyano-4*H*-imidazo[4,5,1-*ij*]quinoline-4-thiones **85a-d** through a pericyclic reaction. The quinolinic

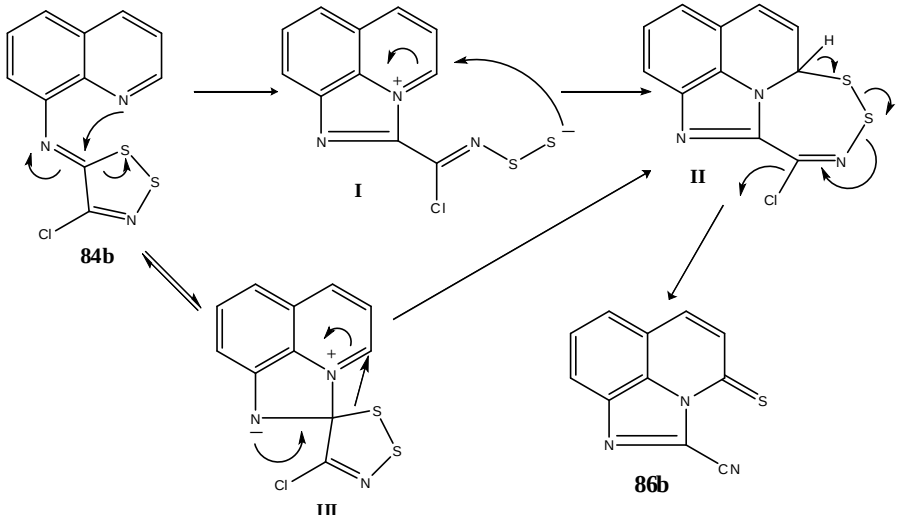
nitrogen atom participates in this reaction with the formation of the imidazole ring and the insertion of a sulphur atom in 4-position of the delineated ring. Those thiones (**85a-d**) are easily oxidized to their corresponding 4-one derivatives **86a-d** upon stirring with cupric nitrate in acetic anhydride at room temperature (**Scheme 30**).[73]



	R_1	R_2	R_3
a	Ph	OMe	H
b	H	H	H
c	Ph	H	H
d	H	H	Me

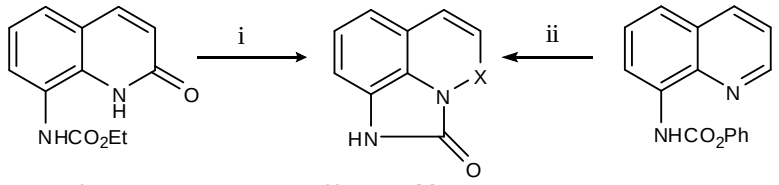
Scheme 30. Reagents and conditions; i) 250 °C; $Cu(NO_3)_2.8\ H_2O$, Ac_2O, stirring, rt.

A plausible mechanism for this thermo-rearrangement reaction is explained by the contribution of the quinoline nitrogen as a nearby nucleophile to divert the reaction to the imidazoquinolinium species **I**. This species could form a tetracyclic intermediate **II** to deliver the sulfur atom to the 2-position on the quinoline ring. Elimination of a hydrogen chloride and sulfur from **II** leads to the formation of the desired ring system **86b** (**Scheme 31)**.[73]



Scheme 31. Thermo-rearrangement reaction mechanism

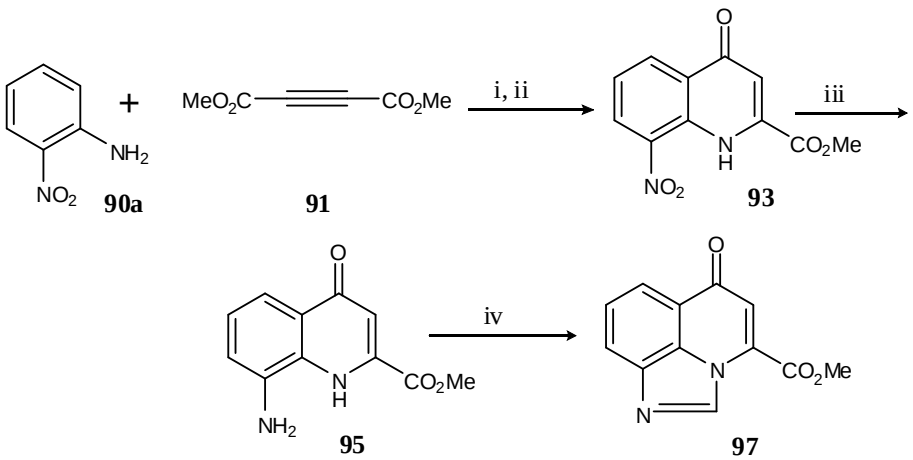
Furthermore, the synthesis of 1,2-dihydro-4*H*-imidazo[4,5,1-*ij*]quinoline-2,4-dione (**89a**) and 4*H*-imidazo[4,5,1-*ij*]quinolin-2-one (**89b**) have been reported to proceed either *via* the thermolysis of the ethyl *N*-(2-oxo-1,2-dihydroquinolin-8-yl)carbamate derivative **87**[74] or the reaction of the phenyl carbamate **88** with sodium borohydride respectively.[75] It is worth mentioning that the thermolysis of **87** is associated with the elimination of an ethanol molecule. In case of the phenyl carbamate **88**, the ring cyclization is facilitated through the addition of the hydride to the 2-position of the quinoline ring with the elimination of a phenoxide ion (**Scheme 32**).



87 **89a**; X = CO **89b**; X = CH_2 **88**

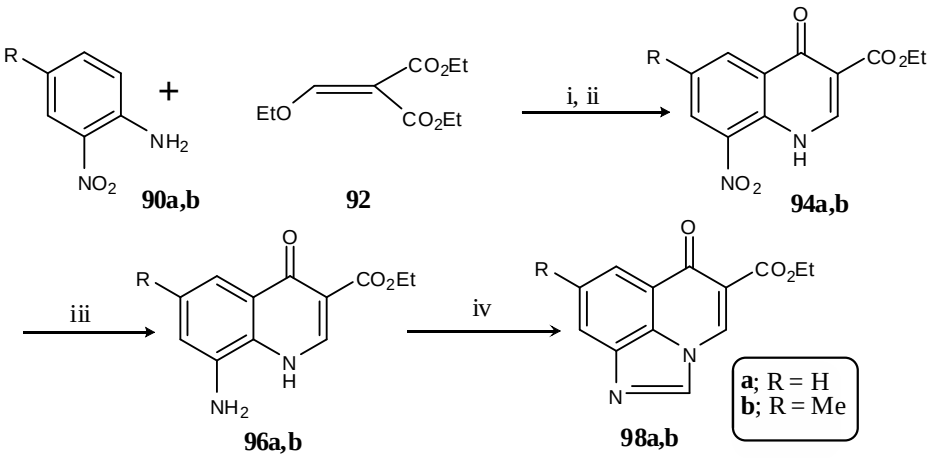
Scheme 32. Reagents and conditions; i) 190 °C; ii) $NaBH_4$, EtOH-THF.

Preparation of 6-oxo-6*H*-imidazo[4,5,1-*ij*]quinoline-4-carboxylic acid methyl ester (**97**) and 5-carboxylic acid ethyl esters **98a,b** were reported to proceed *via* the corresponding 8-amino-4-oxo-1,4-dihydroquinoline-2- and -2,3-(di)carboxylates **95** and **96a,b**, respectively. Stepwise total syntheses of compounds **97** and **98a,b** are illustrated in Schemes **33** and **34**, respectively. Namely, reacting the 2-nitroaniline (**90a)** with dimethyl acetylenedicarboxylate (**91**) (as illustrated in **Scheme 33**) or **90a** and its 4-methyl derivative **90b** with diethyl ethoxymethyenemalonate **92** (as illustrated in **Scheme 34**) afforded the 2-substituted quinolin-4-one **93** and the 3-substiuted quinolin-4-ones **94a,b**, respectively. Reduction of the 8-nitro group on the quinoline ring followed by the reaction with triethyl orthoformate afforded compounds **97** and **98a,b**, respectively.[76]



90a **91** **93** **95** **97**

Scheme 33. Reagents and conditions; i) MeOH; ii) Dowtherm A or PPA; iii) Pd/C, H_2; iv) $HC(OEt)_3$, reflux.



Scheme 34. Reagents and conditions; i) Dowanol DM; ii) Dowtherm A; iii) Pd/C, H_2; iv) $HC(OEt)_3$, reflux.

2.1. LINEAR IMIDAZOQUINOLINES

2.1.1. 1*H*-IMIDAZO[4,5-*b*]QUINOLINES

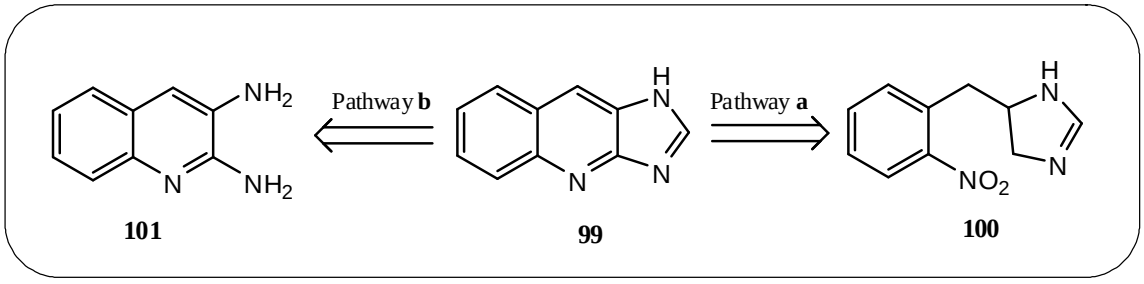
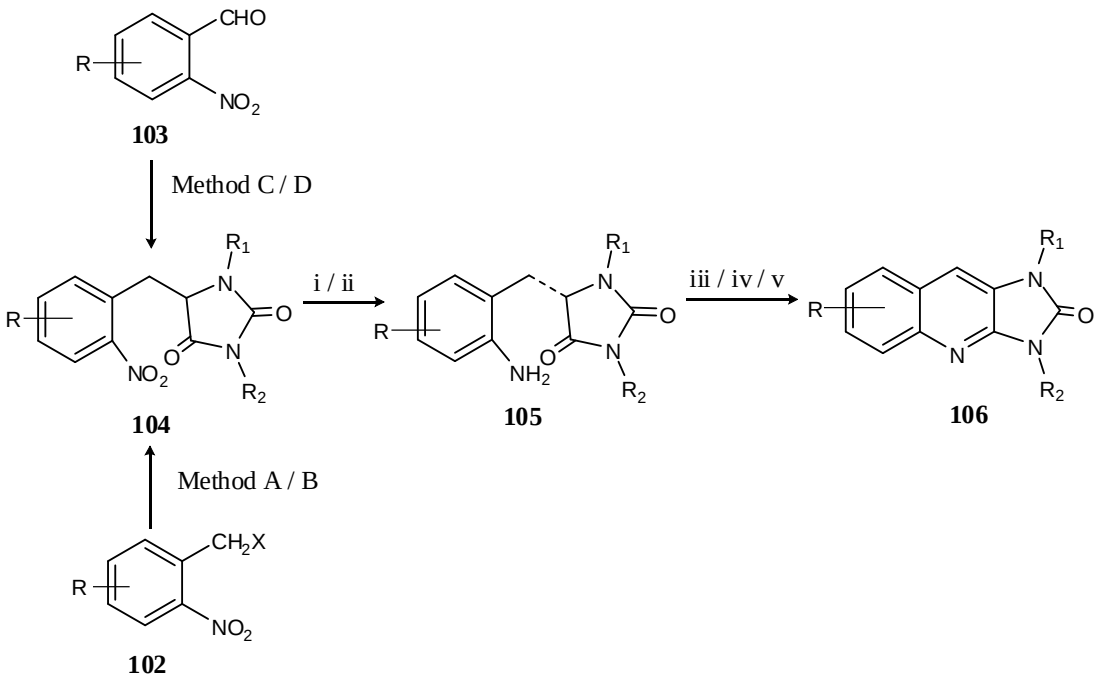


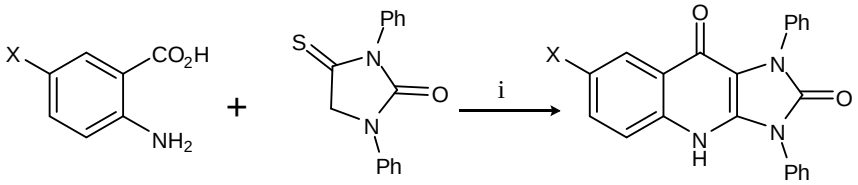
Figure 11. Retrosynthetic pathways for the imidazo[4,5-*b*]quinolines

Investigating the retrosynthetic routes for this imidazoquinoline (**99**) lead us to two main possibilities; namely, a central *pyridine*-ring closure of compound **100** (Pathway **a**, **Figure 11**) or *imidazole*-ring formation from compound **101**[67] (Pathway **b**, **Figure 11**). In reality, Pathway **a** is the most common, well-accessed protocol while none of the reported procedures refers to making use of Pathway **b** as a synthetic approach. Other minor pathways, e.g. ring contraction,[77] and Beckmann rearrangement,[78] have also been reported. Accordingly, the synthesis of imidazo[4,5-*b*]quinoline-2-one scaffold **106**, as an example for this imidazoquinolines, is described in the following general scheme. The synthetic plan starts with the introduction of an imidazole ring to the substituted 2-nitrobenzyl halides **102** or substituted 2-nitrobenzaldehydes **103** by implementing different methods, e.g. A / B or C / D, respectively. The reduction of the nitro group of the hydantoin derivatives **104** is reported to afford **105**. Finally, the dehydrative cyclization and aromatization of **105** yields the imidazoquinolines **106** (**Scheme 35**).[79-81]



Scheme 35. Reagents and conditions; **Method A**: **a**) AcNHCH(CO_2Et)$_2$ / NaOEt / reflux, **b**) 6*N* HCl / reflux, **c**) KCNO / steam bath, **d**) H_3O^+ / reflux or EtOH / HCl / reflux; **Method B**: **a**) Ethyl hydantoin-5-carboxylate sodium salt / EtOH / reflux, **b**) 6N HCl / reflux; **Method C**: **a**) hydantoin or 1-methylhydantoin / NaOAc / Ac_2O / reflux, **b**) OH^-; **Method D**: **a**) phosphonates / OH^- / rt; i) H_2 / DMF / Pd - C, or PdS-C, or Pd - $BaSO_4$; ii) Fe / $FeSO_4$/ MeOH / H_2O / reflux; iii) I_2 / MeOH / reflux, or Pd - C / DMF / reflux; iv) a) TsOH / MeOH / reflux, b) I_2 / MeOH / reflux; v) *hv* / AcOH / rt.

In a similar manner, anthranilic acid (**43**) or its substituted derivatives **107a,b** were used for the preparation of the imidazo[4,5-*b*]quinoline-2,4-diones **109a-c**. The reaction of diphenylthiohydantoin **108** with **43** and **107a,b** in refluxing methanol yielded the imidazo[4,5-*b*]quinolin-2,9-dione series **109a-c** in 70, 75 and 67% yields, respectively (**Scheme 36**).[82]



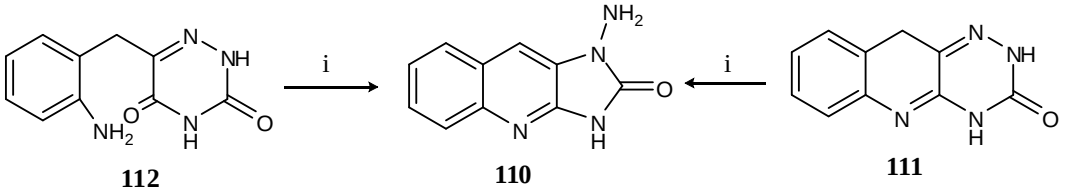
44; X = H
107a; X = Cl
107b; X = I

108

109a; X = H
109b; X = Cl
109c; X = I

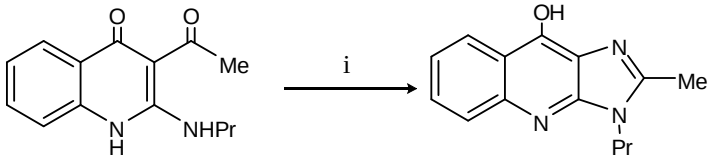
Scheme 36. Reagents and conditions; i) MeONa / MeOH, reflux.

Other derivatives, e.g. 1-aminoimidazo[4,5-*b*]quinolin-2-one (**110**)[77] and 9-hydroxy derivative **113**[78] were reported to be prepared *via* short synthetic pathways. Compound **110** was isolated as an unexpected ring contraction product of 1,2,4-triazine moiety **111** under slightly acidic conditions. The structure was confirmed through an independent preparation from the open-ring precursor **112** (**Scheme 37**).[77]



Scheme 37. Reagents and conditions; i) dil HCl, reflux.

In **Scheme 38**, the 9-hydroxyimidazo[4,5-*b*]quinoline derivative **113** was prepared *via* a Beckmann rearrangement mechanism. This microwave-assisted one-pot reaction of hydroxylamine hydrochloride with 3-acetyl-2-(propylamino)-1,4-dihydroquinolin-4-one (**114)** yielded **113** in 75% yield, along with other minor products.[78]



Scheme 38. Reagents and conditions; i) $NH_2OH.HCl$ / MW.

2.1.2. 3*H*-IMIDAZO[4,5-*g*]QUINOLINES

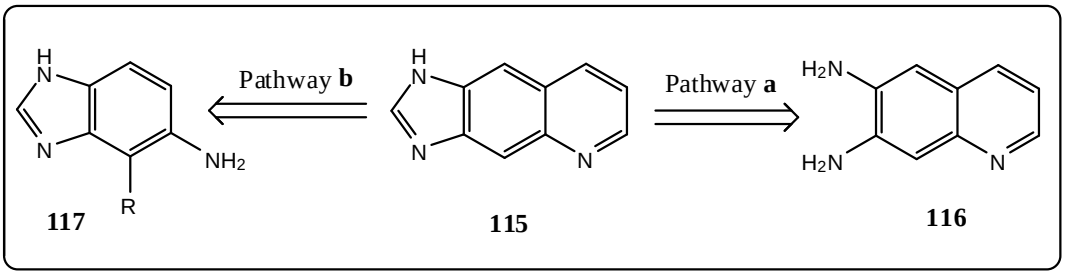
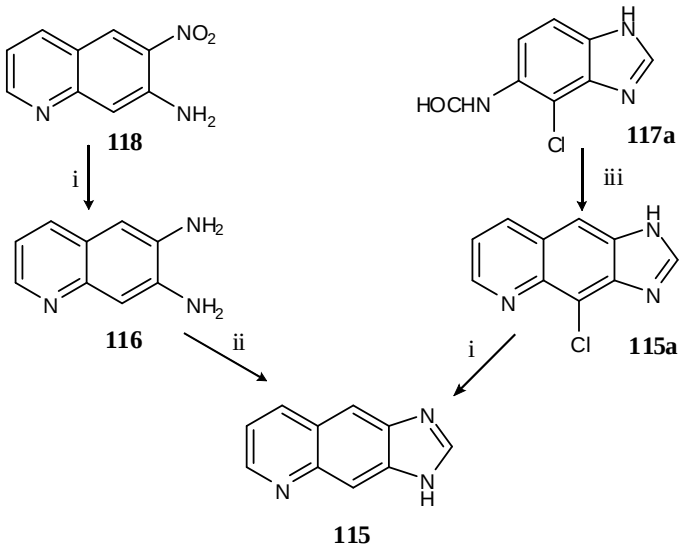


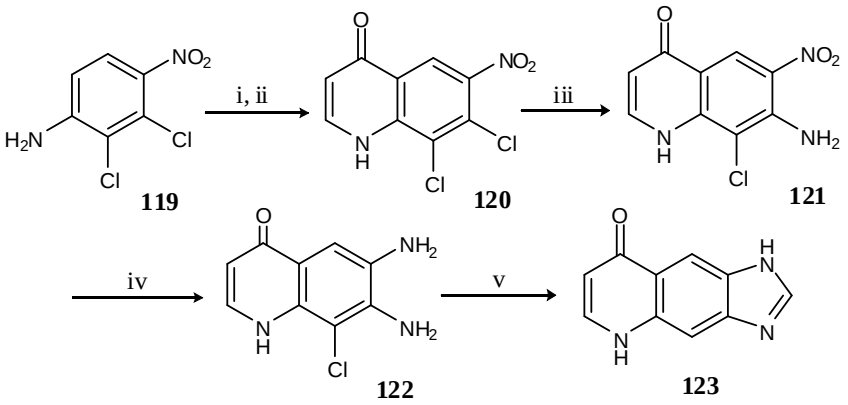
Figure 12. Retrosynthetic pathway for 3*H*-imidazo[4,5-*g*]quinolines

Pertinent to the already discussed synthetic strategies, the imidazo[4,5-*g*]quinolines can be prepared using either from 6,7-diaminoquinoline (**116**) or the 4-substiuted-5-aminobenzimidazole **117**, as starting materials, as shown in **Figure 12**. In the second case, blocking of position 4 (R ≠ H) is necessary to prevent the formation of the angular imidazo[4,5-*f*]quinolines.

Scheme 39 illustrates the two approaches for the preparation of the parent imidazo[4,5-*g*]quinoline **115**.[83] The utilization of other typical quinoline synthetic approaches, e.g. Gould–Jacobs, can lead to the formation of 5,8-dihydroimidazo[4,5-*g*]quinolin-8-one **123** (**Scheme 40**).[84]

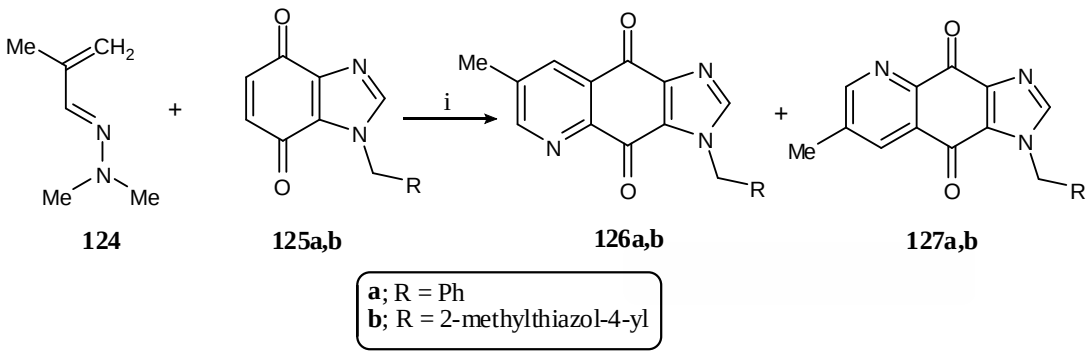


Scheme 39. Reagents and conditions; i) Ra-Ni, H_2; ii) HCO_2H; iii) Skraup's reaction.



Scheme 40. Reagents and conditions; i) Gould-Jacobs; ii) Dowtherm, 250 °C; iii) NH_3; iv) Pd-C, H_2; v) HCO_2H, reflux.

An effective procedure using a Diels–Alder methodology has been developed for the synthesis of 4,9-dihydroimidazo[4,5-*g*]quinolin-4,9-dione derivatives **126a,b** and **127a,b** (**Scheme 41**). The regiochemistry of the cycloadditions of azadiene **124** with quinones **125a,b** agrees with the calculations of the semi–empirical method PM3.[85]



Scheme 41. Reagents and conditions; i) EtOH, rt.

CONCLUSION

The imidazoquinolines are fully synthetic scaffolds with diverse biopharmaceutical applications that are mainly attributed to the variable possible positions of fusion between the imidazole and quinoline rings. Interestingly, their members possess activities ranging from being potent carcinogens to being effective anticancer chemotherapeutic agents. Accordingly, a growing area of research is directly related to the development of new synthetic methodologies and strategies for these significant scaffolds.

In general, this fused heterocyclic system can be prepared *via* two major synthetic plans: *pyridine*-ring formation followed by the *imidazole* one or *vice versa*. According to the type of imidazoquinolines and the nature of substituents, either one of these two synthetic strategies can be adopted. Nevertheless, this field is still in need of future work to improve the methodologies and to implement new approaches to achieve clean, cost-effective, efficient, large-scaled products, as well as to explore and discover novel biological and pharmaceutical applications.

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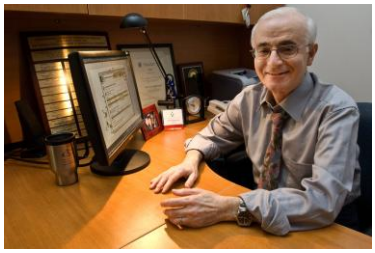

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