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Claudia Lalli. Bicyclic 5-6 Systems With One Bridgehead (Ring Junction) Nitrogen Atom: Two Extra Heteroatoms 0:2. *Comprehensive Heterocyclic Chemistry IV*, Elsevier, pp.659-684, 2022, 10.1016/b978-0-12-409547-2.14939-x . hal-03481501

HAL Id: hal-03481501

<https://univ-rennes.hal.science/hal-03481501v1>

Submitted on 4 Jan 2022

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Bicyclic 5-6 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: Two Extra Heteroatoms 0:2

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1 INTRODUCTION

This chapter reviews bicyclic systems containing five- and six- fused rings with one ring junction nitrogen atom and two extra heteroatoms in the six-membered ring. The heteroatoms are mainly nitrogen, but a number of oxygen, sulfur, boron and phosphorus have also been described in the literature. This chapter is an update of the previous related book chapters, [1] [2] therefore will be concentrated on the literature appeared starting from 2008. No other general review on this topic exists, however the history and the use in medicinal chemistry of the pyrrolo[2,1-f][1,2,4]triazine core has been recently treated in a digest, [3] and their pharmacological activities, structural modifications and structure-activity relationship (SAR) have been reported [4] with a particular attention on their action over fibroblast growth factor receptors (FGFRs). [5] Moreover [1,2,4]triazines condensed with five-membered heterocycles or with bicyclic systems and their use as anticancer compounds have been overviewed. [6]

Among the plethora of ring system fitting within the criteria of this chapter, the most studied are undoubtedly the regioisomeric pyrrolotriazines (**1-6**), both fully conjugated and nonconjugated, and related benzo derivatives (Figure 1). The other known systems are listed with references provided and include: pyrrolo-fused 1,2,4-benzothiadiazines **7a-c**, which structures were assigned by COSY, HMBC and HSQC NMR analysis, IR and mass measurement, and unambiguously confirmed by single crystal X-ray analysis; [7] chiral 2,3,3a,4-tetrahydro-1*H*-pyrrolo[2,1-c][1,2,4]benzothiadiazine 5,5-dioxides **8a** (**S18986**) and **8b**, that make the object of on-column stopped-flow multidimensional HPLC studies for the determination of hydrolysis and enantiomerization rate constants; [8] [9] [10] the achiral **8b** was also synthesized by thermal cyclization under solvent free conditions, starting from chloroacylaminobenzenesulfonamides; [11] (*R*) and (*S*) enantiomers of 7-chloro-9-(furan-3-yl)-2,3,3a,4-tetrahydro-1*H*-benzo[e]pyrrolo[2,1-c][1,2,4]thiadiazine 5,5-dioxide **8c** was synthesized for its pharmacological activity and chemical stability; [12] chiral 2,3,5,6-tetrahydro-[1,2,4]thiadiazino[6,5,4-*hi*]indole 1,1-dioxides **9a-b**, of which the reactivity behaviour towards NaBH₃CN was studied; [13] 3-vinylhexahydro-2*H*-pyrrolo[1,2-*b*][1,2,6]thiadiazine 1,1-dioxide **10**, that was synthesized via intramolecular amination catalysed by Co(II)-based metalloradical catalyst from the corresponding *N*-allylic sulfamoyl azide and which structure was unambiguously confirmed by single crystal X-ray analysis; [14] *trans*-2*H*-pyrrolo[1,2-*b*][1,2,6]thiadiazine 1,1-dioxide **11** were prepared by Pd-catalysed carboamination reaction of 2-allyl and 2,5-diallyl pyrrolidinyl sulfamides via a stereoselective *anti*-aminopalladation pathway; [15] a library of 160 members of isoindoline-thiadiazinanes **12**, obtained via a sequence including a domino Heck-aza-Michael sequence, followed by cyclization with paraformaldehyde or 1,1'-carbonyldiimidazole (CDI), [16] sequence optimized by a combination of microwave heating and continuous-flow organic synthesis; [17] 2,3,3a,4-tetrahydro-1*H*-pyrrolo[1',2':4,5][1,3,4]oxadiazino[2,3-*a*]isoindol-10(5*aH*)-ones **13a-g** which structure was unambiguously confirmed by single crystal X-ray analysis; [18] diethyl-7-methyldihydro-4*H*-pyrrolo[2,1-*d*][1,3,5]dioxazine-6,6(7*H*)-dicarboxylate **14** was accidentally synthesized as single diastereomer from diethylaminomalonate, crotonaldehyde and formaldehyde under secondary amine catalysis; [19] oxadiazine salt **15** was synthesized by a two step procedure involving a Co(II)- [20] or Ni(II)- [21] catalysed cross coupling of 2-benzamidopyridine 1-oxide with terminal alkyne, followed by oxidation; bicyclic and tricyclic aza-peroxides **16** and **17** were obtained via a photooxygenation key step; [22] meso-1,3,5-oxadiazines **18** were obtained by electrochemical decarboxylative oxidation of *N*-acyl-aminoacids; [23] pyrrolo[2,1-*d*][1,2,5]oxadiazines **19** were synthesized by (3+3)-cycloaddition of *N*-vinylpyrroles and nitrones; [24] psycotripine **20**, an alkaloid isolated from *Psychotria pilifera* leaves, which structure was confirmed by mono and bidimensional

NMR experiments, high resolution ESI MS and by comparison of calculated and experimental ECD; [25] the enantioselective total synthesis of (-)-terengganensine A **21** was accomplished by a key Noyori's catalytic enantioselective transfer hydrogenation [26] and a formal total synthesis involving a photoredox catalytic nitrogen-centered radical cascade reaction has also been reported. [27] Heterocycles containing phosphorus as heteroatom such as 1*H*-pyrrolo[1,2-*c*][1,3,2]oxazaphosphorines **22** have also been described. [28] Manganese (III) complexes **23** have been described as potent orally active peroxynitrite scavengers. [29] Systems containing a boron atom, of general formula **24** are having great success, if we judge by the number of publications that has literally exploded in the last 10 years. Indeed, about one hundred articles and patents can be counted in the 2008-2018 period covered by this chapter. The most described systems are BODIPYs and derivatives, which are widely used in different fields of application: in materials science as dyes and fluorescent organic pigments, [30] in catalysis, [31] in analytical chemistry such as fluorescent probes, [32] and in biology as labelling molecules to probe protein-protein interactions. [33] Finally heterocycles of general formula **25** have also been synthesized. [34]

Since no systematic studies of experimental structural as well as theoretical methods exist for those compounds, a little space is devoted to this topic. The synthesis and the chemical reactivity of pyrrolotriazines (**1-6**) will be deeply described instead.

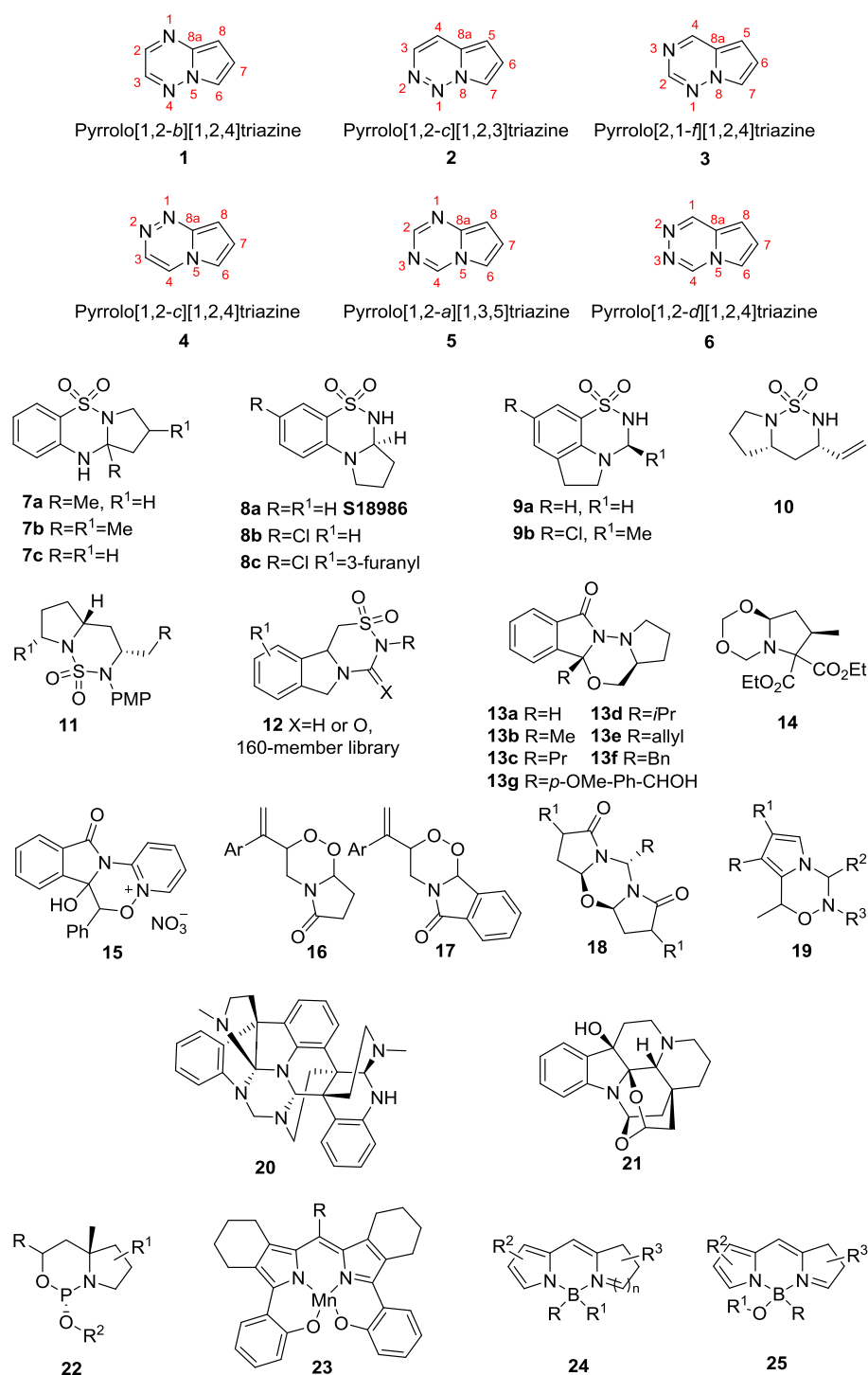


Figure 1.

2 THEORETICAL METHODS

Systematic studies, falling within the scope of this chapter, do not exist. The only two exceptions rely on the prediction of biological properties for drug discovery. Quantum mechanical calculations can be used to explain the inhibition provided by heteroaromatic rings containing nitrogen atoms towards Cytochrome P450s. [35] In particular the complexation energies of Fe(III) heme in its doublet and sextet state with a set of heteroaromatic rings has been calculated. For pyrrolo[1,2-*c*][1,2,3] triazine (**2**) the $\Delta E = 2.2$ kcal/mol for Fe(III) in doublet state and $\Delta E = 4.3$ Kcal/mol in sextet

state if Fe(III) is complexed on the nitrogen in the 2 position. If Fe(III) is linked to the nitrogen in position 3 the $\Delta E = -2.1$ kcal/mol for Fe(III) in doublet state and $\Delta E = 4.1$ Kcal/mol in sextet state. These energies do not represent a risk of P450s inhibition since the barrier is below $\Delta E = -4.5$ kcal/mol for Fe(III) in doublet state. The hydrogen-bond acceptor ability of pyrrolo[1,2-*c*][1,2,3]triazine (**2**) has also been calculated using the Gaussian09 program. [36] To do so two quantum descriptors have been investigated, the $\Delta E(H)$, which is the energy change of a hydrogen atom after complexation, relative to a H-bond complex property; and the V_{\min} , that is the local minimum electrostatic potential value on the hydrogen-bond accepting sites, relative to a H-bond acceptor site property. For pyrrolo[1,2-*c*][1,2,3]triazine (**2**) $\Delta E(H) = 70.1$ kJ/mol, and $V_{\min} = -184.1$ kJ/mol for the nitrogen in position 2; instead for the nitrogen in position 3 $\Delta E(H) = 71.4$ kJ/mol, and $V_{\min} = -225.5$ kJ/mol, indicating that the nitrogen sites are effective H-bond acceptor sites.

3 EXPERIMENTAL STRUCTURAL METHODS

3.1 X-Ray Studies

No systematic studies of this type have been undertaken. The structures of some compounds listed in Figure 2 have been confirmed by single crystal X-ray analysis. Heterodiquinanes containing triazine **26** [37] and **27** [38] have been isolated from the photochemical reaction of 7-methoxy-3-[1-(methoxyimino) ethyl]-*N*-phenyl-1,2,3-dihydrocinnoline 1,2-dicarboximide with diethyl 1,3-acetonedicarboxylate. Their structure and stereochemistry were determined by X-ray diffraction. The structure and the relative stereochemistry of compound **28a** were unambiguously confirmed by single crystal X-ray diffraction. [39] Compound **29** was synthesized as *cis* diastereomer (96:4) via a domino cyclohydrocarbonylation/addition sequence. [40] The ORTEP plot of molecule **30** is also represented [41], in the same manner the structure of compound **31** was determined by X-ray crystallographic analysis and the synthesis of this compound is described in Scheme 28. [42] The absolute stereochemistry assignment of compound **32** [43] as well as the one of the *C*-nucleoside Hepatitis C virus inhibitors, **GS-6620 33** and **GS-5734 34**, adenosine analogues, have been determined by X-ray analysis. [44] [45]

A serie of molecules was co-crystallized with the enzyme active site and the crystal structures are reported (Figure 2). The one of compound **35** co-crystallized with the Met kinase domain was obtained in order to understand the binding mode of the pyrrolo triazine in the enzyme ATP binding site. [46] The key binding interactions have been pointed out: the N1 of the pyrrolotriazine core donates a H to the Met1160, the terminal NH₂ on the piperidine ring creates an ionic interaction with the residue of Asp1164, the central fluorinated phenyl ring is involved in π stacking interaction with Phe1223, and finally the acylurea carbonyl is implicated in a H bond with the backbone NH of Asp1222. X-ray structures of compounds **36a-e** co-complexed with unphosphorylated p38 α were solved shedding light on the nature of the binding interactions between these molecules and the enzyme. Three key H-bonds are identified in common for the four molecules: one between the C6-amide carbonyl and the Met 109 residue, and two for the 5'-R¹ substitution, which is an hydroxamate or amide, between the carbonyl and the NH with the residues Asp168 and Glu71 respectively. For **36a-b** [47] and **BMS 582949 36e** [48] Asp168 forms an extra H-bond with the N3 of the pyrrolotriazine, while for **36c** [49] the pyrrolotriazine core interacts via the N1 with the Leu 171 residue. Finally, for **36d** [50] an enhanced hydrophobic interaction due to the phenyl ring on the C6 ketone is thought to be responsible of an improved enzyme activity. An X-ray co-crystal structure of compounds **37a-c** complexed with the IGF-1R kinase domain was solved revealing the hydrogen bond donor-acceptor-donor triad across the amino-pyrazole substituent to the Glu1050, Leu1051

and Met1052 residues (Figure 2). [51] [52] Compounds **38**, **39** and **40** have been co-crystallized as complex with MAP4K4. The three molecules fit the folded P-loop and create three hydrogen bonds with Glu106 and Cys108. Compound 16 and 25 bring a 4-pyridine which allows better interaction with Lys54, otherwise the phenyl group of 16 in the 6 position of the pyrrolotriazine as well as the pyrazole on the same position of compound 25 fit a partially hydrophobic pocket formed by the residues Phe107, Cys108 and Val31. [53]

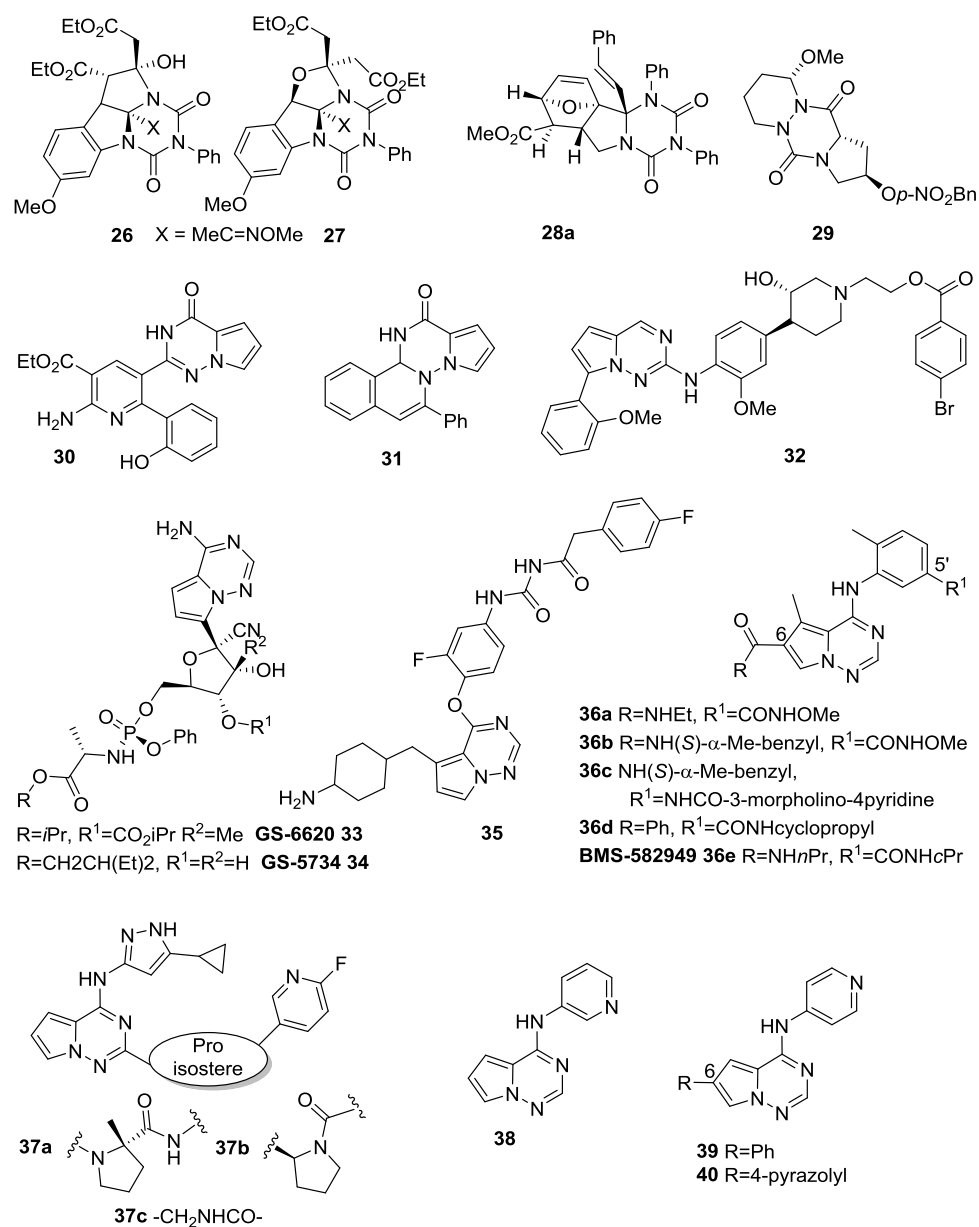


Figure 2.

3.2 NMR Studies

The structure and the relative stereochemistry of compounds **28a-c** were confirmed by NOESY (Figure 3).[39] Detailed assignments of the ¹H and ¹³C signals of Nocarsine A **41**, isolated from a soil sample collected in China, were unambiguously accomplished by NMR techniques including COSY, HSQC, ROESY and HMBC (Figure 3). [54] The NMR spectroscopic properties of several furo[2',3':4,5] pyrrolo[1,2-*d*][1,2,4]triazin-ones **42** and -thiones **43** were investigated. In particular it was put in

evidence the influence of various substituents on the triazine ring on ^1H - and ^{13}C -NMR chemical shifts (Figure 3). [55]

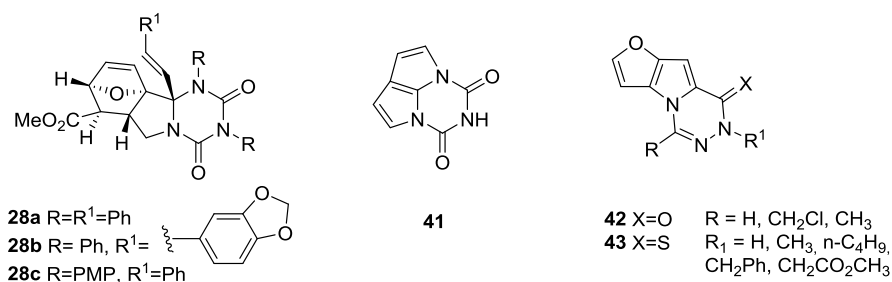


Figure 3.

3.3 Mass Spectrometry Studies

There have been no systematic studies on the use of mass spectroscopy in the series of systems falling within this chapter.

4 THERMODYNAMIC ASPECTS

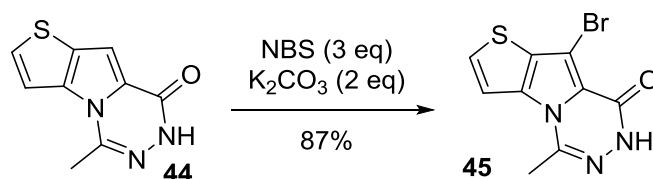
No thermodynamic studies have been systematically undertaken for this class of compounds.

5 REACTIVITY OF FULLY CONJUGATED RINGS

The pyrrolo triazines can be described as a five-membered π -electron rich heterocycle fused with a six-membered π -electron poor one. For this reason, it can be considered that the expected reactivity of the pyrrole ring is towards electrophilic reagents while the nucleophilic agents react preferentially with the six-membered ring.

5.1 Electrophilic Attack at Carbon

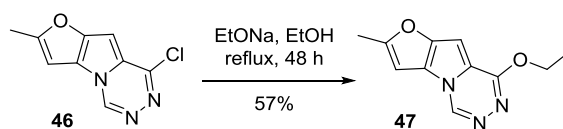
As expected, the pyrrole ring undergoes electrophilic attack to the carbon atoms. Only one study has been reported on the electrophilic substitution reaction at C-9 atom on the tricyclic thieno[2',3':4,5]pyrrolo[1,2-*d*][1,2,4]triazin-8(7*H*)-one **44**. Regioselective bromination of the pyrrole ring with excess of NBS in the presence of K_2CO_3 gave product **45** (Scheme 1). [56]



Scheme 1

5.2 Nucleophilic Attack at Carbon

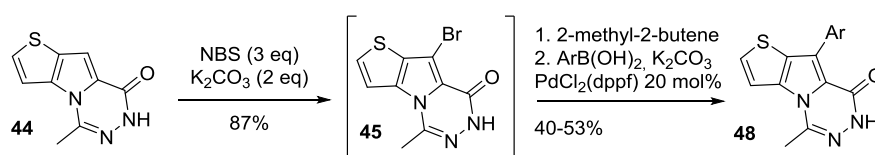
Due to the nature of the six-membered π -electron deficient triazine ring, these systems undergo nucleophilic attack at carbon atoms. The only example reported describes the nucleophilic substitution reaction of 8-Cl-furo[2',3':4,5]pyrrolo[1,2-*d*][1,2,4]triazine **46** with sodium ethoxide to deliver the ethoxy derivative **47** in 57% yield (Scheme 2). [57]



Scheme 2

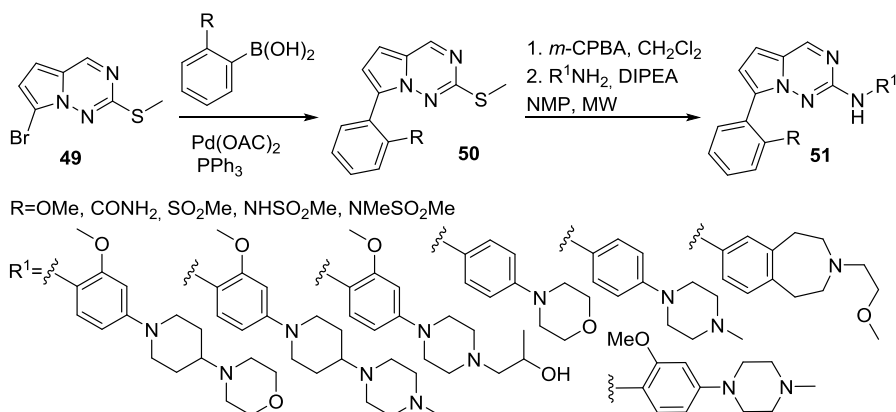
5.3 Other reactions

Compound **44** undergoes Pd catalysed Suzuki coupling with different arylboronic acids to yield C-9 substituted compounds **48** (Scheme 3). The sequence bromination/Suzuki coupling was performed in one pot. [56]



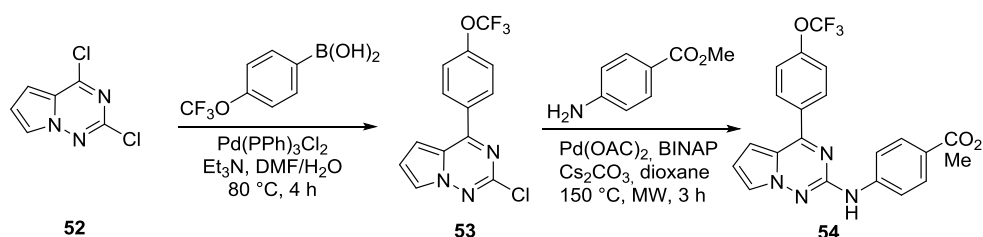
Scheme 3

Starting from intermediate **49** a library of substituted pyrrolo[2,1-f][1,2,4]triazines **51** has been synthesized. The Suzuki coupling on the C-7 position has been performed with *ortho*-substituted arylboronic acids in the presence of Pd(OAc)₂ to give compounds **50** and then the oxidation of the sulphide to sulfoxide with *m*-CPBA followed by the coupling with the suited amine, under MW irradiation, delivered the desired compounds **51**. These latter can be obtained as well reversing the two steps described above (Scheme 4). [58]



Scheme 4

2,4-dichloropyrrolo[2,1-f][1,2,4]triazine **52** underwent Pd-catalysed Suzuki then Buchwald coupling reactions on the position C-4 and C-2 respectively. Compound **52** was thus treated with 4-trifluoromethoxyphenylboronic acid in the presence of Pd(PPh)₃Cl₂ to yield **53**, followed by reaction with methyl 4-aminobenzoate in the presence of Pd(OAc)₂ and BINAP under MW irradiation, to lead to compound **54** (Scheme 5). [59]



Scheme 5

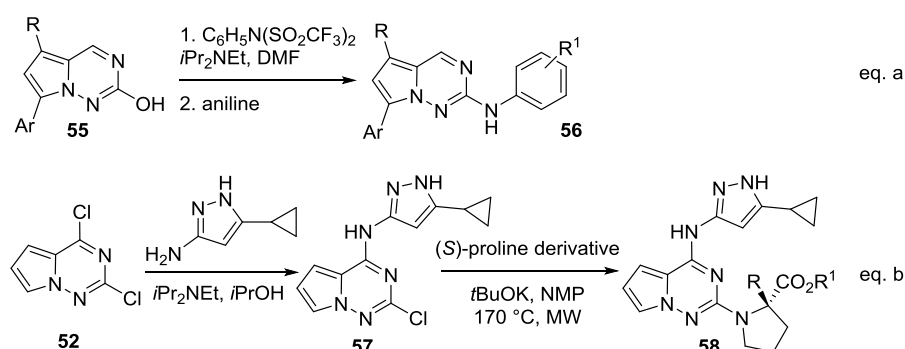
The Suzuki coupling has been also used to functionalize the C-5 position of the pyrrolo[2,1-*f*][1,2,4]triazine skeleton, as an example see compound **35** figure 2.

6 REACTIVITY OF NONCONJUGATED RINGS

Undoubtedly the most studied systems fitting within the criteria of this chapter are bicycles containing one or two oxo groups in the six-membered ring, and their equilibrium forms containing the corresponding hydroxyl group. The reactivity of the cycle can be compared to the one of cyclic amides, therefore they react with nucleophiles.

6.1 Nucleophilic attack at Carbon

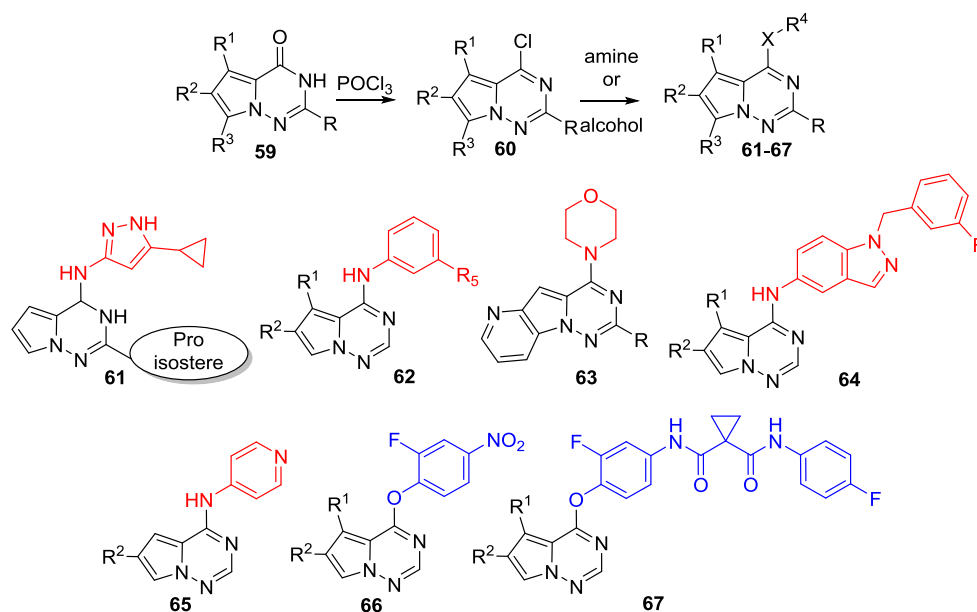
The majority of references deal with the nucleophilic attack at the carbonyl group resulting in substitution rather than ring opening. Most of the reactions consist in the transformation of the pyrrolo[2,1-*f*][1,2,4]triazin-(one)s into the fully aromatic C-2 and/or C-4 chlorinated derivatives followed by nucleophilic substitution of the chloroimidates with alcohols or amines to deliver the corresponding ethers or amines. Substitution of the position C-2 has been treated for only two examples, depicted in scheme 6. In the first case the hydroxyl group in C-2 position of compound **55** was transformed into the corresponding triflate before substitution with the appropriate aniline to give **56** (eq a). [43] [60] In the second example both position C-2 and C-4 of compound **52** were modified by displacement of Cl before on position C-4, with 5-cyclopropyl-3-aminopyrazole, to deliver **57** and then on C-2 with a (*S*)-proline derivatives to lead to compounds **58** (eq. b). [51]



Scheme 6

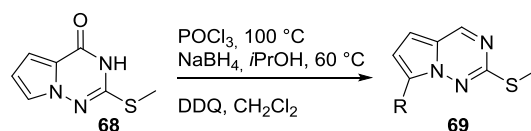
Most of the examples deal with the substitution of the C-4 position, by transformation of the pyrrolo[2,1-*f*][1,2,4]triazinone **59** into the heteroaryl chloride **60** upon treatment with POCl₃, then reaction with different amines such as 5-cyclopropyl-3-aminopyrazole [51] [52], *m*-anisidines [46] [47] [48] [49] [50] [61], morpholine [62], 1-(3-fluorobenzyl)-1H-indazol-5-amine [63] and finally 4-aminopyridine [53] to give the corresponding amines **61-65**. The substitution of **60** with 2-fluoro-4-

nitrophenol [46] or with 2-fluoro-4-aminophenol derivatives [64] can alternatively lead to the corresponding ethers **66-67** (Scheme 7).



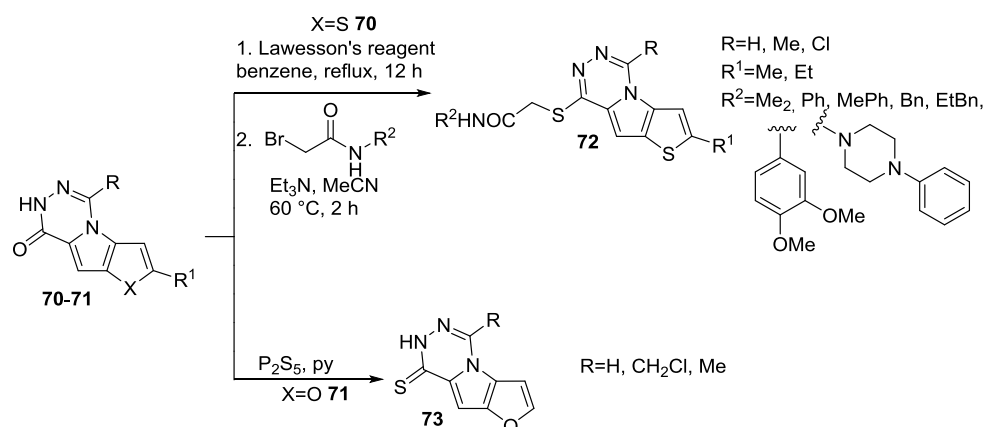
Scheme 7

Treatment of pyrrolo[2,1-*f*][1,2,4]triazinone **68** with POCl_3 , followed by reduction with NaBH_4 and reoxidation with DDQ gave the aromatic triazine **69** (Scheme 8). [65]



Scheme 8.

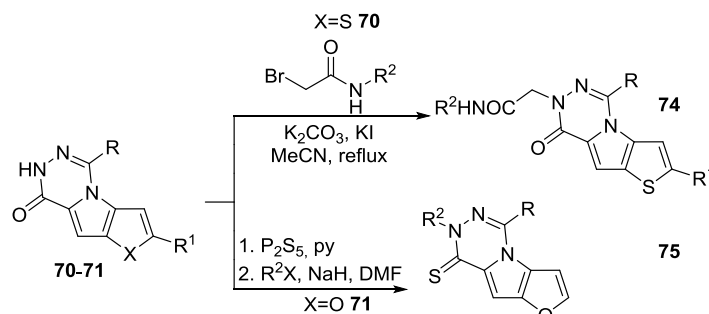
Thionation of thieno[2',3':4,5]pyrrolo[1,2-*d*][1,2,4]triazin-8(7*H*)-ones **70** in the presence of Lawesson's reagent followed by *S*-alkylation with 2-bromo-*N*-substituted acetamides gave compounds **72** [66] while thionation of furo[2',3':4,5]pyrrolo[1,2-*d*][1,2,4]triazin-8(7*H*)-ones **71** with P_2S_5 yielded compounds **73** [67] (Scheme 9).



Scheme 9

6.2 Electrophilic attack at Nitrogen

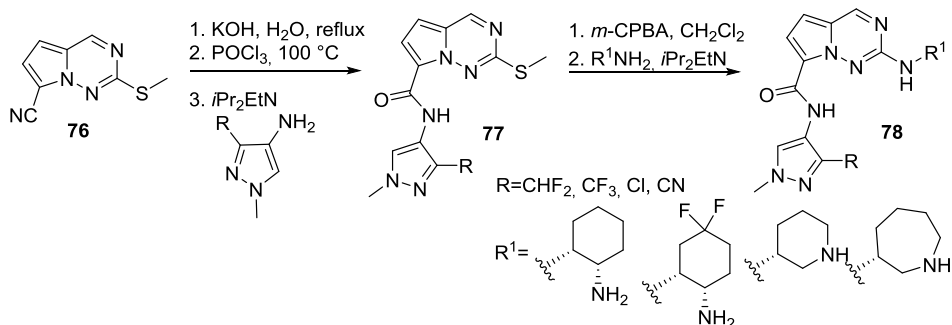
Direct *N*-alkylation of cyclic amide nitrogen of thieno or furo[2',3':4,5]pyrrolo[1,2-*d*][1,2,4]triazin-8(7*H*)-ones **71** and **72** with 2-bromo-*N*-substituted acetamides [66] or with alkyl halides [67] respectively, lead to compounds **74** and **75** (Scheme 10)



Scheme 10

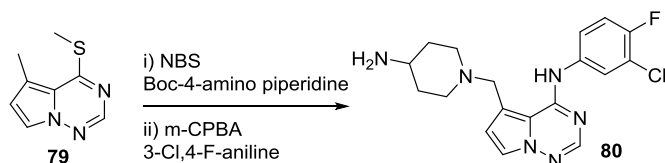
7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

Several functional groups have been introduced on the different positions of the pyrrolotriazine core. The substitution of position C-2 and C-7 of the pyrrolo[2,1-*f*][1,2,4]triazine **76** has been explored by conversion of the cyano group, before into carboxylic acid, and then into amides, to give **77**, while the thioether was before oxidized to sulfone and then replaced with amines to deliver compounds **78** (Scheme 11). [68]



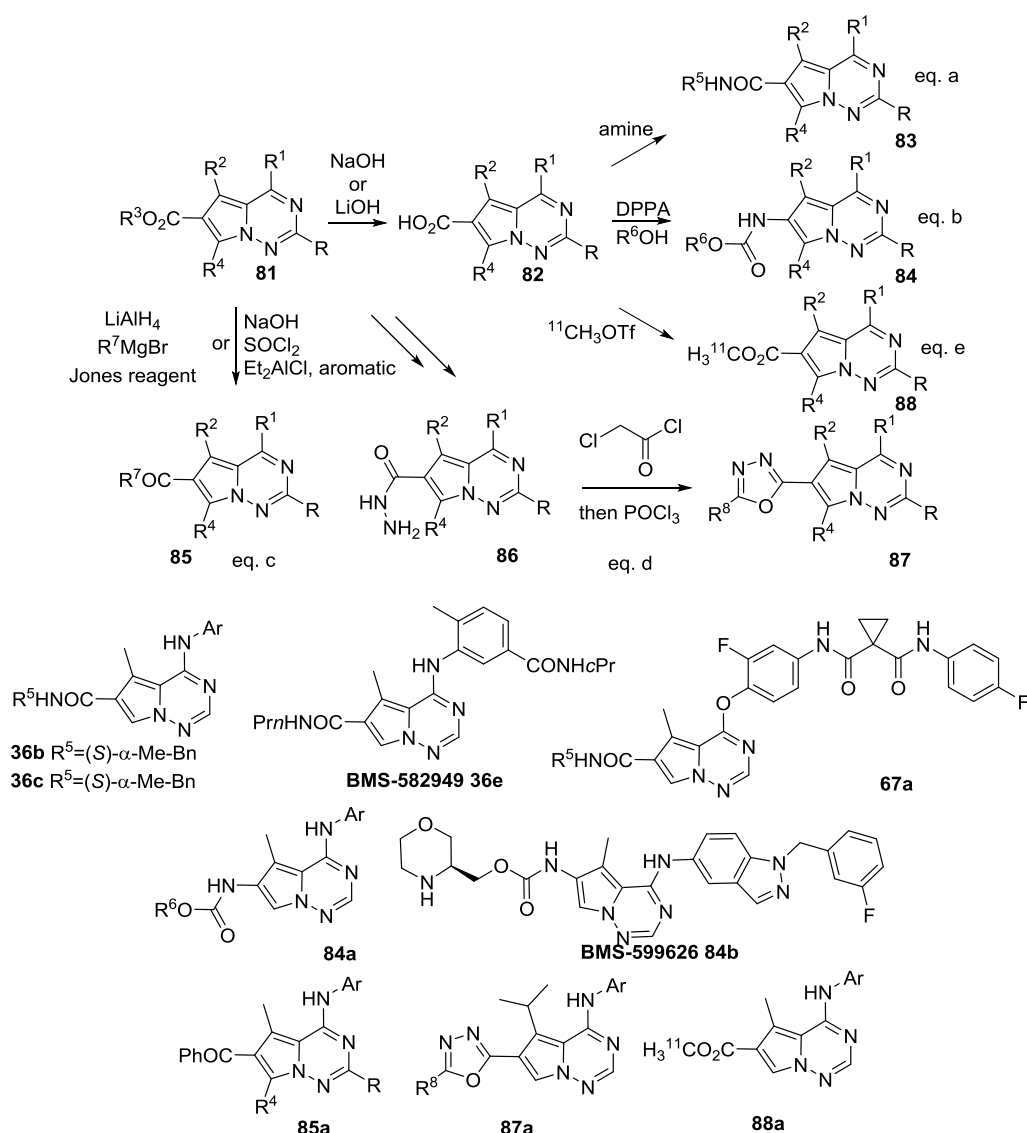
Scheme 11

Compound **80** has been synthesized by reaction of 5-methyl-4-(methylthio) pyrrolo[2,1-*f*][1,2,4]triazine **79** with: i) NBS followed by addition of 4-amino piperidine derivative; ii) oxidation of the C-4 thiomethyl ether with *m*-CPBA followed by addition of anilines (Scheme 12). [69]



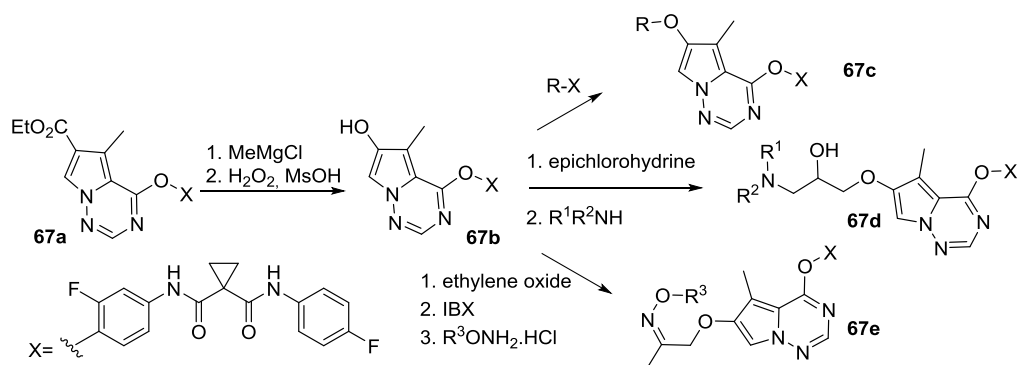
Scheme 12

The majority of the references deal with the C-6 and C-7 substitution of the pyrrolo[2,1-*f*][1,2,4]triazines. The C-6 position of compounds **81** is frequently substituted with an ester that undergoes saponification to carboxylic acid (compounds **82**). This latter is generally coupled with amines giving the corresponding amides **83** such as for example **36b** [47], **36c** [49], **BMS-582949 36e** [48], and **67a** [64]. (Scheme 13, eq. a). Alternatively, a sequence including Curtius rearrangement in the presence of diphenylphosphoryl azide (DPPA) and reaction of the isocyanate intermediate with alcohols, yields a serie of carbamates **84** such as for instance **84a** [47], and **BMS-599626 84b** [63] (Scheme 13, eq. b). Another example consists in the preparation of ketones **85** on one hand by reduction of the ester directly to aldehyde, followed by addition of the appropriate organo magnesium bromide and oxidation or on the other hand by conversion of the ester into acyl chloride followed by Friedel-Crafts acylation; as an example see **85a** [50] (Scheme 13, eq. c). Finally, hydrazides **86** can be obtained from esters by known procedures and transformed into oxadiazole ring **87** by treatment with 2-chloroacetyl chloride followed by heating in neat POCl₃, see compound **87a** [61] (Scheme 13, eq. d). Only one example has been reported on the synthesis of carbon-11-labeled pyrrolo[2,1-*f*][1,2,4]triazines **88** prepared from the carboxylic acid in presence of [¹¹C]CH₃OTf through O-[¹¹C]methylation, to give compound **88a** (Scheme 13, eq. e). [70]



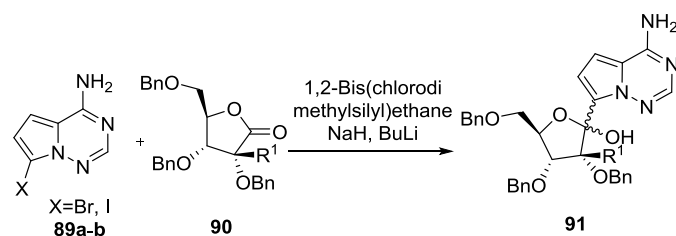
Scheme 13

Several analogues of compound **67a** modified on the C-6 position have been obtained by transformation of the ethyl ester group into alcohol by Grignard reaction followed by Baeyer-Villiger rearrangement to give the intermediate **67b**. Further decoration of the C-6 position relies basically on the *O*-alkylation and brings to molecules **67c-e** (Scheme 14). [64]



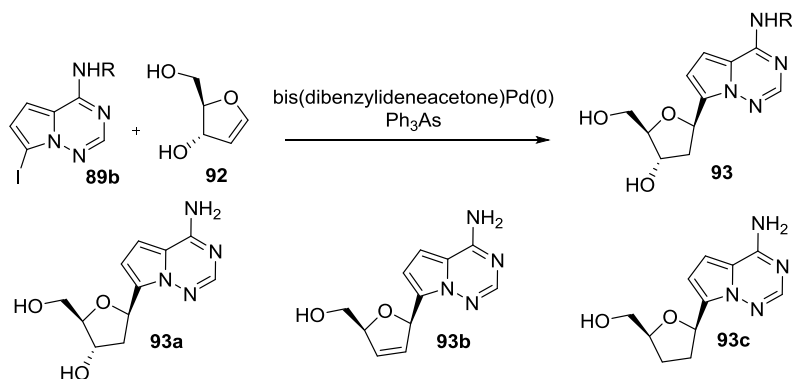
Scheme 14

Concerning the functionalization of the C-7 position the majority of the examples deal with the synthesis of C-nucleosides. The common strategy is to react the bromo or iodo derivative **89a-b** with the ribonolactone **90** in order to obtain the hemiketal intermediate **91** (Scheme 15). [71] This latter undergoes different reaction to introduce several groups such as the CN group, for the most popular compounds in terms of biological activity see **GS-6620 33** and **GS-5734 34**, figure 2.



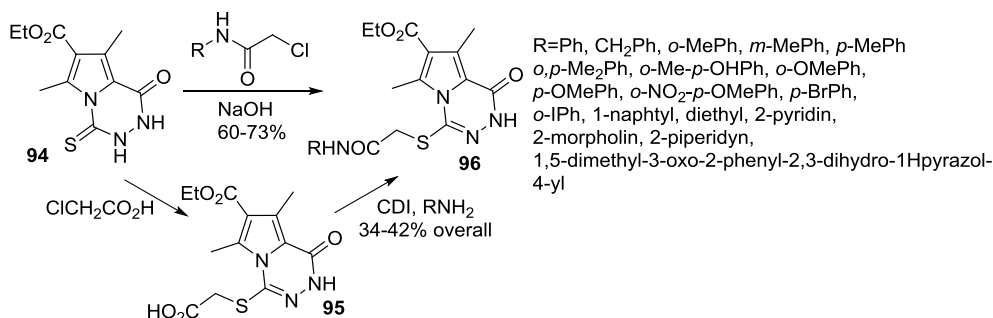
Scheme 15

2'-deoxy and 2',3'-dideoxyribose C-nucleosides **93a-c** have also been synthesized by Heck-type coupling between glycal **92** and the 7-iodo pyrrolo[2,1-f][1,2,4]triazine **89b** (Scheme 16). [72]



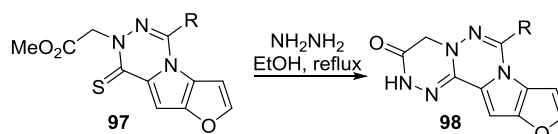
Scheme 16

Two examples concern the 5-alkylation of the pyrrolo[1,2-*d*][1,2,4]triazine **94**. Compounds **96** were obtained in one step by reaction with 2-chloro acetamide derivatives or via a two steps procedure involving the reaction with chloroacetic acid to deliver the intermediate **95** followed by amidation with different amines in the presence of *N,N*-carbonylimidazole (CDI) in globally lower yields (Scheme 17). [73]



Scheme 17

Furo[2',3':4,5]pyrrolo[1,2-*d*][1,2,4]triazin-8(7*H*)-thione **97** can cyclize upon reaction with hydrazine to deliver the triazino-triazinone **98** (Scheme 18). [67]

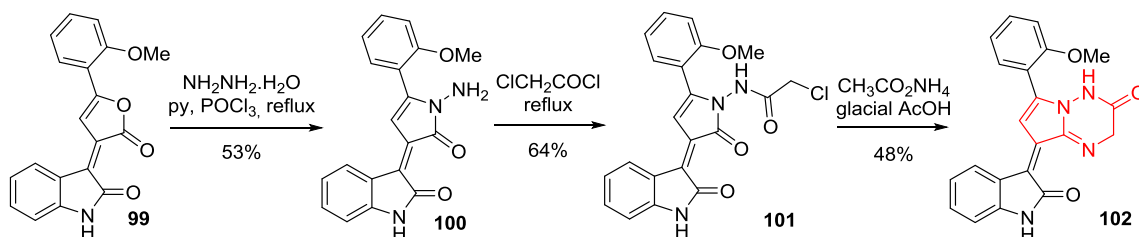


Scheme 18

8 RING SYNTHESSES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

8.1 Pyrrolo[1,2-*b*][1,2,4]triazine

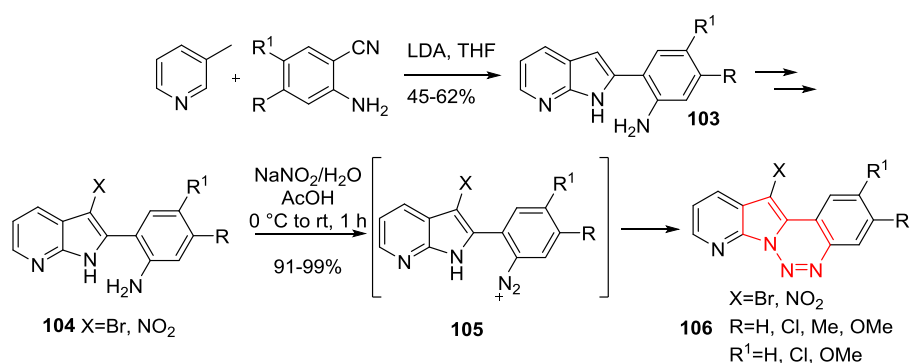
6-(2-methoxyphenyl)-8-(2-oxoindolin-3-ylidene)-2,8-dihydropyrrolo[1,2-*b*][1,2,4]triazin-3(4*H*)-one **102** was synthesized in three steps starting from 3-(2-oxofuran-3(2*H*)-ylidene)indolin-2-one **99**. The reaction with hydrazine hydrate in refluxing pyridine in the presence of POCl₃ gave in 53% yield the corresponding hydrazine **100** that was in turn alkylated with chloroacetylchloride to yield 64% of **101**. The cyclization to deliver the dihydropyrrolo[1,2-*b*][1,2,4]triazinone skeleton was achieved in presence of ammonium acetate in acidic conditions (48% yield) (Scheme 19). [74]



Scheme 19

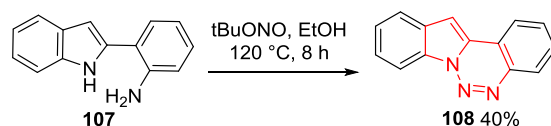
8.2 Pyrrolo[1,2-*c*][1,2,3]triazine

This class of compounds was the less studied until 2009, when a group of scientists have generated a virtual exploratory heterocyclic library of small aromatic ring systems useful for the development of novel synthetic protein ligands. [75] This list includes pyrrolo[1,2-*c*][1,2,3]triazines which is an under- or not yet explored class of heterocycles. In 2014 the synthesis of pyrrodo[3',2':4,5]pyrrolo[1,2-*c*][1,2,3]benzotriazines **106** was described and involves the intramolecular cyclization of diazonium intermediates **105** generated in situ from anilines **103**. These latter were synthesized by Chichibabin type reaction starting from commercially available 3-methylpyridine and 2-aminobenzonitriles to give anilines **103**, followed by transformations on the 3-position of the pyrrole ring in order to block the spontaneous cyclization of the diazonium on this position delivering the pyrrolocinnoline skeleton (Scheme 20). [76]



Scheme 20

6 π electrocyclization of 2-indolo aniline **107** with *tert*-butyl nitrite gave pyrrolo[1,2-*c*][1,2,3]benzotriazines **108** in 40% yield. *tert*-butyl nitrite plays the dual role of N source and oxidant. (Scheme 21). [77]

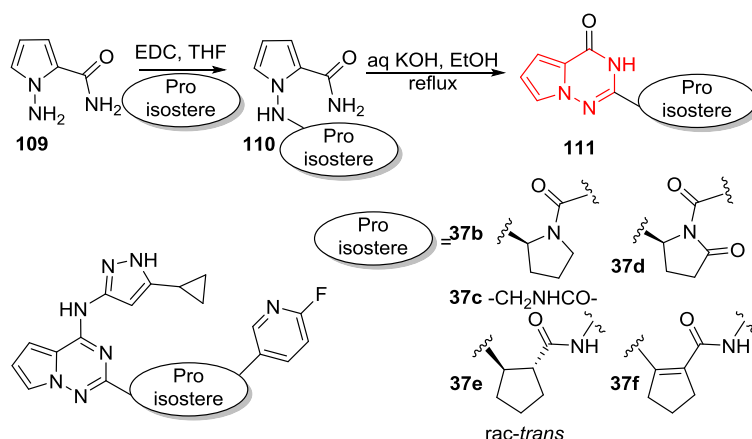


Scheme 21

8.3 Pyrrolo[2,1-*f*][1,2,4]triazine

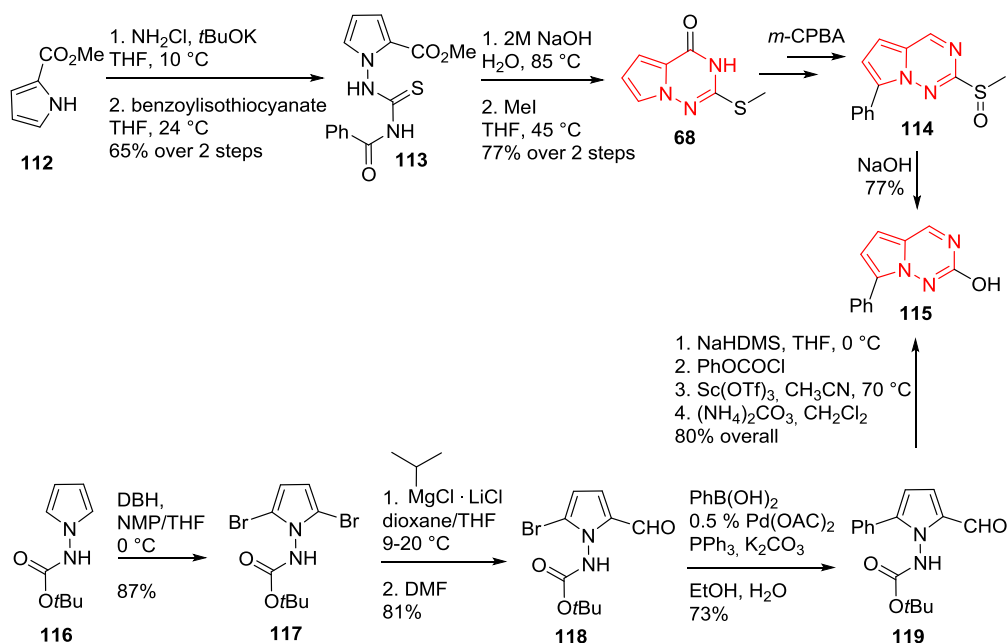
Together with pyrrolo[2,1-*d*][1,2,4]triazines this is undoubtedly the most studied class of heterocycles falling within the scope of this chapter.

The synthesis of pyrrolo[2,1-*f*][1,2,4]triazines bringing C-2 carbon-linked proline isosteres such as pyrrolidin(on)e, cyclopentane and simple acyclic, has been achieved starting from the common 1-amino-1*H*-pyrrole-2-carboxamide **109**. A coupling reaction with the appropriate proline isostere in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) delivered the intermediate **110** that undergoes cyclization, upon treatment with refluxing ethanolic KOH solution, to give compound **111** (Scheme 22). [52] Examples of biologically relevant compounds prepared with this methodology are compounds **37b-f**.



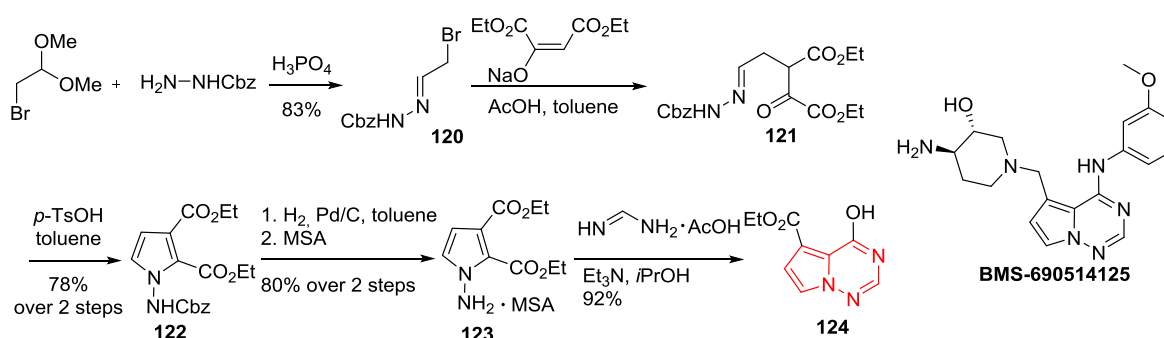
Scheme 22

Pyrrolo[2,1-f][1,2,4]triazine **115** substituted in C-2 and C-7 positions have been synthesized starting from methyl-2-pyrrole carboxylate **112**. Treatment of **112** with chloramine followed by the addition of benzoylthiocyanate yielded 65% of **113**, which cyclizes into **68** upon basic hydrolysis. After the modifications in the C-4 and C-7 positions, discussed above in the paragraphs 5.3 2 and 6.1 2, the oxidation of the sulphide to sulfoxide with *m*-CPBA gave **114**. Follow the hydrolysis step to lead to **115** in 77% yield (Scheme 23). The development of a scalable process has also been established starting from **116** which was converted into the dibrominated **117** in the presence of 5,5-dimethyl-1,3-dibromohydantoin (DBH) in 87% yield. The halogen-metal exchange in the presence of the Knochel "Turbo Grignard" followed by quenching with DMF selectively gave **118** in 81% yield. Suzuki coupling with only 0.5 mol% of Pd catalyst in aqueous EtOH gave **119**. The cyclization to obtain the pyrrolo[2,1-f][1,2,4]triazine core **115** takes place after treatment with NaHMDS and addition of phenyl chloroformate, by the action of a Lewis acid, namely Sc(OTf)₃, followed by addition of ammonium carbonate (Scheme 23). [65]



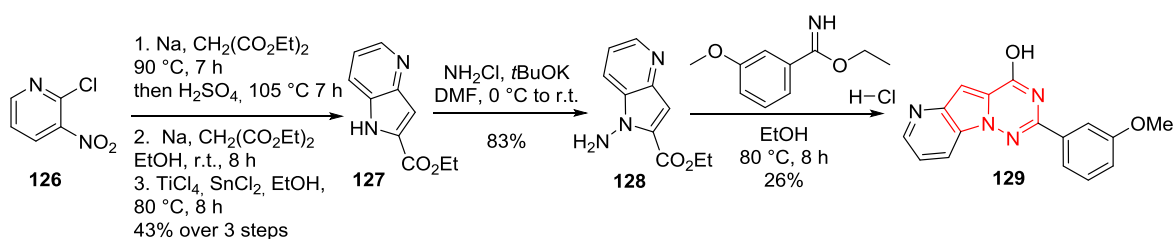
Scheme 23

A kg scale synthesis of functionalized pyrrolotriazine **124**, as intermediate building block in the synthesis of **BMS 690514 125** [46] [47] [61] and analogues, as potent anticancer agents, has been established. [78] Bromohydrazone intermediate **120** was obtained in 550 Kg over five batches by condensation of commercially available bromoacetal and Cbz-hydrazine in the presence of H_3PO_4 . The following alkylation in the presence of acetic acid delivered the intermediate **121** which undergoes cyclization to pyrrole **122** in acidic conditions (*p*-TsOH) in 78% yield over two steps. The deprotection of the Cbz group was achieved in standard 10% Pd/C and H_2 conditions. For stability reasons the amine **123** was recovered as methylsulfonate salt in 80% yield over two steps. Acid catalysed annulation of **123** with formamidine acetate provided the key pyrrolotriazine ester **124** in 92% yield (Scheme 24).



Scheme 24

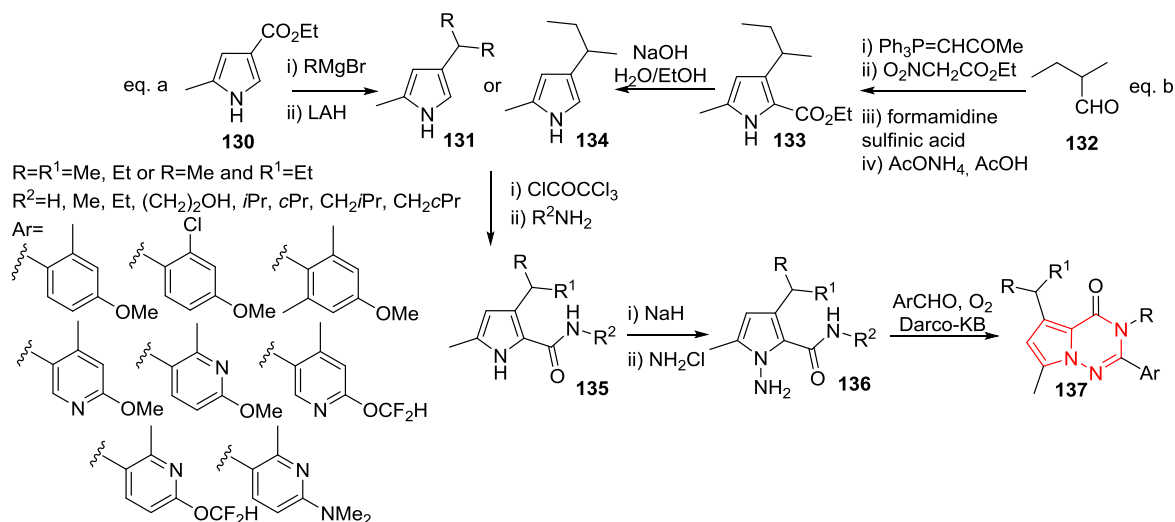
4-(2-arylpyrido[3',2':3,4]pyrrolo[1,2-*f*][1,2,4]-triazine **129** was synthesized following scheme 8.3 5. Starting from 2-chloro-3-nitropyridine **126** the 1*H*-pyrrolo[3,2-*b*]pyridine skeleton **127** was formed in three steps in 43% overall yield. The hydrazine function was installed by treatment with chloramine and intermediate **128** was submitted to annulation in the presence of ethyl 3-methoxybenzimidate hydrochloride in refluxing ethanol to deliver **129** in only 26% yield (Scheme 25). [62].



Scheme 25

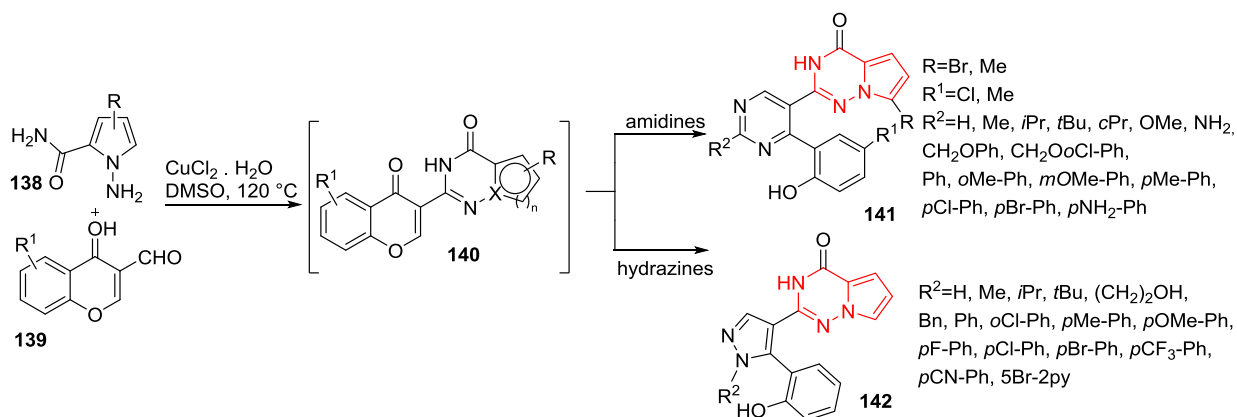
The synthesis of substituted pyrrolo[2,1-*f*]triazin-4(3*H*)-ones **137** has been achieved from intermediate **131** or the unsymmetrical **134**. The synthesis of **131** is depicted in scheme 26, eq. a, and relies on the addition of Grignard reagent on the 2-methylpyrrole-4-carboxylate **130**, followed by reduction with lithium aluminium hydride. The synthesis of unsymmetrical **134**, bearing three different substituents on the C-3 of the pyrrole unit, is described in scheme 26, eq. b. 2-methylbutanal **132** was submitted to Wittig reaction in the presence of the appropriate phosphorane, follow the addition of ethyl nitroacetate, reduction of the nitro group and intramolecular cyclisation to get the pyrrole ring **133**. The alkaline hydrolysis and decarboxylation gave **134**. C-acylation with triphosgene followed by addition of different amines resulted in the amides **135**. *N*-amination to give **136** was achieved with chloroamine and finally the cyclization step

to obtain the pyrrolotriazine core **137** was carried out with arylaldehydes in the presence of O₂ and activated charcoal Darco-KB. [79]



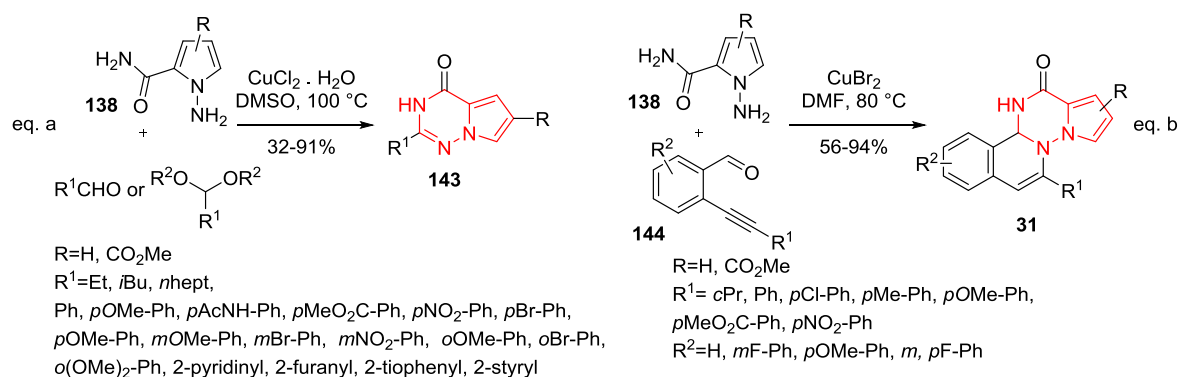
Scheme 26

2-substituted pyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-ones **141-142** have been synthesized by pot, atom, step economic and six bond forming reaction. The reaction of pyrrolo carboxamides **138** with substituted 4-oxo-4*H*-chromene-3-carbaldehyde **139** is catalysed by Cu(II) in DMSO to deliver intermediate **140** which reacts with benzamides or hydrazines to give the final compounds **141-142** respectively (Scheme 27). [41]



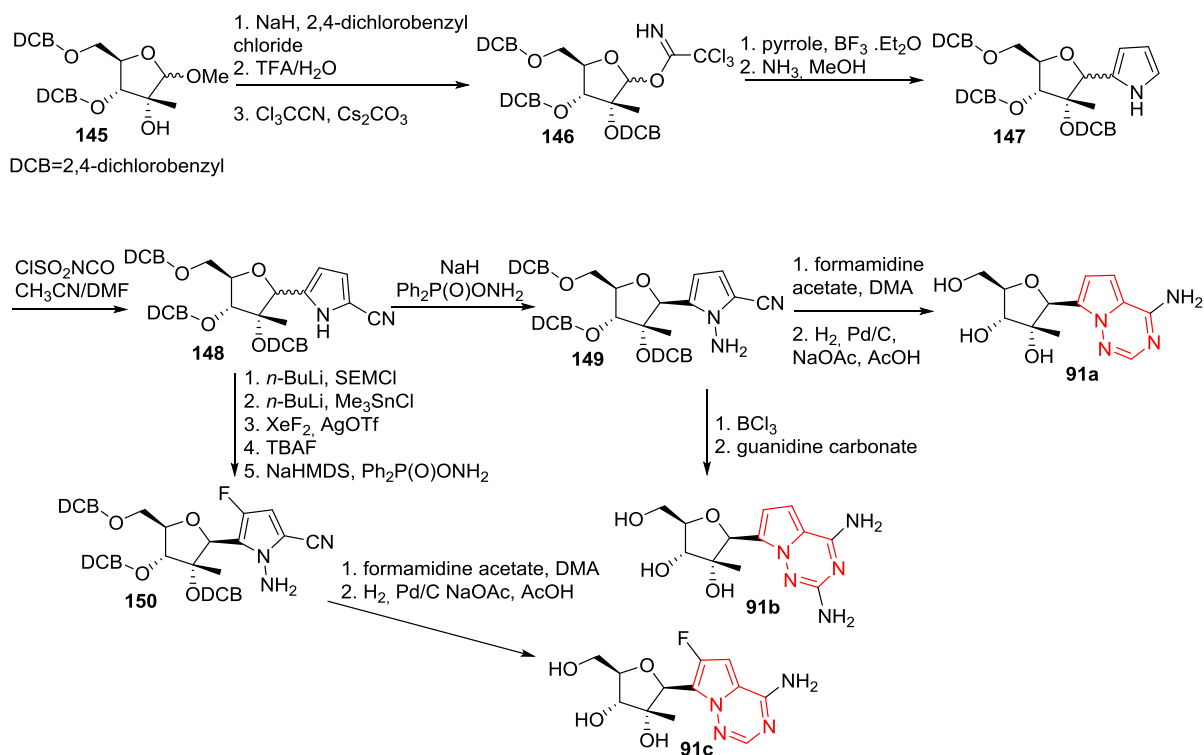
Scheme 27

A variant to this reaction relies on copper(II) promoted annulation of pyrrolo carboxamides **138** with different aldehydes and acetals, to yield compounds **143** as shown in scheme 28, eq. a. [80] With the same strategy more complex pyrrolo[2,1-*f*][1,2,4]triazines fused to isoquinolines **144** were also obtained when using 2-ethynylbenzaldehyde derivatives **144** (Scheme 28, eq. b). [42]



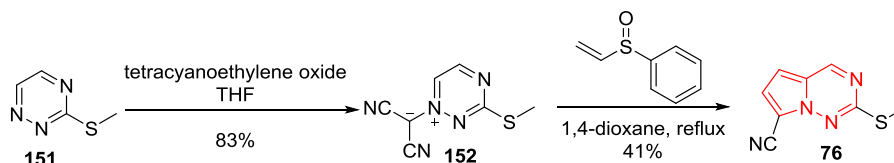
Scheme 28

Pyrrolotriazine C-nucleosides with increased anti-hepatitis C virus (HCV) activities were synthesized following a linear route starting from riboside **145**. After protection of the different hydroxy groups the activated trichloroacetimidate **146** was obtained. Addition of the pyrrole in the presence of BF₃·Et₂O delivered an anomeric mixture of the pyrrolo-nucleosides **147**, which were submitted to reaction with chlorosulfonyl isocyanate to give the pyrrolonitrile nucleoside **148**. *N*-amination of the desired β-anomer, to deliver **149**, followed by ring closure with formamidine acetate, yielded the adenosine analogue **91a**. [71d] Alternatively ring closure by condensation with guanidine carbonate after deprotection delivered the 2,6-diamino-pyrrolotriazine nucleoside **91b**. Finally, intermediate **148** was also decorated with a F atom on the 3-position of the pyrrole ring before proceeding to the *N*-amination that allowed the synthesis of the intermediate **150**. This last underwent ring closure and deprotection to give compound **91c** (Scheme 29). [71c-d]



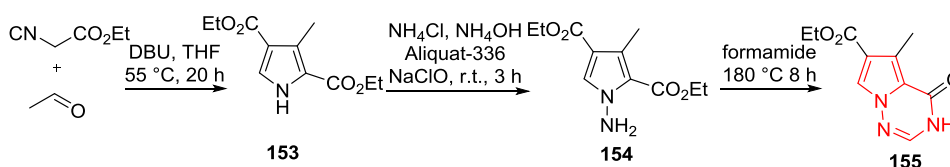
Scheme 29

C-7 substituted pyrrolo[2,1-*f*][1,2,4]triazine **76** was obtained from 3-(methylsulfanyl)-1,2,4-triazine **151** by treatment with tetracyanoethylene oxide, to yield 83% of **152**, followed by [2+3] cycloaddition with phenyl vinyl sulfoxide (Scheme 30). [68]



Scheme 30

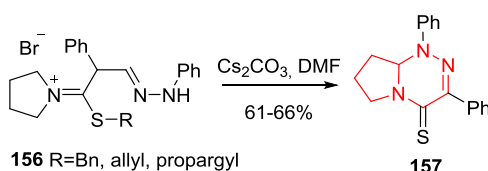
Reaction of ethyl 2-isocyanoacetate and acetaldehyde in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the substituted pyrrole skeleton **153**, which undergoes then *N*-alkylation in the presence of chloramine to give **154**. Its reaction with formamide allowed the synthesis of C-5 and C-6 substituted dihydropyrrolo[2,1-*f*][1,2,4]triazinone core **155** (Scheme 31). [64]



Scheme 31

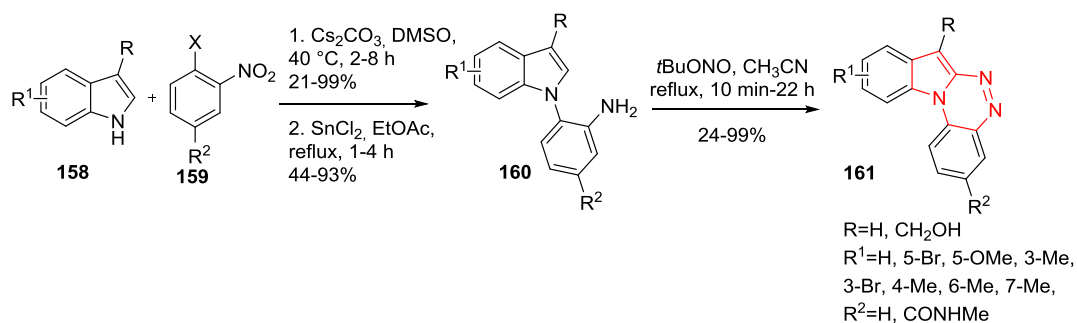
8.4 Pyrrolo[1,2-*c*][1,2,4]triazine

The synthesis of 1,3-diphenyl-6,7,8,8a-tetrahydropyrrolo[2,1-*c*]-1,2,4-triazine-4(1*H*)-thione **157** has been reported starting from sulfanyl derivatives of pyrrolidinium salts **156**, in the presence of cesium carbonate, via an intramolecular cyclization (Scheme 32). [81]



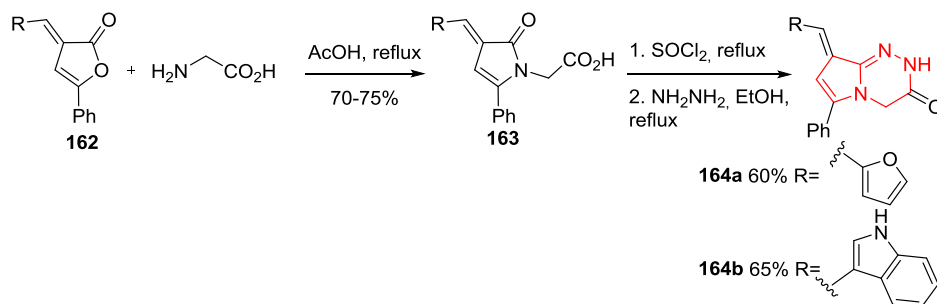
Scheme 32

Indole[1,2-*c*][1,2,4]triazines **161** were obtained by a three steps procedure involving the reaction of substituted indole derivatives **158** with 2-nitrophenyl halides **159** in the presence of cesium carbonate, and reduction of the nitro group into amine operated by SnCl_2 , to yield **160**. Modified intramolecular Sandmeyer reaction in the presence of *tert*-butylnitrite gave the desired **161** (Scheme 33). [82]



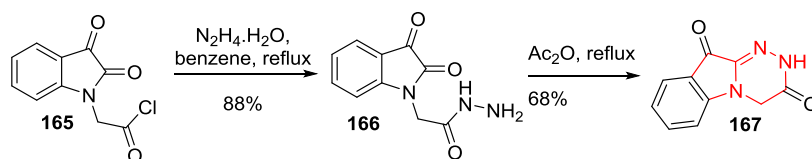
Scheme 33.

2,8-dihydropyrrolo[2,1-c][1,2,4]triazin-3(4H)-ones **164a-b** have been obtained by transformation of 2(3H)-furanones **162** via opening of the lactone and formation of the lactam ring **163** in the presence of glycine in acidic conditions. The carboxylic acid was then used for the construction of the triazinone ring by treatment with hydrazine upon activation in the presence of SOCl_2 (Scheme 34). [83]



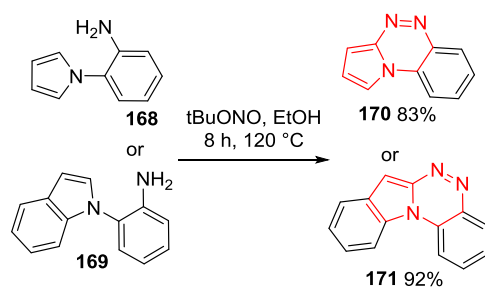
Scheme 34

Indole [1,2,4]triazin-dione **167** has been synthesized starting from isatin-*N*-acetyl chloride **165** by reaction with hydrazine hydrate in refluxing benzene to yield 88% of the corresponding hydrazide **166**. The cyclization into indole-triazine was achieved by refluxing in acetic anhydride in 68% yield (Scheme 35). [84]



Scheme 35

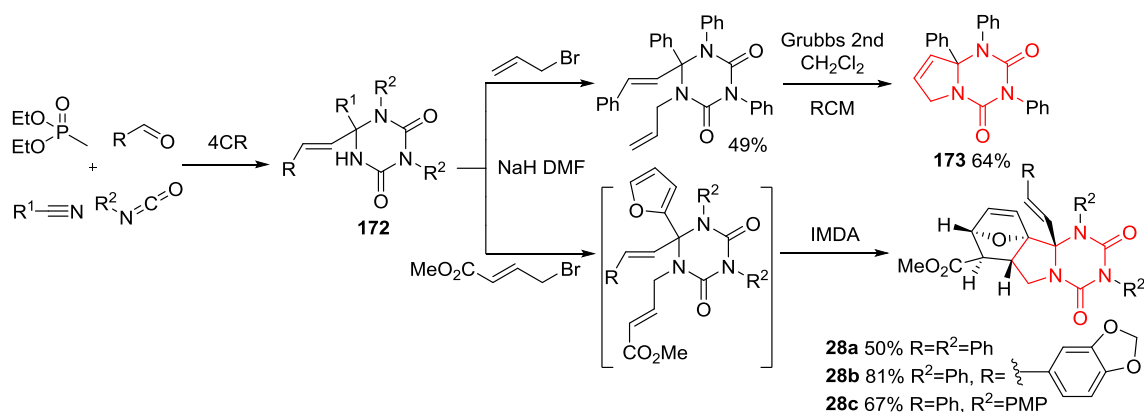
6π electrocyclic of 2-pyrrolo and 2-indolo anilines **168-169** with *tert*-butyl nitrite gave benzo[*e*]pyrrolo[2,1-c][1,2,4]benzotriazines **170** and **171** respectively, in good yields. *Tert*-butyl nitrite plays the dual role of N source and oxidant. (Scheme 36). [85] [77]



Scheme 36

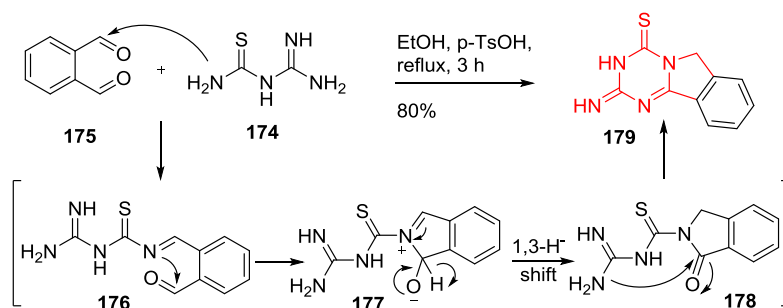
8.5 Pyrrolo[1,2-*a*][1,3,5]triazine

Triazinane diones **172** have been synthesized by a four component reaction (4CR) involving a phosphonate, different nitriles, aldehydes and isocyanates. The ring-closing metathesis (RCM) or cycloaddition reaction such as intramolecular Diels-Alder (IMDA) of intermediates **172** delivered the bicyclic skeleton of nonconjugated pyrrolo[1,2-*a*][1,3,5]triazines. With those methodologies, compounds **173** and **28a-c** were respectively obtained (Scheme 37).[39]



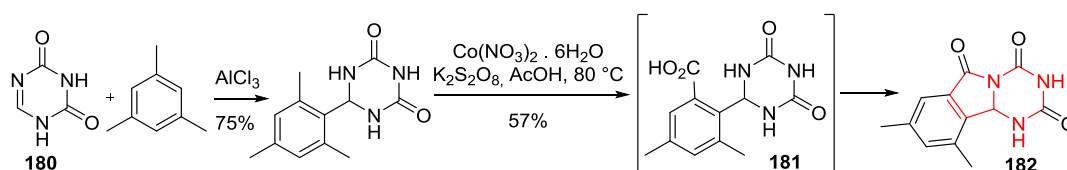
Scheme 37

The reactivity of *N*-amidinothiourea **174** towards *o*-phthalaldehyde **175** have been studied. [86] The condensation of the amino group onto the aldehyde gave the azomethine intermediate **176**. The attack of the azomethine N atom on the second carbonyl group gave the cyclic **177** which undergoes 1,3-hydride shift to deliver the adduct **178**. Further cyclization yielded the isoindolo triazine scaffold **179**. (Scheme 38).



Scheme 38

Direct arylation of [1,3,5]triazine-2,4(1*H*, 3*H*)-dione **180** with mesitylene promoted by AlCl₃ followed by oxidation in mild conditions yielded 8,10-dimethyl-1,10*b*-dihydro[1,3,5]triazino-[2,1-*a*]isoindole-2,4,6(3*H*)-trione **182** via the intermediate **181** (Scheme 39). [87]

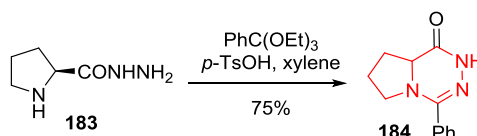


Scheme 39

8.6 Pyrrolo[1,2-*d*][1,2,4]triazine

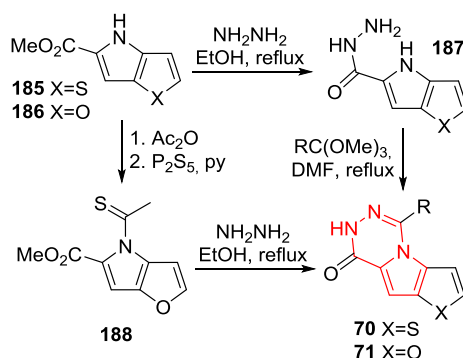
In general, the 1,2,4-triazin-6-one skeleton has been constructed by two main strategies: the cyclocondensation of α -aminocarbohydrazides with orthoesters or the cyclisation of *N*-thioacyl- α -aminoesters with hydrazines.

Concerning the first route three examples have been described in the period covered by this chapter. 4-phenyl-6,7,8,8*a*-tetrahydropyrrolo[1,2-*d*][1,2,4]triazin-1(2*H*)-one **184** was obtained in 75% yield by reaction of proline hydrazide **183** with triethyl *ortho*benzoate in the presence of *p*-TsOH. Partial racemisation occurred and this can be explained by the keto-enol tautomerism of the bicyclic [1,2,4]triazin-6-one product (Scheme 40). [88]



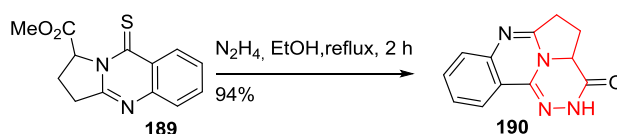
Scheme 40

Thieno- **185** and furo-pyrrole skeleton **186** undergo reaction with hydrazine to deliver the corresponding hydrazones **187** which were further cyclized in the presence of orthoesters to the tricyclic thieno **70** [66] and furo[2',3':4,5]pyrrolo[1,2-*d*][1,2,4]triazinones **71** [57] [67]. Alternatively, the acetylation of the furo-pyrrole unit **186** followed by thionation yielded the *N*-thioacyl- α -aminoesters **188** which undergoes cyclization upon treatment with hydrazine to give **71** as well (Scheme 41).



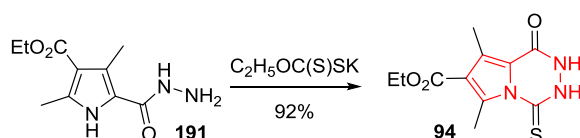
Scheme 41

Other two examples of cyclisation of *N*-thioacyl- α -aminoesters with hydrazines are described below. 5-methoxycarbonyldesoxythiovasicinone **189** was reacted with hydrazide monohydrate to yield 94% of heterocycle **190** (Scheme 42). [89]



Scheme 42

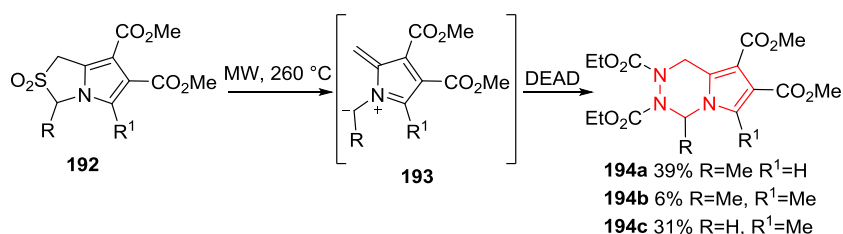
The heterocyclization of hydrazide **191** by heating in EtOH in the presence of potassium(ethoxycarbonothioyl)sulphide delivered the pyrrolo[1,2-*d*][1,2,4]triazine **94** in 92% yield (Scheme 43). [73]



Scheme 43

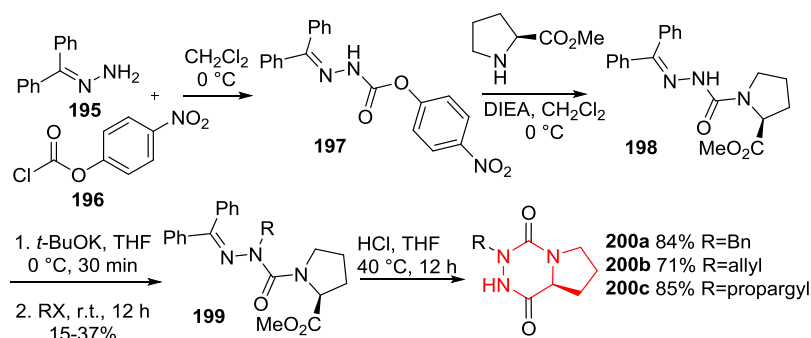
Beyond these methods, more recently new routes to access the pyrrolo[1,2-*d*][1,2,4]triazine core have been developed.

1*H*,4*H*-pyrrolo[1,2-*d*][1,2,4]triazines **194a-c** were obtained by a $[8\pi+2\pi]$ cycloaddition reaction of diethyl azodicarboxylate (DEAD) with azafulvenium methides **193**, in situ generated from pyrrolo[1,2-*c*]thiazoles **192** under MW irradiation (Scheme 44). [90] [91]



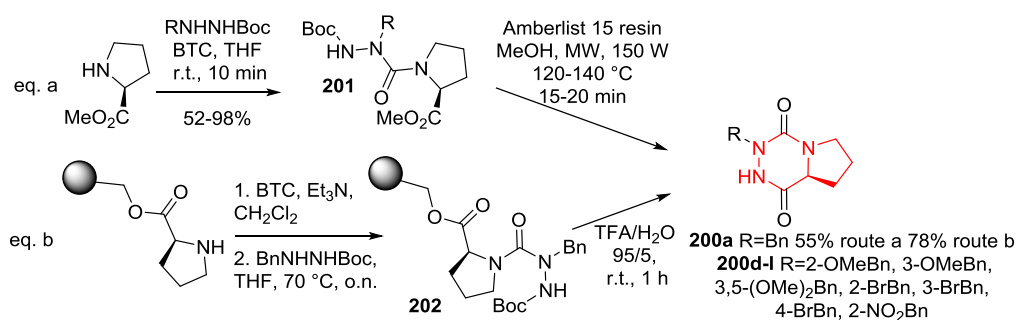
Scheme 44

Aza-diketopiperazines (aza-DKPS) have been synthesized starting from aza-dipeptides **199**. These latter are obtained by reaction of diphenylhydrazone **195** activated by *p*-nitrophenyl chloroformate **196** and subsequent coupling of the resulting **197** with proline methyl ester. After alkylation of the benzophenone semicarbazone aza-dipeptide **198** with alkyl bromides in the presence of *t*BuOK, the *N*-terminal deprotection of the aza-dipeptides **199** in HCl/THF yielded the cyclic aza-diketopiperazines **200a-c** (Scheme 45). [92]



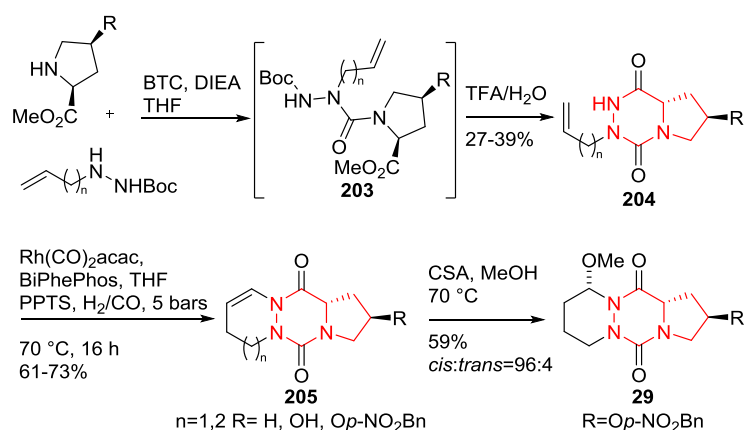
Scheme 45

Aza-DKPs **200** have been also synthesized thanks to solution- and solid-phase strategies via semicarbazides key intermediates **201** and **202**. Concerning the solution-phase approach (Scheme 46, eq. a), two steps are involved in the formation of the target *c*-[aza-alkylGly-Pro] derivatives: coupling of proline ester with Boc-carbazates, in the presence of bis(trichloromethyl)carbonate (BTC) as activation reagent, to deliver the semicarbazides **201**, concomitant deprotection of the Boc group and cyclization in the presence of Amberlist 15 resin. The solid-phase strategy relies on the use of Wang-PS resin in order to have access to **200a** and **200d-I**. Following the same sequence as in solution-phase, the semicarbazide intermediate **202** is obtained and readily submitted to cleavage and cyclization by treatment with TFA/H₂O (95/5) (Scheme 46, eq. B). [93] Comparison of the three methods reveal that, at least for aza-DKP **200a**, the first methodology [92] is more powerful (84%) than the solid-phase approach (eq. b 78%) and that the route a gave the less good yields (eq. a 55%).



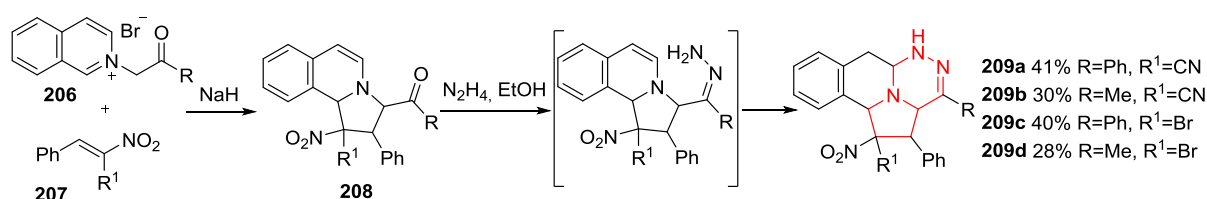
Scheme 46

Another approach to this class of molecules consists in the reaction of L-proline derivatives activated with BTC, with allyl or homoallyl *t*-butyl carbazate, and cyclization of the intermediate **203** in the presence of TFA. The pyrrolo[1,2-*d*][1,2,4]triazine core **204** was thus further submitted to Rh(I)-catalysed cyclohydrocarbonylation, by applying a 5 bar pressure mixture of H₂/CO gas in the presence of Rh(CO)₂acac and BiPhePhos under acidic catalysis conditions (pyridinium *p*-toluenesulfonate PPTS) in THF (Scheme 47). The obtained **205** was then decorated in acidic conditions (canforsulfonic acid CSA) in MeOH as nucleophile to give compound **29** in 59% yield as *cis* diastereomer (96:4), as unambiguously established by X-ray analysis. [40]



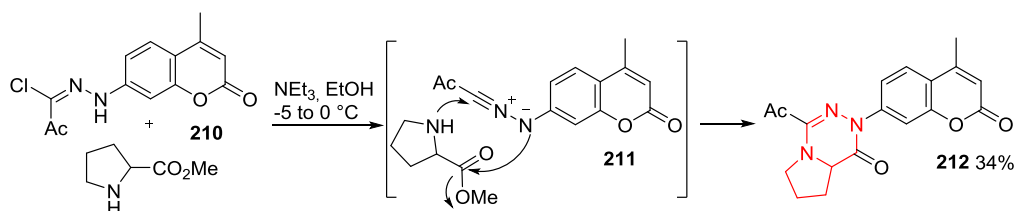
Scheme 47

Hexahydro-1*H*-benzo[*g*][1,2,4]triazino[5,4,3-*cd*]indolizines **209a-d** were obtained via a two steps procedure involving a 1,3-dipolar cycloaddition between in situ generated azomethine ylides derived from isoquinolinium bromides **206** and phenylethylene dipolarophiles **207**, followed by a heterocyclization of the cycloaddition adducts **208** upon treatment with hydrazines (Scheme 48). [94]



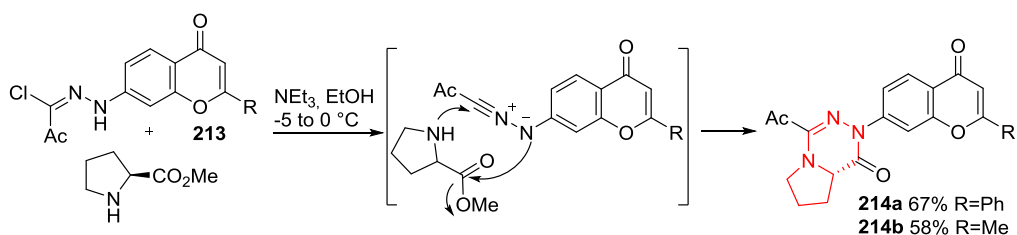
Scheme 48

The synthesis of pyrrolo[1,2-*d*][1,2,4]triazin-1-one **212** was achieved by addition of proline methyl ester onto the nitrile imine **211** generated in situ, from the corresponding hydrazonoyl chloride **210**. In the presence of trimethylamine, the transient amidrazone ester undergoes intramolecular cyclization to deliver 34% of **212** (Scheme 49). [95]



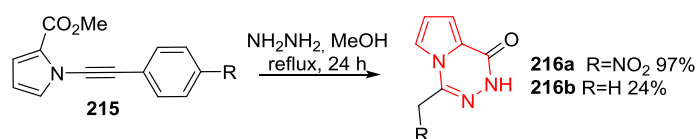
Scheme 49

By the same strategy, starting from hydrazonoyl chlorides **213**, flavonoyl pyrrolo[1,2-*d*][1,2,4]triazin-1-ones **214** were obtained (Scheme 50). [96]



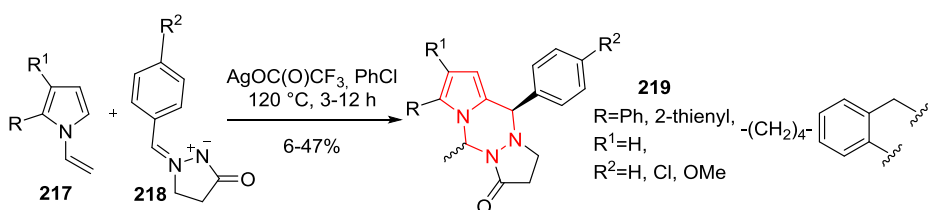
Scheme 50

Pyrrolotriazinones **216a-b** can also be obtained by cyclization of N-substituted pyrrole **215a-b** in the presence of hydrazine in 97% and 24% yield respectively (Scheme 51). [97]



Scheme 51

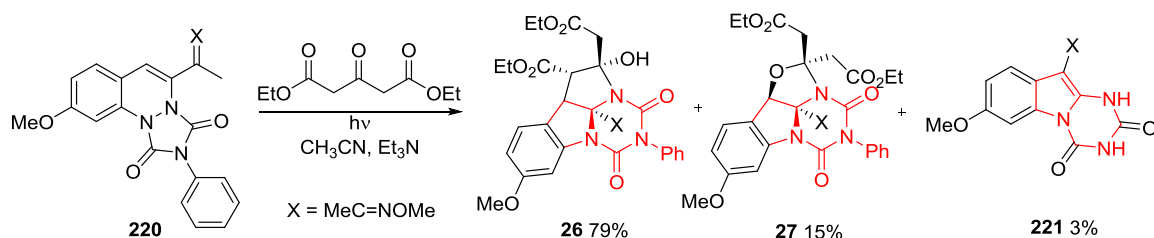
The formal (3+3)-cycloaddition of azomethine imines **218** with N-vinylpyrroles **217**, catalysed by AgOC(O)CF_3 as Lewis acid, leads to the formation of pyrazolo[1,2-*a*]pyrrolo[1,2-*d*][1,2,4]triazines **219** (Scheme 52). [24]



Scheme 52

9 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

Photochemical reaction of urazole **220** and 1,3-acetonedicarboxylate gave a mixture of three products, **26**, **27** and **221** (Scheme 53). [37]



Scheme 53

10 IMPORTANT COMPOUNDS AND APPLICATIONS

All the compounds described in this chapter exhibited a panel of different biological activities. Among the heterocycles which fall within the scope of this chapter, undoubtedly the pyrrolo[2,1-*f*][1,2,4]triazine skeleton is a privileged fragment that constitute the core of several pharmaceutical candidates exhibiting anticancer and anti-inflammatory activities. [98]

This scaffold makes the object of a recent reviews which explore its history and use in medicinal chemistry. [3] Remarkably the original therapeutic use of this nucleus as a C-nucleoside anti-viral agent is still and again of actuality, since recently the therapeutic efficacy of **GS5734** against Ebola virus has been proved. [99]

In the period covered by this book chapter a plethora of patents have been deposited about the preparation of pyrrolo[1,2-*f*][1,2,4]triazines and their use as kinase inhibitors for the treatment of cancer and proliferative disorders or for treating virus infections. [100]

Another class of biologically relevant compound are molecules containing the pyrrolo[1,2-*d*][1,2,4]triazine core, which have been evaluated for their activities as potent Rho-associated protein kinase (ROCK) inhibitors, [101] antiproliferative [102] and anticancer agents, [103] potassium ion channel [104] and acetylcholinesterase inhibitors. [105]

Some pyrrolo[1,2-*b*][1,2,4]triazines have been evaluated as protein kinases modulators. [106]

Pyrido[3',2':4,5]pyrrolo[1,2-*c*][1,2,3]benzotriazines inhibit topoisomerase I activity, which is unprecedented for compounds bearing the triazine core. In particular these compounds exhibit high cytotoxic activity against around 60 human tumor cell lines, with a particular efficacy against leukemia cell lines and they are also useful in treating drug-refractory patients. [76]

Finally several pyrrolo[1,2-*a*][1,3,5]triazines are effective as therapeutic agents for Alzheimer's and Parkinson's diseases. [107]

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Bibliographical Sketch



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