Pyrrolo[1,2-*a*]quinazolines. Synthesis and biological properties

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Abstract

Pyrrolo[1,2-*a*]quinazolines have raised some interest as bioactive scaffolds but their synthetic strategies based mainly on the anthranilic acid route have been rather limited. The last two decades have brought new approaches to the synthesis of pyrrolo[1,2-*a*]quinazoline framework and thus their potential could be valued in the obtaining of new lead compounds from the important class of quinazolines. Herein we present the synthetic strategies towards compounds containing the pyrrolo[1,2-*a*]quinazoline scaffold and their biological properties.

Keywords: Pyrrolo[1,2-*a*]quinazoline, isoindolo[2,1-*a*]quinazoline, pyrimidine *N*-heterocycles, bioactivity

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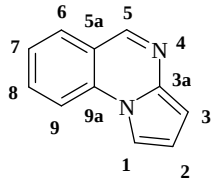
1. Introduction

Pyrrolo[1,2-*a*]quinazoline **1** is a pyrrolo-fused quinazoline *N*-bridgehead aromatic tricyclic system. The structure and numbering of the atoms in the pyrrolo[1,2-*a*]quinazoline skeleton are presented in formula **1**.



1

Quinazolines are known to possess important biological properties[1] and thus their pyrrolo-fused derivatives are good candidates for the discovery of new lead compounds in medicinal chemistry. The main focus was on their linear pyrrolo-condensed natural products (i.e vasicinone) and consequently on their synthetic analogs.[2]

However, the angular tricyclic system of pyrrolo[1,2-*a*]quinazoline has been rather seldom investigated regarding its biological properties and studies of its synthesis are quite limited prior to the last two decades. Nevertheless, new reports presented herein give reason to expect that efficient synthetic pathways could renew interest in this class of pyrrolo[1,2-*a*]quinazolines.

A review on syntheses and properties of these and related compounds was published in 1986,[3] and a short chapter focused on heterocycles containing the pyrimidine moiety was reported in 1991.[4] This paper presents an up-to-date classification of the synthetic strategies, reviews the biological properties of pyrrolo[1,2-*a*]quinazoline, and covers all the relevant literature available.

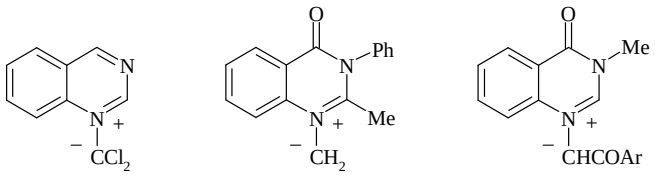
2. The Synthesis of Pyrrolo[1,2-*a*]quinazolines

There are three known strategies for the synthesis of pyrrolo[1,2-*a*]quinazolines: syntheses starting from substituted quinazolines, synthetic routes starting from substituted *N*-arylpyrroles, and syntheses by double cyclisation of different starting reagents.

2.1 Syntheses starting from quinazoline and its derivatives

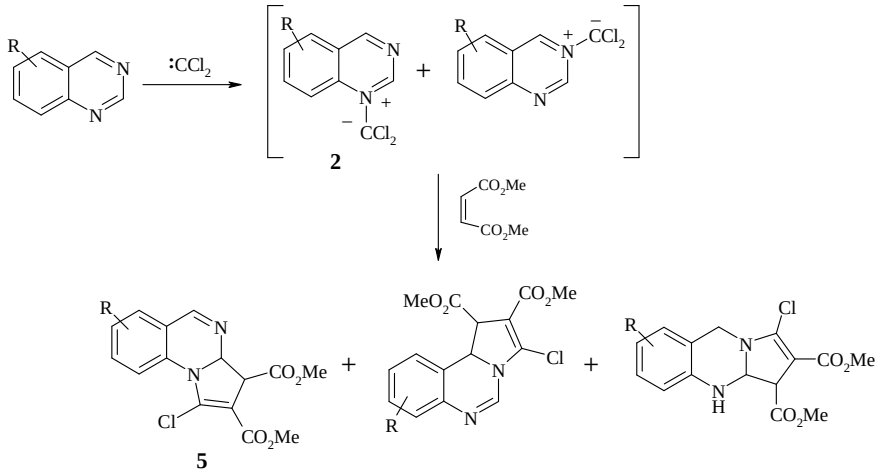
2.1.1 From quinazolinium *N*-ylides. 1,3-Dipolar cycloaddition reactions of the heteroaromatic *N*-ylides are one of the most versatile synthetic routes to pyrroloazines with a bridgehead nitrogen

atom.[5-7] The *N*-ylide approach to pyrrolo[1,2-*a*]quinazolines is versatile in providing series of compounds by simple procedures. In the literature are known three main routes to these compounds *via* quinazolinium *N*-ylides, starting either from dichloroquinazolinium ylide (**2**) or the unsubstituted (**3**) or a monosubstituted quinazolinium *N*-ylide (**4**).



2 **3** **4**

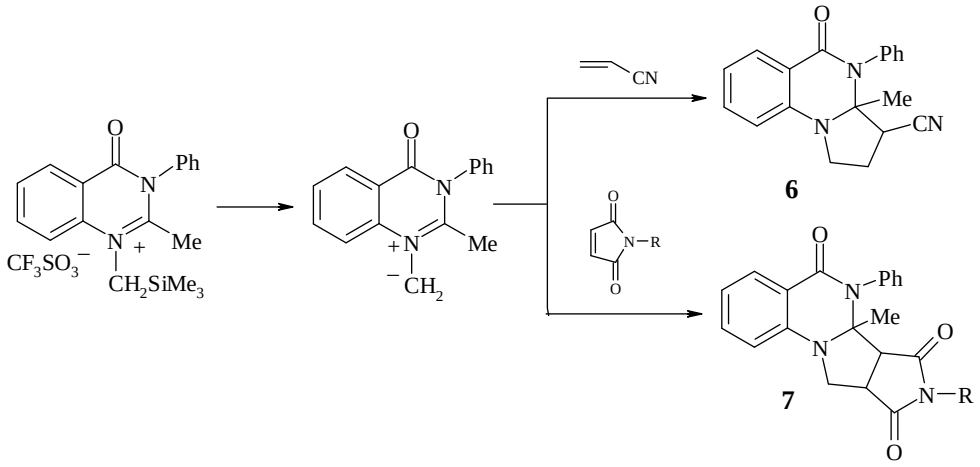
The pyrrolo[1,2-*a*]quinazoline **5** (Scheme 1) was obtained by Khlebnikov *et al.*[8] in mixture with other two isomers from the corresponding dichloroquinazolinium N-ylide **2**. Their synthetic strategy in obtaining pyrrolo-fused compounds was the 1,3-dipolar cycloaddition of the quinazolinium dichloromethanides generated *in situ* by the reaction of the quinazoline with dichlorocarbenes, in presence of different dipolarophiles such as dimethyl maleate. The result of the reaction was a mixture of isomeric pyrroloquinazolines, as the dichlorocarbene could also react at the N3 of the quinazoline generating the corresponding *N*-ylide. In some cases the fully aromatic compounds were obtained by using an oxidizing agent.



2 **5**

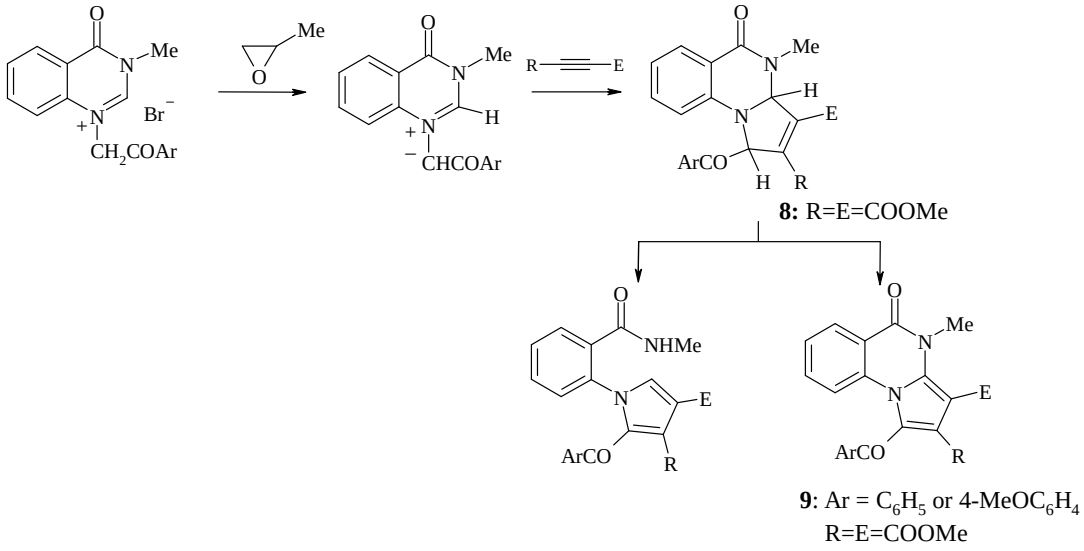
Scheme 1

Azouz *et al.*[9] obtained the tetrahydropyrrolo[1,2-*a*]quinazolines **6** and **7** starting with carbanion-unsubstituted quinazolinium *N*1-ylides using activated olefinic dipolarophiles (Scheme 2). The yields however were not high. When they employed dimethyl acetylenedicarboxylate (DMAD) as dipolarophile, an *in situ* ring-opening of the pyrroloquinazoline was observed with the formation of the corresponding *N*-arylpyrrole, but no further studies were performed in this direction.[9]



Scheme 2

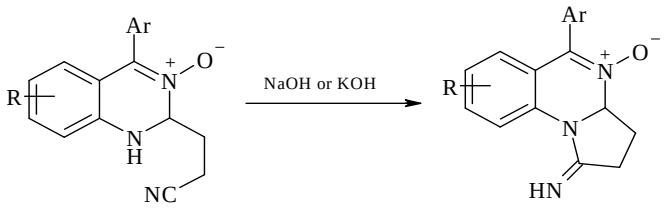
Recently, during the investigation on the cycloaddition reaction between monosubstituted quinazolinium ylides and symmetrical or unsymmetrical acetylenic dipolarophiles with the aim of obtaining pyrrolo[1,2-*a*]quinazolines,[10] the formation of substituted *N*-arylpyrroles[10,11] was observed. The dihydropyrrolo[1,2-*a*]quinazoline **8** was obtained however by using triethylamine as base in ethanol as solvent, and was characterized by NMR (Scheme 3). The pyrrolo[1,2-*a*]-quinazoline derivatives **9** were observed in mixtures with the pyrroles only in the case when dimethyl acetylenedicarboxylate was used as dipolarophile (R = E = COOMe) and were isolated in two cases with moderate yields.[12]



Scheme 3

2.1.2 From substituted quinazolines. The pyrrolo[1,2-*a*]quinazoline skeleton was successfully constructed starting from the corresponding 2-susbtituted quinazolines, by intramolecular cyclization.[13-20]

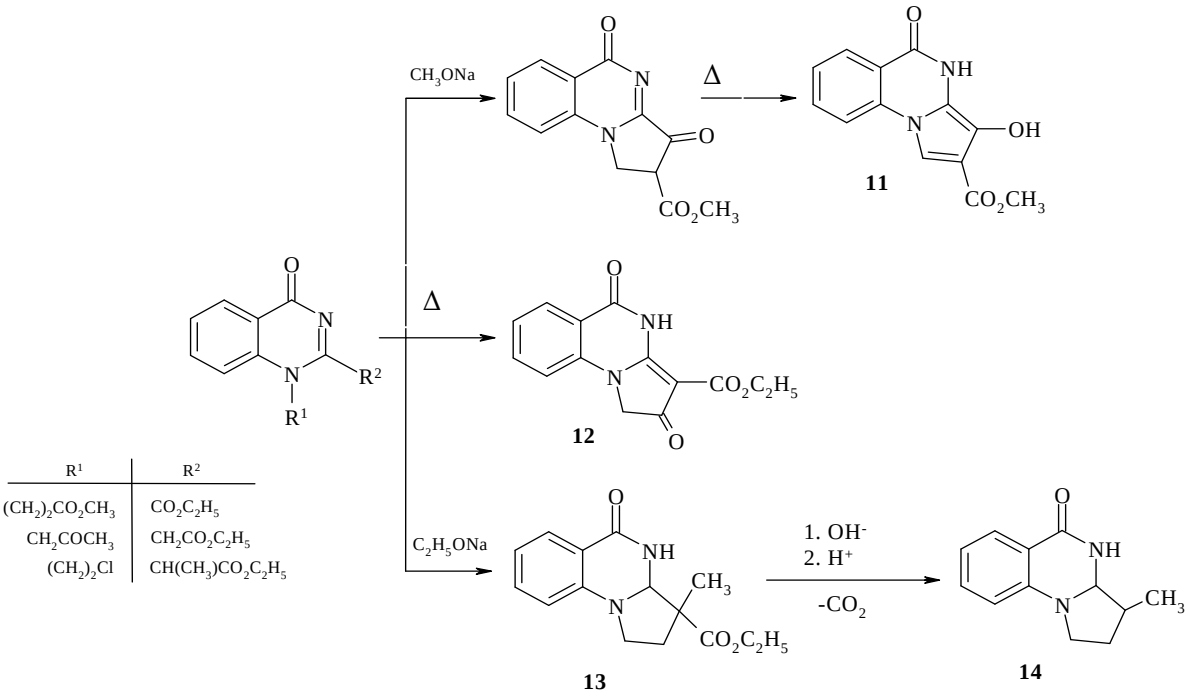
By intramolecular cyclisation of the 1,2-dihydroquinazolinepropionitrile 3-oxides in alkaline media (Scheme 4) the corresponding 1-iminotetrahydropyrrolo[1,2-*a*]quinazoline-4-oxides **10** were obtained.[13]



10

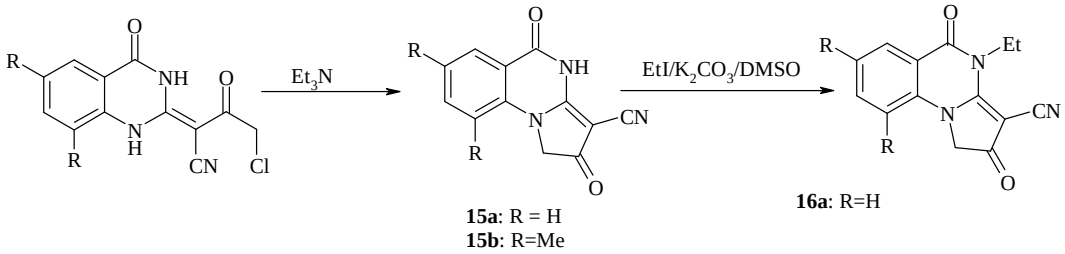
Scheme 4

Another approach to the pyrrolo[1,2-*a*]quinazoline skeleton is by the interlinking of substituents in the positions 1 and 2 of a disubstituted quinazolin-4-one in a Dieckmann type reaction such as is depicted in Scheme 5. The four pyrrolo[1,2-*a*]quinazolines **11**-**14** were obtained from suitable substituted starting materials.[14]



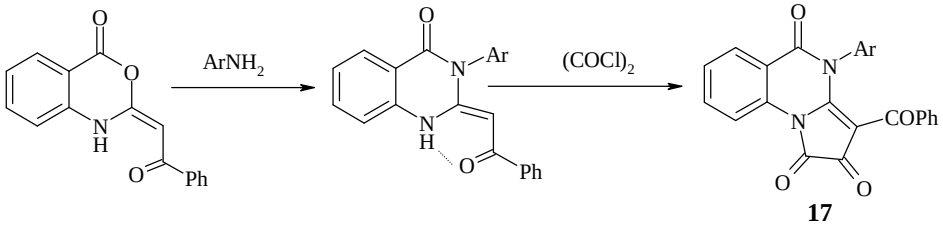
Scheme 5

The regioselective intramolecular alkylation of corresponding 2-substituted quinazolin-4-ones gave the 2,5-dioxo-1,2,4,5-tetrahydropyrrolo[1,2-*a*]quinazolines **15a,b** according to Scheme 6.[15] The pyrroloquinazoline **15a** was alkylated at N4 to the 4-ethyl derivative **16a** by ethyl iodide.



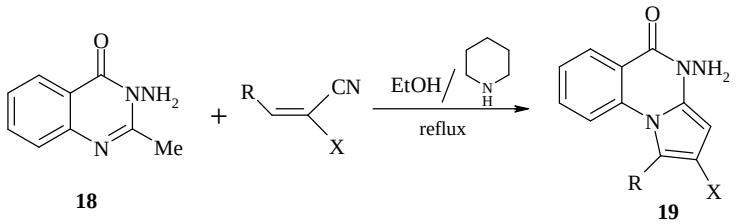
Scheme 6

Starting from 2-phenacylidene-1,2-dihydro-4*H*-3,1-benzoxazin-4-one, in a two-step synthesis the pyrrolo[1,2-*a*]quinazolones **17** were obtained in yields of over 90% (Scheme 7).[16]



Scheme 7

More recently the synthesis of pyrrolo[1,2-*a*]quinazolinones **19** was achieved starting from 3-amino-2-methylquinazolinone (**18**) by cyclisation with cinnamonitrile derivatives in ethanol at reflux, in the presence of a catalytic amount of piperidine (Scheme 8).[20] The compound **18** was obtained from anthranilic acid.



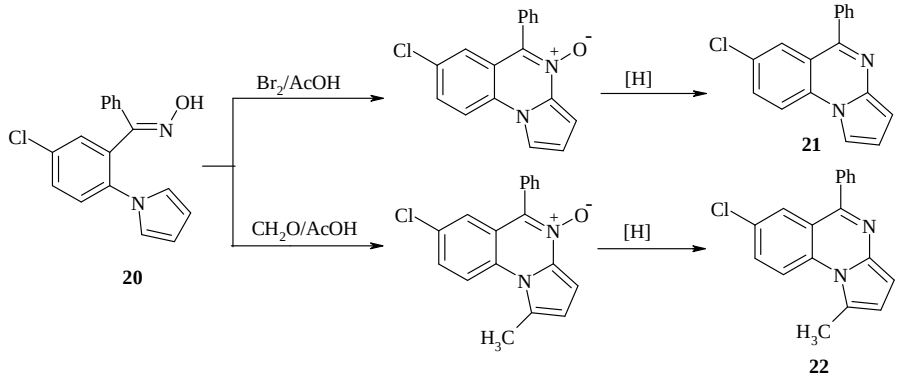
Scheme 8

2.2 Syntheses starting from *N*-arylpyrroles

The interest in syntheses of heterocycles starting from substituted *N*-arylpyrroles has been also directed on the obtaining of pyrrolo[1,2-*a*]quinazolines.[18-30]

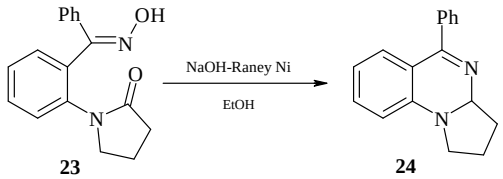
Noticing the availability of the 2-aminobenzophenones in the synthesis of certain heterocycles, Garcia *et al*.[24] extended these studies to pyrrole and pyrrolo-fused derivatives. Thus, starting from

the oxime of the 2-(1-pyrroly1)benzophenone **20** the fully aromatic pyrrolo[1,2-*a*]quinazolines **21** and **22** were obtained in moderate yields by reducing the corresponding pyrrolo[1,2-*a*]quinazoline *N*-oxides obtained in the first reaction step (Scheme 9).



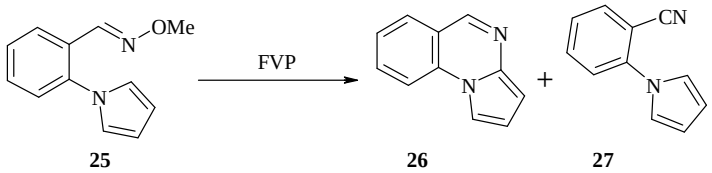
Scheme 9

Using a similar strategy, Ishikawa *et al.* succeeded in cyclizing the oximes **23** over a catalyst of NaOH and Raney nickel as shown in Scheme 10, to obtain **24**.[25,26]



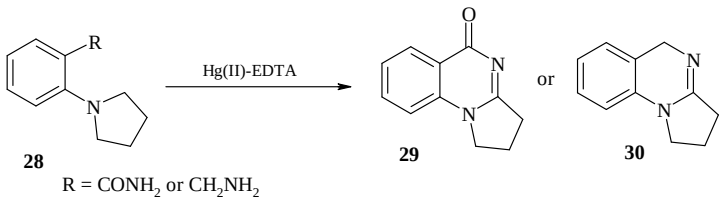
Scheme 10

There is also a report that on flash vacuum pyrolysis (FVP) of the pyrrole oxime **25** the parent pyrrolo[1,2-*a*]quinazoline (**26**) is obtained (Scheme 11) as the major product in a mixture with the pyrrole **27**.[27] The author also presents a study on the reaction mechanism leading to the pyrrolo[1,2-*a*]quinazoline and extends his work on the reactivity of this parent heterocycle.



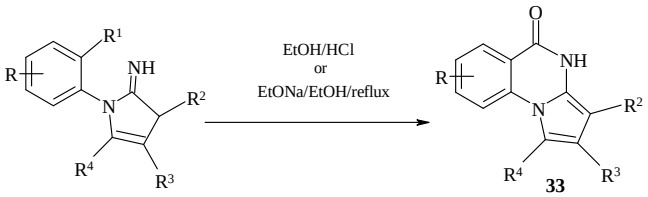
Scheme 11

Mohrle *et al.*[28,29] cyclized different hydrogenated pyrroles to form pyrrolo[1,2-*a*]quinazolines. From **28** by cyclization in presence of Hg(II)-EDTA as oxidizing agent they obtained the corresponding pyrrolo[1,2-*a*]quinazolines **29** and **30** (Scheme 12).



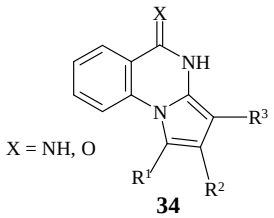
Scheme 12

Recent studies on the formation of pyrrolo[1,2-*a*]quinazolines starting from conveniently substituted *N*-arylpyrrole intermediates **31** and **32** were reported (Scheme 13). The pyrrolo[1,2-*a*]-quinazolines **33** were obtained (Scheme 13) by two similar synthetic pathways by two independent research groups.[30,31]



Scheme 13

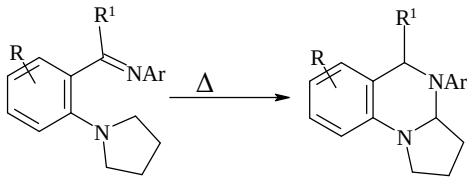
Pyrrolo[1,2-*a*]quinazolin-5-imines and pyrrolo[1,2-*a*]quinazolin-5-ones of type **34** were obtained by Abdelrazek *et al. via* intramolecular cyclisation of the corresponding *N*-aryl-pyrroles.[32,33]



Other reactions involving pyrrole intermediates were reported by Schaefer starting from *N*-aryl-4-amino-5-cyano-2,3-dihydro-1*H*-pyrrol-2-ones.[34]

2.3 Synthesis by the tert-amino effect

By the cyclisation of the *ortho* substituted anilines of type **35**, also known as tert-amino effect, the compounds **36** were obtained in medium yields.[35] Recently, using the tert-amino effect Akyiama *et al.*[36] have isolated the pyrrolo[1,2-*a*]quinazoline **36** having as substituents R = H, R^1 = H and Ar = C_6H_5 (Scheme 14).



35 **36**

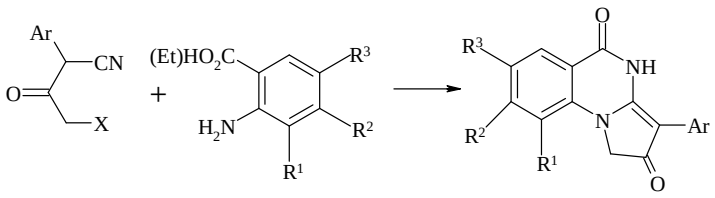
Scheme 14

2.4 Syntheses by double cyclisation reactions

Various substituted quinazolines were obtained in two step reactions involving in the first step the formation of the bicyclic quinazoline or a *N*-arylpyrrole system followed in the second step by intramolecular cyclisation to the desired tricyclic pyrrolo[1,2-*a*]quinazoline system.

2.4.1. Double cyclisation starting from anthranilic acid and its derivatives. The anthranilic acid route is one of the most facile synthetic route to quinazolines.[37] Pyrrolo[1,2-*a*]quinazolines derivatives were obtained[38-86] starting from suitable anthranilic acid derivatives by reaction with aliphatic acids, esters or acid halides containing keto groups, followed by intramolecular cyclisation of the corresponding intermediates.

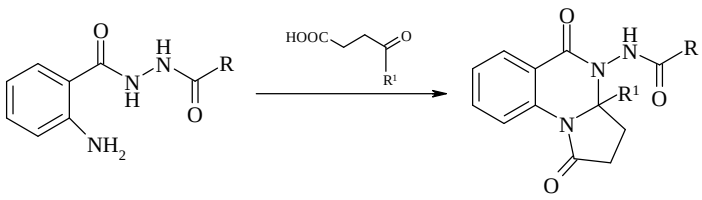
Recent reports[67-70] state that starting with substituted anthranilic acid or its derivatives the pyrrolo[1,2-*a*]quinazolines **37** are obtained by cyclisation with substituted 3-oxo-4-halo-butanenitriles. (Scheme 15) Most probably the reaction goes *via* a *N*-arylpyrrole intermediate.



37

Scheme 15

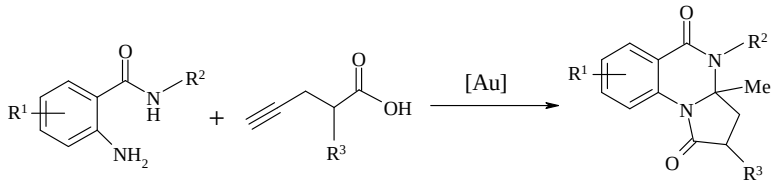
Starting from anthranilic hydrazides, Zicane *et al.*[71-73] obtained the pyrrrolo[1,2-*a*]quinazolines **38** when the cyclisation was made with 2-oxoglutaric or 4-oxopentanoic acid (Scheme 16).



38

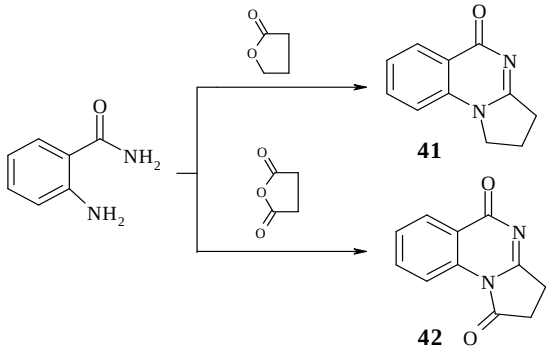
Scheme 16

Starting from the anthranilic acid amides **39** the pyrrolo[1,2-*a*]quinazolinones **40** were obtained by a gold-catalyzed cascade reaction with suitable alkynoic acids (Scheme 17).[74,75] There were also obtained more complex structures containing the pyrrolo[1,2-*a*]quinazoline framework.[75] Earlier studies by Patil *et al.*[76] showed that from alkynes tethered with hydroxyl groups, by double hydroamination with various substituted 2-aminobenzamides in presence of $PtCl_4$, compounds similar to **40** were obtained.



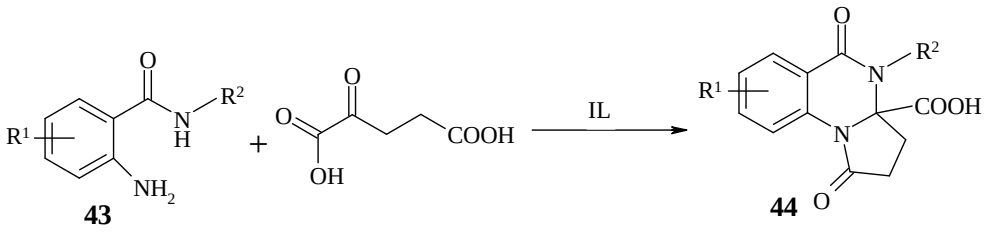
Scheme 17

Many syntheses are also known starting from substituted 2-aminobenzamides with different acyclic compounds.[77-81] Cyclisations of 2-aminobenzamides with 2,4-dioxovalerate derivatives were also investigated[77,78] or, as reported by Suh *et al.*,[79] by employing γ-butyrolactone or succinic anhydride as in the case of compounds **41** and **42** (Scheme 18).



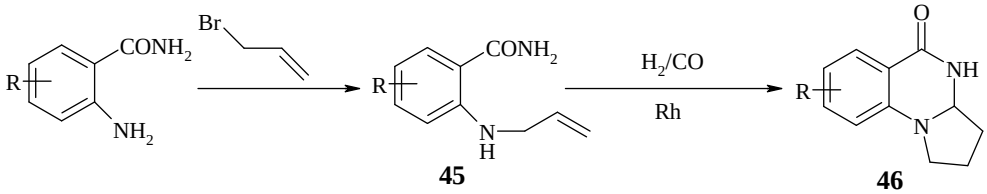
Scheme 18

More recently, also starting from 2-aminobenzamides, Wang *et al.*[80,81] synthesized carboxylic acids (**44**), derivatives of pyrrolo[1,2-*a*]quinazoline, using 2-oxopentanedioic acid as cyclisation reagent. The main feature of the reaction is the use of ionic liquids (IL) as reaction medium (Scheme 19).



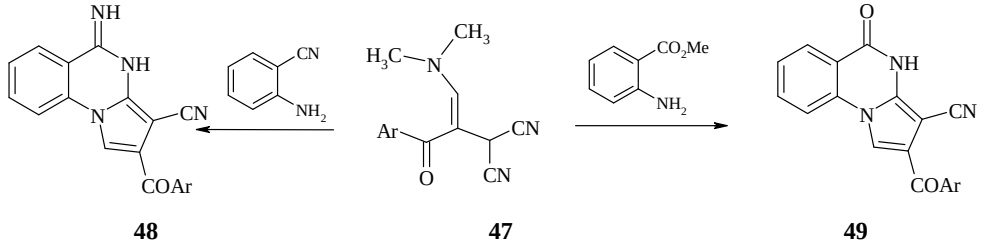
Scheme 19

An interesting application of rhodium catalyzed hydroformylation of compounds of type **45**, obtained starting from anthranilamides, was reported by Campi *et al.*[82,83] The reaction led to the reduced pyrrolo[1,2-*a*]quinazolines **46** (Scheme 20).



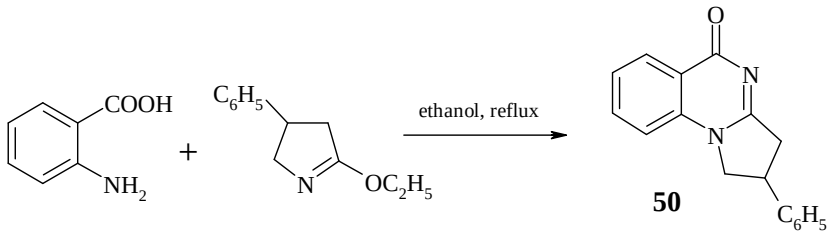
Scheme 20

On reaction with anthranilonitrile or methyl anthranilate the enaminones **47** afforded the pyrrolo[1,2-*a*]quinazolines **48** and **49**.[84] A similar approach was described earlier by Dave and Upadhyaya (Scheme 21).[85]



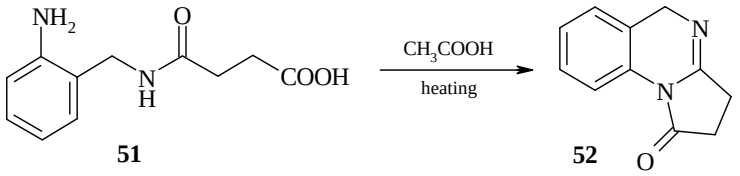
Scheme 21

Compounds **50** were obtained by a cyclization reaction starting from anthranilic acid and 2-ethoxypyrroline in ethanol by heating at reflux (Scheme 22).[86]



Scheme 22

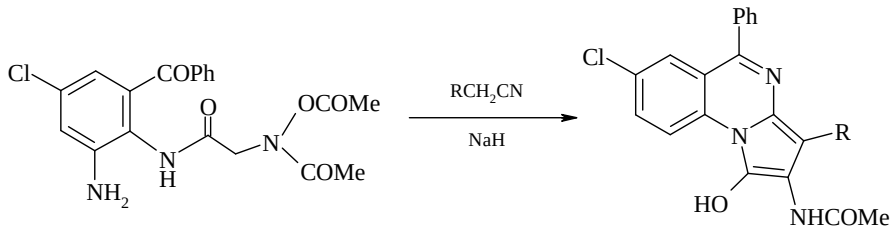
2.4.2 Other double cyclisation reactions. Double cyclisation reactions leading to the pyrrolo[1,2-*a*]quinazoline skeleton are known, starting with the early work of Juneja *et al.*[87] who at that time were looking for the structure of vasicine, which in fact has a linear pyrroloquinazoline skeleton. Thus, starting from the succinic acid amide **51** the pyrrolo[1,2-*a*]quinazoline **52** was obtained (Scheme 23) on heating in acetic acid. Further studies by Spath *et al.* established the correct structure.[88]



51 **52**

Scheme 23

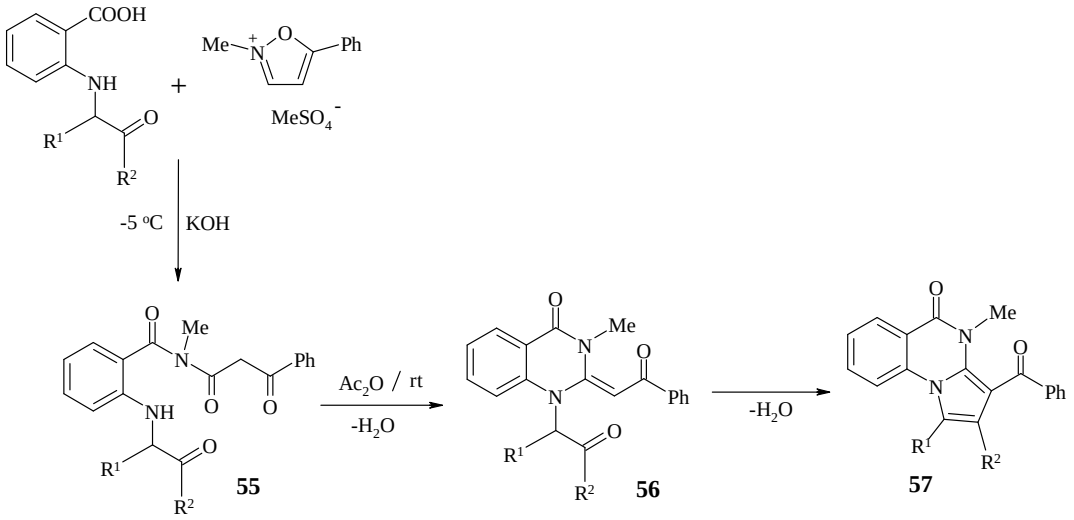
Since these early syntheses,[87,88] other synthetic strategies were reported,[89-92] until the first review[3] on the pyrrolo[1,2-*a*]quinazolines appeared in 1986. Of importance was the work of Bell and Wei[89-91] who studied the synthesis of pyrrolo[1,2-*a*]quinazolines **54** by reaction of compounds **53** with nitrile derivatives bearing acid methylene protons in DMF as reaction medium and in the presence of sodium hydride (Scheme 24).[91]



53 R=COOEt, $PO(OEt)_2$ **54**

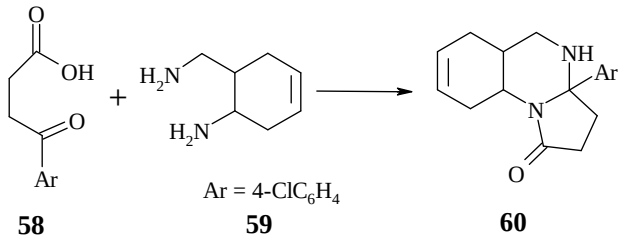
Scheme 24

Henning and Haber[93] reported that at room temperature in acetic anhydride, anthranilic derivatives **55** eliminate water yielding 2-benzoylmethylene-quinazolinones **56**, which at 60 °C cyclize to pyrrolo[1,2-*a*]quinazolin-5-ones **57** (Scheme 25). The compounds **55** were obtained from anthranilic acid derivatives and isoxazolium salts.



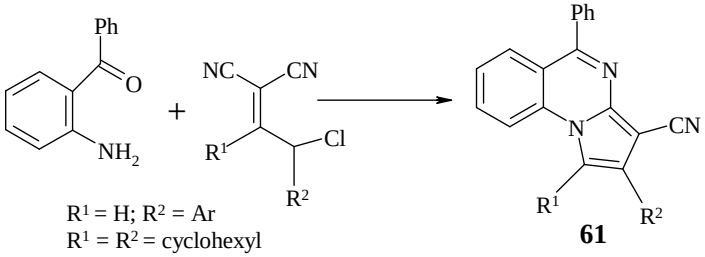
Scheme 25

By condensating 3-(4-chlorobenzoyl)propionic acid **58** with the amine **59** the hydrogenated pyrrolo[1,2-*a*]quinazoline **60** was obtained (Scheme 26).[94,95] Studies were made in order to obtain specific stereoisomers of **60** starting from specific stereoisomers of the amine **59**. Some studies regarding the fragmentation of such compounds by mass spectrometry should be mentioned.[96]



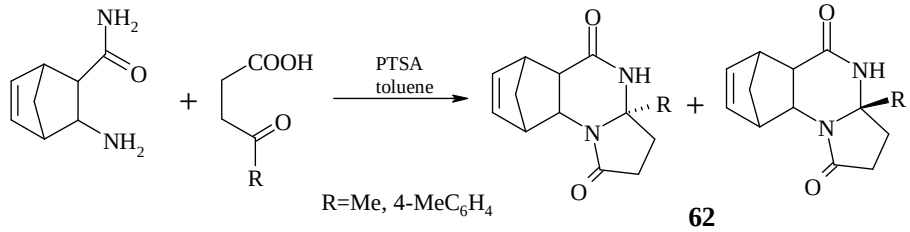
Scheme 26

In a one step reaction starting from substituted 2-aminobenzophenones and 2-haloalkylidene propanedinitriles Dave and Shah obtained (Scheme 27) the pyrrolo[1,2-*a*]quinazolines **61**.[97]



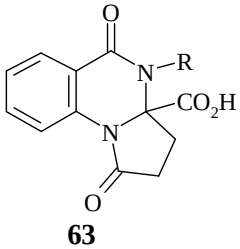
Scheme 27

Fulop *et al.*[98] synthesized the stereoisomeric pyrrolo[1,2-*a*]quinazolines **62** starting from racemic *diexo*-3-aminonorbornane-2-carboxylic acid, condensing it with levulinic or (4-methyl-benzoyl)propionic acid (Scheme 28) in the presence of *p*-toluenesulfonic acid (PTSA).

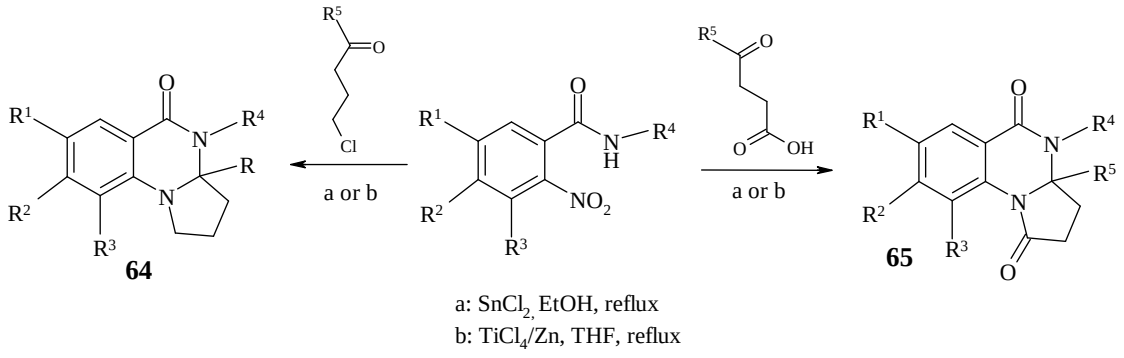


Scheme 28

The compounds **63** were prepared in 70-100 gram scale by reaction of 2-amino-*N*-alkyl(aryl)benzamides with 2-oxoglutaric acid.[99]



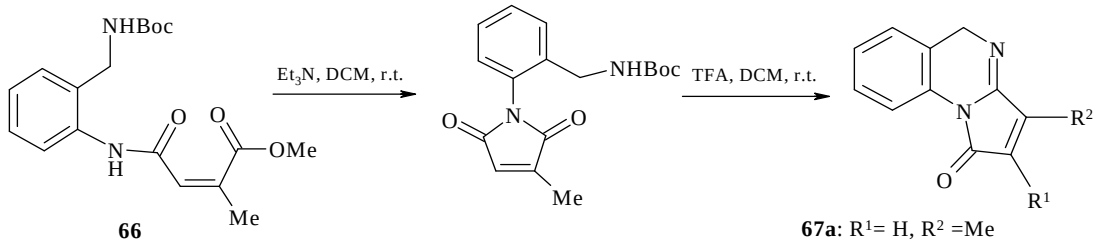
By reductive cyclization of 2-nitrobenzamides with haloketones or keto acids mediated by $SnCl_2 \cdot 2H_2O$[100] or $TiCl_4/Zn$[101] systems Shi *et al.* obtained compounds of type **64** and **65** in good yields according to Scheme 29. The authors cite some reports also presented herein[41,64,74,75] by highlighting the disadvantages of these synthetic strategies compared to the one they proposed.



Scheme 29

By the same strategy of metal reduction-condensative cyclization strategy Bunce and Nammalwar obtained similar compounds using Fe as metal catalyst and starting from the unsubstituted 2-nitrobenzamide in reaction with linear keto bearing compounds.[102]

Recently a synthesis[103] starting from different substituted anilic esters **66** was reported to yield pyrrolo[1,2-*a*]quinazolines **67a,b**. The reaction goes through an isolable cyclic imide.



66

67a: R^1= H, R^2 =Me
67b: R^1= Me, R^2 =H

Scheme 30

3. Biological Properties of the Pyrrolo[1,2-*a*]quinazolines

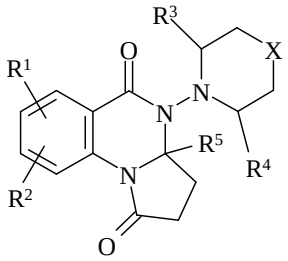
The biological properties of the pyrrolo[1,2-*a*]quinazoline system have not been much investigated, perhaps because of the scarcity of preparative routes to such compounds. However, there are some reports and patents claiming potentially bioactive pyrrolo[1,2-*a*]quinazolines and these will be presented briefly in this chapter.

3.1 Antibiotic activity

Compounds **54** (Scheme 24) are reported as antibiotics,[91] but the author did not mention the specific antibiotic activity.

3.2 Analgesic, anti-inflammatory and antipyretic activity

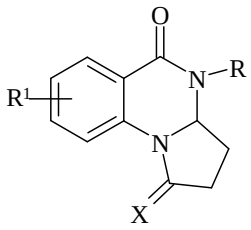
Compounds of structure **68** are known to possess analgesic, anti-inflammatory and antipyretic properties. The patent contains also the pharmaceutical formulation of the active ingredients as capsules or tablets.[52]



68

R^1 = H, X, NH_2, NO_2
R^2 = H, X, NH_2, NO_2
R^3, R^4 = H, alkyl
R^5 = alkyl
X = O, $(CH_2)_m$ (m = 0,1,2)

Compounds of type **69** are reported as anti-edema agents. The tests were carried out on mice which are subjected to strong inflammatory response induced by carrageenin with 25-100 mg doses of compounds of type **69**.[56]



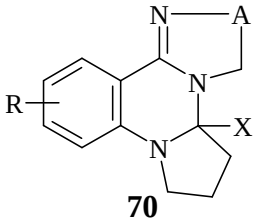
R = H, Et, Bu, diethylamino-alkyl
R^1 = Br, I, F, Me, Et, MeO, EtO, etc
X = O, NH

69

3.3 Cardiovascular potential activity

Compounds of type **24** (Scheme 10) present antihypotensive activity and thus possess potential as cardiovascular therapeutics.[25,26]

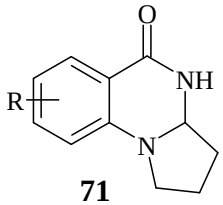
Compounds of quinazoline class are hypotensive and bronchodilatators.[104,105] Formula **70** presents some compounds with antiarrhythmic properties being therapeutics in treatment of atrial or ventricular arrhythmias.



R = H, X, NH_2, alkyl, etc.
R^1 = Phenyl, Thienyl, Naphthyl

70

The pyrrolo[1,2-*a*]quinazolines **71** are claimed to possess hypotensive activity by regulating the blood pressure.[40] The authors propose also pharmaceutical formulations for the compounds. Compounds similar to **71** substituted at N4 or possessing a carbonyl at C-1 are also claimed to possess antihypertensive properties.[48] The inventors also present possible formulations as tablets for orally administration. The mechanism of action is not clearly defined; thus the compounds could have CNS depressant action also.

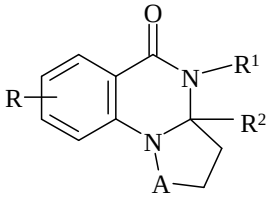


71

R = H, F, Cl, alkyl, alkoxy, aryloxy, NH_2, etc

3.4 Bioactive compounds acting on the respiratory system

Compounds with general formula **72** were tested on guinea pigs and found to possess bronchodilatator properties.[106] The patent includes a pharmacological formulation and possible administration methods. These compounds are claimed to be suited to the treatment of bronchial asthma.



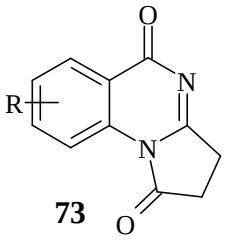
72

A = CH_2 or CO
R = H, Cl
R^1 = H or Ph
R^2 = alkyl (methyl, ethyl, propyl, isopropyl, amyl, hexyl) or substituted benzene

There are also other reports[104,105] of pyrrolo[1,2-*a*]quinazoline derivatives having broncho-dilatator properties.

3.5 Central nervous system activity

Compounds with general formula **73** were tested as CNS depressants. The tests on mice showed decreased motor-activity, respiration and sedative-ataxic effects.[47] The compounds **71** with similar structure were also claimed to possess CNS depressant activity.[40] The same authors present some pyrrolo[1,2-*a*]quinazolines with potential tranquilizant activity,[90] but the patent lacks details on how this activity was tested and measured.



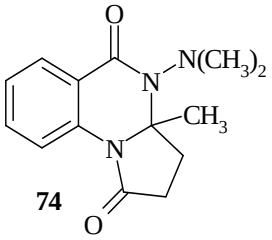
73

R = H, alkyl, alkoxy, SO_2NH_2

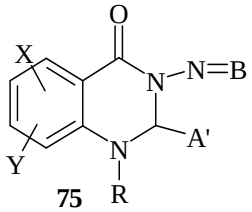
Compounds of formula **10** are reported only as intermediates in obtaining open cycle compounds as CNS depressants.[13] The authors don't seem to provide biological data on the compounds **10** included in the patent.

The pyrrolo[1,2-*a*]quinazoline **74** was tested together with other quinazoline structure related compounds as sedatives, having potentiating barbiturate properties and are thus claimed to be useful as adjuvants in the treatment of convulsions, insomnia or mental disorders.[53] This work is a continuation of a previous report by the same authors.[46] The patent could refer to other analogs of

the general formula **75**. Pyrrolo[1,2-*a*]quinazolines with anticonvulsant properties are also reported in a German patent.[64]



74



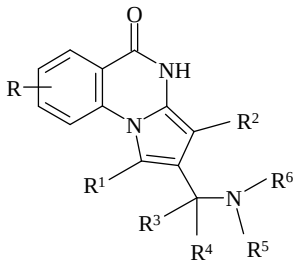
75

R and A' = $(CH_2)_3$
X, Y= alkyl, alkoxy, X, NO_2, CF_3, etc.
B = pair of two alkyl groups

Compounds **54** (Scheme 23) are also claimed to possess CNS depressant activity, mydriasis being one of the effects.[91]

3.6 Anticancer activity

Compounds of formula **76** are claimed as PARP (poly ADP ribose polymerase) inhibitors[107] and thus to have potential as anticancer therapeutics.

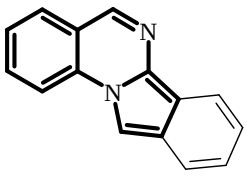


76

R = X, CN, NO_2, OH, RO, alkyl;
R^2, R^3 = H, X, alkyl;
R^3, R^4 = H, D, C=O, alkyl;
R^5 and R^6 i.e cycloalkyl, piperazine, etc

3.7 Bioactive isoindolo[2,1-*a*]quinazolines

The isoindolo[2,1-*a*]quinazolines are tetracyclic compounds which possess a pyrrolo-[1,2-*a*]quinazoline substructure. The structure of such compounds corresponds to the formula **77**.



77

Isoindolo[2,1-*a*]quinazolines were synthesized[102,108-116] and studied for a broad range of medicinal applications including TNF-α inhibitors[110] antibacterial and antifungal activity[116] or CNS depressants.[108]

4. Conclusions

Pyrrolo[1,2-*a*]quinazolines are tricyclic compounds with great potential and combine the quinazoline substructure, a privileged structure in the medicinal chemistry, with a pyrrole. The synthetic methods are rather scarce but the past ten years have brought efficient new synthetic strategies which could lead to an increased interest in pyrrolo[1,2-*a*]quinazolines in the near future, mainly for their potential applications in medicinal chemistry.

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