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Synthesis of pyrrolo(pyrido)[1,2-a]quinazolinones and their benzoannulated analogues: An overview

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A B S T R A C T

Angular pyrrolo(pyrido)[1,2-*a*]quinazolinones, being structurally isomeric to linear pyrrolo(pyrido)[2,1-*b*]quinazolinone alkaloids, are attractive molecular systems for both synthetic transformations and targeted biomedical research. The pyrrolo(pyrido)[1,2-*a*]quinazolinone scaffold has proven to be quite effective in the search for compounds with a wide range of pharmacological activities, e.g. anti-inflammatory, antioxidant, antibacterial, antiarrhythmic, and inhibitors of important biotargets. The present review summarises the methods for the synthesis of pyrrolo(pyrido)[1,2-*a*]quinazolinones as a comprehensive research object, especially in the past decade. They are systematised according to the type of heteroannulation and include the processes of cascade annulation of the pyrimidine and pyrrole (pyridine) cycles to anthranilamides (hydrazides); formation of a pyrimidine nucleus based on *ortho*-pyrrolyl(pyridinyl) substituted aromatic compounds; annulation of the pyrrole (pyridine) nucleus to a quinazolinone scaffold. It is expected that the generalised material presented will serve as a reliable guide for the rational design of new pharmacologically oriented compounds.

1. Introduction

Nitrogen containing heterocyclic compounds constitute a unique class of organic structures endowed with a wide range of synthetic and biological applications.[1-4] Pyrrolo- and pyridoquinazolinone systems are important representatives of tricyclic nitrogen-containing compounds that are part of many natural products and a significant number of pharmaceuticals.[5-8] For example, a linearly condensed pyrrolo[2,1-*b*]quinazolinone fragment is a key structure element of deoxyvasicinone **I** alkaloids.[9] Prominent representatives of linearly condensed alkaloids containing the pyrido[2,1-*b*]quinazolinone fragment are mackinazolinone **II**,[10] rutaecarpine **III**[11] and related structures[12-14] (**Fig. 1**). Of particular pharmacological interest are synthetic exofunctionalised analogues of pyrrolo[2,1-*b*]quinazolones, which are characterised by antitumour[15,16] and antimicrobial activity,[17] are effective in the treatment of Alzheimer's disease,[18,19] as well as pyrido[2,1-*b*]quinazolinones, with biological effects including anticancer, antimalarial,[20] antihypertensive, anti-inflammatory,[14,21] and anti-tuberculosis activities.[22]

Just as significant are the angular pyrroloannulated quinazoline-4(3*H*)-ones, among which it is worth noting the isomeric to deoxyvasicinone **I** pyrrolo[1,2-*a*]quinazolone **IV** (**Fig. 1**), first found in the Chestnut honey[23] in 2015, though synthetically obtained much earlier.[24] Quite promising for medicinal chemistry are the derivatives of angular pyrroloquinazoline-4(3*H*)-ones, which demonstrate a wide range of biological effects, e.g. anti-inflammatory **V**,[25] antioxidant and antibacterial **VI**,[26-28] antiarrhythmic **VII**,[29] and inhibitors targeting bromodomains **VIII**.[30] Their indolo[1,2-*a*]quinazolinone analogues have attracted considerable attention as inhibitors of protein kinase CK2[31] and poly(ADP-ribose)polymerase-1 (PARP-1) **IX**.[32]

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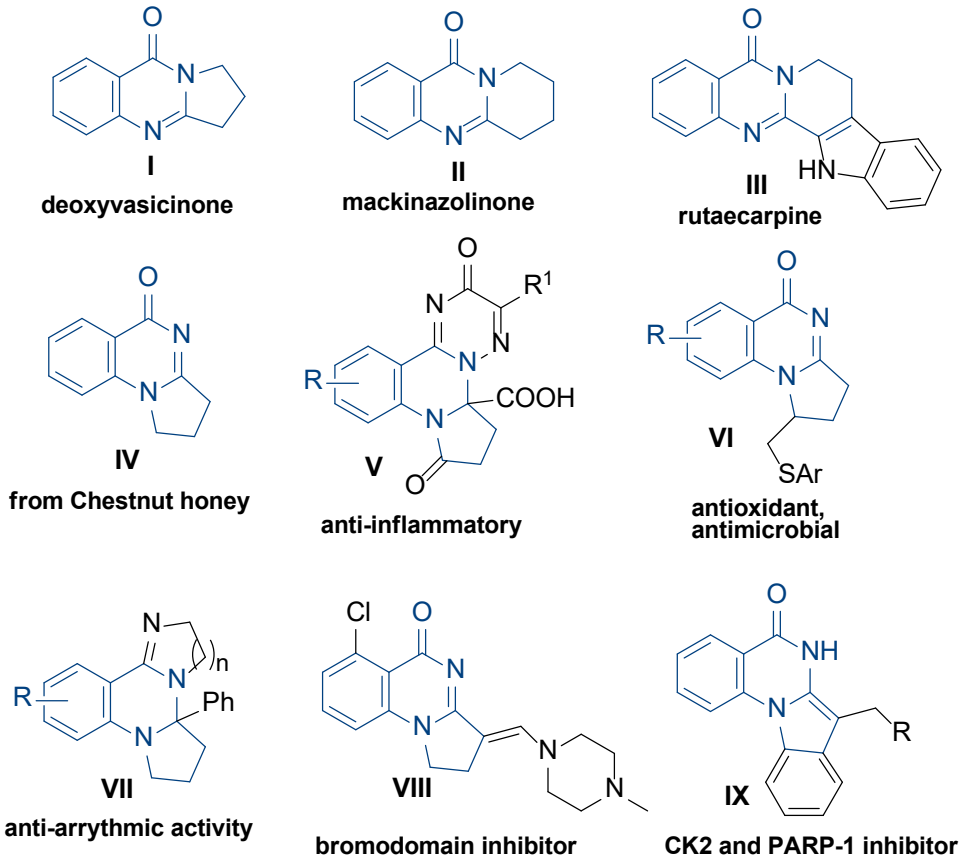


Fig. 1. Structures of pyrrolo(pyrido)[2,1-*b*]quinazolone alkaloids and some bioactive derivatives of pyrrolo[1,2-*a*]quinazolinones.

Overall, pyrrolo(pyrido)[1,2-*a*]quinazolines seem to be very attractive compounds for both structural and biomedical research. Some aspects of the approaches to their synthetic design were reflected in previously published literature reviews.[6,33-35] However, no attempt was yet made to systematise and generalise the methods for the preparation of angular pyrido[1,2-*a*]quinazolinones and to discuss them together with pyrroloannulated analogues. Therefore, a systematic analysis and compilation of the literature on the methods of synthesis of angular pyrrolo(pyrido)[1,2-*a*]quinazolinones and their annulated analogues was reasonable and justified.

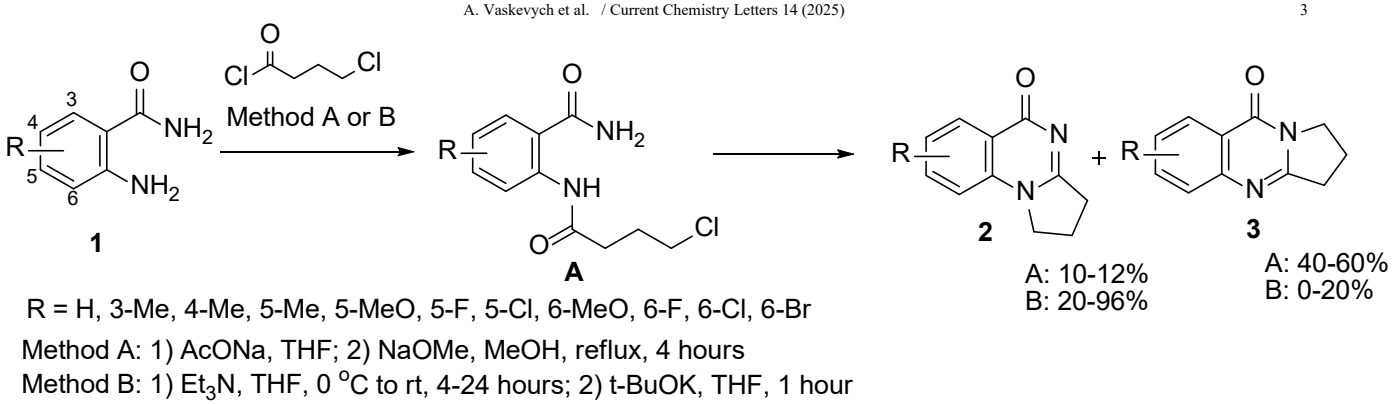
2. Synthesis of pyrrolo[1,2-*a*]quinazolinone derivatives

Several general synthetic approaches were developed for the construction of angular pyrrolo[1,2-*a*]quinazolones, which include a) cascade annulation of the pyrimidine and pyrrole cycles to the aromatic nucleus of anthranilamides or anthranilhydrazides; b) formation of a central pyrimidine nucleus based on some *ortho*-pyrrolyl-substituted aromatic compounds; c) annulation of the pyrrole cycle to the basic quinazolinone nucleus.

2.1. Tandem cyclizations of ortho-substituted benzamides(hydrazides)

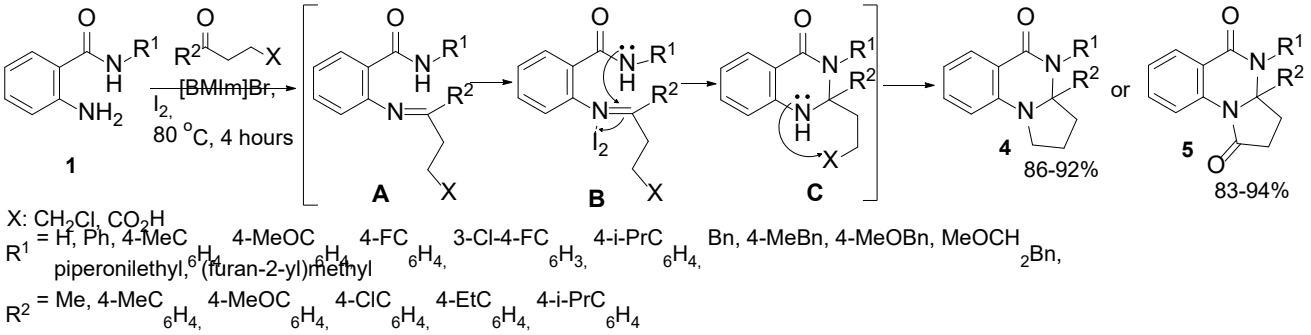
2.1.1 Cyclocondensations with bielectrophilic reagents

Dunn and Kinnear[36] proposed to synthesise pyrrolo[1,2-*a*]quinazolinone systems by condensation of 2-aminobenzamides **1** with 4-chlorobutanoyl chloride **2** in the presence of AcONa as a base, which proceeded through the stage of intermediate 2-[(4-chlorobutanoyl)amino]benzamides **A**, with further cyclization under the action of NaOMe. As a result, a mixture of two isomers, pyrrolo[1,2-a]quinazolinones **2** (yield 10-12%) and pyrrolo[2,1-b]quinazolinones **3** (yield 40-60%), was obtained (**Scheme 1**, Method A). In 2016, Satterell and Lei[30,37] improved the above mentioned method using t-BuOK as a stronger base, thereby increasing the yield and changing the ratio of products towards the formation of angular pyrrolo[1,2-*a*]quinazolinone **2** (**Scheme 1**, Method B).



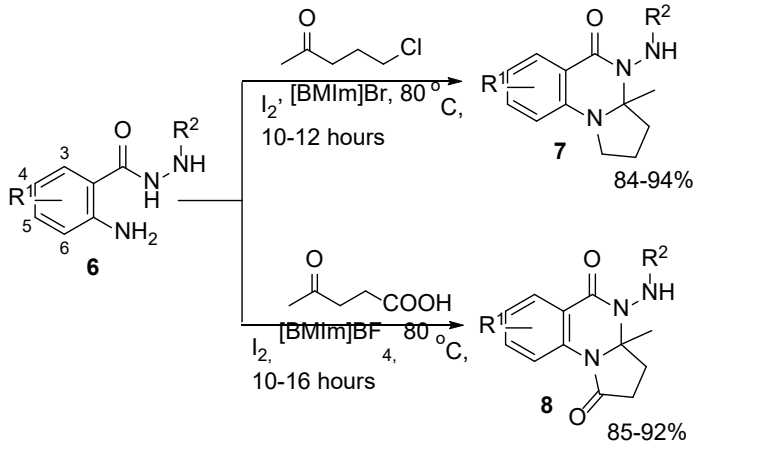
Scheme 1. Synthesis of pyrrolo[1,2-*a*]quinazolinones **2** by condensation of 2-aminobenzamides **1** with 4-chlorobutanoyl chloride.

The reaction of 2-aminobenzamides **1** with γ-chloropentanones or 4-oxoacids with a catalytic amount of iodine in ionic liquid [BMIm]Br was used for the synthesis of a series of derivatives 2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazoline-5(1*H*)-ones **4** and 2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-diones **5** (**Scheme 2**).[38,39] In both cases, the reactions proceed through the formation of Schiff bases **A**, whose subsequent activation with iodine (intermediate **B**) provides tandem intramolecular cyclizations leading *via* the intermediate quinazolinone **C** to the target products **4** or **5**.



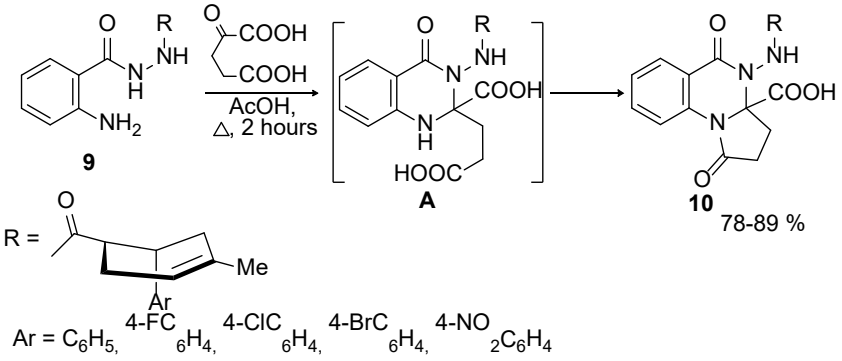
Scheme 2. Synthesis of 2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazoline-5(1*H*)-ones **4** and 2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-dione **5** by iodine-catalyzed tandem cyclization of 2-aminobenzamides **1**.

The chemoselective iodine-catalysed reaction of 2-amino-*N*′-arylbenzohydrazide **6** with 5-chloropentan-2-one or levulinic acid which was used for the facile synthesis of 4-arylamino-pyrrolo[1,2-*a*]quinazolinones **7** and pyrrolo[1,2-*a*]quinazoline-1,5-dione **8** is likely to proceed in a similar manner (**Scheme 3**).[40,41]



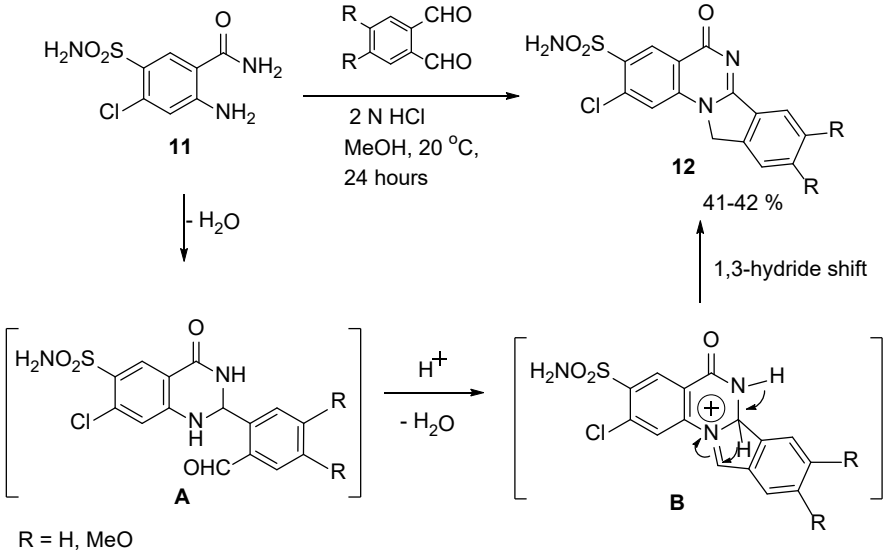
Scheme 3. Synthesis of 4-arylamino pyrrolo[1,2-*a*]quinazolinones **7** and 4-arylamino pyrrolo[1,2-*a*]quinazoline-1,5-dione **8** by iodine-catalyzed tandem cyclization of 2-amino-N'-arylbenzohydrazide **6**.

Chemoselective condensation of *N′*-(6-aryl-4-methylcyclohex-3-enecarbonyl) anthranilhydrazides **9** with 2-oxoglutaric acid afforded 4-amino-1,5-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a]quinazolines **10** in good yields (**Scheme 4**).[42]



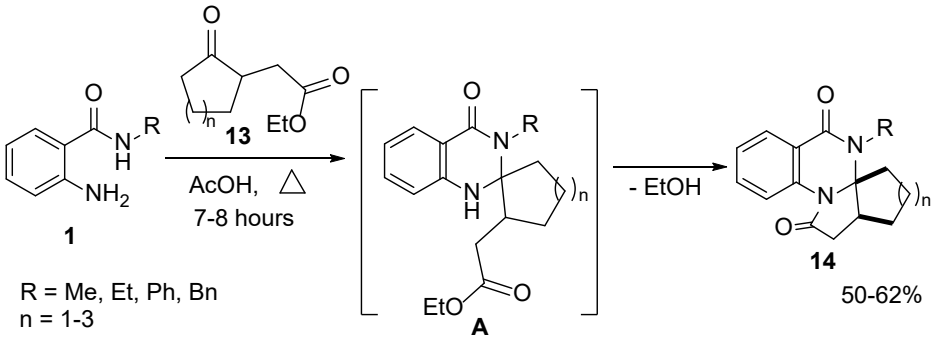
Scheme 4. Synthesis of 4-amino-1,5-dioxo-2,3,4,5-tetrahydro-pyrrolo[1,2-*a*]quinazoline-3a(1*H*)-carboxylic acid **10**.

Isoindolo[2,1-*a*]quinazolinones **12** were obtained by the reaction of 2-aminobenzamide **11** with phthalaldehydes in MeOH/HCl at room temperature (**Scheme 5**).[43] The formation of the isoindole cycle was most likely caused by the elimination of H_2O in N,N-acetal **A**. Mechanistic studies in a deuterated solvent show that the reaction proceeds through the stage of intramolecular 1,3-hydride shift in the intermediate **B**.[40]



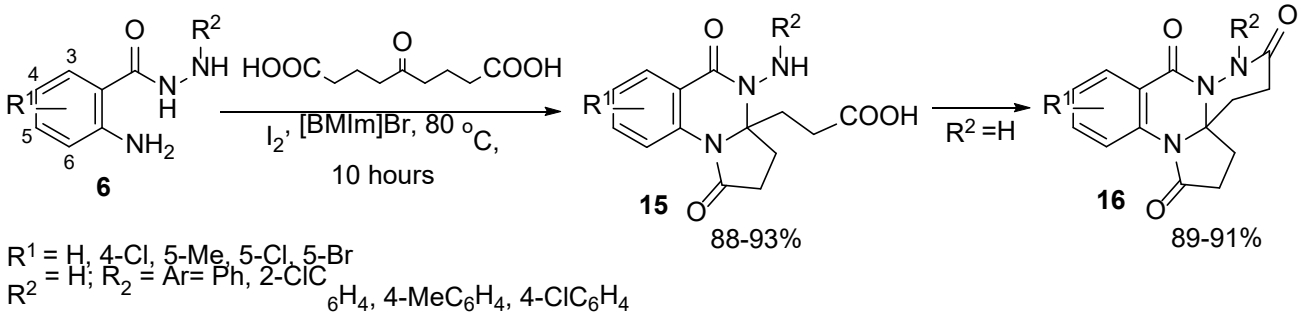
Scheme 5. Synthesis of 2-chloro-5-oxo-11*H*-isoindolo[2,1-*a*]quinazoline-3-sulfonamides **12** *via* condensation of 2-amino-4-chloro-5-sulfamoylbenzamide **11** with phthalaldehydes.

The interaction of 2-aminobenzamides **1** with carbocyclic oxoesters **13** in acetic acid proved to be an accessible route for the stereoselective synthesis of condensed cyclo(penta-hepta)[2,3]pyrrolo[1,2-*a*]quinazoline-6,12(7*H*,11*H*)-diones **14** with *cis*-condensed lactam and cycloalkane fragments (**Scheme 6**).[45]



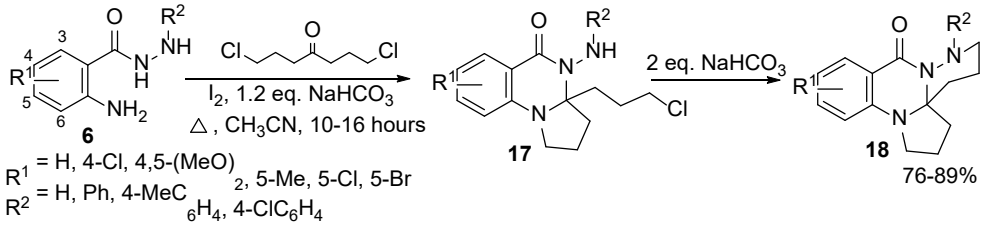
Scheme 6. Synthesis of hydrogenated cyclo(penta-hepta)[2,3]pyrrolo[1,2-*a*]quinazoline-6,12(7*H*,11*H*)-diones **14**.

The synthesis of pyridazino[6,1-*b*]pyrrolo[1,2-*a*]quinazoline-1,6,9(7*H*)-ones **16** through intermediate (2-aminodioxopyrrolo[1,2-*a*]quinazolinyl)propionic acids **15** was achieved by a one-pot iodine-catalysed process of three new ring constructions from 2-aminobenzohydrazide **6** (R^2 = H) and 4-oxopimelic acid in ionic liquid [BMIm]Br.[46] However, with *N′*-aryl hydrazides **6** (R^2 = Ar), the reaction stopped at the stage of formation of propionic acid derivatives **15**, which is most likely due to the hindrances of the *N′*-aryl substituent (**Scheme 7**).



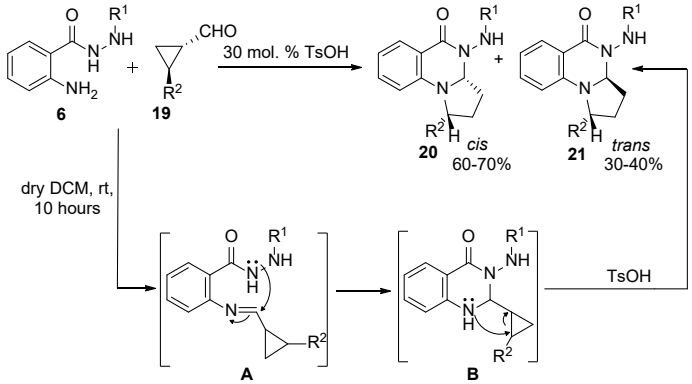
Scheme 7. Synthesis of tetrahydropyrrolo[1,2-*a*]quinazolin-3*a*(1*H*))-propionic acids **15** and pyridazino[6,1-*b*]pyrrolo[1,2-*a*]quinazoline-1,6,9(7*H*)-triones **16**.

Another noteworthy method proposed by Wang et al.[47] is a simple and versatile iodine-catalysed synthesis of pyridazino[6,1-*b*]pyrrolo[1,2-*a*]quinazoline-9(1*H*)-ones **18** by the interaction of anthranil hydrazides **6** with 1,7-dichloroheptane-4-one in the presence of a threefold excess of $NaHCO_3$ (**Scheme 8**). The primary stable products of this two-step cyclocondensation were pyrrolo[1,2-*a*]quinazolinones **17** isolated when 1.2 equiv. of the base was used.



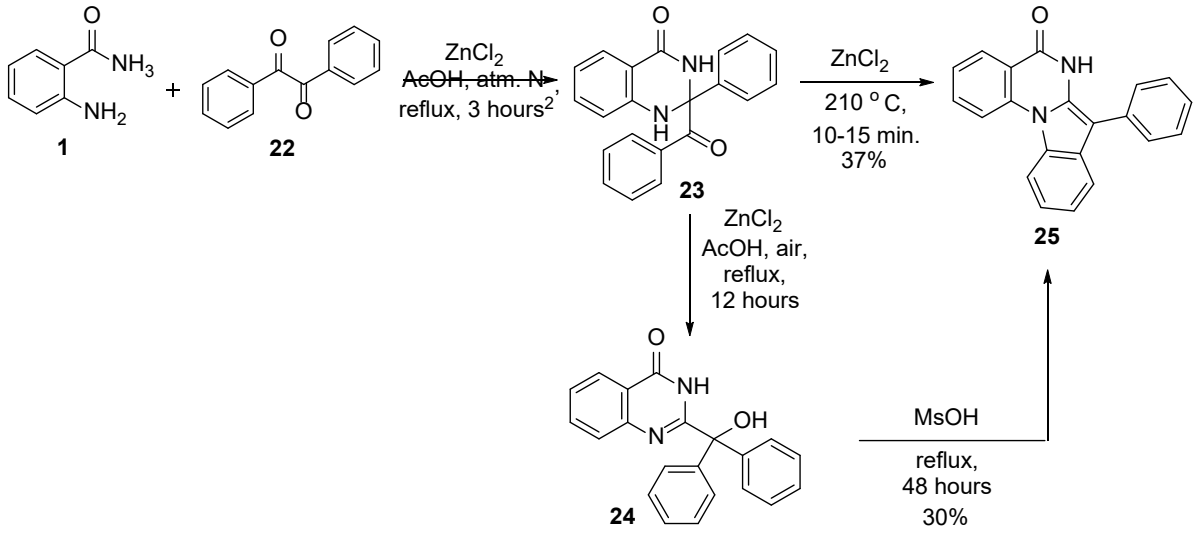
Scheme 8. Synthesis of 3a-(3-chloropropyl)-2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-ones **17** and 2,3,4,5,6,7-hexahydropyridazino[6,1-*b*]pyrrolo[1,2-*a*]quinazolin-9(1*H*)-ones **18** by iodine-catalysed reaction of 2-amino-*N′*-arylbenzohydrazides 6 with 1,7-dichloroheptan-4-one.

Recently, the authors[48] reported the facile synthesis of diastereoisomeric tetrahydropyrrolo[1,2-*a*]quinazoline-5(1*H*)-ones **20** and **21** by the reaction of *N′*-arylanthranilhydrazides **6** with formyl cyclopropanes **19** in the presence of *p*-toluenesulfonic acid (TsOH) (**Scheme 9**). The reaction proceeded through the initial formation of imines **A**, the intramolecular cyclization of which generated dihydroquinazoline-4-one intermediates **B** with an intact cyclopropane ring. The nucleophilic cyclopropane ring opening upon the attack of the N1 quinazoline atom yielded diastereomeric products **20** and **21**.



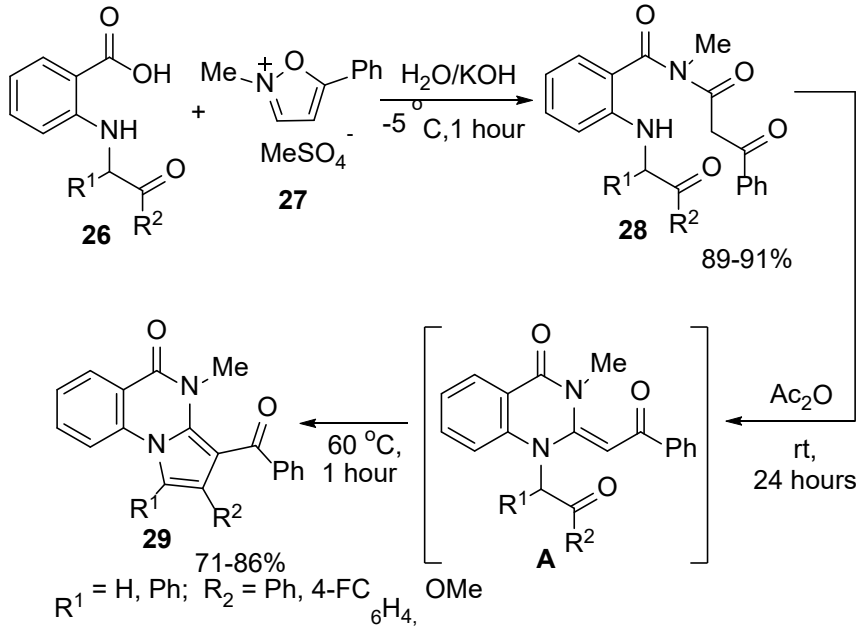
Scheme 9. Domino construction of tetrahydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-ones **20**, **21** *via* annulation of cyclopropane aldehydes **19** with *N'*-aryl anthranilhydrazides **6**.

A readily available method for the synthesis of 7-phenylindolo[1,2-*a*]quinazolin-5(6*H*)-one **25** proved to be the $ZnCl_2$-catalysed condensation of anthranilamide **1** with benzil **22**, proceeding through the initial formation of dihydroquinazolinone **23** (**Scheme 10**).[49] The latter is easily rearranged in the acetic acid medium into 2-(hydroxydiphenylmethyl)quinazolin-4(3*H*)-one **24**, and its dehydration finally gave indoloquinazolinone **25** in 30% yield. Optionally, the melting of dihydroquinazolinone **23** with anhydrous $ZnCl_2$ for 10-15 min resulted in indoloquinazolinone **25** in 37% yield in one step.



Scheme 10. Synthesis of 7-phenylindolo[1,2-*a*]quinazolin-5(6*H*)-one **25** by condensation of anthranilamide **1** with benzil **22**.

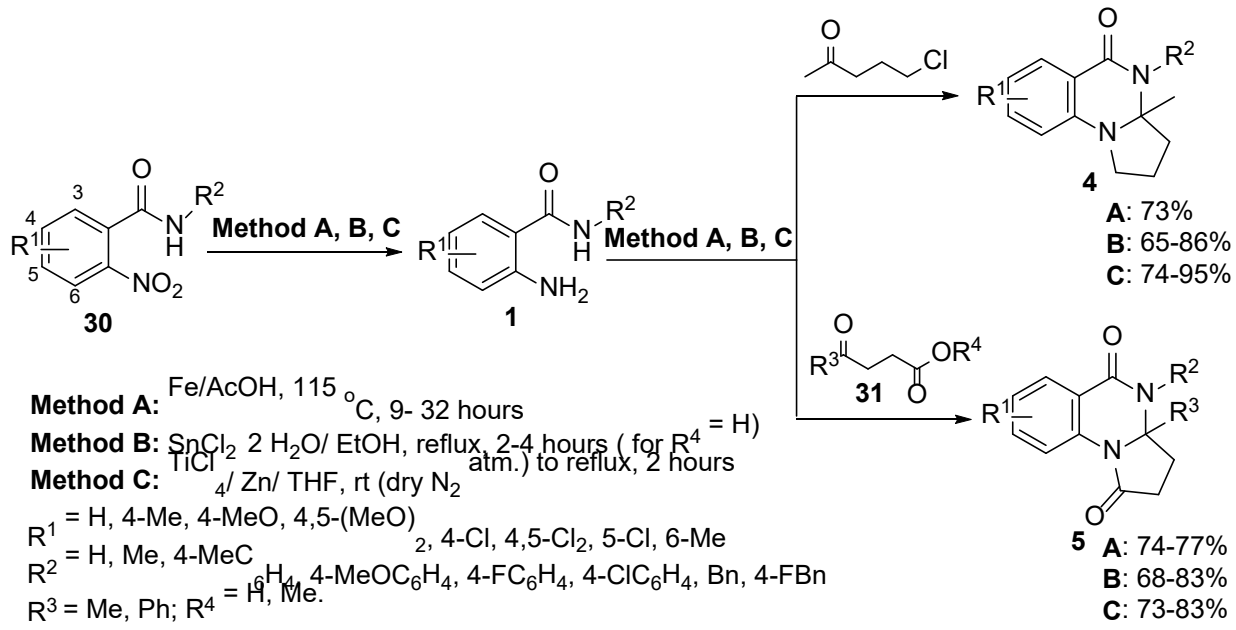
N-Aroyl-*N*-methyl-benzoylacetamides **28**, synthesised by the interaction of the corresponding anthranilic acids **26** with 5-phenylisoxazoline methyl sulfate **27**, were found to be good precursors of pyrrolo[1,2-*a*]quinazolinone systems (**Scheme 11**).[50] Compounds **28** in acetic anhydride at room temperature cyclized through intermediate 2-benzoylmethylenequinazolinones **A** to pyrrolo[1,2-*a*]quinazolin-5-ones **29** in 55-86% yields.



Scheme 11. Synthesis of 3-benzoyl-4-methylpyrrolo[1,2-*a*]quinazolin-5-ones **29** from anthranilic acids **26** and 5-phenylisoxazolium methyl sulfate **27**.

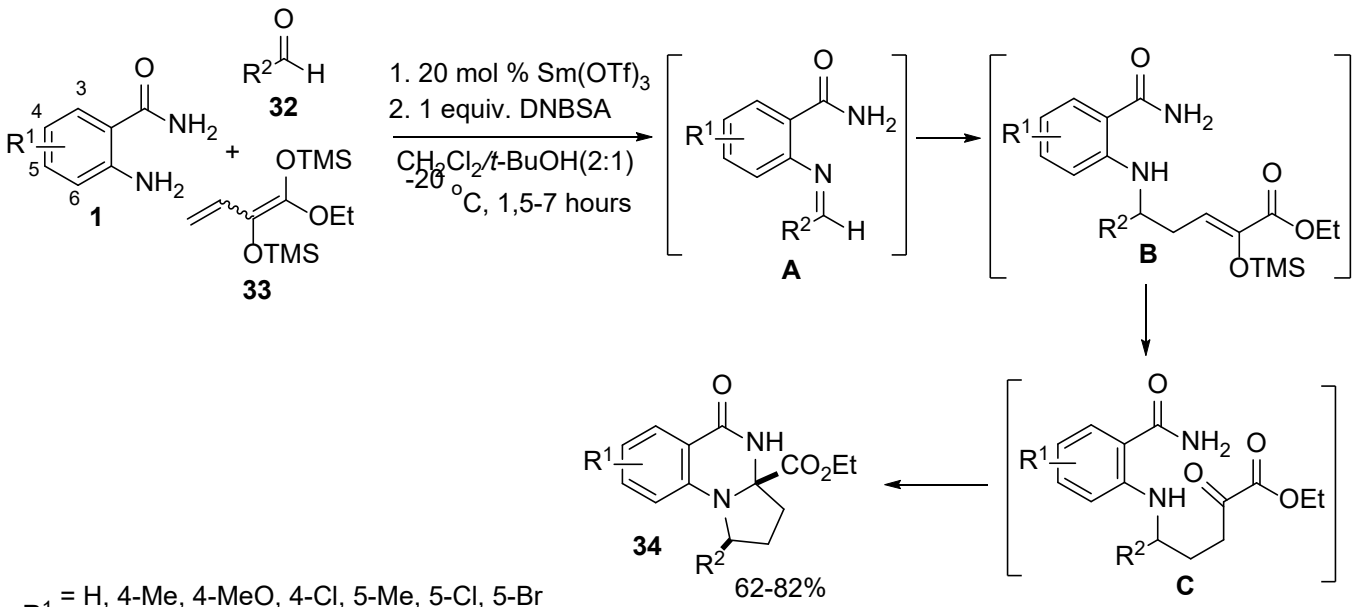
In the tandem processes for angular pyrroloquinazolinone systems construction, besides 2-aminobenzamides as starting materials, their 2-nitro analogues were used. Bunce and Nammalwar[51] reported a convenient approach to pyrrolo[1,2-*a*]quinazolinones 4 and 5 *via* the tandem reduction-cyclocondensation of nitrobenzamide **30** (R^2 = H) with 5-chloro-2-pentanone and methyl levulinate(3-benzoylpropionate) **31** using Fe in boiling acetic acid (**Scheme 12**, method A).

Alternatively, the authors[52,53] proposed $SnCl_2 \cdot 2H_2O$ in ethanol (method B) or $TiCl_4$/Zn in THF (method C) as reducing agents in this reaction.



Scheme 12. Synthesis of 2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-ones **4** and 2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-diones **5** *via* reductive cyclization of 2-nitrobenzamides **30** with 5-chloro-2-pentanone or ketoesters(acids) **31**.

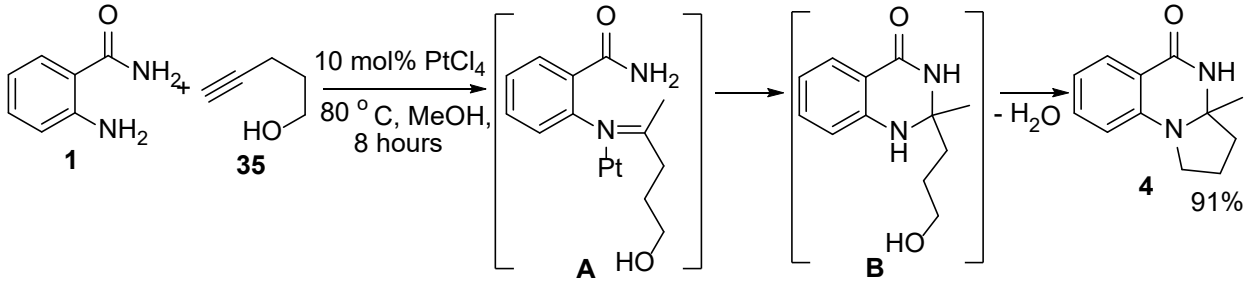
The diastereoselective synthesis of 5-oxopyrrolo[1,2-*a*]quinazoline-3a-carboxylates **34** (R^2=Ar) was achieved by the interaction of anthranilamides **1** with benzaldehydes **32** and bis-silyldiendiolate **33** in the presence of catalytic amounts of $Sm(OTf)_3$ and 2,4-dinitrobenzene sulfonic acid (DNBSA) (**Scheme 13**).[54] In the process, the primary condensation product imine **A** was converted to silylene ester **B** *via* the vinylogenic Mannich reaction. The hydrolysis of the latter to the ketoacid ester **C** was accompanied by the closure of the pyrimidine and pyrrole cycles.



Scheme 13. Three component cyclocondensation of anthranilamides **1** with benzaldehydes **32** and bis-silyldiendiolate **33** to ethyl 5-oxopyrrolo[1,2-*a*]quinazolinon-3a-carboxylates **34**.

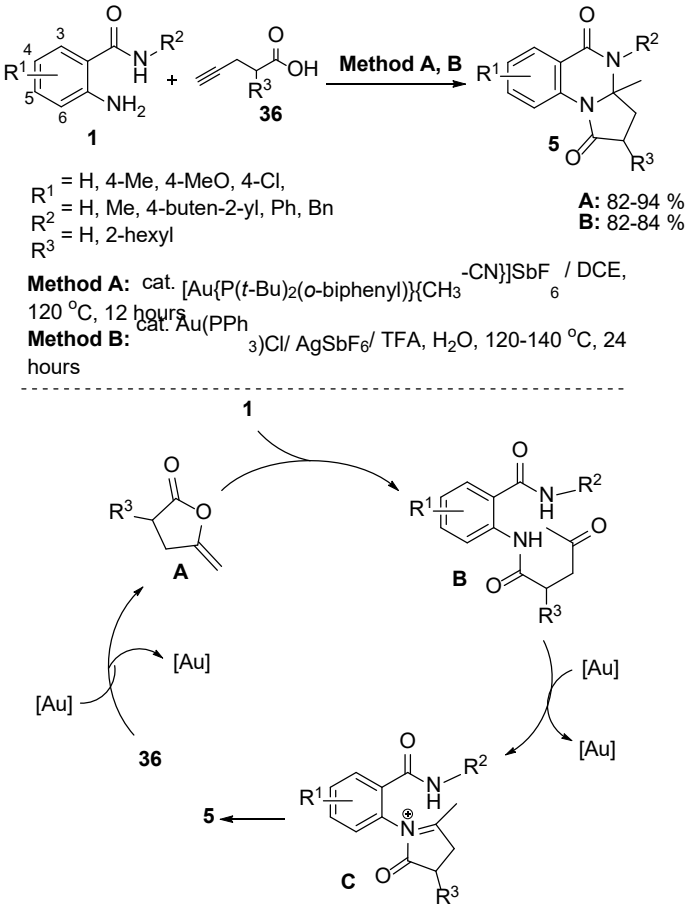
2.1.2 Cyclizations involving functionalized alkynes

The synthesis of 3a-methyl-2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one **4** in high yields was achieved by the $PtCl_4$-catalyzed cyclization-hydroamination-dehydration cascade of 2-aminobenzamide **1** with pentynol **35** *via* intermediates **A** and **B** (**Scheme14**).[55]



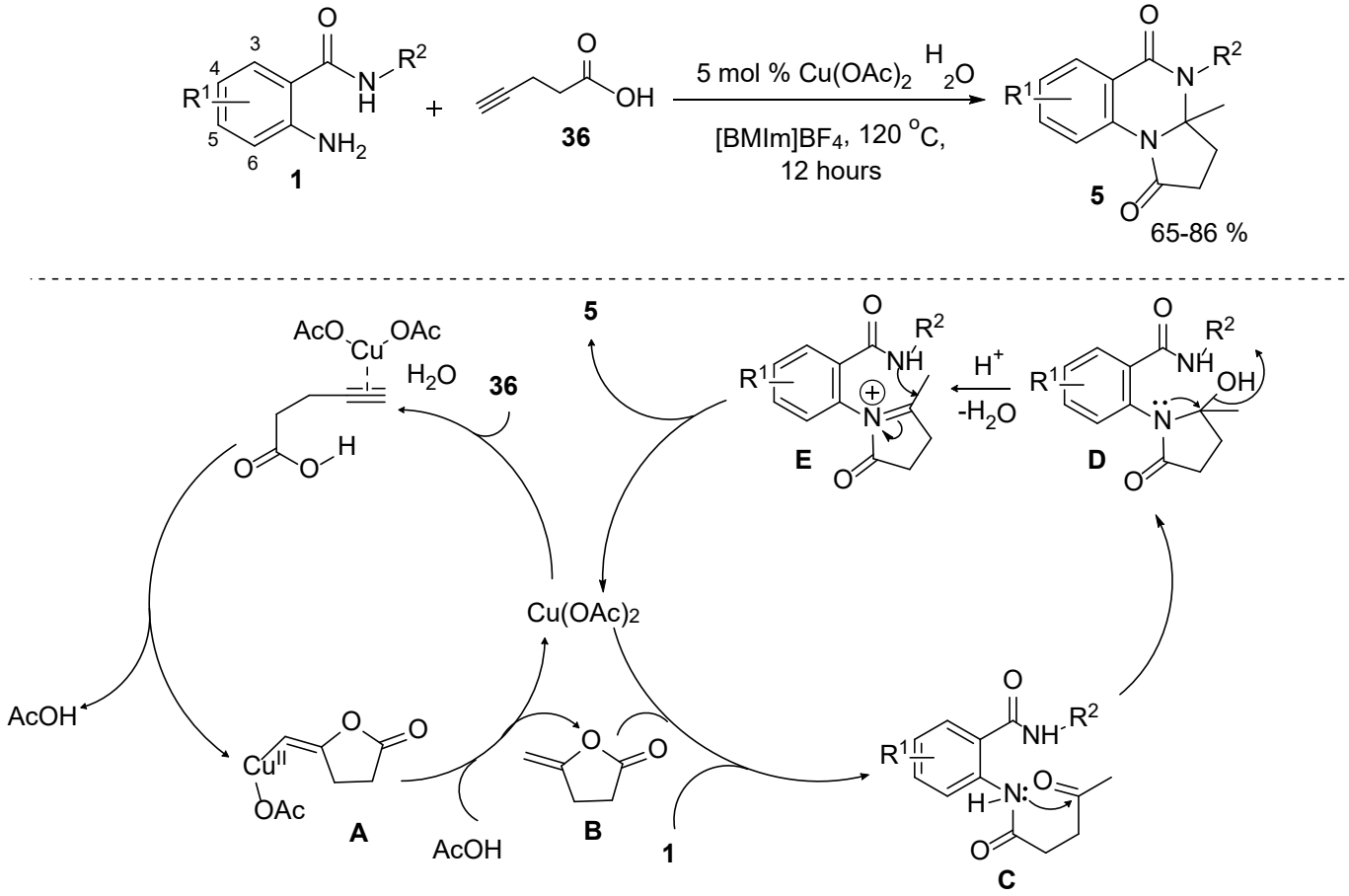
Scheme 14. Synthesis of 3a-methyl-2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one **4** *via* $PtCl_4$-catalysed double hydroamination-dehydrative cyclization cascade.

The authors of[56,57] presented an environmentally benign and facile assembly of angular pyrroloquinazolines which involves the cascade formation of pyrimidine and pyrrole ring by the Au(I)-catalyzed tandem addition/cyclization of 2-aminobenzamides **1** to 4-pentynoic acids **36** (**Scheme 15**). In particular, a wide range of 3a-methyl-2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-diones **5** in high yields was obtained in the reaction of N-alkyl- and N-aryl-substituted anthranilamides **1** with alkynoic acids **36** under the catalysis of $[Au\{P(t\text{-}Bu)_2(o\text{-biphenyl})\}\{CH_3CN\}]SbF_6$ in dichloroethane at 120 °C (method A).[56] The use of the $Au(PPh_3)Cl/AgSbF_6$ catalytic system (method B) in aqueous THF proved to be successful for the synthesis of the target structures **5** ($R^1 = R^3 = H$, R^2 = H, Me).[58] It is assumed that the catalyst activates alkynoic acids **36**, converting them into methylenelactones **A**, which further form ketoamides **B** under the action of nucleophilic substrate **1**. Gold(I) also catalyses the subsequent transformation of ketoamides **B** into N-acylimine intermediates **C**, then cyclized to the target products **5**.



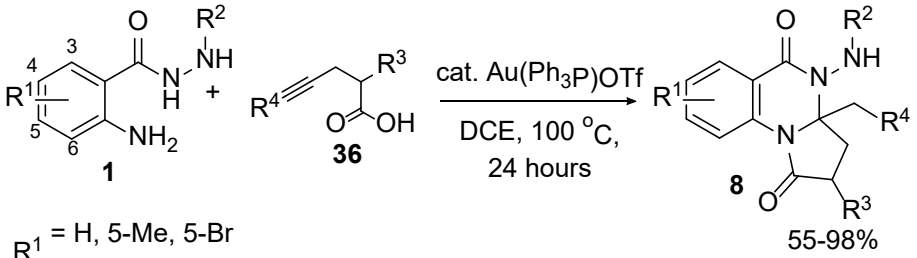
Scheme 15. Gold-catalysed synthesis of 2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-diones **5**.

A similar tandem reaction of aminobenzamides **1** with pentanoic acids **36** was achieved by $Cu(OAc)_2$ catalysis in the ionic liquid [BMIm]BF_4 (**Scheme 16**).[59] The promoting effect of Cu(II) in this process is generally very close to the catalysis with Au(I) complexes.



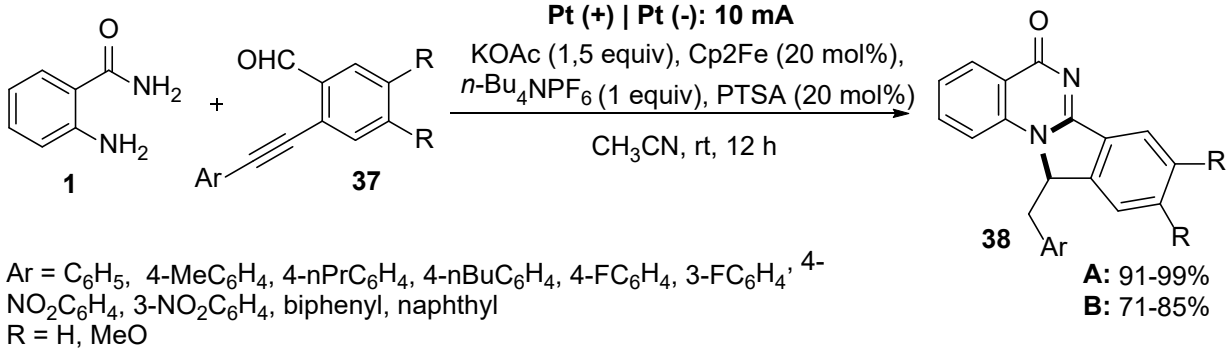
Scheme 16. $Cu(OAc)_2$ and ionic liquid catalytic system in the synthesis of 2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-diones **5**.

Patil[59] used in the analogous tandem reaction *N'*-arylanthranil hydrazides **6**, which with alkynoic acids **36** under $Au(Ph_3P)OTf$ catalysis in dichloroethane underwent regioselective cyclization to 3a-methyl-4-(phenylamino)-2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-diones **8** (**Scheme 17**).



Scheme 17. Au(I)-catalysed synthesis of 4-(arylamino)-2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-diones **8**.

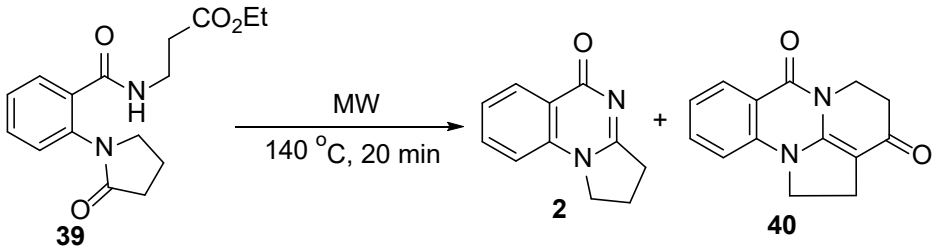
Recently, the authors[60] developed an environmentally friendly approach to isoindolo[1,2-*a*]quinazoline-5-ones **38** *via* cascade cyclization of anthranilamide **1** with ortho-(arylethynyl)benzaldehydes **37** under electrochemical reduction conditions (**Scheme 18**). The reaction proceeds through proton-coupled electron transfer (PCET) under electrolysis, and allowed to synthesize the target compounds **38** in one step. The proposed protocol tolerated electron-donating and electron-accepting aryl substituents of alkynes **37** and resulted in isoindolo[1,2-*a*]quinazoline-5-ones **38** in moderate yields of 48-58%.



Scheme 18. Synthesis of isoindolo[1,2-*a*]quinazolin-5-ones **38** *via* electrochemical reductive cascade cyclization 2-aminobenzamide **1** with 2-(arylethynyl)benzaldehydes **37**.

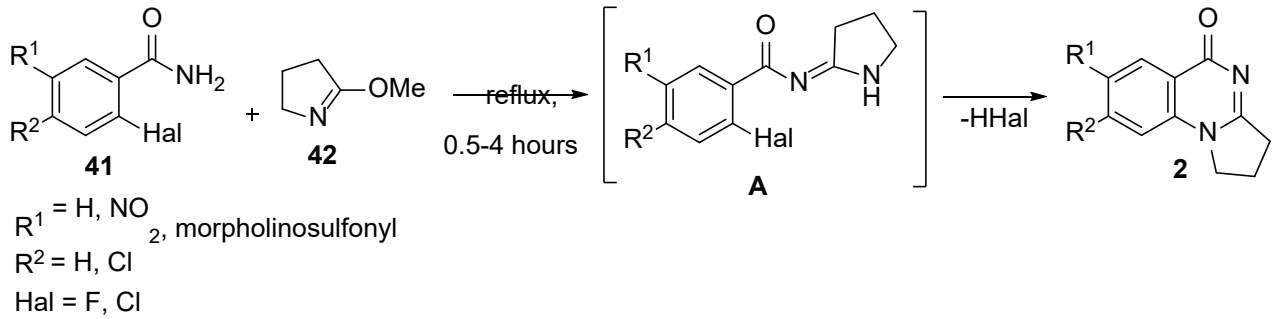
2.2. Annulation of the quinazolinone nucleus to the pyrrolidine(indoline)

Annulation of the quinazoline nucleus to the pyrrole was achieved *via* intramolecular cyclocondensation of N-substituted *o*-oxopyrrolidinyl benzamide **39** under microwave irradiation at 140 °C.[61] The major product of this process was unsubstituted 2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one **2** in 54% yield, whereas pyrrolo[1,2-*a*]pyrido[2,1-*b*]quinazolinedione **40** was formed in 16% yield (**Scheme 19**).



Scheme 19. Synthesis of pyrrolo[1,2-]quinazolinone **2** and 1,2,3,4,5,7- hexahydropyrrolo[1,2-*a*]pyrido[2,1-*b*]quinazoline-3,7-dione **40** *via* microwave-assisted cyclocondensation of ethyl 3-(2-(2-oxopyrrolidin-1-yl)benzamido)propanoate **39**.

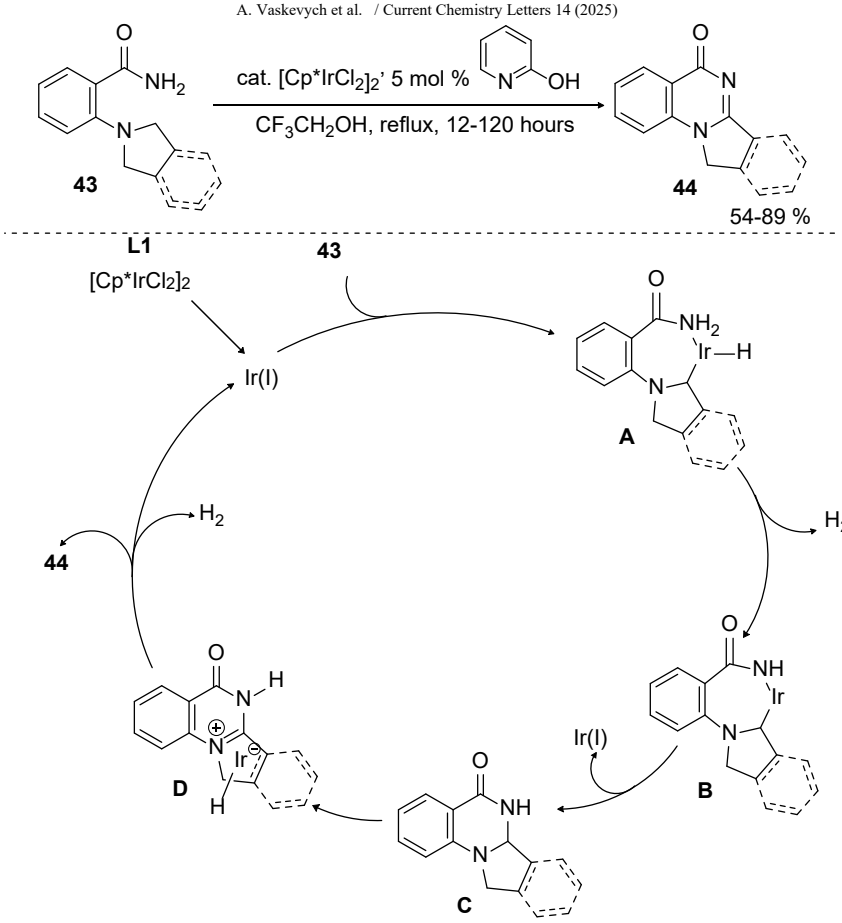
It was shown[62] that iminopyrrolidines A, easily generated *in situ* in the reaction of 2-halogenobenzamides **41** with lactim ether **42,** underwent further intramolecular *N*-arylation to pyrrolo[1,2-*a*]quinazolinones **2** in 46-67% yields (**Scheme 20**).



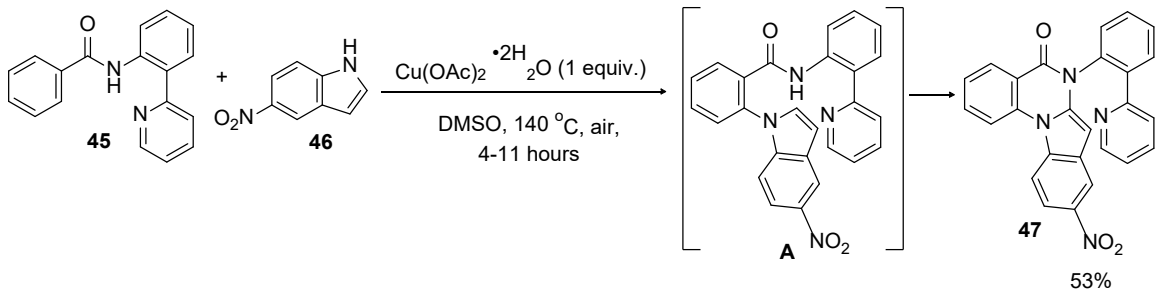
Scheme 20. Synthesis of 1,2,3,4-tetrahydropyrrolo[1,2-*a*]quinazolin-5-ones **2** by condensation of amides of 2-halogeno-substituted aromatic acids **41** with lactim ethers **42**.

The intramolecular Ir-catalyzed dehydrogenative cross-coupling of 2-(pyrrolidin-1-yl)benzamides or their indolinyl analogues **43** in the presence of 2-hydroxypyridine as a ligand in trifluoroethanol was successfully used for the synthesis of 2,3-dihydro-1*H*-pyrrolo(indolo)[1,2-*a*]quinazoline-5-ones **44** (**Scheme 21**).[63]

Zhang and co-workers[64] proposed to synthesize indolo[1,2-*a*]quinazolinone **47** by heating *N*-benzoyl-2-(pyridin-2-yl)aniline **45** with 5-nitroindole **46** in DMSO in the presence of $Cu(AcO)_2$, which is likely realized *via* Cu-mediated successive C-H activation of benzoyl and indole moieties through the formation of intermediate **A**. The reaction proceeds in a highly selective manner, with the 2-(pyridin-2-yl)aniline fragment in compound **45** acting as a directing group in the C-H amination and subsequent intramolecular *N*-arylation processes (**Scheme 22**).

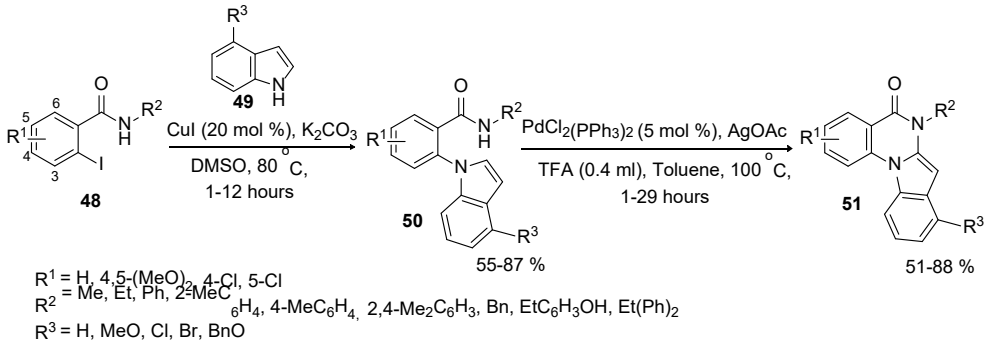


Scheme 21. Ir-catalysed synthesis of 2,3-dihydro-1*H*-pyrrolo(indolo)[1,2-*a*]quinazolin-5-ones **44**.



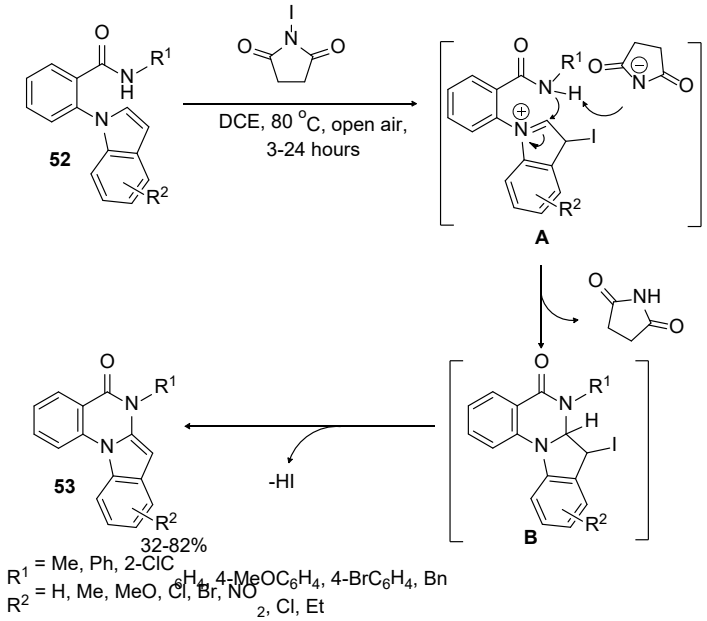
Scheme 22. Synthesis of 9-nitro-6-(2-(pyridin-2-yl)phenyl)indolo[1,2-*a*]quinazolin-5(6*H*)-one **47** *via* Cu(II)-mediated C–H amination/amidation reaction.

An alternative two-step procedure for the synthesis of indolo[1,2-*a*]quinazolinones **51** is based on the Ullmann N-arylation of indoles **49** with 2-iodobenzamide derivatives **48** and involves the preparation of 2-(1*H*-indol-1-yl)benzamides **50** followed by Pd-catalysed intramolecular C–N bond formation (**Scheme 23**).[65]



Scheme 23. Syntheses of indolo[1,2-*a*]quinazolinone derivatives **51** *via* Pd- catalysed intramolecular C–H amidation.

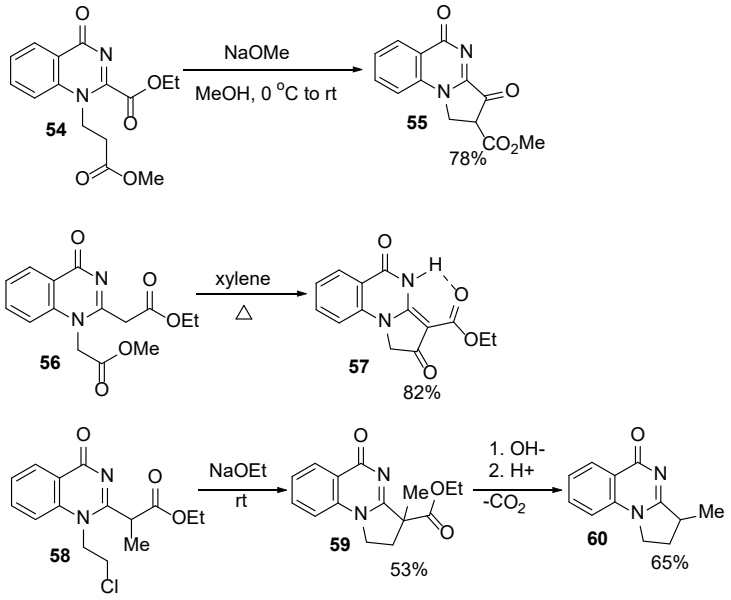
A series of indolo[1,2-*a*]quinazolinones **53** were obtained by NIS-initiated intramolecular *N*-hetarylation of indolyl-substituted benzamides **52**.[66] The plausible mechanism of this reaction suggested the initial iodination of the C3 indole atom to form an unstable iminium cation **A**, followed by a nucleophilic attack of amide nitrogen on the C2 indole atom, leading to the intermediate **B**. Finally, the HI elimination from **B** yielded the desired product **53** (**Scheme 24**).



Scheme 24. Synthesis of 6-substituted indolo[1,2-*a*]quinazolin-5(6*H*)-ones **53** *via* NIS mediated C(sp^2)–N bond formation.

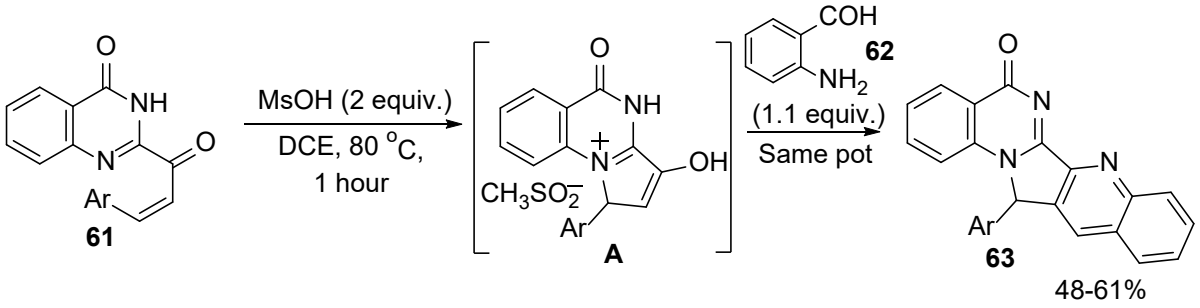
2.3. Annulation of the pyrrole ring to the quinazoline nucleus

4(1*H*)-Quinazolinones functionalized at positions 1 and 2 with alkoxycarbonylalkyl or chloroalkyl groups proved to be convenient substrates for the pyrrole ring annulation.[67] For instance, the NaOMe-induced intramolecular cyclocondensation of 2-ethoxycarbonyl-1-(2-methoxycarbonylethyl)-4(1*H*)-quinazolinone **54** was used to afford 2-methoxycarbonylpyrrolo[1,2-*a*]quinazoline-3,5(1*H*,2*H*)-dione **55**. In turn, quinazoline diacetate **56** was converted to 3-ethoxycarbonylpyrrolo[1,2-*a*]quinazoline-2,5(1*H*,4*H*)-dione **57** in boiling xylene. Treatment of 1-chloroalkyl-2-(1-ethoxycarbonylethyl)-4(1*H*)-quinazolinone **58** with NaOEt yielded the ester **59**, which was decarboxylated to 3-methylpyrrolo[1,2-*a*]quinazolinone **60** upon hydrolysis (**Scheme 25**).



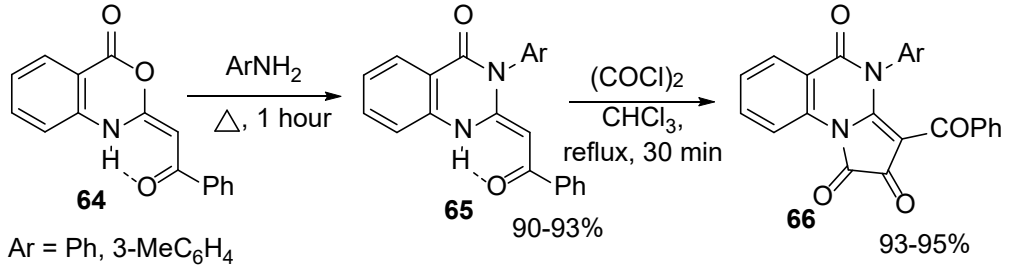
Scheme 25. Synthesis of 2-methoxycarbonylpyrrolo[1,2-*a*]quinazoline-3,5(1*H*,2*H*)-dione **55**, 3-ethoxycarbonylpyrrolo[1,2-*a*]quinazoline-2,5(1*H*,4*H*)-dione **57** and 3-methylpyrrolo[1,2-*a*]quinazolinone **60**.

The aza-Nazarov-Friedlander condensation sequence was successfully used by Rasapalli and co-workers[68] for the methanesulfonic acid-initiated one-pot synthesis of angular luotonines **63** from 2-(3-arylprop-2-enoyl)quinazoline-4(3*H*)-ones **61** and 2-aminobenzaldehyde **62** (**Scheme 26**).



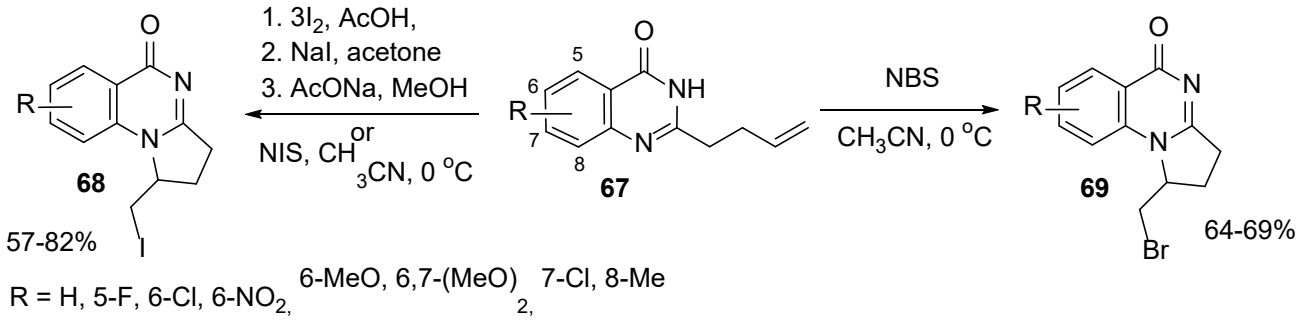
Scheme 26. Synthesis of angular luotonines **63** *via* a one-pot aza-Nazarov-Friedlander sequence.

2-Phenacylidenequinazolinones **65**, synthesized by the reaction of 2-phenacylidenebenzoxazinone **64** with aromatic amines, reacted with oxalyl chloride to form 4-aryl-3-benzoyl-1,2,4,5-tetrahydropyrrolo[1,2-*a*]quinazoline-1,2,5-trione **66** (**Scheme 27**).[69]



Scheme 27. Access to 4-aryl-3-benzoyl-1,2,4,5-tetrahydropyrrolo[1,2-*a*]quinazoline-1,2,5-trione **66** from phenacylidene benzoxazinone **64**.

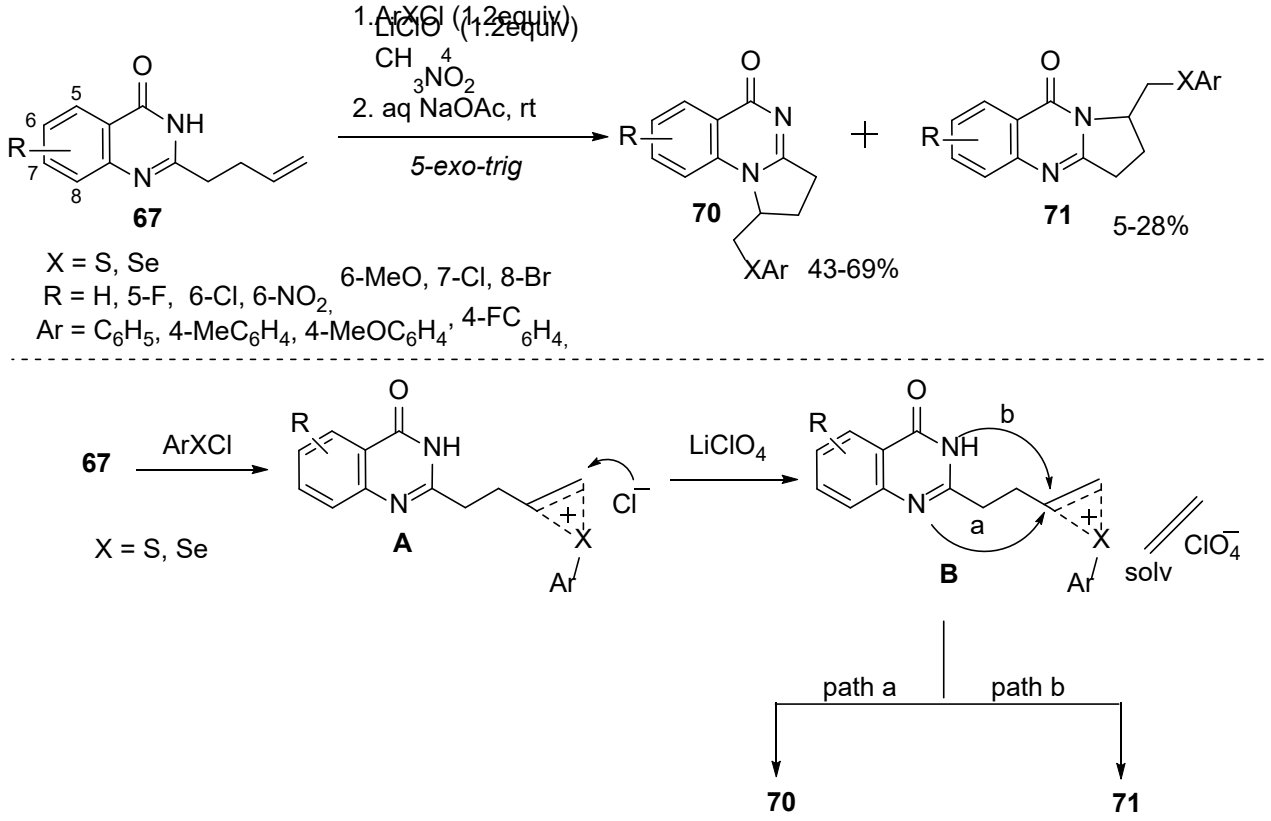
The halogenation of 2-(3-butenyl)quinazolinones **67** is of particular interest as a method for the synthesis of functionally substituted pyrrolo[1,2-a]quinazolinones **68** and **69**.[70] It was reported that the reaction of **67** with a 3-fold excess of iodine in acetic acid, followed by treatment with sodium iodide and acetate or N-iodosuccinimide in acetonitrile at 0°C, afforded the angular 1-iodomethylpyrrolo[1,2-*a*]quinazolinones **68** in moderate to high yields (**Scheme 28**). At the same time, the one-step bromocyclization of substrates **67** under the action of NBS led to the formation of 1-bromomethyl-substituted products **69** in 64-69% yields. It is noteworthy that both reactions are highly regioselective and follow the electrophilic 5-*exo-trig* cyclization pathway with ring closure at the N1 atom.



Scheme 28. The halogen-induced cyclization of 2-(3-butenyl)quinazolin-4(3*H*)-ones **67** in synthesis of 1-iodo(bromo)methylpyrrolo[1,2-*a*]quinazoline-5-ones **68,69**.

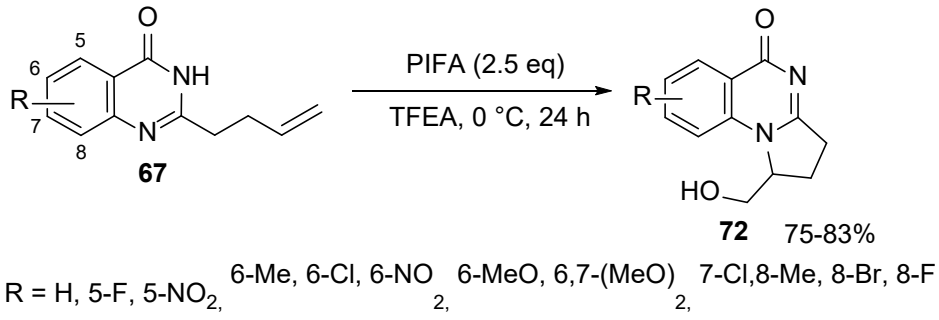
The above strategy of intramolecular cyclization of 2-(3-butenyl)quinazolinones **67** was also studied using arylchalcogenyl chlorides as electrophilic reagents.[71] It was found that compounds **67** with ArSCl or PhSeCl in nitromethane at room temperature in the presence of $LiClO_4$ undergo pyrroloannulation according to the 5-*exo-trig* cyclization scheme on both nitrogen atoms, giving a mixture of isomeric compounds **70** and **71** (**Scheme 29**). The plausible mechanism of the

cyclochalcogenation found involves the formation of a cyclic electrophilic intermediate **A** in the form of a contact ion pair with a chlorine anion in the first step. When $LiClO_4$ is added to the reaction medium, a solvate-separated ion pair **B** is formed in which nitrogen atoms act as internal nucleophiles to attack the episulfonium(selenonium) cation, resulting in the formation of the cyclisation products **70** and **71**.



Scheme 29. Arylsulfenylation(selenylation) of 2-(3-butenyl)quinazolin-4(3*H*)-ones **67** in the synthesis of 1-(arylchalcogenylmethyl)-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-ones **70**, 1-(arylchalcogenylmethyl)-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-ones **71**.

A facile method for the synthesis of 1-(hydroxymethyl)-2,3-dihydropyrrolo[1,2-*a*]quinazoline-5(1*H*)-ones **72** is based on the highly selective oxidative 5-*exo-trig* cyclisation of 2-(3-butenyl)quinazoline-4(3*H*)-ones **67** initiated with [bis(trifluoroacetoxy)iodo]benzene (PIFA) (**Scheme 30**).[72] Reaction condition screening revealed that the most efficient result was achieved by using 2.5 equivalents of PIFA in trifluoroethanol solution at 0 °C for 24 hours.

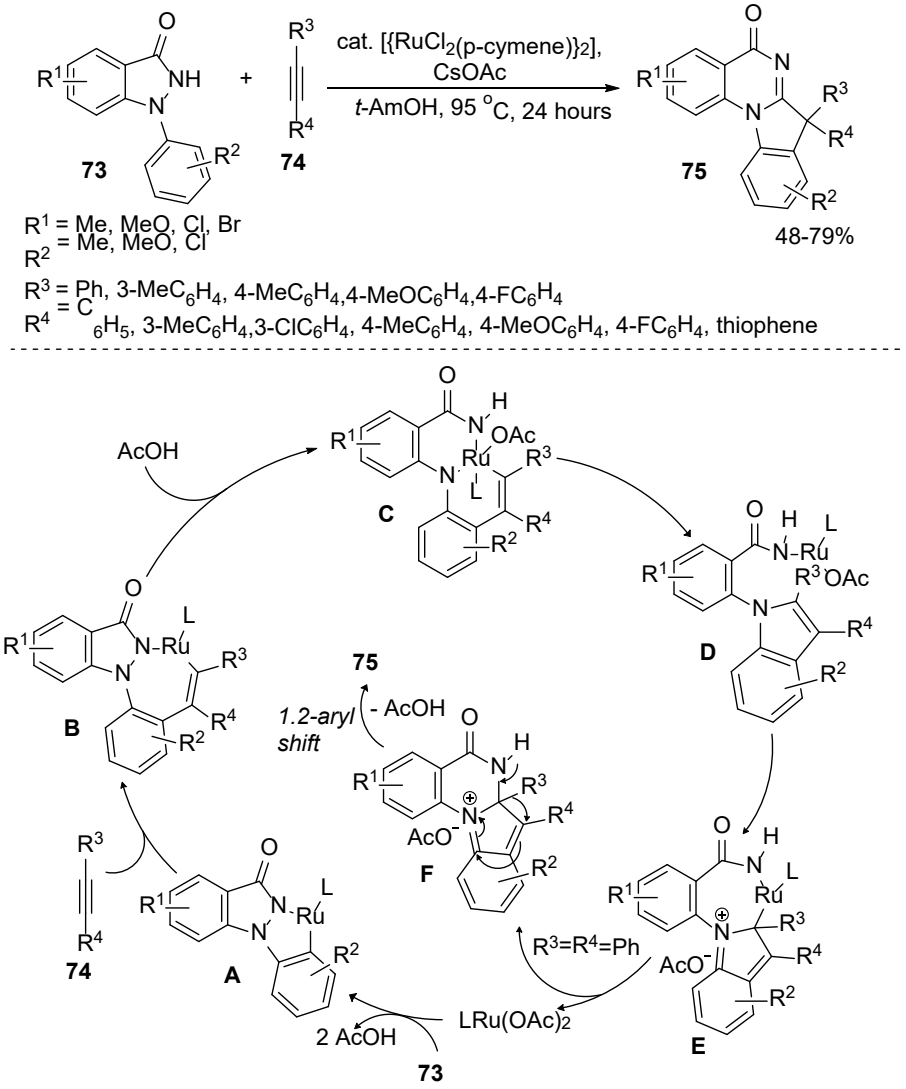


Scheme 30. Synthesis of 1-(hydroxymethyl)-2,3-dihydropyrroloquinazolin-5(1*H*)-ones **72** via PIFA-initiated oxidative 5-*exo-trig* cyclization of 2-(3-butenyl)quinazolin-4(3*H*)-ones **67**.

2.4. Other synthetic methods

The Ru(II)-catalysed reaction of arylindazolones **73** with diarylalkynes **74**, involving activation of the Csp^2–H bond in the N-aryl substituents, proved effective for the synthesis of indolo[1,2-*a*]quinazolinones **75** (**Scheme 31**).[73] According to the mechanism proposed by the authors, the catalyst activates the C-H bond in the N-aryl fragment of the indazolone **73** with the formation of the Ru(II) complex **A**. Further coordination of intermediate **A** with alkyne **74** leads to its incorporation into the C–Ru bond, forming the Ru(II) complex **B**, which then transforms into the six-membered cyclic Ru(IV) complex

C. Subsequent recyclization to complex **D** and reductive metal elimination gives intermediate **E.** Removal of the acetic acid and the concomitant migration of the 1,2-phenyl group yields the target compounds **75.**

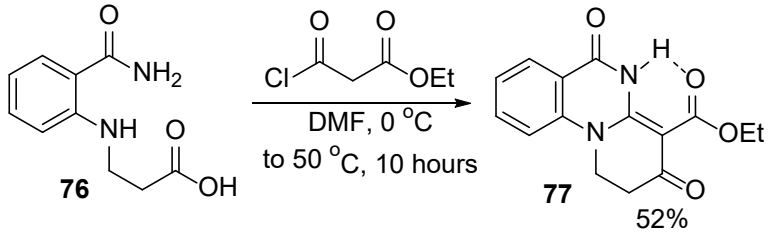


Scheme 31. Synthesis of indolo[1,2-*a*]quinazolinones **75** *via* Ru(II)-catalysed Csp^2-H bond activation/annulation reaction of phenylindazolones with diaryl substituted alkynes **74**.

3. Synthesis of pyrido[1,2-*a*]quinazolinone derivatives

3.1 Tandem cyclization with ortho-aminobenzoic acid derivatives

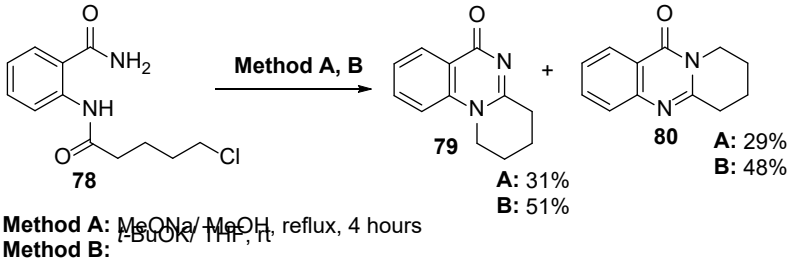
In 1983, Ozaki and colleagues[67] reported the synthesis of 4-ethoxycarbonyl-1*H*-pyrido[1,2-*a*]quinazoline-3,6(2*H*,5*H*)-dione **77** by reaction of 2-(2-carboxyethylamino)benzamide **76** with ethyl chloroformylacetate in DMF in 52% yield (**Scheme 32**).



Scheme 32. Synthesis of 4-ethoxycarbonyl-1*H*-pyrido[1,2-*a*]quinazoline-3,6(2*H*,5*H*)-dione **77**.

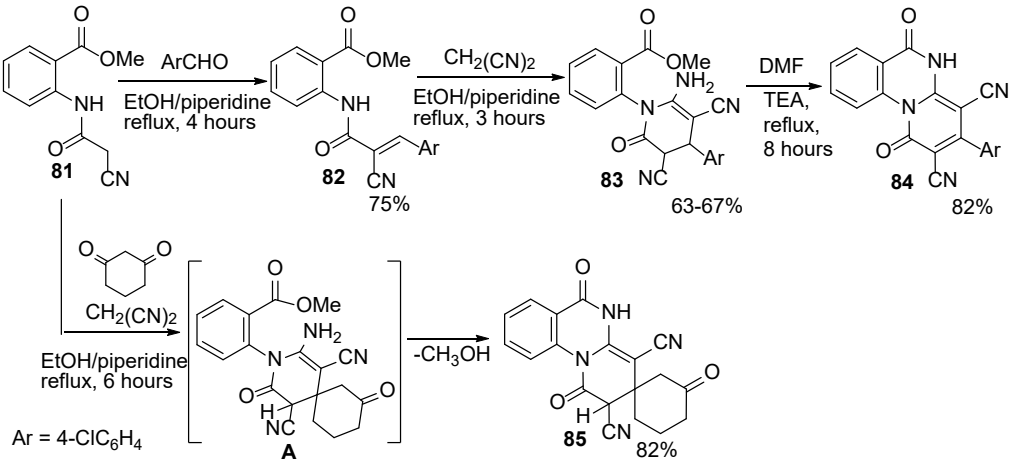
Otherwise, the MeONa-mediated intramolecular cyclisation of 2-[(5-chloropentanoyl)amino]benzamide **78** (**Scheme 33**, method A) was not highly selective and resulted in a mixture of angular pyrido[1,2-*a*]quinazolinone **79** and linear

pyrido[2,1-*b*]quinazolinone **80** in relatively low yields.[36] The use of *t*-BuOK as the base (method B) did not significantly affect the process selectivity, although an increase in product yields was observed.[37]



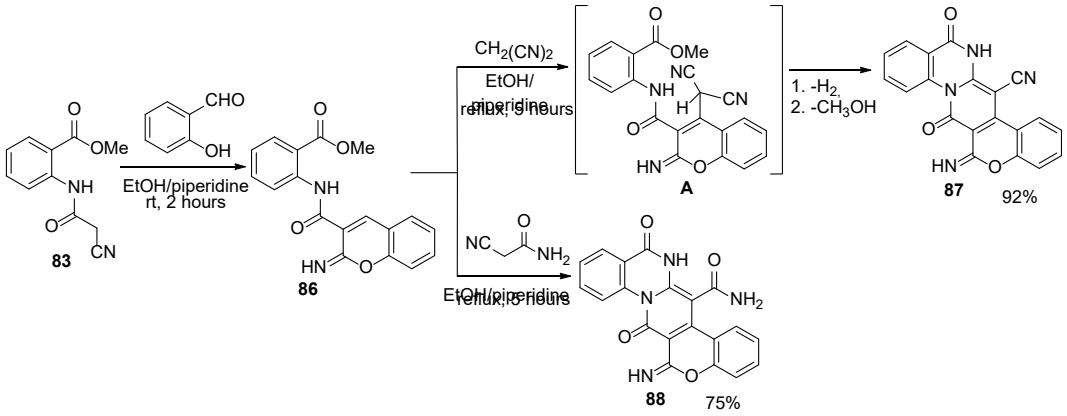
Scheme 33. Synthesis of pyrido[1,2-*a*]- and pyrido[2,1-*b*]quinazolinones **79** and **80** by cyclocondensation of 2-(5-chloropentanamido)benzamide **78**.

Ammar and co-workers[74] proposed the use of amidoester **81** as a key substrate for the preparation of pyrido[1,2-*a*]quinazolinones **84** and their spiro-analogues **85**. Thus, the Knevenagel condensation of **81** with aromatic aldehydes afforded cinnamic acid amides **82**, whose interaction with malononitrile led to aminopyridone derivatives **83**. The latter were cyclized to the tricyclic system **84** by boiling in DMF in the presence of triethylamine. The synthetic versatility of cyanoacetanilide **81** was illustrated in the synthesis of spiropyrido[1,2-*a*]quinazoline **85** by interaction with malononitrile and 1,3-cyclohexandione through intermediate **A** (**Scheme 34**).



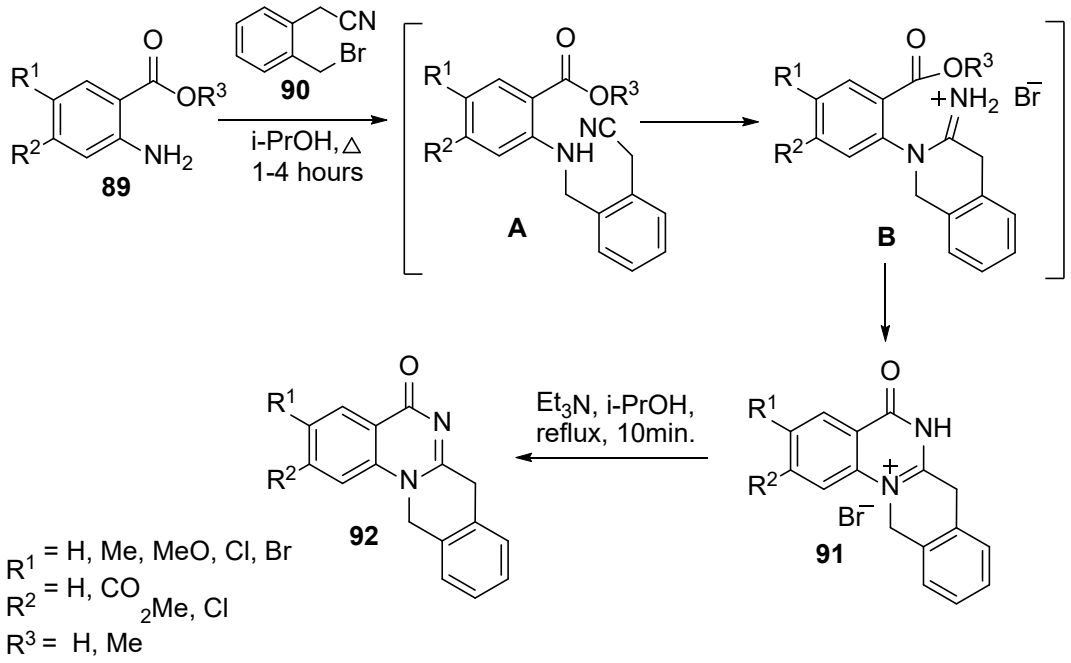
Scheme 34. Synthesis of 3,5-dicyanopyrido[1,2-a]quinazoline-2,7-dione **84** and its 3-spirocyclohexane analogue **85** by condensation of methyl 2-(2-cyanoacetamido)benzoate **81** with aldehydes and malononitrile.

Following the above method, researchers[74] used 2-(2-imino-2*H*-chromen-3-carboxamido)benzoate **86** derived from cyanoacetanilide **81** and salicylic aldehyde for the synthesis of chromeno[3',4':4,5]pyrido[1,2-*a*]quinazolines **87** and **88** in high yields (**Scheme 35**).



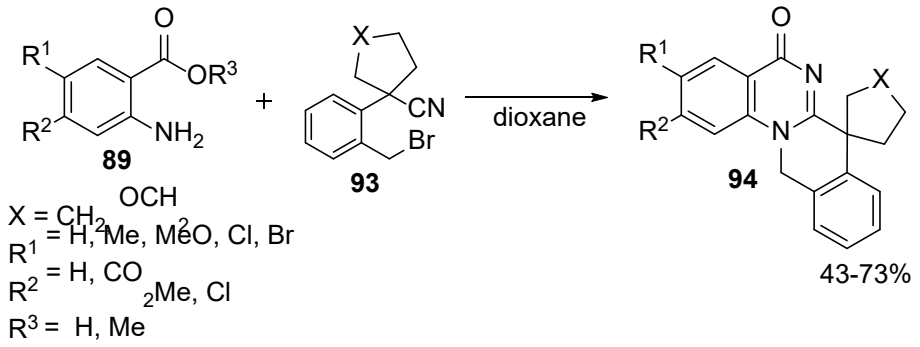
Scheme 35. Synthesis of 6-imino-7-oxo-12,13-dihydro-6*H*,7*H*-chromeno[3‘,4‘:4,5]pyrido[1,2-*a*]quinazolinone-14-carbonitrile **87** and -14-carboxylic acid amide **88**.

Potikha[75] reported a convenient approach for the construction of condensed isoquinolinequinazoline scaffolds. By melting an equimolar mixture of substituted anthranilic acids or their esters **89** with *ortho*-bromomethylphenylacetonitrile **90** at 130-150 °C or by heating their 2-propanol solutions, hydrobromides of 2,3-substituted 7,12-dihydro-5*H*-isoquino[2,3-*a*]quinazoline-5-ones **91** were obtained, which were converted to free bases **92** by Et_3N treatment (**Scheme 36**).



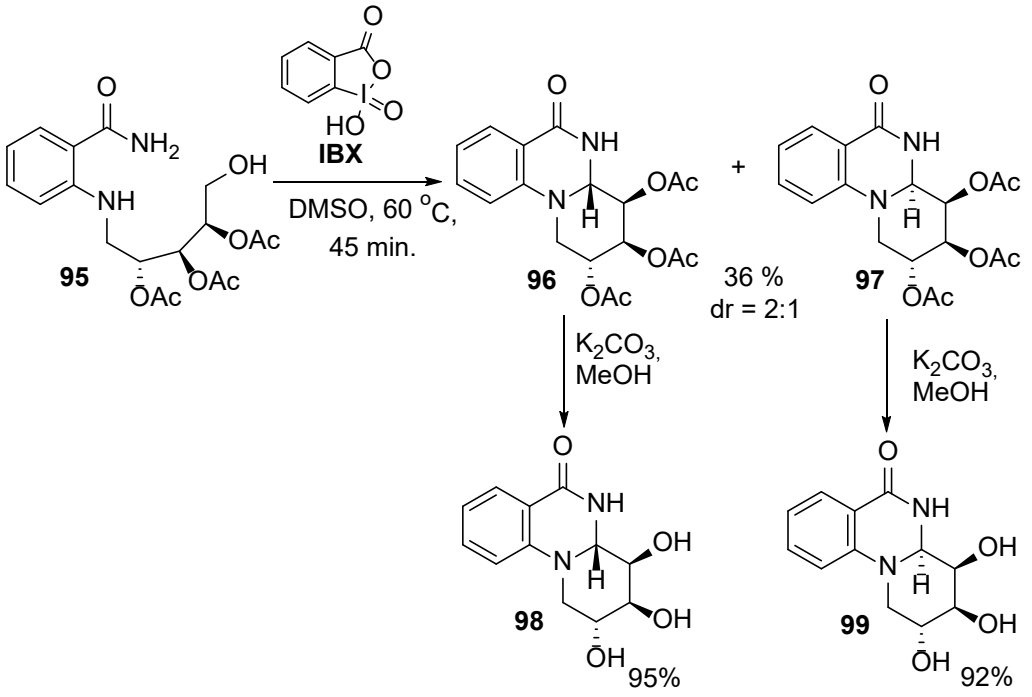
Scheme 36. Synthesis of 7,12-dihydro-5*H*-isoquino[2,3-*a*]quinazolin-5-ones **92** by condensation of substituted anthranilic acids **89** with *o*-bromomethylphenylacetonitrile **90**.

New derivatives **94** with cyclopentane or tetrahydropyran spiro-linked to the isoquinolino[2,3-*a*]quinazoline-5-one framework were synthesised by condensation of anthranilic acid or its esters **89** with (2-bromomethylphenyl)-1-cyclopenta(pyran)carbonitriles **93** (**Scheme 37**).[76,77]



Scheme 37. Synthesis of spiro[5*H*-isoquino[2,3-*a*]quinazoline-7,4'-2*H*-pyran]-5-ones **94**.

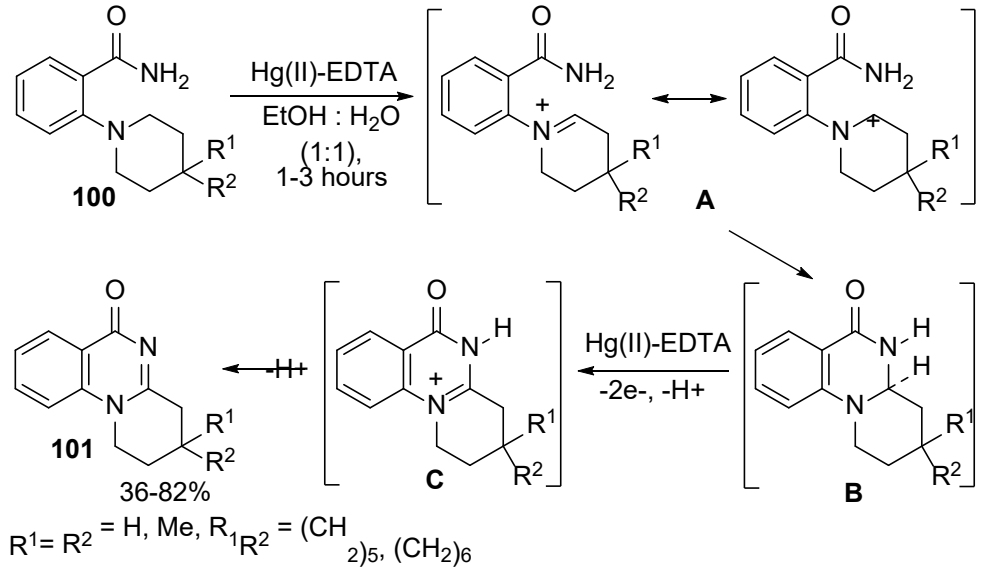
The methodology of cascade formation of a pyridoquinazoline skeleton from N-amino-substituted anthranilamides was applied to the synthesis of epimeric 2,3,4-trihydroxy-1,2,3,4,4a,5-hexahydro-6*H*-pyrido[1,2-*a*]quinazoline-6-ones **98** and **99**, the aza analogues of the antiviral agent transdihydrolikoricidin.[78] The procedure proposed by the authors was based on the 2-iodobenzoic acid (IBA)-induced tandem cyclization of the arabinose derivative **95**, yielding a mixture of diastereomers **96** and **97**, which after separation and hydrolysis were converted into polyhydroxy derivatives **98** and **99** (**Scheme 38**).



Scheme 38. Synthesis of epimeric 2,3,4-trihydroxy-1,2,3,4,4a,5-hexahydro-6*H*-pyrido[1,2-*a*]quinazolin-6-ones **98,99**.

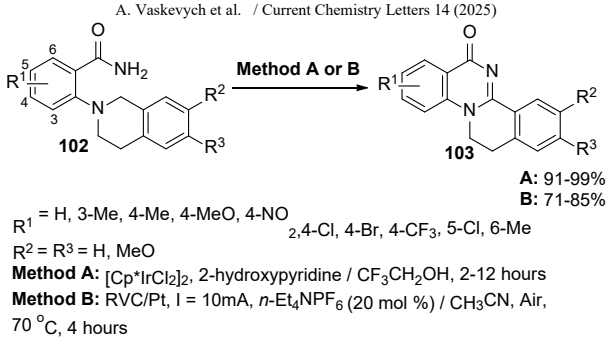
3.2. Annulation of quinazoline nucleus to piperidine or tetrahydroisoquinoline rings

Authors[79] found that the cyclodehydration of *N*-[2-(aminocarbonyl)phenyl]piperidines **100** using the Hg(II)-EDTA system allows the synthesis of substituted pyrido[1,2-*a*]quinazolinones **101** in 36-82% yields (**Scheme 39**). According to the proposed mechanism, the reaction proceeds *via* the formation of the mesomerically stabilised carbocation **A** which then undergoes intramolecular cyclization to intermediate **B**. Its rapid dehydrogenation to intermediate **C** and subsequent deprotonation leads to the target products **101**.



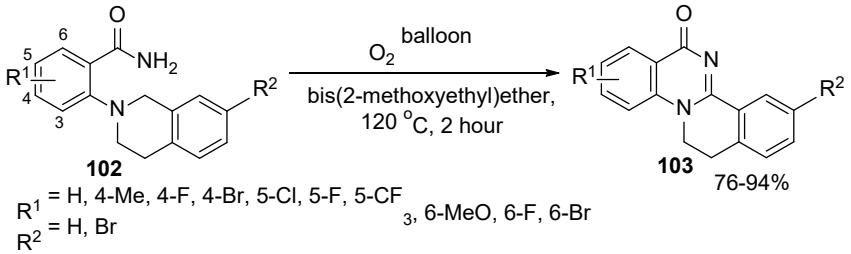
Scheme 39. Synthesis of pyrido[1,2-*a*]quinazolinones **101** by Hg(II)-EDTA-induced cyclodehydrogenation of *N*-[2-(aminocarbonyl)phenyl]piperidines **100**.

The annulation of the quinazolinone nucleus to the hydrogenated isoquinoline backbone, which allows to obtain dihydroisoquinolino[2,1-*a*]quinazolinones **103** in hight yields, was achieved by the Ir-catalysed intramolecular dehydrogenative cross-coupling of 2-(3,4-dihydroisoquinolin-2-yl)benzamides **102** in trifluoroethanol in the presence of 2-hydroxypyridine as ligand (**Scheme 40**, method A).[63] Another environmentally benign method for designing products **103** is the electrochemical version of this reaction proposed by Li's research group (Method B).[80]



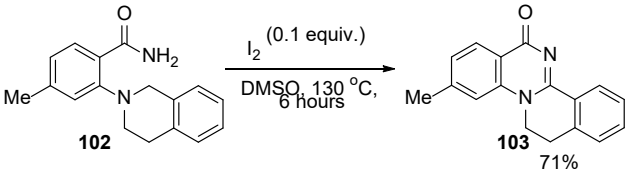
Scheme 40. Synthesis of dihydroisoquinolino[2,1-*a*]quinazolinones **103** *via* Ir-catalyzed and electrochemical intramolecular dehydrogenation cross-coupling reaction.

Recently, Zhao and co-workers[81] proposed a simpler 'green' method for the synthesis of tetracyclic systems **103** in 76-94% yields, which avoids the use of an external initiator, catalyst or additives and is based on the oxidation of benzamides **102** with a peroxy radical generated from bis(2-methoxyethyl)ether (BME) (**Scheme 41**).



Scheme 41. Bis(2-methoxyethyl)ether-oxygen mediated intramolecular dehydrogenative coupling reaction for the synthesis of dihydroisoquinolino[2,1-*a*]quinazolinones **103**.

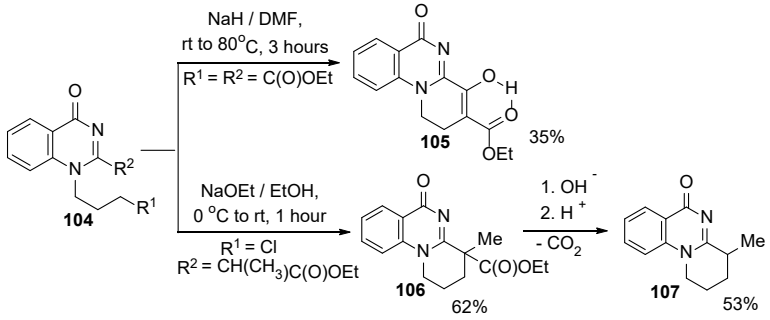
Also notable for its preparative simplicity is the recently described iodine-catalysed intramolecular oxidative C(sp^3)-H/N-H cross-coupling of 2-(3,4-dihydroisoquinoline-2(1*H*)-yl)-4-methylbenzamide **102** in DMSO to give 9-methyl-12,13-dihydro-6*H*-isoquinolino[2,1-*a*]quinazoline-6-one **103** (**Scheme 42**).[82]



Scheme 42. Access to dihydroisoquinolino[2,1-*a*]quinazolinones **103** through intramolecular oxidative C(sp^3)–H/N–H cross-coupling mediated by I_2/DMSO.

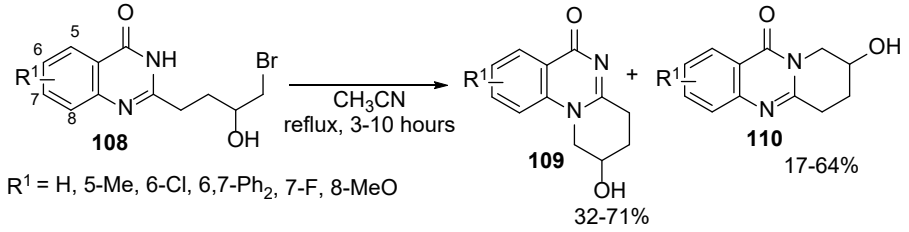
3.3 Pyrrolidine/dihydroisoquinoline annulation to the quinazolinone nucleus

It was reported that the cyclocondensation of 1-alkyl-2-functionalised quinazolinones **104** in the presence of bases is governed by the nature of the C2 substituent and the base used, but in either case, angular quinazolinone derivatives **105** and **107** were formed (Scheme 43).[67]



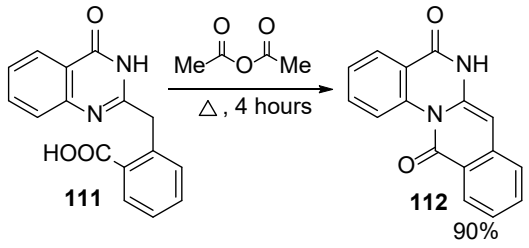
Scheme 43. Synthesis of 1,2-dihydro- and 1,2,3,4-tetrahydropyrido[1,2-*a*]quinazoline-6-ones **105, 107** by cyclocondensation of 1-alkyl-2-functionalized quinazolinones **104**.

2-(*δ*-Bromo)alkyl-substituted quinazolinones **108** were evaluated as substrates for the annulation of the piperidine ring by intramolecular N-alkylation.[83] However, with these compounds the process was not characterised by high regioselectivity and yielded two regioisomeric products, **109** and **110**, of angular and linear structure, respectively (**Scheme 44**).



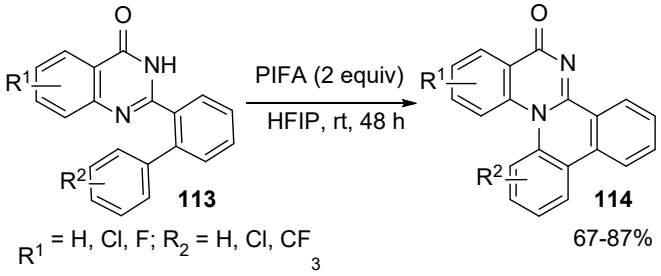
Scheme 44. Synthesis of 2-hydroxydihydropyrido[1,2-*a*]quinazoline-6-ones **109** and 3-hydroxypyrido[2,1-*b*]quinazoline-6-ones **110**.

On the other hand, the intramolecular condensation of 2-(2-carboxybenzyl)quinazolinone **111** in acetic anhydride proceeded in a highly selective manner to form 5*H*-isoquinolino[2,3-*a*]quinazoline-5,12(6*H*)-dione **112** in 90% yield (**Scheme 45**).[84]



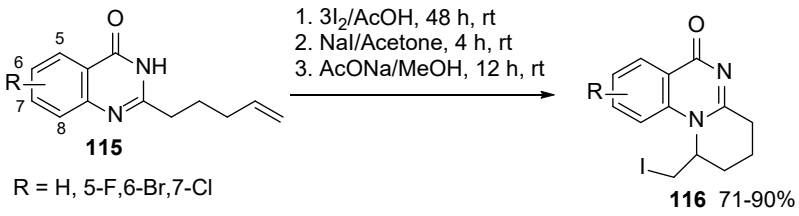
Scheme 45. Synthesis of 5*H*-isoquinolino[2,3-*a*]quinazoline-5,12(6*H*)-dione **112**.

Of particular interest is the regioselective synthesis of 6*H*-quinazolino[1,2-*f*]phenanthridin-6-ones **114** by PIFA-mediated intramolecular oxidative cyclization of 2-([1,1′-biphenyl]-2-yl)quinazoline-4(3*H*)-ones **113**.[85] The most efficient protocol for cyclization to the quinazoline N1 atom requires 2.0 equiv of PIFA in hexafluoroisopropanol (HFIP) at room temperature (**Scheme 46**).



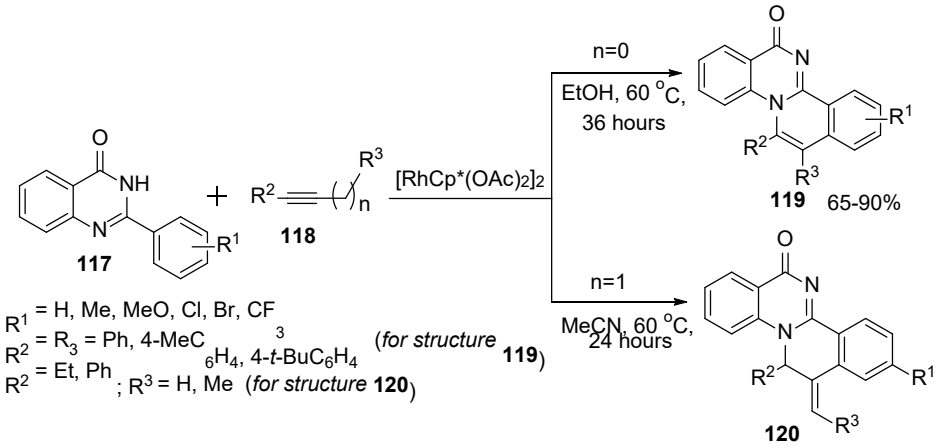
Scheme 46. Synthesis of 6*H*-quinazolino[1,2-*f*]phenanthridin-6-ones **114** *via* PIFA-mediated intramolecular C−N coupling reaction.

Recently, some authors proposed the use of 2-(4-pentylquinazolin-4(3*H*)-ones **115** as efficient substrates for the synthesis of angular 1-(iodomethyl)-1,2,3,4-tetrahydro-6H-pyrido[1,2-*a*]quinazolin-6-ones **116**.[86] It was found that the iodine-induced cyclization of quinazolinones **115** proceeds selectively according to the 6-*exo*-*trig* scheme, with the pyridine ring closing on the N1 atom (**Scheme 47**).



Scheme 47. Synthesis of 1-(iodomethyl)-1,2,3,4-tetrahydro-6*H*-pirido[1,2-*a*]quinazolin-6-ones **116** *via* iodocyclization of 2-(4-pentylquinazolin-4(3*H*)-ones **115**.

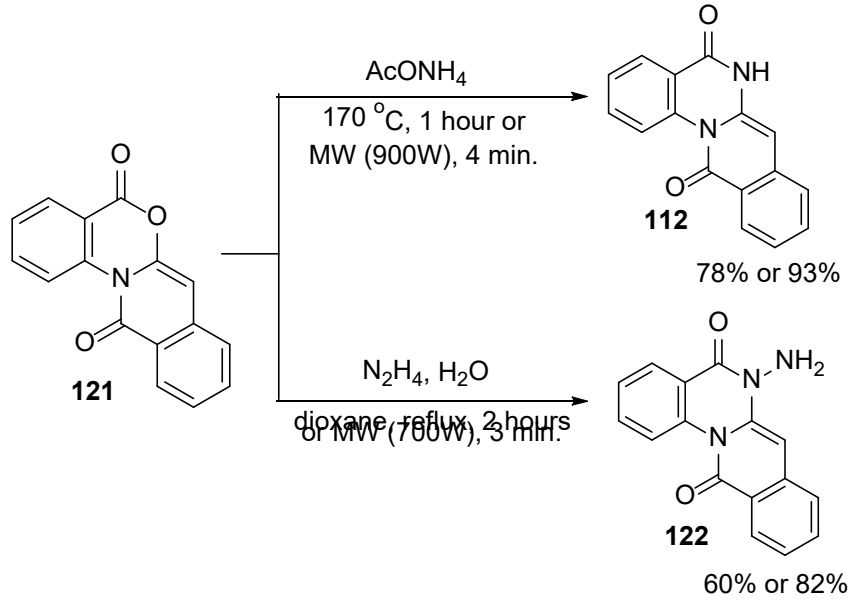
The Rh-catalysed cascade C-H olefination/annulation reaction widely used for the design of various polyheterocycles with directing groups proved to be effective for the construction of the isoquinolinopyrrolo[2,1-*a*]quinazolinone structure.[87] In particular, the [4+2]-annulation process leading to the formation of target products **119** in high yields was achieved by the reaction of 2-phenylquinazoline-4-(3*H*)-ones **117** with acetylenes **118** (n=0) in EtOH with the catalytic amount of $[RhCp^*(OAc)_2]_2$. When alkyl-substituted alkynes **118** (n=1) were used with MeCN as solvent, the Rh-catalysed C-H olefination/annulation was followed by double bond migration resulting in the products **120**. It is speculated that such migration may be caused by the isomerisation of alkynes **118** to alenes under the reaction conditions (**Scheme 48**).



Scheme 48. Rh(III)-catalysed synthesis of isoquinolinopyrido[2,1-*a*]quinazo-linones **119,120**.

3.4 Other synthetic methods

Some authors reported an unusual approach to the synthesis of isoquinoline-annulated quinazolinones **112** and **122** in high yields by amidation or hydrazidation of the oxazine cycle of [1,3]oxazino[3,2-*b*]isoquinoline **121** under microwave irradiation (**Scheme 49**).[88]



Scheme 49. MW-Assisted synthesis of 5*H*-isoquinolino[2,3-*a*]quinazoline-5,12(6*H*)-dione **112** and 6-amino-5*H*-isoquinolino[2,3-*a]*quinazoline-12(6*H*)-one **122** from [1,3]oxazino[3,2-*b*]isoquinolinone **121**.

4. Conclusions

The analysis and systematization of the literature reveals a diversity of synthetic strategies to the design of pyrrolo(pyrido)[1,2-*a*]quinazolinones, their benzo analogues and functional derivatives. Such approaches can become a reliable platform for the search and synthesis of new original compounds with a pyrrolo(pyrido)[1,2-*a*]quinazolinone scaffold. In addition to summarising the classical cyclization methods used to form target structures, modern highly selective metallocatalytic methods, which promise to be significantly extended in the future, are duly reviewed. Special emphasis is given to the electrophilic cyclization of alkenyl-substituted quinazolinones as an efficient atom-economical method for the

synthesis of functionalised pyrrolo(pyrido)[1,2-*a*]quinazolinones. It can therefore be concluded that this study will facilitate their further widespread application for medicinal chemistry purposes..

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