Review

Fused 1,5-Naphthyridines: Synthetic Tools and Applications

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Abstract: Heterocyclic nitrogen compounds, including fused 1,5-naphthyridines, have versatile applications in the fields of synthetic organic chemistry and play an important role in the field of medicinal chemistry, as many of them have a wide range of biological activities. In this review, a wide range of synthetic protocols for the construction of this scaffold are presented. For example, Friedländer, Skraup, Semmler-Wolff, and hetero-Diels-Alder, among others, are well known classical synthetic protocols used for the construction of the main 1,5-naphthyridine scaffold. These syntheses are classified according to the nature of the cycle fused to the 1,5-naphthyridine ring: carbocycles, nitrogen heterocycles, oxygen heterocycles, and sulphur heterocycles. In addition, taking into account the aforementioned versatility of these heterocycles, their reactivity is presented as well as their use as a ligand for metal complexes formation. Finally, those fused 1,5-naphthyridines that present biological activity and optical applications, among others, are indicated.

Keywords: fused 1,5-naphthyridines; heterocycle synthesis; biological activity; metal complexes

1. Introduction

Several reviews have appeared in the area of naphthyridines [1–4] including some references to fused 1,5-naphthyridines. Among them, in 2005, Ivanov et al. [5] published a generic review on benzo[b]naphthyridines. However, there are no previous reviews that specifically address the chemistry and application of fused 1,5-naphthyridines. For these reasons, to avoid overlapping with previous contributions, our wish in this review is coverage since 2003.

Heterocyclic compounds, such as fused 1,5-naphthyridines, are significantly important in the field of medicinal chemistry, because many of them present a wide variety of biological activities. For example, it was reported that pyronaridine I (Figure 1) has a high activity against Plasmodium falciparum and Plasmodium vivax [6,7]. Benzo[b][1,5]naphthyridine II (Figure 1) presented noticeable cytotoxicity against human HL-60 and HeLa cells grown in culture and topoisomerase II inhibition [8]. Moreover, through chemotherapy of solid-tumor-bearing mice, this compound II resulted as potent as amsacrine (m-AMSA) but less toxic towards the host. In 1994, Sliwa et al. showed that benzo[b]1,5-naphthyridine III (Figure 1) presented higher activity against Gram-positive than Gram-negative strains [9]. Years later, 5H-benzo[c][1,5]naphthyridin-6-ones IV (Figure 1) showed poly ADP ribose polymerase (PARP)-1 inhibition and protective effects in rat models of stroke and heart ischemia [10].
Regarding the organization of this review, first of all, the synthesis of 1,5-naphthyridines fused with carbocycles will be addressed, followed by the synthesis of 1,5-naphthyridines fused with nitrogen heterocycles, fused with oxygen heterocycles, and fused with thieno heterocycles. Afterwards, the reactivity of fused 1,5-naphthyridines is classified by $N$-alkylation, electrophilic substitution reactions (SEAr), nucleophilic substitution reactions (SNAr), oxidations, reductions, side chain modifications, and metal complex formation. Finally, some properties and applications of these heterocycles studied during this period are reviewed.

2. Synthesis of Fused 1,5-Naphthyridines

2.1. Synthesis of 1,5-Naphthyridines Fused with Carbocycles

In this section, general methods of synthesis for 1,5-naphthyridines fused with benzene, naphthalene, and indene rings (Figure 2) are analyzed.
The most commonly used synthetic routes for the synthesis of benzo\([b][1,5]\)naphthyridines are based on the Friedländer reaction and on the Skraup synthesis using 3-aminopyridine or 3-aminoquinoline derivatives and carbonyl compounds. There are numerous examples collected in the excellent reviews published previously [1,3,4,5] describing these approaches. As an example, the reaction of 3-aminopicolinaldehyde 1 with 2-methylcyclohexanone 2 (Scheme 1) in \(\text{^1BuOH}\) in the presence of \(\text{^1BuOK}\) followed by dehydrogenation of the 6,7,8,9-tetrahydrobenzo\([b][1,5]\)naphthyridine 3, formed at reflux with \(\text{Pd/C}\) in \(\text{Ph}_2\text{O}\), afforded benzo\([b][1,5]\)naphthyridine 4 [4].

![Scheme 1](image1)

Scheme 1. Preparation of benzo\([b][1,5]\)naphthyridines by Friedländer reaction.

Similarly, the ligand 2-(pyridin-2-yl)benzo\([b][1,5]\)naphthyridine 7 (pbn) was prepared by a modified Friedländer reaction of 3-aminoquinaldehyde 6 with 2-acetylpyridine 5 (Scheme 2) in ethanol in the presence of \(\text{NaOH}\) [11,12]. As will be seen later, this compound has been used as a ligand in the preparation of Ru, Rh, and Pd complexes to study its electrochemical behavior.

![Scheme 2](image2)

Scheme 2. A modified Friedländer reaction for the preparation of pbn ligand.

An analogous reaction was used for the preparation of 2-acetyl-6-benzo\([b][1,5]\)naphthyridin-2-yl-4-\(\text{tert}\)-butylpyridine 9 (abnp, Scheme 3) and 2,6-bis(benzo\([b][1,5]\)naphthyridin-2-yl)-4-\(\text{tert}\)-butylpyridine 10 (bbnp, Scheme 3) [13]. In this case, the Friedländer reaction between equimolar amounts of quinoline 6 and 2,6-diacetyl-4-\(\text{tert}\)-butylpyridine 8 gave derivative 9 (abnp), while compound 10 (bbnp) was obtained by condensing 2,6-diacetyl-4-\(\text{tert}\)-butylpyridine 8 with two equivalents of 3-aminoquinaldehyde 6.

![Scheme 3](image3)

Scheme 3. Friedländer reaction for the synthesis of benzo\([b][1,5]\)naphthyridine derivatives 9 and 10.
In a similar way, 3-aminoquinoline-2-carboxylate 11 (Scheme 4) was transformed into benzo[b][1,5]naphthyridine 13 in two steps [14]. The reaction of quinoline 11 with the DMF acetal gave amidine 12, whose reaction with the acetonitrile anion followed by chlorination with phosphorus oxychloride provided derivative 13.

![Diagram](attachment:Scheme_4.png)

**Scheme 4.** Formation of a cyano benzo[b][1,5]naphthyridine derivative in two steps.

A modified Skraup synthesis allows the preparation of 5,10-dihydrobenzo[b][1,5]naphthyridin-10-one 17 (Scheme 5) by heating at 75 °C the 2,6-dichloro-3-nitrobenzoic acid 14 in 6-methoxy-3-pyridinamine 15. Thus, the 6-chloro-2-[(6-methoxy-3-pyridyl)amino]-3-nitrobenzoic acid 16 was obtained. Heating of 16 at 100 °C in H2SO4 leads to the 9-chloro-2-methoxy-6-nitro-5,10-dihydrobenzo[b][1,5]naphthyridin-10-one 17 [15].

![Diagram](attachment:Scheme_5.png)

**Scheme 5.** Modified Skraup synthesis of 5,10-dihydrobenzo[b][1,5]naphthyridin-10-one.

In a similar way, when anthranilic acid derivative 19 was stirred with POCl3 at 140 °C (Scheme 6, route a), the 9-chloroacridine derivative 20 was obtained [16]. A new approach to the preparation of anthranilic acid 19 is a nucleophilic substitution reaction by heating 2,4-dichlorobenzoic acid 18 with 5-amino-2-methoxypyridine 15 in the presence of Cu (Scheme 6).

The process has been applied to the industrial preparation of pyronaridine tetraphosphate 21 (Scheme 6), a well-known antimalarial drug, by introducing several modifications [17]. The cyclization of compound 19 to derivative 20 is the most important stage in the synthesis of pyronaridine tetraphosphate 21. However, purification of compound 20 was difficult because of its poor solubility in common solvents. In order to reduce undesired impurities produced during reaction, ethylene dichloride (EDC) was used as solvent and short reaction times were applied to the process (Scheme 6, route b). Following this improved manufacturing process, 9-chloroacridine 20 was synthesized in a high purity, increased yield and lower production cost.
Synthetic routes based on Skraup synthesis are also convenient approaches to obtain benzo[\textit{c}][1,5]naphthyridines. A modified Skraup method, namely, Michael addition of \textit{N}-acyliminium salt 26 followed by the opening of the lactam ring. 

On the other hand, the treatment of oximes 25a–c with acid (Scheme 8), allows the formation of 3,4-dihydrobenzo[\textit{c}][1,5]naphthyridin-2(1H)-ones 27a–c [18]. The formation of derivatives 27a–c takes place through a Semmlere–Wolff transposition (Scheme 8) with good yields. It is important to note that the mechanism leading to derivatives 27a–c involves the formation of a stabilized \textit{N}-acyliminium salt 26 followed by the opening of the lactam ring.

The preparation of benzo[\textit{c}][1,5]naphthyridines can be also performed by [4+2] cycloaddition reaction. Thus, the microwave-mediated intramolecular Diels–Alder (DA) reaction [19] of \textit{o}-furyl(allylamino)pyridines 28a–c, in the presence of a catalytic amount of acid, gave 5,6-dihydrobenzo[\textit{c}][1,5]naphthyridines 30a–c (Scheme 9, method A). The initially formed DA-adduct 29 spontaneously underwent ring opening and subsequent aromatization to afford the 5,6-dihydrobenzo[\textit{c}][1,5]naphthyridines 30a–c. Electron-withdrawing substituents, especially \textit{R}1 = \textit{Cl}, seem to stabilize the 5,6-dihydrobenzo[\textit{c}][1,5]naphthyridines 30. Some of these dihydro compounds 30 were oxidized, with high yields, to the aromatic compounds 31 during workup and purification. When the reaction mixture was bubbled through air in the presence of UV light (Scheme 9, method B) or stirred with 2,3-dichloro-5,6-dicyano-\textit{p}-benzoquinone (DDQ, 1.2 equivalent) at room temperature (Scheme 9, method C) aromatic benzo[\textit{c}][1,5]naphthyridine compounds 31a–c were obtained.
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Through metabolomics, several benzo[c][1,5]naphthyridine alkaloids, known as fumisoquins, have been prepared. For this purpose, groups of microbial biosynthetic gene clusters (BGC) in the human pathogen Aspergillus fumigatus called fsq have been used [20]. The authors demonstrated that fsqF, which lacks a canonical condensation domain, is necessary for the formation of carbon–carbon bonds between the amino acids \( \text{L-serine} \) and \( \text{L-tyrosine} \) in the fumisoquin biosynthetic pathway. The fsqD appears to activate tyrosine for subsequent condensation with serine-derived dehydroalanine (Scheme 10), which is the first example of a new strategy for the formation of carbon–carbon bonds in fungi. Optimization of the extraction conditions and reverse phase fractionation followed by
two-dimensional NMR spectroscopy and HRMS analysis allowed the identification of fumisoquin C (Scheme 10) as the deep purple metabolite. While standing or during chromatography, fumisoquin C decomposes into 32 and 33 (Scheme 10) which are more stable and were isolated.

A visible-light-catalyzed synthesis of 5-phenyldibenzo[b,h][1,5]naphthyridine 36 from 3-isocyanato-2-phenylquinoline 34 and bromobenzene 35 at room temperature has been discovered [21]. This metal-free cross-coupling reaction offers rapid and sustainable access to a series of structurally complex dibenzo[b,h][1,5]naphthyridines 36 (Scheme 11). The usage of inexpensive Rhodamine 6G (Rh-6G) as the catalyst with easy operation makes this protocol very practical. A plausible mechanism was proposed through a radical anion [Rh-6G•−] formed by the use of the visible-light irradiation, that triggers a single electron transfer to bromobenzene producing the transient [Ph-Br•−] radical anion and regenerating Rh-6G completing the catalytic cycle.

A novel procedure for hydride-induced anionic cyclization has been developed. It includes the reduction of a biaryl bromonitrile 37 with a nucleophilic aromatic substitution (S_NAr). Dibeno[b,h][1,5]naphthyridine 38a and benzo[b]naphtho[2,3-h][1,5]naphthyridine 38b were so obtained in moderate-to-good yield with good substrate tolerance (Scheme 12). In addition, the analogue of trisphaeridine 38c could be also obtained in moderate yield [22]. This method involves a concise transition-metal-free process, and it was applied to synthesize natural alkaloids. A tentative reaction pathway can be proposed as below (Scheme 12). The reaction is likely to be initiated by the chelating of compound 37 to lithium (complex A). Subsequent addition of hydride to nitrile provides the iminyl lithium complex (complex B). A subsequent nucleophilic aromatic substitution then takes place to generate the anionic intermediate C. Elimination of halide affords desired products 38 and precipitate LiBr.
was carried out by Palacios and colleagues [24–26]. Buchwald-Hartwig (Palladium-catalyzed arylamination) with benzylamine (Bn-NH₂) was achieved with glycerol in THF, 100 °C, N₂, 48 h. The reaction pathway can be proposed as below (Scheme 12). The reaction is likely to be initiated by the formation of compound A, which is the central intermediate for the synthesis of naphtho[1,8-bc][1,5]naphthyridines by reduction of biaryl bromonitriles. A subsequent nucleophilic aromatic substitution then takes place to generate the anionic intermediate B. Elimination of halide affords desired products C. Subsequent addition of hydride to nitrile provides 38a-c.

Naphtho[2,1-b][1,5]naphthyridines can also be prepared by the Skraup synthesis. Thus, annulated naphthonaphthyridine 41 (Scheme 13) was synthesized starting from 2-aminobenzo[ f]quinoline 39 [4,5]. This reaction was carried out with glycerol 40 in the presence of an oxidant (nitrobenzenesulfonic acid) formed in situ upon the reaction of nitrobenzene with oleum.

Nitropyridylnaphthalene 42 is the central intermediate for the synthesis of naphtho[1,8-bc][1,5]naphthyridine derivatives [23]. Transformation of the nitro group to iodo followed by oxidation and cyclization results in an iodonium salt 43 (Scheme 14). Using the successful protocol for the transformation of annulated iodolium salts to pyrroles, Buchwald-Hartwig (Palladium-catalyzed arylamination) with benzylamine (Bn-NH₂) was achieved with 43 to give compound 44. The unsubstituted 7H-naphtho[1,8-bc][1,5]naphthyridine 45 was obtained in nearly quantitative yield via base-induced debenzylation of 44 (Scheme 14).

The first report for the synthesis of substituted 7H-indeno[2,1-c][1,5]naphthyridine derivatives was carried out by Palacios and colleagues [24–26].
The process consists of a Povarov-type [4+2]-cycloaddition reaction, by both step-by-step and by multicomponent strategies (MCRs). First, the hetero-Diels-Alder reaction between indene 49 (Scheme 15, route a) and N-(3-pyridyl) aldimines 48, prepared in situ by reaction of 3-pyridylamine and aldehydes 47, in the presence of two equivalents of BF3·Et2O in refluxing chloroform were performed. Afterwards, the corresponding tetracyclic endo-1,2,3,4-tetrahydro[1,5]naphthyridines 50 were selectively obtained with good yields (route a, Scheme 15) in a regio- and stereospecific way. Alternatively, three-component synthetic protocol was carried out (Scheme 15, route b) by reacting commercially available 3-pyridylamine 46, aromatic aldehydes 47 and indene 49 in the presence of 2 equivalents of BF3·Et2O in refluxing chloroform to afford also the corresponding endo-1,2,3,4-tetrahydro[naphthyridines 50 with good yields. The presence of electron-donating groups (OMe and SMe) seems to favor the direct formation of indeno[1,5]naphthyridines 51. Formation of these derivatives could be reasoned by a [4+2]-cycloaddition reaction between aldimines 48 and indene 49 and, subsequent, dehydrogenation of tetrahydroindeno[1,5]naphthyridines 50. The scope of this strategy is very wide, given that compounds 50 and 51 substituted not only with a pyridine group (R = 4 pyr) but also with a wide range of ortho, meta, and para aromatic substrates containing electron-releasing and -withdrawing groups, including fluorine substituents can be prepared.

R = 4-MeC6H4, Ph, 4-CF3C6H4, 3-FC6H4, 4-FC6H4, 2,4-F2C6H3, 3,4-F2C6H3, 4-NO2C6H4, 3-MeOC6H4, 4-MeOC6H4, 4-MeSC6H4, 4-pyr, 2-naphthyl, CO2Et

Scheme 15. Povarov reaction for the preparation of substituted 7H-indeno[2,1-c][1,5]naphthyridines.
2.2. Synthesis of 1,5-Naphthyridines Fused with Nitrogen Heterocycles

Nitrogen atoms are ubiquitous in biologically significant secondary metabolites (alkaloids, cytokinins), in biomacromolecules (proteins, peptides, DNA, RNA) as well as in synthetic organic substances, and often belong to atomic centers of importance for intra- and intermolecular interactions. Therefore, the addition of nitrogen atoms to a structure can contribute to the discovery and development of new therapeutic agents for the treatment of different diseases, which represents one of the most important objectives in medicinal chemistry.

This section, firstly, will analyze the general methods of synthesis of 1,5-naphthyridine fused with five-membered nitrogen heterocycles (Figure 3).

![Diagram of fused 1,5-naphthyridines with five-membered nitrogen heterocycles](image)

**Figure 3.** Examples of fused 1,5-naphthyridines with five-membered nitrogen heterocycles.

An efficient enantioselective total synthesis of the potent antibiotic GSK966587 [27] was accomplished. After the synthesis of the corresponding fused 1,5-naphthyridine and several structural modifications, the desired allylic alcohol [53] was obtained. A Sharpless asymmetric epoxidation of allylic alcohol [53] gives epoxy alcohol [54]. When the unpurified epoxy alcohol [54] was treated with concentrated HCl and after aqueous workup, the solution was heated in butyronitrile to 100 °C for 1.5 h, causing cyclization and demethylation in one pot. Cooling to room temperature allowed the crystallization of tricyclic diol [55] from allylic alcohol [53] (Scheme 16). The preparation of the fully elaborated side chain and various final transformations gave GSK966587 as a precipitate directly from the reaction mixture.

The synthesis of 4,5-dihydro-6λ4pyrrolo[3,2,1-ij][1,5]naphthyridine derivatives, including a new synthesis of GSK966587 [52], has also been reported [28]. In this case, a Suzuki cross-coupling of 8-bromo-7-fluoro-2-methoxy[1,5]naphthyridine [56] (Scheme 16) with pyridine-tris (1-methylethenyl) boroxin [57] gives [58] (Scheme 16). Then, chlorination with cerium (III) chloride heptahydrate gave a chloride whose cyclisation using NaI in acetone during 18 h of reflux afforded 3-fluoro-4-methylene-4H-pyrrolo[3,2,1-de][1,5]naphthyridin-7(5H)-one [59]. Then, subsequent dihydroxylation yielded the previously described diol [55] (Scheme 16).
Scheme 16. Enantioselective total synthesis of the potent antibiotic GSK966587.

The preparation of imidazo[1,2-α][1,5]naphthyridinic systems was achieved by a modified Friedländer’s reaction [29]. In this case, from 6-aminoimidazo[1,2-α]pyridine-5-carbaldehyde 60 and ketones, such as acetone, butanone, acetophenone, cyclohexanone, ethyl 4-oxocyclohexane carboxylate, 1,3-cyclohexandione, α- or β-tetralone, the corresponding compounds were obtained using EtOH/KOH 10% (Scheme 17, method A) or AcOH (Scheme 17, method B). The protocol is effective for the synthesis of imidazo[1,2-α][1,5]naphthyridines 61a–c and 62 and also for the synthesis of benzo[g]imidazo[1,2-α][1,5]naphthyridines 63a and 63b, from cyclohexanone and ethyl 4-oxocyclohexane, respectively (Scheme 17, method A). In contrast, compound 64 could be prepared by reaction of 60 with 1,3-cyclohexadione in an acetic acidic medium (Scheme 17, method B). Imidazo[1,2-α]naphtho[1,5]naphthyridines 65–67 were prepared from α- or β-tetralone, respectively. Under alkaline conditions (Scheme 17, method A) α-tetralone gave the single dihydro compound 65, while β-tetralone yielded the compounds 66 and 67. It is interesting to note that the use of acidic conditions (Scheme 17, method B) afforded only compound 66.
Scheme 17. Modified Friedländer reactions for the synthesis of imidazo[1,2-a][1,5]naphthyridines.

The tricyclic system of imidazo[4,5-c][1,5]naphthyridine present in a series of compounds 71a (R1 = H) and in the potent and selective PI3K/mTOR dual kinase inhibitor PF-04979064, was prepared [30] from 68 after several modifications to obtain 69 (Scheme 18). When 69 is treated with diphenylphosphoryl azide (DPPA) and Et3N, the initially formed nitrene intermediate gives isocyanate 70 which by Curtius rearrangement reacts with the amine group at 4-naphthyridine to undergo intramolecular cyclization producing the 1,3-dihydro-2H-imidazo[4,5-c][1,5]naphthyridin-2-ones 71 (Scheme 18). Following these strategies, tricyclic derivatives 71a were designed with phenyl substituted cyclohexane and piperidine substituents. In a similar way, imidazo [4,5-c][1,5]naphthyridines 71b (Scheme 18), that possess an isoxazole substituent (R1 = 3,5-dimethylisoxazol-4-yl), were synthesized from the corresponding previously prepared carboxylic acids 69b [31].
Scheme 18. Preparation of tricyclic imidazo[4,5-c][1,5]naphthyridine derivatives.

Indole framework holds a very high affinity to multiple receptors and enzymes and, accordingly, it is considered a privileged structure in many active medicine compounds for human health and represents a promising scaffold for drug development (Figure 4) [32–35].

Figure 4. Examples of indolo and indazolo[1,5]naphthyridine derivatives.
Indol systems fused to the 1,5-naphthyridine nucleus can be obtained by heating oximes in an acidic medium, through a Semmier-Wolf transposition, similar to the preparation of 3,4-dihydrobenzo[\(c\)][1,5]naphthyridin-2(1H)-ones 27 previously described (Scheme 8, *vide supra* [18]). No general conditions were found for the transformation of oximes 72a–d into the corresponding tetrahydro-2\(H\)-indolo[3,2-c][1,5]naphthyridin-2-ones 73a–d (Scheme 19), and it was necessary to adjust the media according to the substituents present in the aromatic group. The advantage of using triflic acid mixtures in trifluoroacetic or methanesulfonic acid is the easy quenching of the reaction media when large amounts of oximes are employed.

![Scheme 19. Preparation of indol 1,5-naphthyridines by a Semmier-Wolf transposition of oximes.](image)

Two high-yielding and flexible syntheses of canthin-6-ones 77 (\(R = H\), Scheme 20) were developed and optimized [36]. In the first one, through a stepwise approach, the desired 8-(2-chlorophenyl)-2-methoxynaphthyridine derivatives 75 were prepared from 8-bromo-2-methoxynaphthyridine 74 and 2-chlorophenylboronic acids via a Suzuki–Miyaura coupling. Reflux of the corresponding 2-methoxy[1,5]naphthyridine derivatives 75 with aqueous HCl in dioxane gave naphthyridones 76. The C-N coupling using Cul (10 mol%) and \(N,N'\)-dimethylethylenediamine (DMEDA, 20 mol%) gave six new 6\(H\)-indolo[3,2,1-de][1,5]naphthyridin-6-ones 77 as well as canthin-6-one (\(R = H\)) in good overall yields.

![Scheme 20. Syntheses of canthin-6-ones through a Suzuki-Miyaura coupling.](image)

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\begin{align*}
\text{Scheme 19. Preparation of indol 1,5-naphthyridines by a Semmier-Wolf transposition of oximes.} \\
\text{Scheme 20. Syntheses of canthin-6-ones through a Suzuki-Miyaura coupling.}
\end{align*}
\]
The second one was a simple and useful one-pot protocol involving a sequential application of a Pd-catalyzed Suzuki-Miyaura coupling of naphthyridine 78 prepared from 8-bromo-2-methoxynaphthyridine 74 (Scheme 20), followed by a Cu-catalyzed amidation, of general use for synthetic chemists. Using this new one-pot protocol, nine 6H-indolo[3,2,1-de][1,5]naphthyridin-6-ones 77 with various substituents in the aromatic ring were quickly obtained in excellent yields (Scheme 20).

Via a copper-catalyzed Buchwald cyclization, ethyl canthin-6-one-1-carboxylate 80 (R = H, Scheme 21) and nine analogues were obtained from ethyl 4-(2-haloaryl)-6-oxo-5,6-dihydro[1,5]naphthyridine-3-carboxylates 79. Thus, treatment of 79 with typical Buchwald conditions [CuI (5 mol%), DMEDA (10 mol%), Cs₂CO₃ (2 equivalents), water (2 equivalents)] in refluxing dioxane, gave the ethyl canthinone-1-carboxylates 80 [37]. A series of eight ethyl 6-oxo-6H-indolo[3,2,1-de][1,5]naphthyridine-1-carboxylates 80 was prepared bearing various substituents in the aromatic ring, together with the 8-aza and 9-aza analogues (Scheme 21).

![Scheme 21. Copper-catalyzed Buchwald cyclization to ethyl canthin-6-one-1-carboxylates.](image)

Tryptamine, tryptophan, and their derivatives are widely used in the synthesis of benzoindolo[3,2,1-de][1,5]naphthyridine derivatives [4]. Thus, refluxing tryptamine 81 with 2-formylbenzoic acid 82 in ethanol followed by the addition of concentrated hydrochloric acid afforded hexahydrobenzo[hi]indolo[3,2,1-de][1,5]naphthyridine hydrochloride 83 (Scheme 22).

![Scheme 22. Formation of hexahydrobenzo[hi]indolo[3,2,1-de][1,5]naphthyridine hydrochloride.](image)

The synthesis of a library of β-carboline fused systems was carried out via intramolecular 1,3-dipolar cycloaddition reactions [38] starting from β-carboline protected aldehydes 84 (Scheme 23). Thus, protected aldehydes 84a–c reacted with allyl bromide in the presence of Cs₂CO₃ as base in dry DMF, the acetal group was deprotected by heating in the presence of AcOH/water (2:3, v/v) at 120 °C and aldehydes 85a–c were obtained. In the next step, the aldehydes 85a–c reacted with NH₂OH-HCl in the presence of NaOAc to furnish the substituted oximes, whose treatment with NaOCl in the presence of Et₃N at room temperature for three days resulted in the formation of the desired 9a,10-dihydro-9H-indolo[3,2,1-i]isoxazolo[4,3-c][1,5]naphthyridines 86a–c (Scheme 23).
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When the reaction of compound 84a (R¹ = H, R² = CO₂Me) with several substituted allyl bromides 87a–d in the presence of Cs₂CO₃ in dry DMF is performed (Scheme 23) and the acetal group of obtained substituted alkenes (E-isomer exclusively) is deprotected as described earlier, the aldehydes 88a–d were obtained in high yields and good purity. The reaction of aldehydes 88a–d with NH₂OH·HCl gave rise to the corresponding oximes which, upon treatment with NaOCl in the presence of Et₃N, afforded the substituted isoxazoline derivatives 89a–d, respectively, as a mixture of diastereomers (Scheme 23). Similarly, the reaction of aldehydes 84a–c with propargyl bromide in dry DMF using Cs₂CO₃ and the deprotection of the acetal moiety in the presence of AcOH/H₂O resulted in the formation of aldehydes 90a–c (Scheme 23). The transformation of 90a–c was achieved by their reaction with NH₂OH·HCl and with NaOCl to produce the required isoxazole derivatives 91a–c.

Scheme 23. Synthesis of fused isoxazole and pyrro[1,5]naphthyridine derivatives.
In order to further diversify the range of the products which could be generated by applying intramolecular 1,3-dipolar cycloaddition reaction, the aldehydes 90a–c were treated with sarcosine in dry toluene under refluxing conditions. This reaction yielded the β-carboline-fused pyrroles 92a–c (Scheme 23).

A series of dihydroindazolo[4,3-bc][1,5]naphthyridines 94 was prepared by condensation of 9-chloro-2-methoxy-6-nitro-5,10-dihydrobenzo[b][1,5]naphthyridin-10-one 17 (previously prepared Scheme 5, vide supra) [15]. Thus, condensation of 17 with appropriate (ω-aminoalkyl) hydrazines 93 in tetrahydrofuran/methanol (1:1) at room temperature afforded the desired 2,6-dihydroindazolo[4,3-bc][1,5]naphthyridine 94 (Scheme 24).

![Scheme 24](image_url)

Scheme 24. Condensation reaction of chloro benzo[b][1,5]naphthyridinone with hydrazines.

Recently [39], starting from 2-iodo-5,10,15-tris(3,5-di-tert-butylphenyl)porphyrin niquel(II) complex 95 (Scheme 25), β-to-bethynylene-bridged NiII porphyrin dimer 96 was obtained by a two-fold Stille coupling reaction with a half equivalent of bis(tributylstannyl)acetylene.

![Scheme 25](image_url)

Scheme 25. Synthesis of fused 1,5-naphthyridine porphyrin dimers.

Nitration of 96 with AgNO3 and I2, hydrogenation by using Pd/C, NaBH4, and then PtII-catalyzed intramolecular cyclization with a catalytic amount of PtCl2 and oxidation with PbO2 afforded the 1,5-naphthyridine-fused porphyrin dimer 97. In the next step, the dimer 97 was reduced with an excess of NaBH4 to give dimer 98 (Scheme 25). This product is quite electron-rich owing to the presence of a 1,2-diaminoethene bridge and oxidizes back to 97 within several hours in solution under ambient conditions. Furthermore, treatment of 98 with PbO2 cleanly afforded 97.
The pyridonaphthyridines, are difficult to chemical access, but pyrido[4,3 or 3,4 or 2,3-c][1,5]naphthyridines were obtained with good yields after chlorodehydroxylation and dehalogenation reactions starting from the parent pyridonaphthyridinones [45]. These pyridonaphthyridinones 102a–c were synthesized (Scheme 26) in a two-step procedure using a Suzuki cross-coupling reaction between 2-chloro-3-fluoropyridine 99 and ortho-cyanopyridylboronic esters 100a–c followed by a KOH-mediated anionic ring closure which was performed under microwave heating conditions. The three expected pyrido[c][1,5]naphthyridin-6-ones 102a–c were isolated in good yield (Scheme 26).

The synthesis of quinolino[4,3-b][1,5]naphthyridines and quinolino[4,3-b][1,5]naphthyridin-6(5H)-ones was described recently [46]. The hybrid substituted quinolino[4,3-b][1,5]naphthyridines were prepared by an intramolecular Povarov [4+2]-cycloaddition reaction of functionalized aldimines 106 (X = CH₂) or 107 (X = CO), obtained by the condensation of 3-aminopyridines 103 and unsaturated aldehydes 104 (X = CH₂) or 105 (X = CO), respectively, in refluxing chloroform in the presence of Lewis acid as BF₃·Et₂O (Scheme 27). In this sense, the corresponding tetracyclic endo-5-tosyl-5,6,6a,7,12,12a-hexahydroquinolino[4,3-b][1,5]naphthyridines 110 (X = CH₂) or endo-5-tosyl-6a,7,12,12a-tetrahydroquinolino[4,3-b][1,5]naphthyridin-6(5H)-ones 111 (X = CO) were selectively obtained with good yields (Scheme 27). Formation of derivatives 110 and 111 may be explained by a regio- and stereospecific intramolecular [4+2]-cycloaddition reaction of aldimines 106/107 to give intermediates 108/109 followed by prototropic tautomerization. The methodology tolerates a wide range of electron-releasing and electron-withdrawing substituents in the starting 3-aminopyridines 103.

Figure 5. Examples of fused 1,5-naphthyridines with six-membered nitrogen heterocycles.

**Scheme 26.** Preparation of pyrido[4,3 or 3,4 or 2,3-c][1,5]naphthyridinones.
The preparation of 5-tosyldihydroquinolino[4,3-b][1,5]naphthyridines 115 (Scheme 27) in a single step may be also performed. When aldehyde 112 with a triple bond in their structure reacts with 3-aminopyridines 103 would give the corresponding aldimines 113, which after a subsequent intramolecular cycloaddition in the presence of BF$_3$·Et$_2$O yielded the 5-tosyldihydroquinolino[4,3-b][1,5]naphthyridines 115 with good yields. Formation of 5-tosylquinolino[4,3-b][1,5]naphthyridine derivatives 115 may be explained in a similar way that previously, by a regiospecific intramolecular [4+2]-cycloaddition reaction of aldimines 113 to give intermediates 114 followed by protodehydrogenation under the reaction conditions (Scheme 27).

2.3. Synthesis of 1,5-Naphthyridines Fused with Oxygen-Containing Heterocycles

The low toxicity of the natural products containing chromene and their broad pharmacological properties are attractive feature for medicinal chemists and a source of inspiration for the design of novel therapeutic agents [47,48]. Therefore, naphthyridines fused with 1,3-oxazines, chromenes or chromenones are very interesting substrates in the search of new drug candidates (Figure 6).
1,3-dipole A was accomplished in high yields via the one-pot three-component reaction of 3-aminopyridine with the experimental results. Indeed, the reversible formation of 1,3-dipole complex A (Scheme 28). So, when reactants

The authors propose a mechanism in which the first step is the reversible formation of the intermediate phenyltrifluoroacetylacetylene

at 100 °C [50]. The process gave the derivatives 46. The authors propose a mechanism in which the first step is the reversible formation of the intermediate 1,3-dipole A. Subsequent addition of the second molecule of acetylene 117 proceeds selectively to its carbonyl group. Afterwards, the oxygen center of formed anion B attacks position 2 of the naphthyridine ring to cause the product 118 (Scheme 28). The suggested mechanism is in agreement with the experimental results. Indeed, the reversible formation of 1,3-dipole complex A is supported by the fact that at a higher temperature, yields of the target products are not improved.

![Chemical structure](image)

Figure 6. Examples of fused 1,5-naphthyridines with oxygen-containing heterocycles.

Metal- and solvent-free reaction of 1,5-naphthyridine 116 with two molecules of phenyltrifluoroacetylacetylene 117 afforded 3,4a-dihydro-[1,3]oxazino[3,2-α][1,5]naphthyridine 118 (Scheme 28). So, when reactants 116 and 117 were allowed to contact at room temperature in the absence of water and solvent, compound 116 appeared to be capable of assembling with two molecules of trifluoroacetylacetylene 117 to form 3,4a-dihydro-[1,3]oxazino[3,2-α][1,5]naphthyridine 118 [49]. The authors propose a mechanism in which the first step is the reversible formation of the intermediate 1,3-dipole A. Subsequent addition of the second molecule of acetylene 117 gives a cyclized intermediate 118C. Subsequently, the double bond isomerization furnishes the final product 118.

![Chemical structure](image)

Scheme 28. Preparation of [1,3]oxazino[3,2-α][1,5]naphthyridine.

A simple and efficient synthesis of chromeno[4,3-b][1,5]naphthyridine derivatives 122 (Scheme 29) was accomplished in high yields via the one-pot three-component reaction of 3-aminopyridine 46, arylaldehydes 119 and 4-hydroxycoumarine 120 in aqueous media catalyzed by sulfamic acid and at 100 °C [50]. The process gave the derivatives 122 in high yields. The nature of substituents on aromatic ring did not show obvious effects in terms of yields. In the mechanism proposed by the authors, first, an imine 121A is formed via condensation of aldehyde 119 with 3-aminopyridine 46 (Scheme 29). Then, Povarov reaction of 4-hydroxycoumarin moiety with the imine 121A gave a cyclized intermediate 121C. Subsequently, the double bond isomerization furnishes the final product 122.
A mild and efficient method for the synthesis of chromenonaphthyridine derivatives via domino reaction of 3-aminopyridine 46 and different O-propargylated salicylaldehydes 123 (Scheme 30) using CuI/InCl$_3$ as an efficient catalyst, refluxed in acetonitrile have been reported [51]. Mild reaction conditions, operational simplicity, good-to-excellent yield, and easy isolation of product is the silent feature of this reaction to afford the corresponding 6H-chromeno[4,3-b][1,5]naphthyridine derivatives 124 in high yields (Scheme 30). Different O-propargylated salicylaldehydes 123, containing electron-withdrawing and electron-donating substituents, exhibited equal activity towards the formation of product in good to excellent yields. Plausible mechanistic rationalization for the formation of chromenonaphthyridine derivatives 124 is depicted in Scheme 30. Initially, imine A is formed which contained the aza-heterodiene moiety. This aza-heterodiene undergoes intramolecular aza Diels-Alder reaction with the propargyl triple bond, which is activated by indium chloride followed by aromatization to give the desired products 124.

A domino reaction for the synthesis of chromeno[4,3-b][1,5]naphthyridine derivatives.
aldimines and aldehydes containing a double or triple carbon-carbon bond in ortho position and allows the selective generation of three stereogenic centers in a short, efficient and reliable synthesis (Scheme 31). Aldimines 128 (X = CH$_2$), prepared in situ by condensation reaction of 3-aminopyridines 125 and previously prepared functionalized aldehydes 126 (X = CH$_2$), cyclized intramolecularly in refluxing chloroform and in the presence of BF$_3$·Et$_2$O (Scheme 31) to give 129 by a regio- and stereospecific intramolecular [4+2]-cycloaddition reaction which after prototropic tautomerization afforded compounds 127. When 2-(allyloxy)benzaldehyde 126 (R$^2$ = R$^3$ = H) and 6-bromo-3-aminopyridine 125 (R$^1$ = Br) were used, after formation of the corresponding tetrahydro[1,5]naphthyridine 127, subsequent dehydrogenation under the reaction conditions gave dehydrogenated derivative 130 (Scheme 31).

**Scheme 31.** Intramolecular aza-Diels-Alder reaction to obtain hybrid, fused naphthyridines.
In order to increase the molecular diversity, the methodology was extended to the preparation of angularly fused tetracyclic derivatives (X = CO), in which the chromene scaffold was substituted by a coumarin (chromen-2-one). As before, functionalized aldehydes (X = CO) were condensed with 3-aminopyridines to give aldimines (X = CO). These imines cyclized intramolecularly in refluxing chloroform in the presence of two equivalents of Lewis acid (BF₃·Et₂O) to afford endo-附加值6Hchromeno[4,3-b][1,5]naphthyridin-6-ones with good yields in a regio- and stereospecific way (Scheme 31). The formation of these polycyclic compounds may be explained, as before, by a regio- and stereospecific intramolecular [4+2]-cycloaddition reaction of aldimines (X = CO) to give intermediates followed by prototropic tautomerization. The methodology tolerates electron-releasing and electron-withdrawing substituents in the aromatic aldehydes, even fluorinated ones that allow the preparation of fluoro-containing compounds, interesting substrates from a biological point of view.

If acetylenes are used as dienophiles instead of olefins, the corresponding 1,5-naphthyridine compounds may be directly obtained. The formation of these chromeno[4,3-b][1,5]naphthyridines can be performed by initial condensation reaction between 3-aminopyridine and functionalized aldehydes containing an alkyne group in the ortho position. Subsequent intramolecular [4+2]-cycloaddition reaction in refluxing chloroform, in the presence of two equivalents of BF₃·Et₂O, would give intermediates followed by dehydrogenation under the reaction conditions to afford chromeno[4,3-b][1,5]naphthyridines with good yields (Scheme 31).

2.4. Synthesis of 1,5-Naphthyridines Fused with Sulphur-Containing Heterocycles

A one-stage procedure has been collected by Litvinov et al. for the preparation of isomeric 1,5-naphthyridines fused with a thiophene ring [4]. The procedure used Pd(PPh₃)₄-catalyzed cross-coupling of 2-chloropyridin-3-amine with thiopheneboronic acids (Scheme 32) containing an ortho-formyl group. The cross-coupling products cyclized spontaneously during the reaction to give thiophen-1,5-naphthyridines with all possible types of ring fusion. The effects of the catalyst amount, the nature of the base, and the reaction time on the yield of the naphthyridine have been studied.

A synthetic route previously reported by Bisagni et al. was modified for the synthesis of 4,9-bis(2-hexyldecyl)-4,9-dihydridothieno[3,2-c;3,2-]naphthyridine-5,10-dione (NT) and the poly(2,5-thiophene-4,9-bis(2-hexyldecyl)-4,9-dihydridothieno[3,2-c;3,2-]naphthyridine—5,10-dione (PTNT, Scheme 33). Nitration of derivative at low temperature seemed to be selective.
for the proton on the 7-position and offered 146. Reduction with hydrogen/Pd/C and subsequent reaction with ethyl chloroformate offered the derivative with a carbamate group 147. Subjecting 147 to high temperatures caused nucleophilic attack of the thiophene to the carbonyl, after which the NT unit 148 was obtained.

![Scheme 33](image)

**Scheme 33.** Preparation of dithieno[3,2-c:3,2-h][1,5]naphthyridine NT, a precursor of PTNT.

### 3. Reactivity of Fused 1,5-Naphthyridines

#### 3.1. N-Alkylation

The N-alkylation of the fused dihydro- or tetrahydro[1,5]naphthyridines is one of the reactions frequently carried out in the fused system. They are generally S_N reactions on alkyl halides or reductive alkylation reactions.

Methyl 3-ethyl-2,3,3a,4-tetrahydro-1H-indolo[3,2,1-de][1,5]naphthyridine-6-carboxylate 151 (Scheme 34) was prepared by the N-alkylation of ester 150 with iodoethane in DMSO [4]. In a similar way, 2,3,9,13b-tetrahydro-1H-benzo[c]indolo[3,2,1-ij][1,5]naphthyridine 152 (Scheme 34) has been used in the synthesis of 153 [4]. Thus, the reductive methylation of 152 with formaldehyde and sodium cyanoborohydride as a source of hydride gives compound 153 (Scheme 34).

![Scheme 34](image)

**Scheme 34.** N-alkylation of fused 1,5-naphthyridines.
NT, (4,9-bis(2-hexyldecyl)-4,9-dihydrodithieno[3,2-c:3,2-\textit{h}][1,5]naphthyridine-5,10-dione) 148, can be N-alkylated (Scheme 35) with 2-hexyldecyl bromide to give 154 the necessary compound in the polymerization of NT to obtain PTNT polymer 149 [54].

Scheme 35. N-alkylation of dithieno[3,2-c:3,2-\textit{h}][1,5]naphthyridine NT.

3.2. Electrophilic Substitution Reactions (SEAr)

It is known that the nitration of benzonaphthyridines with a HNO\textsubscript{3}/H\textsubscript{2}SO\textsubscript{4} mixture occurs exclusively in the benzene ring. Thus, nitration of 6-methylbenzo[\textit{h}][1,5]naphthyridine 4 gives the corresponding nitro derivative 155 (Scheme 36). In these reactions, the nitro group is also attached to the benzene ring in the \textit{para} position with respect to the methyl substituent [5].

Scheme 36. Nitration and bromination of benzo[\textit{h}][1,5]naphthyridines.

At the same time, 6-methylbenzo[\textit{h}][1,5]naphthyridines are brominated at the peripheral pyridine ring in the \textit{β}-position with respect to the nitrogen atom (rather than at the benzene ring). This reaction pathway cannot be explained in terms of the electrophilic substitution mechanism (aromatic SE (AE)). In this case, the behavior of benzonaphthyridine 4 (Scheme 36) is similar to that of quinoline and isoquinoline, when its bromination in weakly acidic media also occurs at the pyridine ring in the \textit{β}-position with respect to the nitrogen atom giving 156, rather than at the benzene ring [5]. The mechanism for the bromination of these compounds entails nucleophilic addition-elimination [S\textsubscript{N}(AE)].

More recently, the synthesis of benzo[c][1,5]naphthyridine-6-carbonitrile 158, starting from benzonaphthyridine \textit{N}-oxide 157 [58], has been achieved following the methodology of cyanation of two unsubstituted 1\textit{H}-imidazole 3-oxides [56]. Benzo[c][1,5]naphthyridine-5-oxide 157 in dry CH\textsubscript{2}Cl\textsubscript{2} in the presence of Et\textsubscript{3}N was treated with Me\textsubscript{3}SiCN at 0–5 °C and benzo[c][1,5]naphthyridine-6-carbonitrile 158 was obtained in good yield. The reaction mechanism for the formation of compounds 158 is analogous to that proposed for the cyanation of azine \textit{N}-oxides, silylation of the \textit{N}-oxide leads to the benzonaphthyridinium ion \textit{A}, which adds a cyanide ion to give the intermediate \textit{B} and which, in turn, eliminates Me\textsubscript{3}SiOH (Scheme 37).
Scheme 37. Cyanation of benzo[c][1,5]naphthyridine by means of N-oxide derivative.

3.3. Nucleophilic Substitution Reactions (SNAr)

One of the major procedures used in the synthesis of biologically active fused 1,5-naphthyridines is based on the replacement (SNAr) of the halogen atom at position 4 of the benzo[β][1,5]naphthyridine ring. Thus, coupling of 13 (Scheme 38) with 2,4-dichloro-5-methoxyaniline 159 gave target compound 160 [4].

Similarly, the replacement (SNAr) of the halogen atom at position 10 of the benzo[β][1,5]naphthyridine system occurred. The reaction of 20 with aniline derivatives 161 in the presence of a few drops of concentrated hydrogen chloride (Scheme 39) afforded the amino derivatives benzo[β][1,5]naphthyridines 162a–e [15] or 162f [57]. The same reaction was used in the industrial preparation of pyronaridine tetraphosphate 21 (Scheme 6, vide supra) a well-known antimalarial drug. Thus, the halogen atom at position 10 of the benzo[β][1,5]naphthyridine ring in 20 was replaced (SNAr) by an aminophenol group to give compound 162g (Scheme 39) used later in the preparation of pyronaridine tetraphosphate [17].

Scheme 38. SNAr at position 4 of benzo[β][1,5]naphthyridine ring.

Scheme 39. SNAr at position 10 of benzo[β][1,5]naphthyridine ring.
The same procedure, a double SNAr, if diamines are used can lead to dimers. Thus, dimeric benzo[b][1,5]naphthyridines 164 (Scheme 40) were synthesized by the SNAr reaction of 7,10-dichlorobenzonaphthyridine 20 with di- and polyamines 163 [5].

![Scheme 40](image_url)

\[ X = CH_2CH(OH)CH_2, (CH_2)_3NHCH(2)_3, (CH_2)_4NH(2)_2, (CH_2)_5NH(2)_2NH(2)_3 \]

**Scheme 40.** Double SNAr using diamines for the synthesis of dimeric benzo[b][1,5]naphthyridines.

The reactivity of position 10 of the benzo[b][1,5]naphthyridine system has been used for the synthesis of other functionalized derivatives with a benzo[b][1,5]naphthyridine unit [58]. Benzo[b][1,5]naphthyridin-10(5H)-one 165 (Scheme 41) was converted into the corresponding chloro derivative 166, using the Vilsmeier reagent generated from oxalylo chloride and DMF (Scheme 41). Subsequent reaction with methanethiolate provided 167.

![Scheme 41](image_url)

**Scheme 41.** Methanethiolation of benzo[b][1,5]naphthyridine.

In the preparation of 2,6-dihydroindazolo[4,3-bc][1,5]naphthyridine 94 (Scheme 24, vide supra), the condensation of 9-chloro-2-methoxy-6-nitro-5,10-dihydrobenzo[b][1,5]naphthyridine-10-one 17 (previously prepared) with the appropriate (ω-aminoalkyl)hydrazine 93 in tetrahydrofuran/methanol (1:1) at room temperature proceeds through an intramolecular SNAr of the halogen atom at position 9 giving to desired compounds 94 [15].

Otherwise, chlorodehydroxylation reaction of three pyrido[c][1,5]naphthydin-6-ones 102a–c (Scheme 42) was carried out by using phosphorus oxychloride at 100 °C for 12 h and the 6-chloropyrido[c][1,5]naphthyridines 168a–c were easily obtained in good yields [45]. Subsequently, derivatives 168a–c (Scheme 42) were submitted to a dehalogenation with four equivalents of ammonium formate and palladium on charcoal in methanol. Reacting 6-chloropyrido[2,3-c][1,5]naphthyridine 168a (X = N, Y = Z = CH) to reflux, the total conversion into 1,5-naphthyridine 169 was observed. Similarly, compound 168b was submitted to the same conditions and at this time the reaction afforded the pyrido[3,4-c][1,5]naphthyridine 170 in a high yield. Finally, the 1,5-naphthyridine 168c after 12 h of stirring in MeOH, showed a total conversion and the formation of two inseparable compounds: the expected compound 171 and a hydrogenated 5,6-dihdropyrido[4,3-c]-1,5-naphthyridine 172 (Scheme 42).
The aromatization of compounds

3.4. Oxidation and Reduction

The most common reduction reaction of 1,5-naphthyridine system fused with carbocycles or heterocycles is the transformation of naphthyridinones into naphthyridines or what is the same, the transformation of the carbonyl group into methylene group in different conditions. For instance in Reference [4], tetrahydro-1H-benzo[c]indolo[3,2,1-ij][1,5]naphthyridin-9(2H)-one hydrochloride 83 previously obtained (Scheme 22, vide supra) gave the reduced compound 173 by treatment with LiAlH₄ and AlCl₃ (Scheme 43).

However, the most usual is the oxidation (dehydrogenation) of tetrahydro- or dihydro[1,5]naphthyridines fused with carbocycles to give the corresponding dehydrogenated heterocycles and these transformations can be carried out under different oxidation conditions. The aromatization of compounds 27a–c (Scheme 8, vide supra) under different conditions allowed to obtain 3,4-dihydrobenzo[c][1,5]naphthyridin-2(1H)-ones 174 and 175 (Scheme 44) or benzo[c][1,5]naphthyridines 176 and 177 [18]. So, bromine in AcONa/AcOH led only, in an irreproducible manner, to very few amounts of pyridones 83 from lactams 27a–c. However, when lactam 27a (R₁ = R₂ = R₃ = H) was refluxed with 1.2 equivalents of bromine in bromobenzene for 12 h, pyridine 174a, accompanied by monobrominated compound 175 (position of the bromine atom was not determined), was obtained. Alternatively, by heating 27a with thionyl chloride for 9 h, it furnished a mixture of 176 containing a chlorine and a sulphur atom (position of substituents was not determined) and chloronaphthyridine 177 (Scheme 44).
DDQ is generally used for the transformation of hydrogenated compounds into the corresponding aromatic compounds. Thus, the addition of DDQ to the crude reaction mixture of pyrido[4,3-c][1,5]naphthyridine 171 and a hydrogenated product 172 (Scheme 42, vide supra), showed a total conversion into pyrido[4,3-c][1,5]naphthyridine 171 [45].

The transformation of 1,2,3,4-tetrahydroindenof[1,5]naphthyridine 50 into dehydrogenated derivatives 51 was performed by our group [24,25] by dehydrogenation under microwave irradiation (150 W), with one equivalent of DDQ (Scheme 45) with total conversion of starting material. Alternatively, dehydrogenation of tetrahydroindenof[1,5]naphthyridine 50 with a ethyl carboxylate group (R = CO₂Et) was performed by using Mn(AcO)₃ as oxidant in acetic acid at room temperature and the corresponding 7H-indeno[2,1-c][1,5]naphthyridine 51 (R = CO₂Et) was obtained.

On the other hand, dehydrogenation of tetrahydro-2H-indolo[3,2-c][1,5]naphthyridin-2-ones 73a–d previously described (Scheme 19, vide supra) to fused naphthyridinones 178a–d (Scheme 46) proceeded with good yields by refluxing them with selenium oxide in acetic acid for 15–36 h [18].
As recently described [46], the dehydrogenation of 110 (X = CH₂, Y = NTs) and 111 (X = CO, Y = NTs) with four equivalents of MnO₂ in toluene at 111 °C for 48 h (Scheme 47) led to the corresponding more unsaturated dihydro[1,5]naphthyridines 115 and [1,5]naphthyridin-6(5H)-one derivatives 179 in quantitative yields.

Similarly, the dehydrogenation of tetrahydro-6H-chromeno[4,3-b][1,5]naphthyridines 127 (X = CH₂, Y = O, Scheme 47) and naphthyridin-6-ones 132 (X = CO, Y = O, Scheme 47) with 1 equivalent of DDQ in toluene at 40 °C under microwave irradiation for 2 h would afford chromeno[4,3-b][1,5]naphthyridines 130 and chromeno[4,3-b][1,5]naphthyridin-6-ones 180 (X = CO, Scheme 47) respectively, in quantitative yields [52].

### 3.5. Side Chain Modifications

There are many modifications of functional groups and side chains that can be made in fused 1,5-naphthyridine derivatives, without altering the 1,5-naphthyridine system. For example, with a basic solution of silver oxide at 20 °C for 30 min, a methyl group in 6-methylbenzo[β][1,5]naphthyridine 4 can be oxidized to the formyl group or the carboxyl group (Scheme 48) to get compounds 181 and 182 [4].
Similarly, the nitrile group of benzo[c][1,5]napththyridine-6-carbonitrile 158 can also undergo transformations without any modification occurring in the polycyclic system [56]. Thus, compound 158 is hydrolyzed to the corresponding acid 183 by boiling in aqueous alkali (Scheme 49).

In the industrial preparation of antimalarial drug pyronaridine tetraphosphate 21, the compound 162g previously described (Scheme 39, vide supra) underwent a Mannich reaction with pyrrolidine in the presence of formaldehyde to give pyronaridine 184 (Scheme 50) and the yield increased about 20% [17]. Finally, 184 was treated with phosphoric acid to yield pyronaridine tetraphosphate 21.

The reduction of NO₂ group in 162f (Scheme 39, vide supra) using SnCl₂ as reducing agent (Scheme 51) led to the key intermediate 185 [57]. Then 185 and different aromatic aldehydes 186 were mixed in boiling ethanol affording the target compounds 187 bearing the C=N linkage moiety.
Tridentate ligand 2-(benzo[b][1,5]naphthyridin-2-yl)-6-(quinolin-2-yl)-4-tert-butylpyridine 189 (bnqp, Scheme 52) was synthesized by the Friedländer condensation of equimolar amounts of acetyl compound 9 (abnp) and aromatic α-aminoaldehyde 188 in dry ethanol in the presence of KOH [13].

Scheme 52. Preparation of tridentate ligand bnqp.

For the synthesis of indenyl ligand functionalized with a benzo[b][1,5]naphthyridine unit 192 (Scheme 53) the organosulphide 167 was oxidized to the sulfoxide 190 by using one equivalent of m-chloroperbenzoic acid (MCPBA) [58]. The ligand-coupling reaction was carried out using lithium-2-methylindenide (Li-2-MeInd) 191, the 2-methyl substituent being used to raise the barrier to rotation around the heteroaryl–indenyl bond. To isolate the 1-heteroaryl-1H-indene tautomer, the reaction was carried at −110 °C with 1.3 equivalents of 191 (Li-2-MeInd) for only 30 min. Then, the 1-heteroaryl-1H-indene tautomer 192 was isolated (Scheme 53).

Scheme 53. Preparation of the 10-indenylbenzo[b][1,5]naphthyridine ligand.

The presence of hydroxyl groups in the heterocyclic molecules may offer some advantages such as the enhancement of the solubility of such molecules in the physiological media or the formation of hydrogen bonds with the surrounding amino acids present in the target protein. Reaction between 7H-indeno[1,5]naphthyridines 51 with three equivalents of Mn(OAc)₃ in a microwave reactor in acetic acid (Scheme 54) generated indeno[1,5]naphthyridin-7-ones 193 [24]. The results demonstrated that a wide range of substituents with electron-donating and -withdrawing groups participated in this process. After, by the hydride reduction of carbonyl group present in 7H-indeno[1,5]naphthyridine-7-ones 193 with NaBH₄ in methanol at room temperature the corresponding 7H-indeno[2,1-c][1,5]naphthyridin-7-ols 194 were quantitatively obtained (Scheme 54).

Scheme 54. Oxidation and reduction reactions over indeno[1,5]naphthyridines.
To complete the efficient enantioselective total synthesis of the potent antibiotic GSK966587 \( \text{52} \) (Scheme 16, vide supra), diol \( \text{55} \) was first converted to spiro-epoxide \( \text{195} \) (Scheme 55) using \( \text{Et}_3\text{N} \) and perfluorobutanesulfonfonyl fluoride \( \text{[27]} \). After 1 h at room temperature and filtration through silica gel, epoxide \( \text{195} \) was treated with functionalized piperidine \( \text{196} \) (1.5 equivalents) at room temperature for 14 h. Afterwards, GSK966587 \( \text{52} \) precipitated directly from the reaction mixture.

A modification of the above procedure for the total synthesis of \( \text{52} \), the antibiotic GSK966587 \( \text{[28]} \) was the transformation of racemic diol \( \text{55} \) by activation of the primary hydroxyl group as the tosylate using dibutyltin oxide (Scheme 56), reaction with tert-butylicarbamate \( \text{197} \) and displacement with \( \text{N-Boc} \) piperidine to afford the \( \text{N-Boc} \) protected intermediate \( \text{198} \). The free amine \( \text{199} \) was liberated by Boc deprotection and then separated into enantiomers by preparative chiral HPLC. The desired (4S)-enantiomer was placed under reductive alkylation conditions with aldehyde \( \text{200} \) to give \( \text{52} \) (Scheme 56).

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**Scheme 55.** Enantioselective synthesis of the antibiotic GSK966587.

**Scheme 56.** Synthesis of the antibiotic GSK966587 from a racemic diol.
In the last stage of the general synthetic route for preparing 3-methyl-1H-imidazo[4,5-c][1,5]naphthyridin-2(3H)-one 201 (Scheme 57), 1,3-dihydro-2H-imidazo[4,5-c][1,5]naphthyridin-2-ones 71a (Scheme 18, vide supra) were methylated with MeI in the presence of NaOH to give compound 201 [30].

![Scheme 57. N-methylation reaction of 1,3-dihydro-2H-imidazo[4,5-c][1,5]naphthyridin-2-ones.](image)

Recently [46], the deprotection of the tosyl group in compounds 110a–b (R = H, Br) was performed and the corresponding derivatives 202a–b could be isolated when the 5-tosylhexahydroquinolino[4,3-b][1,5]naphthyridines 110a–b were treated with Mg under acidic conditions and sonicated for 8 h (Scheme 58).

![Scheme 58. Tosyl deprotection of 5-tosylhexahydroquinolino[4,3-b][1,5]naphthyridines.](image)

To brominate the alkylated monomer 154 derived of NT with NBS [54], the authors found that slightly elevated temperatures and a catalytic amount of acetic acid were necessary to drive the reaction and to form 203. After purification, 203 was polymerized with 2,5-bis(trimethylstannyl) thiophene to yield 149 (PTNT, Scheme 59).
3.6. Metal Complex Formation

The relative nucleophilicity of the nitrogen atoms of the 1,5-naphthyridine bicyclic system present in the benzo[\(\beta\)][1,5]naphthyridines allows these compounds to be used as ligands in the preparation of Rh, Ru, and Pd complexes. Rhodium complex bearing benzo[\(\beta\)][1,5]naphthyridine derivatives as ligands have been prepared. Thus, reaction of indenyl ligand functionalized with a benzo[\(\beta\)][1,5]naphthyridine 192 (Scheme 54, vide supra) with \([\text{Rh(CO)}_2\text{Cl}_2]\) leads to the product 204 (Scheme 60), which shows only coordination to the N5 atom [58]. Consistent with these data are isomeric structures 204a and 204b where the CO ligands are mutually cis; however, the structures differ from one another through restricted rotation along the Rh-N bond, due to restricted rotation of the coordinated square-planar Rh(CO)_2Cl unit. The peri-H substituents to 5-nitrogen in the benzonaphthyridene unit are presumably responsible for this behavior (Scheme 60).

A rhodium complex \([\text{RhCp^*}(\text{pbn})\text{Cl}]\) 206 (Scheme 61) which has a 2-(2-pyridyl)benzo[\(\beta\)] [1,5]naphthyridine 7 (pbn, Scheme 2, vide supra) and pentamethylcyclopentadienyl (Cp*) ligands, has been synthesized [59]. The complex 206 was prepared by a procedure similar to the synthesis of polypyridyl RhCp*complexes. A mixture of \([\text{RhCp^*Cl}_2]\) 205 and two equivalents of 7 was stirred in EtOH for 1 h to give 206 (Scheme 61).
was treated with two equivalents of AgPF₆ in 2-methoxyethanol, followed by addition of one equivalent of 7 (pbn) to give [Ru(pbn)(bpy)](PF₆)₂ 207 as a red-purple powder [11].

Scheme 61. Formation of a rhodium complex from pbn.

Also, ruthenium complex bearing benzo[β][1,5]napthyridine derivatives as ligands have been prepared. Thus, Ru(pbn)(bpy)₂][PF₆]₂ 207, [pbn=2-(2-pyridyl)benzo[β][1,5]napthyridine, bpy=2,2′-bipyridine; Scheme 62] was synthesized to study its electrochemical behavior. [RuCl₂(bpy)₂] was treated with two equivalents of AgPF₆ in 2-methoxyethanol, followed by addition of one equivalent of Ru(pbn)(bpy)₂][PF₆]₂ 207 as a red-purple powder [11].

Scheme 62. Preparation of heteroleptic pbn–ruthenium complex.

Ruthenium complexes with more than one pbn (pbn = 2-(2-pyridyl)benzo[β][1,5]napthyridine) group have also been synthesized. The ruthenium complexes [Ru(bpy)(pbn)₂][PF₆]₂ 209 (bpy = 2,2-bipyridyne), and [Ru(pbn)₃][PF₆]₂ 210 were synthesized [60] from a Ru complex with two pbn ligands 208 [RuCl₂(pbn)₂] (Scheme 63). Complex 208 was prepared by the reaction of RuCl₃·3H₂O with two equivalents of pbn in the presence of six equivalents of LiCl in DMF. Two chlorides of [RuCl₂(pbn)₂] 208 were removed by treatment with excess amounts of (CH₃)₃O·BF₄ in 1,2-dichloroethane. After the BF₄ anion of the crude product was exchanged with a PF₆ anion, recrystallization of the product from CH₃CN afforded [Ru(pbn)₂(NCCH₃)₂][PF₆]. Addition of one equivalent of bpy and pbn to [Ru(pbn)₂(NCCH₃)₂][PF₆]₂ in 2-methoxyethanol gave [Ru(bpy)(pbn)₂][PF₆]₂ 209 and [Ru(pbn)₃][PF₆]₂ 210, respectively (Scheme 63).

On the other hand, the reaction of Ru(pbn)₂Cl₂ 208 with CO (2 MPa) at 150 °C in H₂O selectively produced [Ru(pbnHH)₂(CO)₂]²⁺ 211 accompanied by only CO₂ evolution, indicating that [Ru(pbn)₂(CO)₂]²⁺ 212 initially formed in the reaction underwent 4H⁺/4e⁻ reduction under the present reaction conditions (Scheme 64) to form [Ru(pbnHH)₂(CO)₂]²⁺ without evolving H₂ [61]. Furthermore, [Ru(pbnHH)₂(CO)₂]²⁺ 211 was quantitatively oxidized to 212 [Ru(pbn)₂(CO)₂]²⁺ with the treatment of two equivalents of 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ). The reversible 4H⁺/4e⁻ redox reaction of the [Ru(pbnHH)₂(CO)₂]²⁺ 211/[Ru(pbn)₂(CO)₂]²⁺ 212 (Scheme 64) couple without accompanying a reductive Ru-CO bond cleavage is attributable to the proton-coupled electron transfer (PCET) function of the pbn ligands.
On the other hand, the reaction of Ru(pbn)2Cl2 with CO (2 MPa) at 150 °C in H2O selectively produced [Ru(pbnHH)2(CO)2]2+ accompanied by only CO2 evolution, indicating that [Ru(pbn)2(CO)2]2+ initially formed in the reaction underwent 4H+/4e− reduction under the present reaction conditions (Scheme 64) to form [Ru(pbnHH)2(CO)2]2+ without evolving H2 [61]. Furthermore, [Ru(pbnHH)2(CO)2]2+ was quantitatively oxidized to [Ru(pbn)2(CO)2]2+ with the treatment of two equivalents of 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ). The reversible 4H+/4e− redox reaction of the [Ru(pbnHH)2(CO)2]2+/[Ru(pbn)2(CO)2]2+ (Scheme 64) couple without accompanying a reductive Ru-CO bond cleavage is attributable to the proton-coupled electron transfer (PCET) function of the pbn ligands.

A four-electron-reduced ruthenium(II) NADH-type complex, [Ru(bbnpH4)(CO)2Cl](PF6)2 has been successfully synthesized by using the ligand 10 bbnp (bbnp = 2,2′-(4-(tert-butyl)pyridine-2,6-diyl)bis(benzo[b][1,5]naphthyridine)) and [Ru(CO)2Cl2] (Scheme 65) under moderate WGSR conditions (water-gas-shift reaction conditions) in a 1:1 ratio in a 2-methoxyethanol/water mixture (9:1 v/v) and CO pressure: 2.0 MPa, temperature: 140 °C [62].

In a similar way, synthesis of (Scheme 66) involved three simple steps starting from Ru(tpy)Cl3 [63]. Conversion from [Ru(tpy)(pbn)Cl]+ to [Ru(tpy)(pbnHH)(CO)]2+ took place via decarboxylation process under water-gas shift reaction (WGSR) conditions (Scheme 66). [Ru(tpy)(pbnHH)(CO)]2+ was quantitatively oxidized to [Ru(tpy)(pbn)(CO)]2+ (Scheme 66) with the treatment of one equivalent of DDQ.

Scheme 63. Syntheses of pbn–ruthenium complexes.

Scheme 64. Reversible 4H+/4e− redox reactions of the pbn–ruthenium complexes.
A four-electron-reduced ruthenium(II) NADH-type complex, [Ru(bbnp\(\text{H}_4\))(CO)\(_2\)Cl](PF\(_6\)) 213 [Scheme 65, bbnp\(\text{H}_4\) = 2,2'-(4-(tert-butyl)pyridine-2,6-diyl)bis(5,10-dihydrobenzo[\(b\]][1,5]napthyridine)] has been successfully synthesized by using the ligand 10 bbnp (bbnp = 2,2'-(4-(tert-butyl)pyridine-2,6-diyl)bis(benzo[\(b\]][1,5]napthyridine)) and [Ru(CO)\(_2\)Cl\(_2\)] (Scheme 65) under moderate WGSR conditions (water-gas-shift reaction conditions) in a 1:1 ratio in a 2-methoxyethanol/water mixture (9:1 v/v) and CO pressure: 2.0 MPa, temperature: 140 °C [62].

[Scheme 65. Preparation of a four-electron-reduced ruthenium(II) NADH-type complex.]

In a similar way, synthesis of 216 (Scheme 66) involved three simple steps starting from Ru(ppy)Cl\(_3\) [63]. Conversion from 214 [Ru(ppy)(pbn)Cl]\(^+\) to [Ru(ppy)(pbnHH)(CO)]\(^{2+}\) 215 took place via decarboxylation process under water-gas shift reaction (WGSR) conditions (Scheme 66). [Ru(ppy)(pbnHH)(CO)]\(^{2+}\) 215 was quantitatively oxidized to [Ru(ppy)(pbn)(CO)]\(^{2+}\) 216 (Scheme 66) with the treatment of one equivalent of DDQ.

[Scheme 66. Preparation and subsequent transformations of pbn–ruthenium complexes.]
Benzo[6][1,5]naphthyridine derivatives have been used also as ligands in palladium complexes. The palladium(II) complexes having the ligands, [PdCl(bnqp)][PF$_6$] 217 and [PdCl(bbnp)][PF$_6$] 218 (Scheme 67), were prepared by the reaction of equimolar amounts of the corresponding ligands 189 (bnqp) and 10 (bbnp) and [PdCl(CH$_3$CN)$_3$][PF$_6$], generated in acetonitrile solution by the treatment of [PdCl$_2$(CH$_3$CN)$_2$] with AgPF$_6$ [13]. Substitution of ligand Cl by CH$_3$CN was not observed under the reaction conditions, and 217 and 218 were isolated in good yields as hexafluorophosphate salts.

Scheme 67. Formation of bnqp- and bbnp-palladium complexes.

4. Biological Activity of Fused 1,5-Naphthyridines

In the last decade, complex heterocyclic systems containing 1,5-naphthyridines fragments have been synthesized, their reactions have been investigated, and the possibility of their use for the preparation of biologically active compounds have been studied extensively. For example, derivatives of annulated benzoindolo[1,5]naphthyridines attempting to improve memory were described, and these are benzo[b][1,5]naphthyridines which are analogs of inhibitors of neurokinin NK1-receptors [4].

The bromodomain and extra C-terminal (BET) domain family of bromodomains (BRDs) consists of four proteins, each containing two discrete bromodomain “reader” modules which recognize the ε-N-acetylation state of specific lysine residues found within histone tails and other proteins [64]. New naphthyridine analogues were synthesized and tested on BET family bromodomains [31]. Compounds 1H-imidazo[4,5-c][1,5]naphthyridin-2(3H)-ones 71b (Scheme 18, vide supra) that possess an isoxazole substituent have as potent inhibitors of the BET bromodomain family with good cell activity and oral pharmacokinetic parameters. Profiling was carried out against the three BET subtypes, as well as in peripheral blood mononuclear cells (PBMCs), where inhibition of cytokine IL-6 was measured after a lipopolysaccharide (LPS) challenge. The fused indenone naphthyridines were more or less equipotent with BRD2, BRD3, BRD4 and PBMC values of pIC$_{50}$ between 6.1 and 6.8. The best results of pIC$_{50}$ were for compounds 71bd and 71be (Figure 7).
Benzo[b][1,5]naphthyridine derivatives have been shown to be topoisomerase I (TopI) inhibitors. Compound 162b (7-chloro-2-methoxy-N-(p-tolyl)benzo[b][1,5]naphthyridin-10-amine, Figure 8) was found to display good cytotoxicity and can bind with calf thymus DNA (ct DNA). A relaxation assay indicated that 162b inhibits TopI activity at 100 μM [16]. Compound 162b with methyl substitute at the para-position on the aniline ring displayed good antiproliferative activity with IC₅₀ values of 15.9 and 18.9 μM against K562 and HepG-2 cells respectively in vitro. The ability of compound 162b to interact with ct DNA indicated that nuclear enzymes involved in DNA processing such as TopI might be inhibited. These data suggest that 162b might exert antiproliferative activity through TopI inhibition, and it may be a potential lead compound for the development of benzo[b][1,5]naphthyridines as TopI inhibitors.

In general, 7H-indeno[2,1-c][1,5]naphthyridines 50 and 51 (Scheme 15, vide supra), and novel 7H-indeno[2,1-c][1,5]naphthyridine-7-ones 193 and 7H-indeno[2,1-c][1,5]naphthyridine-7-ols 194 (Scheme 45, vide supra) exhibited inhibitory effects against TopI mediated relaxation comparable to those observed for the natural inhibitor, camptothecin (CPT). All the prepared derivatives were further subjected to evaluation of their therapeutic efficacy against three different human cancer cell lines: breast (BT20), lung adenocarcinoma (A549), and ovarian carcinoma (SKOV3). These preliminary studies revealed that some of newly synthesized compounds exhibited a significant antiproliferative activity. Indeno[1,5]naphthyridine derivative 51g (Figure 9) showed a high cytotoxic effect in vitro against A549 cell line proliferation with an IC₅₀ of 2.9 ± 0.9 μM. Some of the fluorinated derivatives were the most cytotoxic, showing good enzyme inhibition and relatively low IC₅₀ values. It is worth noting that indeno[1,5]naphthyridine 51d (Figure 9) showed a very high inhibition of TopI activity and the highest cytotoxic effect, with an IC₅₀ of 1.7 ± 0.1 μM, against the A549 cell line in vitro. The interesting biochemical and biological features found for these derivatives provide a promising basis for further development of biologically active fused naphthyridines [25].
The interesting biochemical and biological features found for the above derivatives provide a promising basis for further development of biologically active fused naphthyridines. Thus, tetrahydro[1,5]naphthyridine derivatives fused with heterocycles, such as chromenes 127 and chromen-2-ones 132 and the corresponding tetracyclic chromeno[4,3-b][1,5]naphthyridine 130 derivatives and/or chromeno[4,3-b][1,5]naphthyridin-6-ones 180 (Scheme 47, vide supra), showed activity as inhibitors of TopI [52]. Additionally, the cytotoxic behavior of these compounds has been studied in A549 and SKOV3 cell lines and on noncancerous lung fibroblasts cell line (MRC-5) where, on the last ones, the absence of cytotoxicity was observed.

7-Phenyl-6H-6a,7,12,12a-tetrahydrochromeno[4,3-b][1,5]naphthyridine 127a (Figure 10) showed excellent cytotoxic activity with an IC\textsubscript{50} value of 1.03 ± 0.30 µM against the A549 cell line and an IC\textsubscript{50} value of 1.75 ± 0.20 µM against the SKOV3 cell line. The obtained results point to these compounds as good antiproliferative candidates.

Topoisomerase I enzymatic inhibition of hybrid quinolino[4,3-b][1,5]naphthyridines 110 and 115 (Scheme 47, vide supra) and quinolino[4,3-b][1,5]naphthyridin-6(5H)-ones 111 and 179 (Scheme 47, vide supra) was investigated [46]. The new polycyclic products show excellent-good activity as TopI inhibitors that lead to TopI induced nicking of plasmids. This is consistent with the compounds acting as TopI poisons resulting in the accumulation of trapped cleavage complexes in the DNA. The cytotoxic effect on cell lines A549, SKOV3, and on non-cancerous MRC-5 was also screened. Tetrahydroquinolino[4,3-b][1,5]naphthyridin-6(5H)-one 179 (Figure 11) resulted the most cytotoxic compound with IC\textsubscript{50} values of 3.25 ± 0.91 µM and 2.08 ± 1.89 µM against the A549 cell line and the SKOV3 cell line, respectively. Moreover, 5-tosylhexahydroquinolino[4,3-b][1,5]naphthyridine 110a and 5-tosyldihydroquinolino[4,3-b][1,5]naphthyridine 115a (R\textsuperscript{1} = H) demonstrated to be cytotoxic with IC\textsubscript{50} values of 7.25 ± 0.81 µM and 7.34 ± 0.17 µM against the A549 cell line, respectively, and with IC\textsubscript{50} values of 8.08 ± 1.39 µM and 8.65 ± 0.57 µM against the SKOV3 cell line, respectively. None of the compounds had cytotoxic effects against non-malignant pulmonary fibroblasts (MRC-5).
The compounds showed good potency against Gram-positive and Gram-negative pathogens [28]. The antitumor activity of fused 1,5-naphthyridines derivatives is closely connected with the intercalation characteristic of many planar ionisable systems. 2-[(Alkylamino)alkyl]-9-methoxy-5-nitro-2,6-dihydroindazolo[4,3-bc][1,5]naphthyridines 94 (Scheme 24, vide supra) represent a new class of aza-acridine derivatives which have noticeable antitumor properties [15]. With enhanced DNA affinity and similar in vitro cytotoxic activity in respect to reference compound (pyrazinamide) PZA, but specially, with a capacity to induce oligonucleosomal DNA fragmentation and apoptotic cell death, not present in PZA. In particular the 9-methoxy-5-nitro-2-[2-(tetrahydro-1H-1-pyrrrolyl)]ethyl]-2,6-dihydroindazolo[4,3-bc][1,5]naphthyridine 94d, which possesses the most relevant biological characteristics in the series, can be regarded as a new lead in the field of potential anticancer derivatives (Figure 13). Thus, the ability of this compound to early induce oligonucleosomal DNA fragmentation and apoptotic cell death of the hormone-refractory PC-3 prostate cancer cells may be particularly relevant to overcoming drug resistance or sensitize tumor cells to the effects of other antineoplastic agents.

![Figure 11](image1.jpg)

**Figure 11.** Cytotoxic activity of 110a, 115a, and 179 on A549 and SKOV3 cell lines.

Novel 4,5-dihydro-6λ4-pyrrolo[3,2,1-ij][1,5]naphthyridine hydroxy-derivatives including 52 GSK966587 (Figure 12) have been discovered as inhibitors of bacterial type IIA topoisomerases. The compounds showed good potency against Gram-positive and Gram-negative pathogens [28]. The hERG inhibition of the compounds described was generally related to their lipophilicity and basicity and several compounds within this series were identified with hERG inhibition (Figure 12).

![Figure 12](image2.jpg)

**Figure 12.** Inhibition of 52 on hERG.
To search for a structurally differentiated backup candidate to PF-04691502 (Figure 14), which is currently in phase I/II clinical trials for treating solid tumors, a lead optimization effort was carried out with a tricyclic imidazo[1,5]naphthyridine series. Integration of a structure-based drug design and physical properties-based optimization (Scheme 18, vide supra) yielded PF-04979064, a potent and selective PI3K/mTOR dual kinase inhibitor [30].

![Figure 14. PI3K/mTOR dual kinase inhibition of PF-04979064.](image)

The manuscript discusses the lead optimization for the tricyclic series, which both improved the in vitro potency and addresses a number of absorption, distribution, metabolism, excretion and toxicity (ADMET) properties including high metabolic clearance mediated by both P450 and aldehyde oxidase (AO), poor permeability, and poor solubility. An empirical scaling tool was developed to predict human clearance from in vitro human liver S9 assay data for tricyclic derivatives that were AO substrates.

11,12-Dihydroimidazo[1,2-a]naphtho[1,2-g][1,5]naphthyridine 65 and 7,8-dihydroimidazo [1,2-a]naphtho[2,1-g][1,5]naphthyridine 66 (Scheme 17, vide supra) exhibited in vitro activity comparable to anticancer agent such as amsacrine [29]. Their mechanism of cytotoxicity action was unrelated to poisoning or inhibiting abilities against TopI. On the contrary, must be highlighted a direct intercalation of the drug into DNA by electrophoresis on agarose gel. The tumor cell growth inhibition was assessed on HT-1080 (fibrosarcoma), HT-29 (colon carcinoma), M-21 (skin melanoma), and MCF-7 (breast carcinoma) cells. Compounds 65 and 66 exhibited good values of GI50 ranging from 2.2 to 52 μM (Figure 15). Compound 66 seems to exhibit some specificity towards breast-derived cells such as MCF-7 where it showed a GI50 at least fourfold higher than in any other tumor cell lines (Figure 15).
A library of dimeric benzo[b][1,5]naphthyridines 164 (Figure 16) was synthesized to explore the effect of structurally diverse linkers on PrP\textsuperscript{Sc} replication in scrapie-infected neuroblastoma cells [4]. The data suggest that bis-acridine analogs may provide a potent alternative to the acridine-based compound quinacrine which is currently under clinical evaluation for the treatment of prion disease.

Pyronaridine, 4-((7-chloro-2-methoxybenzo[b][1,5]naphthyridin-10-yl)amino)-2,6-bis(pyrrolidin-1-ylmethyl)phenol 21 (Figure 17), a new Mannich base, schizontocide, originally developed in China and structurally related to the aminoacridine drug quinacrine, is currently undergoing clinical testing. Pyronaridine targets hematin, as demonstrated by its ability to inhibit in vitro β-hematin formation (at a concentration equal to that of chloroquine), to form a complex with hematin with a stoichiometry of 1:2, to enhance hematin-induced red blood cell lysis (but at 1/100 of the chloroquine concentration), and to inhibit glutathione dependent degradation of hematin. Pyronaridine exerted this mechanism of action in situ, based on growth studies of \textit{Plasmodium falciparum} K1 in culture [65].
The inhibition of leishmania (LTopIB) and human TopIB (HTopIB) of tetrahydroindeno[1, 5]naphthyridines 50 and indeno[1,5]naphthyridines 51 (Scheme 15, vide supra) were studied and their antileishmanial activity on promastigotes and amastigote-infected splenocytes of *Leishmania infantum* were evaluated [25]. Some of the prepared heterocycles showed selective inhibition of LTopIB, while no inhibition of HTopIB was observed at evaluated conditions. In addition, the cytotoxic effects of newly synthesized compounds were assessed on host murine splenocytes in order to calculate the corresponding selective indexes (SI). Tetrahydro indeno[1,5]naphthyridines 50e and 50h (Figure 18) showed good antileishmanial activity (IC₅₀ values of 0.67 ± 0.06 and 0.54 ± 0.17 μM) with similar activity than the standard drug amphotericin B (0.32 ± 0.05 μM) and even tetrahydro indeno[1,5]naphthyridine 50b showed higher (SI) towards *L. Infantum* amastigotes. Likewise, in the family of indeno[1,5]naphthyridines 51, compound 51b (Figure 18) showed good antileishmanial activity (IC₅₀ value 0.74 ± 0.08 μM) and higher selective index towards *L. Infantum* amastigotes than amphotericin.

The anti-intestinal nematode activities against *Nippostrongylus brazilliensis* of a series of benzonaphthyridine derivatives bearing the C=N linkage moiety 187 (Scheme 51, vide supra) were evaluated in vivo by an oral route in male rats [37]. Some of compounds showed significant anti-intestinal nematode activity in a two-day in vivo test in rats. Among these compounds, at concentrations of 10 mg/kg of rat, the compound 7-chloro-2-methoxy-10-(4′-(1H-indol-5′-yl)methylene)aminophenyl)-amino-benzo[b][1,5]naphthyridine 187n (Figure 19) produced the highest activity against *Nippostrongylus brazilliensis*, with 80.3% deparasitization. These compounds may find usefulness in the discovery and development of new anti-intestinal drugs.
Figure 19. Activity of 187n against *Nippostrongylus brazilliensis*.

The dimeric indole alkaloid cimiciduphytine 219 (Figure 20) containing the [1,5]naphthyridine fragment and derivatives of eburnane alkaloids 220 (Figure 20) exhibiting hypotensive and pain-relieving activities have been isolated from naturally occurring sources [4]. These compounds are suitable for the treatment of cerebral circulation disturbance.

![Chemical structure of 187n](image)

Figure 19. Activity of 187n against *Nippostrongylus brazilliensis*.

5. Other Applications of Fused 1,5-Naphthyridines

In biological reactions, on the other hand, the NAD+/NADH redox couple, in which the oxidized form (NAD+) with a pyridinium structure is reversibly converted into the reduced form (NADH) with two electrons and one proton, plays a key role in reversible hydride transfer reactions. Transition-metal complexes operating in the same way as the NAD+/NADH system have been reported. Many of these systems present in their structure model ligands that include benzo[b][1,5]naphthyridin-2-yl groups. The electrochemical reduction of 206 (Scheme 68) under aqueous acidic conditions induces formation of the hydrogenated product [Ru(pbnH2)(bpy)2](PF6)2 [11]. The electrochemical reduction of acetone to generate 2-propanol by using complex 206 as a precatalyst with two electrons and H2O as a proton source was described. The key points of this catalytic system are “hydride” generation and transfer, similar to the function of the NAD+/NADH redox couple. Clear evidence of the photochemical and radiolytic formation of 221 with H+ have been reported in Reference [66]. The mechanistic pathways of formation of the NADH-like [Ru(bpy)2(pbnHH)]2+ species from [Ru(bpy)2(pbn)]2+ were studied in an aqueous medium [67] and D2O [68] showing is controlled by the pH of the solution.

![Chemical structures 219 and 220](image)

Figure 20. Fused 1,5-naphthyridines with hypotensive and pain-relieving activities.

\[ R^1 = H; R^2 = H, CO_2Me, CO_2Et, CH_2OH \]
\[ R^1-R^2 = O; R^3 = H, Cl, NO_2 \]
process to construct a catalytic system that has the ability to catalyze multi-electron reduction of CO\(_2\)pyridine moiety in the pbn ligands played a key role in controlling photo-induced NAD\(^+/\)NADH.

Reduction of CO\(_2\)innovative function, since they are widely used as catalysts in photo- and electrochemical reduction of CO\(_2\) alleviate the global crisis caused by depletion of fossil fuels and the rising atmospheric concentration of reduction of carbon dioxide (CO\(_2\) to produce CO, HCOOH, alcohols, etc., have been pursued to

The use of the multielectron redox reactions of mononuclear metal complexes under visible light irradiation is a fascinating approach to harvesting solar energy. The photoinduced four- and six-electron reduction of [Ru(bpy)(pbn)\(_2\)](PF\(_6\))\(_2\) \(209\) and [Ru(pbn)\(_3\)](PF\(_6\))\(_2\) \(210\) (Figure 21), with two and three pbn ligands, respectively, under irradiation with visible light (\(l > 420\) nm) conducted in dry CH\(_3\)CN/TEA (4:1, \(v/v\)) resulted in only one-electron reduction of these complexes to give \((209)^+\) and \((210)^+\). The high-efficiency storage of photoinduced two-, four-, and six-electron reducing equivalents in \(207\) (Scheme 68, vide supra), \(209\) and \(210\), respectively, using the NAD\(^+\) analogous pbn ligands may provide a new pathway for multiple electron and proton transfer to reaction sites under illumination with visible light [60].

On the other hand, on study demonstrated that the introduction of a methyl group of the pyridine moiety in the pbn ligands played a key role in controlling photo-induced NAD\(^+/\)NADH.

The design and synthesis of new catalysts having a capability for photo- and electro-chemical reduction of carbon dioxide (CO\(_2\)) to produce CO, HCOOH, alcohols, etc., have been pursued to alleviate the global crisis caused by depletion of fossil fuels and the rising atmospheric concentration of CO\(_2\). Among the various catalysts, ruthenium complexes may be viable candidates to realize such an innovative function, since they are widely used as catalysts in photo- and electrochemical reduction of CO\(_2\) as well as a variety of organic syntheses. The development of a renewable hydride donor is a key process to construct a catalytic system that has the ability to catalyze multi-electron reduction of CO\(_2\). Reduction of CO\(_2\) using the renewable hydride donor embarks on a new stage of the construction of a sustainable society [70].
An addition of a base to Ru-pbnHH greatly enhanced the hydride donor ability, since [Ru(bpy)2(pbnHH)]2+ reacted with CO2 in the presence of PhCOO− to give HCOO− with regeneration of 207 [Ru(bpy)2(pbn)]2+ [71]. [Ru(bpy)2(pbnHH)]2+ 212 was mixed with PhCOO− at −40 °C under CO2 (Scheme 69, R = Ph). The ESI-MS and 1H NMR spectra of the reaction mixture at that temperature displayed 1:1 adduct formation between PhCOO− and [Ru(bpy)2(pbnHH)]2+ 222a (Scheme 69, R = Ph). The association constant (Ka) was 7.8 × 10^4 M−1.

![Scheme 69. Photo- and electrochemical reduction of CO2 with bpn–ruthenium complexes.](image)

A drastic difference in the organic hydride transfer reaction converting CO2 to HCO2− using the ruthenium complex containing the NADH model ligand 212 (Scheme 69) was observed by changing the base to either acetate anion (MeCOO−, Scheme 69, R = Me) or trifluoroacetate anion (CF3COO−, Scheme 70, R = CF3) [72]. The study demonstrated that the choice of the base plays a key role in the CO2 reduction system utilizing 212 through the association of the base to the NH moiety of the NADH model ligand pbnHH (Scheme 69); the difference in basicity between MeCOO− and CF3COO− led to notable accelerating and decelerating effects on the rate of the organic hydride transfer reaction as compared to PhCOO−.

In this context, the electrochemical reduction of CO2 using the catalytic performance of Ru-NAD-type complexes [Ru(tpy)(pbn)(CO)]2+ 216; tpy = 2,2,6,2-terpyridine; pbn = 2-(pyridin-2-yl)benzo[8][1,5]naphthyridine and the Ru-CO-bridged metallacycle 223 was investigated in H2O/CH3CN at room temperature [73]. A controlled-potential electrolysis of 216 and 223 afforded formate (HCOO−) as the main product, under concomitant formation of minor amounts of CO and H2 (Scheme 70).
PTNT (poly[thiophene-2,5-diyl-alt-5,10-bis((2-hexyldecyl)oxy)dithieno[3,2-c:3′,2′-h][1,5]-naphthyridine-2,7-diyl]) \(149\) consists of a tetracyclic fused lactim ring (see Figure 22) that offers many favorable properties, such as improved solid-state packing, high charge carrier mobility, and moderate photoluminescence quantum yields (PLQYs), required for fast optoelectronics. Photophysical properties of PTNT were explored in solution and thin film. Thus, a new strategy to improve the speed of organic light-emitting diodes (OLEDs) using a new class of luminescent polymer with high charge carrier mobilities has been demonstrated\(^\text{[74]}\). Aqueous nanoparticle dispersions were prepared from PTNT and fullerene blend utilizing chloroform as well as a non-chlorinated and environmentally benign solvent, \(o\)-xylene, as the miniemulsion dispersed phase solvent. The nanoparticles (NPs) in the solid-state film were found to coalesce and offer a smooth surface topography upon thermal annealing\(^\text{[75]}\). Recently, PTNT-conjugated polymer was used as the donor polymer. The preparation of environmentally friendlier polymer solar cell devices\(^\text{[76,77]}\).

\[
\text{HCOD}^+ + \text{CO} \quad \text{225} \quad + \quad \text{e}^- \quad \text{H}_2\text{O}/\text{CH}_3\text{CN} \quad (1/13) \quad \text{231} \quad \text{HCOD}^- + \text{CO} \quad \text{Scheme 70.} \quad \text{Electrochemical reduction of CO}_2 \text{ using bpn–ruthenium–NAD-type complexes.}
\]

The indeno[2,1-c][1,5]naphthyridine-7-one \(193\) (Figure 23), which has a 2-naphthyl group, has been used as an optical DNA biosensor to unravel the inhibitory mechanism of human topoisomerase I activity by blocking enzyme—DNA dissociation\(^\text{[78]}\). This represents the first characterized example of a small molecule drug that inhibits a post-ligation step of catalysis.

\[
\text{Figure 22.} \quad \text{Fused 1,5-naphthyridine with OLED properties.}
\]

\[
\text{Figure 23.} \quad \text{Fused 1,5-naphthyridine as optical DNA biosensor.}
\]
The dimmer 98 is quite electron-rich owing to the presence of a 1,2-diaminoethene bridge and is oxidized back to 97 (Scheme 71) within several hours in solution under ambient conditions. Furthermore, 97 possesses a redox-active 1,4-diazabutadiene linkage that is interconvertible with its reduced 1,2-diaminoethene linkage upon treatment of 97 with NaBH4 or PbO2. The dimmer 97 exhibits an intense NIR absorption and narrow HOMO-LUMO gap with a remarkably low reduction potential mainly due to the effective bonding interactions in the LUMO through the 1,4-diazabutadiene linkage. In contrast, the reduced dimmer 98 has high HOMO energy and shows a relative large HOMO-LUMO gap compared to that of 97 [39].

![Scheme 71. Redox system of 1,5-naphthyridine-fused porphyrin dimers.](image)

A highly selective and sensitive acridine-base colorimetric sensor 2-((7-chloro-2-methoxybenzo[b][1,5]naphthyridine-10-yl)amino)phenol 224 (NAP, Figure 24) was developed for detection of Cu2+ ions both in aqueous solution and on test papers. Sensor NAP responses to Cu2+ ions by changing its color from yellow to pink, which could be easily observed by the naked eyes [79].

![Figure 24. Fused 1,5-naphthyridine as colorimetric sensor for detection of Cu2+ ions.](image)

6. Conclusions

The contributions published in the last 18 years related to the synthesis and reactivity of the fused 1,5-naphthyridine derivatives were analyzed. According to the data presented, these types of fused heterocycles have attracted great interest, not only for synthetic but also for medicinal chemists.

Some fused 1,5-naphthyridines presented in this review show important biological activity as enzymatic inhibitors with antiproliferative, antiparasitic and antibacterial capacities. Likewise, some polycyclic 1,5-naphthyridines has also been reported as a biological sensor for many techniques. Moreover, some fused heterocycles show applications as light-emitting compounds, CO2 reductors, and hydride donors.

In this sense, this revision could be useful to synthetic and medicinal chemists because of the information related to the synthesis and biological activity of fused 1,5-naphthyridines and, on the other hand, by taking advantage of the electronic and optical properties of the described heterocycles, progress could be made in the development of new technologies.

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