organics

MDPI

Review

Synthetic Pathways to Pyrido[3,4-*c*]pyridazines and Their Polycyclic Derivatives

Temitayo Omowumi Alegbejo Price [1,2], Flavio da Silva Emery [1] and Wim Dehaen [2,*]

[1] Department of Pharmaceutical Sciences, School of Pharmaceutical Sciences at Ribeirao Preto, University of Sao Paulo, Ribeirao Preto 14040-903, SP, Brazil
[2] Department of Chemistry, KU Leuven, Celestijnenlaan 200F, 3001 Leuven, Belgium
* Correspondence: wim.dehaen@kuleuven.be

Abstract: Pyrido[3,4-*c*]pyridazines are nitrogen-containing scaffolds that have been described as being promising in medicinal chemistry, but they are rather rare chemicals. In this review article, the literature on synthetic pathways towards pyrido[3,4-*c*]pyridazines is listed exhaustively, first with the bicyclic systems themselves that are obtained starting either from pyridines, pyridazines or other heterocycles. Then, the reports on the related tricyclic derivatives are discussed, again according to the source heterocycle, and finally we mention some examples on polycyclic systems.

Keywords: pyrido[3,4-*c*]pyridazines; heterocycle; pyridopyridazine; pyridine; bispyridopyridazine

check for updates

Citation: Alegbejo Price, T.O.; Emery, F.d.S.; Dehaen, W. Synthetic Pathways to Pyrido[3,4-*c*]pyridazines and Their Polycyclic Derivatives. *Organics* **2022**, *3*, 430–445. https://doi.org/10.3390/org3040028

Academic Editor: David StC Black

Received: 31 August 2022
Accepted: 10 October 2022
Published: 18 October 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

Nitrogen-containing heterocycles play an important role in nature [1] and are also part of the structure of many small molecule drugs. A 2014 study estimated that 59% of the FDA-approved drugs had a nitrogen-containing ring in their structure [2]. However, among those drugs there are clearly much more of the "common" monoheterocycles such as the six-membered pyridine, piperidine and piperazine, or five-membered thiazole, pyrrolidine and imidazoles. Bicyclic structures are somewhat less popular, and in those cephem, penam, indoles and benzimidazoles constitute the majority. Clearly, medicinal chemists have in the past mainly relied on only a few well-known heterocyclic building blocks. W. R. Pitt et al., in "heteroaromatic molecules of the future", referred to a virtual list of unexplored chemicals selected on synthetic tractability [3]. These 22 bicyclic molecules all had at least one nitrogen in their structure. Among those molecules, one was a derivative of the pyrido[3,4-*c*]pyridazine 1, the 6-oxo-derivative 2. The synthesis of differently fused pyridopyridazine isomers 1, 3–8 (Figure 1) has been previously reviewed [4], but specific derivatives of 1 or 2 were only briefly mentioned in these texts. In a 2019 follow-up article on the "heteroaromatic molecules of the future", the literature of 2009–2019 was reviewed [5] and indeed synthetic chemists had risen to the challenge, with reports appearing on 15 of the 22 aforementioned heteroaromatic molecules, but notably the pyridopyrazidinone 2 was not among these, although there had been two theoretical studies on this scaffold [6,7] concerning enhanced inhibition of cytochrome P450s and hydrogen bonding accepting properties, respectively.

With this short review we hope to increase the interest in the heterocycle 1 and its derivatives by exhaustively summarizing synthetic efforts so far. Earlier reviews on "pyridopyridazines" [5,8,9] focus on the other isomers and have mentioned almost nothing on the title subject. As far as we know, this is the first dedicated effort of bringing together all literature on the synthesis of pyrido[3,4-*c*]pyridazine 1. At the same time, we will also have a detailed look at the related tricyclic and polycyclic analogs of this bicyclic system. Where appropriate, we will also mention any biological properties of the different compounds synthetized.

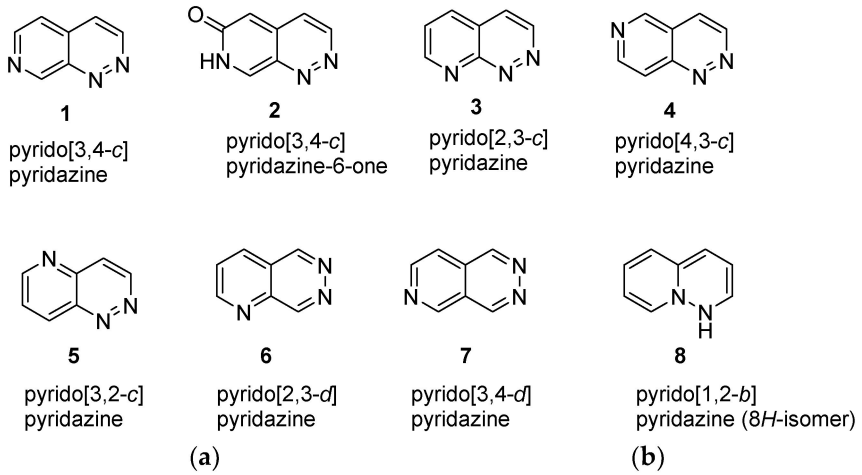


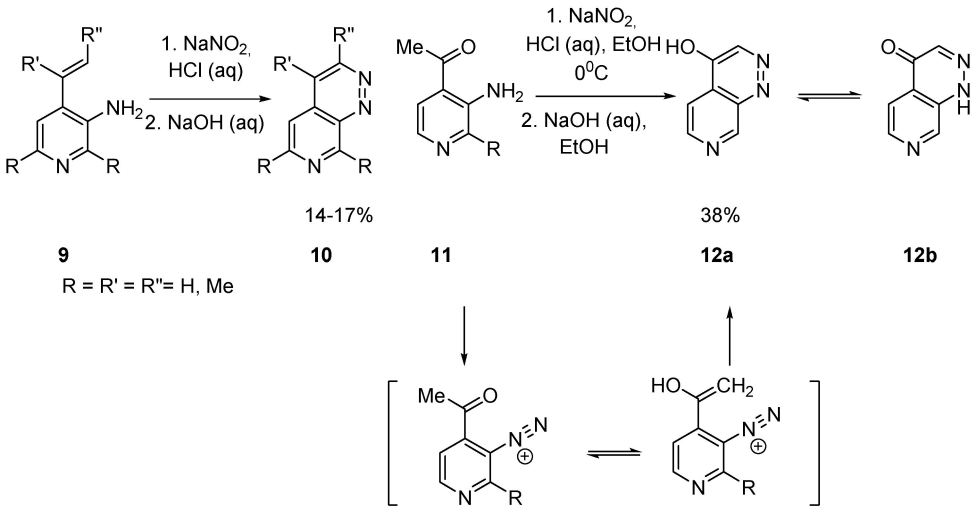
Figure 1. Pyrido[3,4-*c*]pyridazine **1**, oxo derivative **2** and isomers **3**–**8**.

2. Discussion

2.1. Bicyclic Pyrido[3,4-c]pyridazine Derivatives

2.1.1. Starting from Pyridine Derivatives

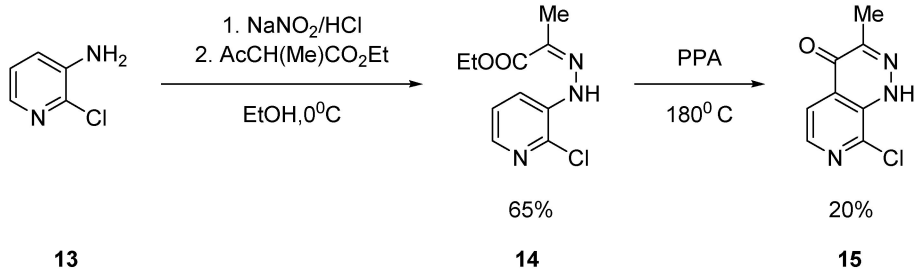
One of the earliest procedures towards pyrido[3,4-*c*]pyridazines led to the synthesis of **10**, named 1,2,7-triazanaphthalenes [10], which was based on the Widman-Stoermer cinnoline synthesis, involving a one- pot diazotisation/cyclization sequence of 4-propenyl-3-aminopyridines **9**. Unfortunately, only a low yield of **10** (14–17%) was obtained after chromatography. In a later effort [11], the same strategy was applied to obtain the corresponding pyrido[3,4-*c*]pyridazine-4-one **12b** from 4-acetyl-3-aminopyridine **11**. This Borsche reaction probably involves the electron rich enol form of the acetyl substituent, to afford (38% yield) a tautomeric equilibrium mixture of **12a,b**. This molecule was referred to as a 7-azacinnolin-4(1*H*)-one. The tautomerism of compound **12** was studied in detail with ^{1}H, ^{13}C and ^{15}N NMR spectroscopy, concluding that the main isomer is indeed **12b** in polar solvents such as deuterated DMSO, methanol and water (Scheme 1). Further examples of pyridopyridazinone analogs of **12** prepared by Borsche cyclization of acyl substituted pyridines have been described in the patent literature [12].



Scheme 1. Widman-Stoermer synthesis of pyrido[3,4-*c*]pyridazine derivatives.

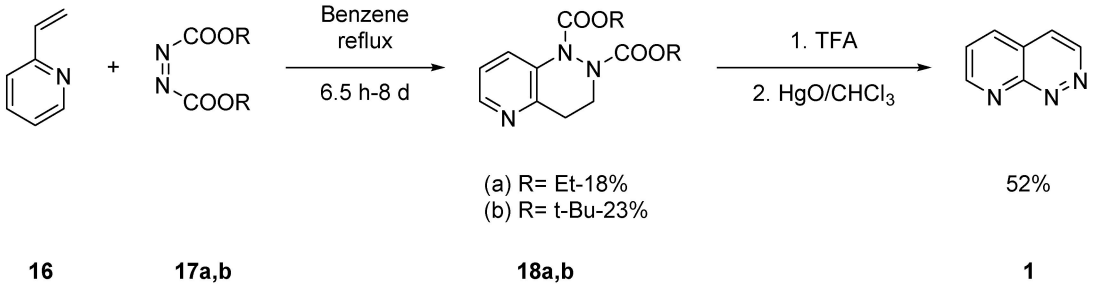
The Japp-Klingemann approach was also used to synthesize 3,8-disubstituted pyridopyridazinone from the reaction with 2-chloro-3-aminopyridine **13**. The corresponding diazonium salt of **9** is combined with Ethyl-2-methyl-acetoacetate to afford the hydrazone

14, which was then cyclized in polyphosphoric acid to give a low yield of the 8-chloro-3-methyl-pyridopyridazine-4-one **15**, which was described as the 4-hydroxy tautomer [13], although probably based on the later study [10] on the analog **12**, the structure should be reassigned as the keto tautomer **15** (Scheme 2).



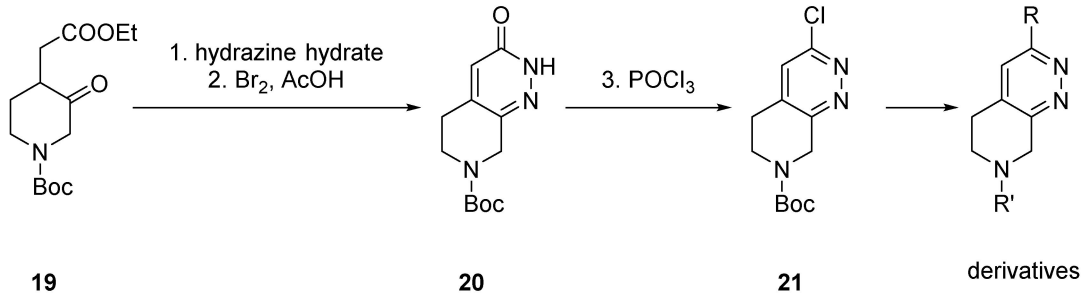
Scheme 2. Synthesis of pyridopyrazin-8-one by acid-catalyzed cyclization of hydrazone.

A Hetero-Diels-Alder cycloaddition reaction of 2-vinylpyridines and electron poor azo derivatives was studied by Gurnos et al. [14,15] as an entry into different pyridopyrimidine isomers, including the pyrido[3,4-*c*]pyrimidine. 2-Vinylpyridine **16** and azodicarboxylates **17** (R = Et, *t*-Bu) to afford the tetrahydropyridopyrimidines **18** (16% yield for R = *t*-Bu), that are subsequently deprotected (R = *t*-Bu) with trifluoroacetic acid (TFA) and oxidized with red mercuric oxide, with a 52% yield for the two final steps leading to the parent compound **1**. The cycloaddition reaction is incomplete and possibly polymerization of **16** occurs, explaining the low yield in the first step (Scheme 3).



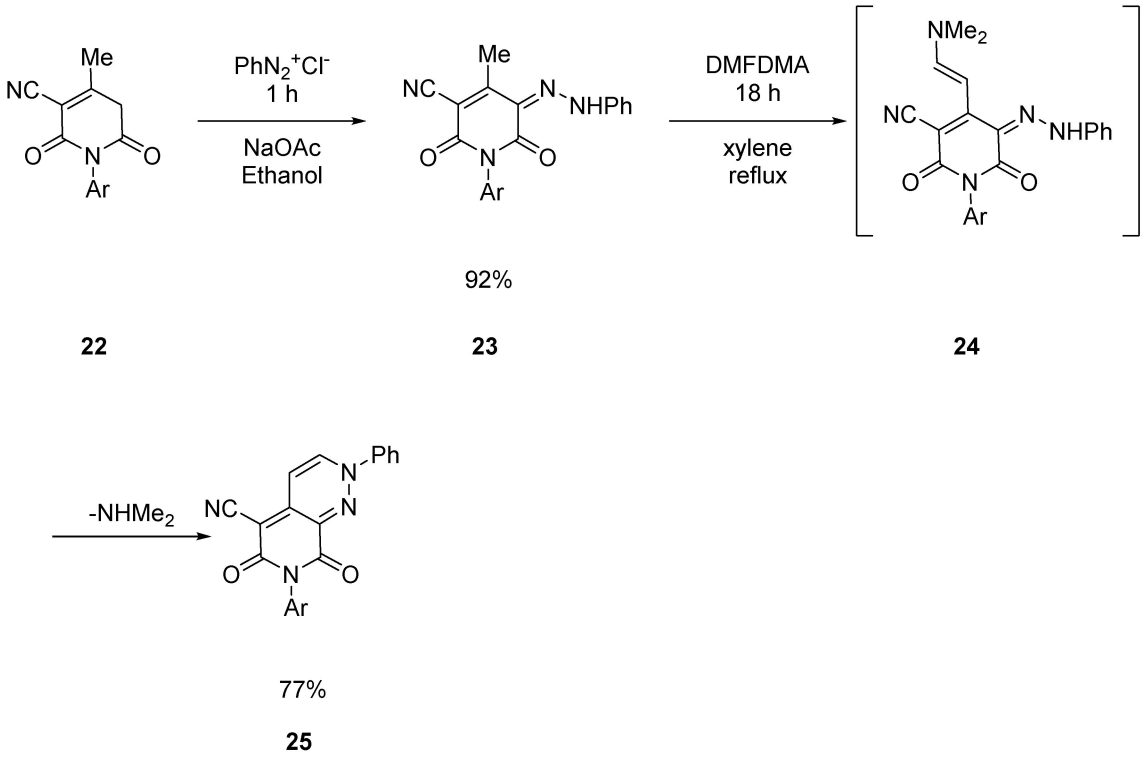
Scheme 3. The parent pyrido[3,4-*c*]pyridazine by cycloaddition/deprotection/oxidation.

Starting from N-protected 3-pyridone-4-acetate derivative **19** [16,17] after condensation with hydrazine and oxidation with bromine in acetic acid, the tetrahydropyridopyridazinone **20** is obtained. The latter can then be chlorinated with phosphoryl chloride to the chloro derivative **21**, which is used as a convenient building block for further derivatization at the piperidine nitrogen (after deprotection) and/or after reaction of the reactive chlorine, e.g., amine substitutions, and Suzuki arylation (Scheme 4). We do not describe these reactions in detail as they are no longer ring forming reactions but rather standard derivatizations. These derivatives constitute the largest and most studied library of pyridopyridazine analogs in the literature. Different biological properties of these compounds were investigated, including inhibitors of the dipeptidyl peptidase-IV enzyme useful in the treatment of type 2 diabetes [18], histamine H3 receptor binders with CNS activity [16], kinase inhibitors [19], gamma-aminobutyric acid A receptor subunit alpha 5 ($GABA_A$ α5) positive allosteric modulators [20] or sphingosine-1-phosphate (S1P) inhibitor activity [21].



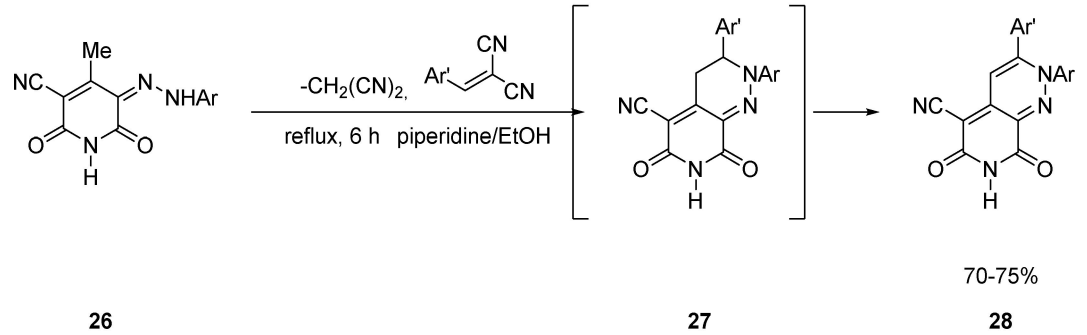
Scheme 4. 5,6,7,8-Tetrahydro derivatives of pyridopyridazines from 3-piperidones.

The 4-methyl-3-cyano-pyridine-2,6-diones **22** are easily available from the condensation reaction of acetoacetate esters and N-arylcyanoacetamide. Azo coupling with phenyldiazonium salt then gave the hydrazone **23**. The latter underwent a one-pot conversion with dimethyl formamide dimethylacetal (DMFDMA) to an enamine **24**, followed by cyclocondensation with evolution of dimethylamine, affording the 6,8-dione derivative **25**. The reaction takes place either in xylene at reflux (77% yield) or solventless after microwave irradiation (no yield given, Scheme 5) [22].



Scheme 5. 5-Cyano derivatives of pyridopyridazine-6,8-diones.

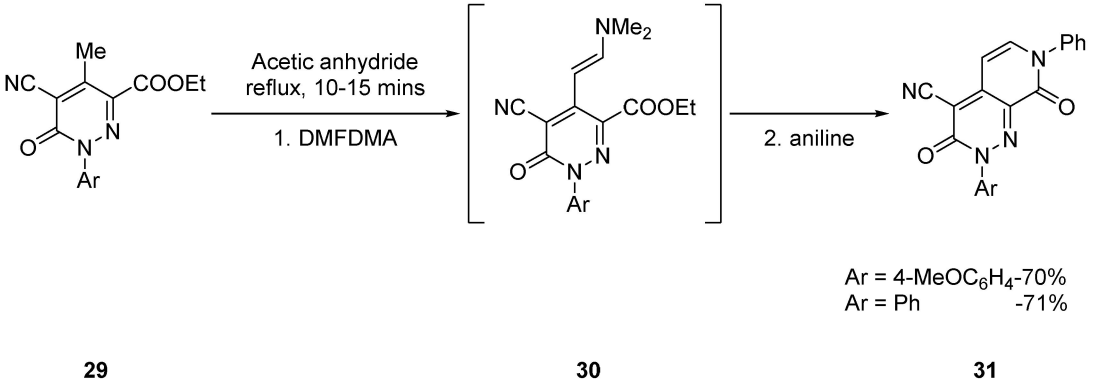
The N-unsubstituted pyridinedione derivatives **26** were condensed with arylidenemalononitrile in the presence of piperidine base in ethanol solvent at reflux. After the Michael addition of the deprotonated methyl to the electron poor alkene, malononitrile is eliminated by intramolecular substitution. The intermediate 3,4-dihydro compounds **27** are aromatized in situ to the final products 28 (6 examples, 70–75% yield) by ambient oxygen (Scheme 6) [23,24]. A similar entry to analogs of **28** (6-C(CN)2 instead of 6-oxo) by Knoevenagel condensation of 4-methyl-6-dicyanomethylpyridones with aromatic aldehydes was reported [25].



Scheme 6. Synthesis of pyridopyridazine-6,8-diones from arylidene-malononitrile and N-substituted pyrimidinedione.

2.1.2. Starting from Pyridazine Derivatives

Pyridopyridazine-3,8-dione **31** was prepared from 4-methyl pyridazine-6-one **29** [26] by a strategy involving condensation of the methyl group with DMFDMA, followed by treatment of enamine intermediate **30** with aniline. On the other hand, the condensation of the 4-ethyl analog of **29** with DMFDMA and subsequent hydrolysis gave ring closure involving the 5-cyano group or the hydrolyzed carboxamide, giving access to isomeric pyrido[3,4-*d*]pyridazinone derivatives (Scheme 7).



Scheme 7. Synthesis of pyrido[3,4-*c*]pyridazine-3,8-dione.

Several variants on this condensation/cyclization strategy starting from pyridazinones have been reported [27–29], leading to different pyridopyridazinedione derivatives **32**–**34** (Figure 2). Compounds **32a,b** were obtained in poor yield (around 10%) from the condensation of 2-(arylhydrazono) -3-oxobutyrates with two equivalents of ethyl cyanoacetate. Pyridazinones analogous to **29a,b** (Ar = 3,4-dimethylphenyl or 3-chloro-4-methylphenyl) were the main isolated products (70% yield), but also the intermediates towards **32a,b**, via an aldol-type of condensation of **29** to a second equivalent of the hydrazine and cyclization were obtained. The structure of **32a,b** was confirmed by an extensive NMR study [27]. Condensation of **29** (Ar = 4-methylphenyl) with triethyl orthoformate and 4-methylaniline in the presence of piperidine gave further analogs of **31**, while condensation of enamine **30** (piperidine instead of dimethylamino) with hydrazine gave the 7-amino derivative **33** [28]. The hydrazones derived from aromatic aldehydes and the carbohydrazide derivative of 29 (Ar = 4-MeOC$_6$H$_5$) were involved in a Knoevenagel condensation/cyclization, affording hydrazones **34** with different combinations of the two aryl groups Ar′ and Ar″ [1997PSS]. Further examples of analogues of **31**–**34** prepared similarly from derivatives of **29** have been reported in the literature [30–32].

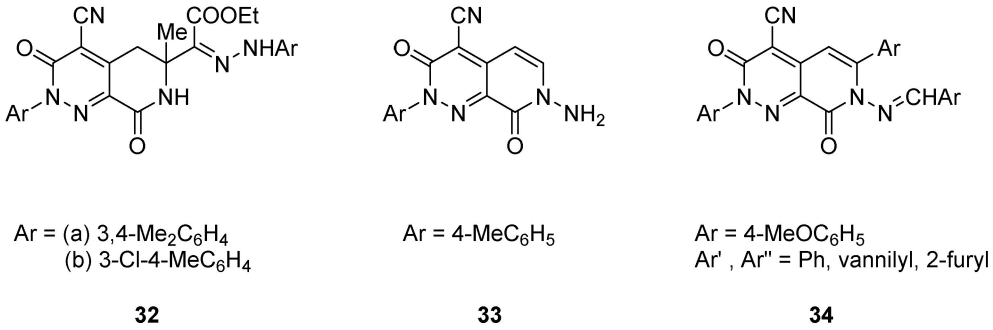
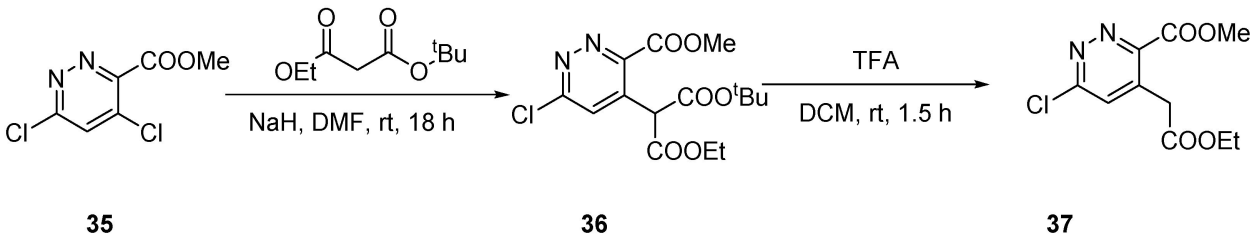
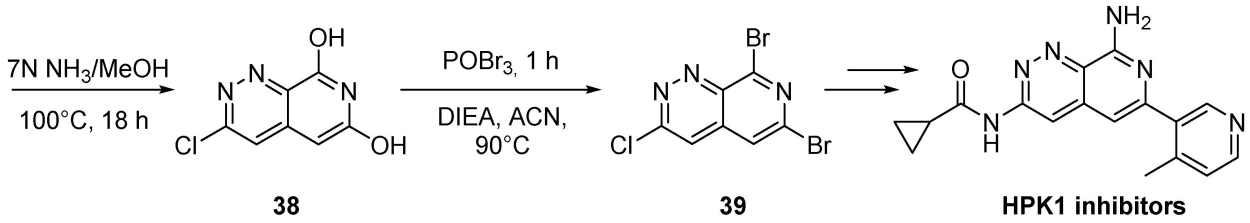


Figure 2. Miscellaneous pyridopyridazine-3,8-dione derivatives.

The 4,6-dichloropyridazine-3-carboxylate **35** could be converted via regioselective nucleophilic substitution at the 4-position with t-butyl ethyl malonate and acid-catalyzed decarboxylation of intermediate **36** to the diester **37**. Subsequent cyclocondensation of **37** with ammonia in methanol lead to the dihydroxypyridopyridazine **38**. This compound was brominated to a trishalogenated pyridopyridazine derivative **39**, which then was converted in a number of synthetic steps, involving nucleophilic substitutions at positions 3 and 8 (reactivity towards nitrogen nucleophiles apparently selective in this order) and then Suzuki arylation on the remaining 6-bromide (Scheme 8). The final compounds were tested as HPK1 inhibitors, of interest in the treatment of certain cancers [33].

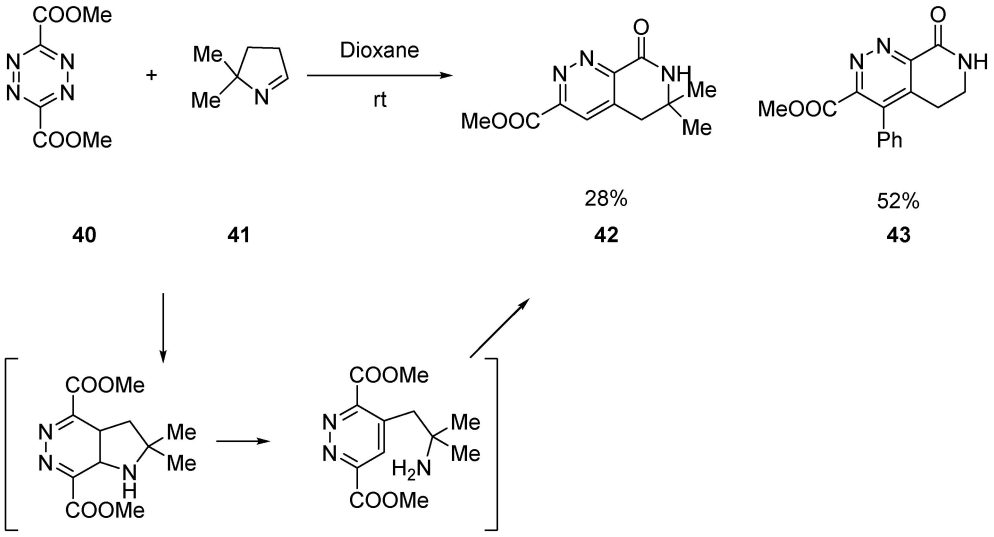




Scheme 8. Synthesis of 3-chloro-6,8-dibromopyridopyridazine.

2.1.3. Starting from Other Building Blocks

Hetero Diels-Alder cycloaddition of 1,2,4,5-tetrazine-3,6vdicarboxylate **40** with the enamine tautomers of cyclic imines such as 5,5-dimethylpyrroline **41** led to fused pyridazine **42** (28% yield) via non-isolable cycloadducts that extruded dinitrogen, then underwent aromatization with liberation of the amine that then formed a lactam with one of the two esters. Likewise, pyridazine **43** was formed in a 52% yield from 2-phenylpyrroline (Scheme 9) [34].

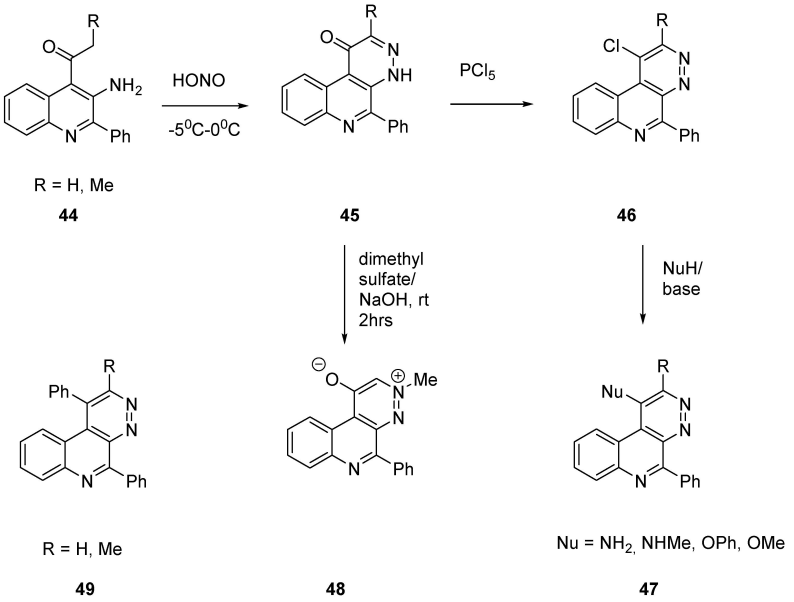


Scheme 9. From tetrazines to pyridopyridazines.

2.2. Tricyclic Derivatives

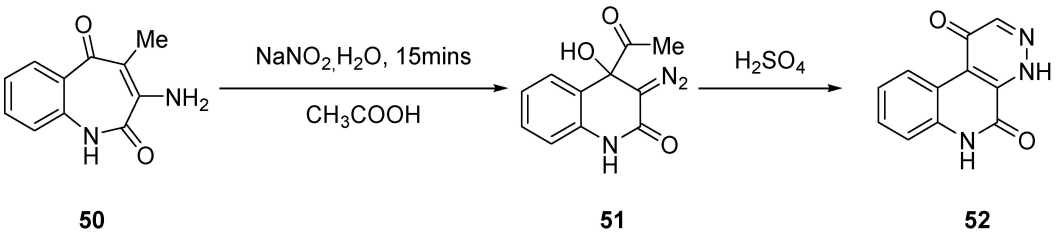
2.2.1. Benzo Fused Tricyclic Derivatives Starting from Quinolines

4-Acetyl-3-amino-2-phenylquinoline **44** (R = H) was diazotized with nitrous acid and ring closed in alkaline medium, forming the pyridazino[3,4-*c*]quinoline named 4-hydroxy-10-phenyl-1,2,9-triazaphenanthrene by the authors (more probable the oxo tautomer **45** shown). The Borsche reaction product **45** was obtained in 80% yield on a 10 g scale by precipitation from the reaction mixture. Chlorination of **45** with phosphorous pentachloride gave the chloro derivative **46**, which could then be converted to a number of derivatives **47** by nucleophilic substitution [35,36]. Some of the above reactions were also carried out on the 4-propionyl derivative **44** (R = Me). Methylation of the compound **45** occurred regioselectively on one of the pyrazine nitrogens, affording a zwitterionic pyridazinoquinoline **48**. Widman-Stoermer reaction starting from 4-alkenyl-3-aminoquinoline substrates as shown before for the synthesis of bicyclic pyridopyridazines **10** analogously gave the tricyclic derivatives **49**, in low to good yields [10] (Scheme 10).



Scheme 10. Borsche and Widman-Stoermer reactions leading to pyridazinoquinoline derivatives.

Starting from the 3-aminobenzazepine-2,5-dione derivative **50**, nitrosation was accompanied by a ring contraction, leading to diazo compound **51**, which in acidic medium underwent a Borsche-like cyclization to form tricyclic pyrazinoquinolinedione derivative **52** in almost quantitative yield. However, there seems to be only this one example in the literature of this interesting transformation [37] (Scheme 11).

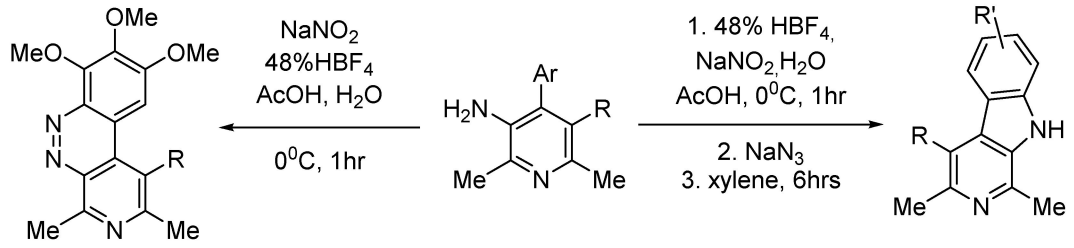


50 **51** **52**

Scheme 11. Pyridazinoquinolines via diazotation, ring contraction and cyclization.

2.2.2. Benzo Fused Tricyclic Derivatives Starting from Pyridines

Diazotation of 4-aryl-3-aminopyridine derivatives **53** resulted in intramolecular electrophilic substitution of the very electron rich 3,4,5-trimethoxyphenyl substituent to afford the tricyclic pyrido[3,4-*c*]cinnolines **54** in 64–84% yield, similar to the Widman-Stoermer approach whereas for other less electron rich aryl groups the diazonium salt can be used without such cyclization to prepared azides, that then were thermolysed in xylene to carboline derivatives **55** (Scheme 12) [38].



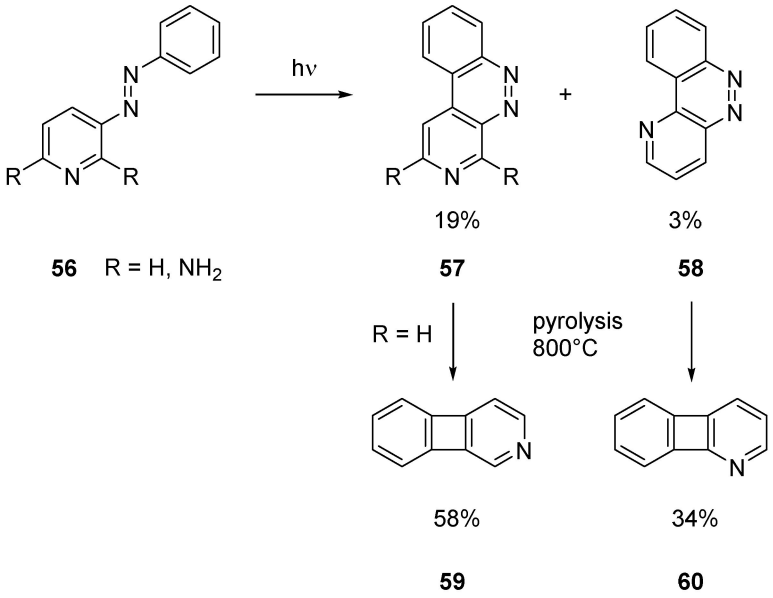
R = COOMe 84%, CN 64%
Ar =3,4,5-MeO-C_6H_2

63-90%

54 **53** **55**

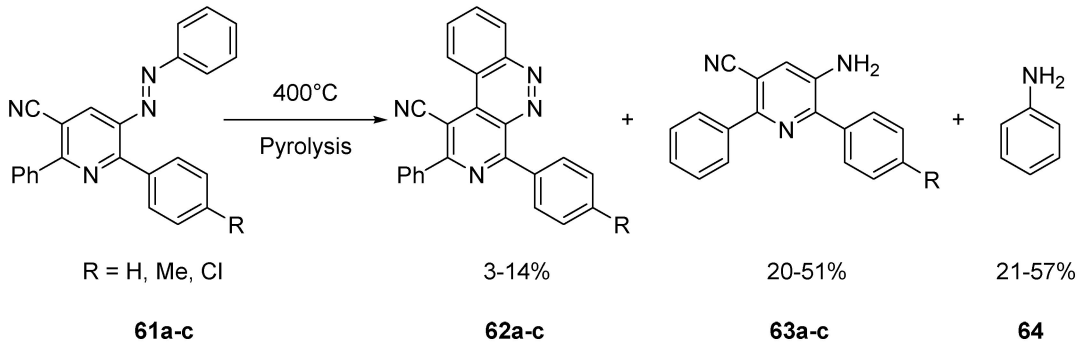
Scheme 12. Cyclization of diazonium salts to pyridocinnolines.

Photocyclization of 3-phenylazopyridine **56** (R=H) in concentrated sulfuric acid by irradiation at 400–450 nm gave a low yield (19%) of the pyrido[3,4-*c*]cinnoline **57**, together with an even smaller amount of the [3,2-*c*] fused isomer **58**. Both isomers were subjected to vacuum pyrolysis at 800 °C, giving the respective azabiphenylenes **59** (58%) and **60** (34%) after dinitrogen extrusion [39]. In a later study, the hydrochloride salt of the diamino analog of **56** (R = NH_2) was irradiated with a 400 W medium pressure mercury vapor lamp in a dilute methanol solution, affording 35% of the product **57** (R = NH_2), together with small amounts of several products resulting from N-N cleavage [40] (Scheme 13).



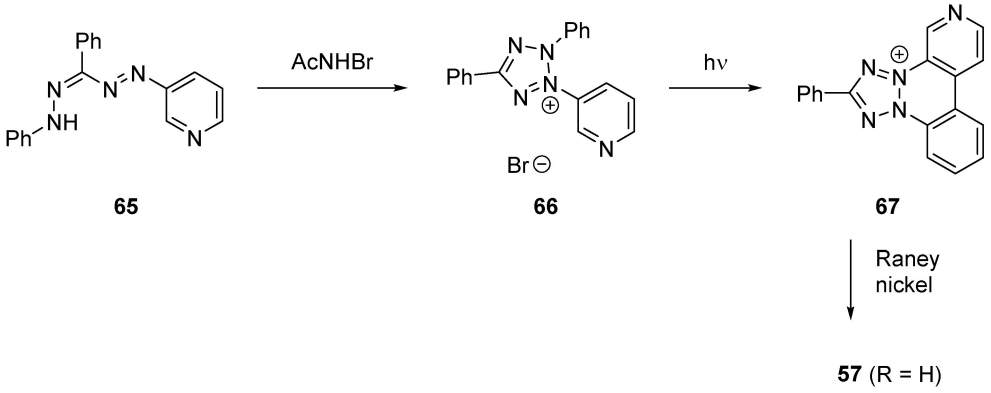
Scheme 13. Pyridocinnolines by photocyclization.

Static pyrolysis of 2,6-diaryl-3-cyano-5-phenylazopyridine **61a–c** at 400 °C gave low yields of pyridocinnolines **62a–c** (3–14%) next to N-N reduction products **63a–c** (20–51%) and aniline **64** (21–57%) (Scheme 14) [41].



Scheme 14. Pyridocinnolines by static pyrolysis.

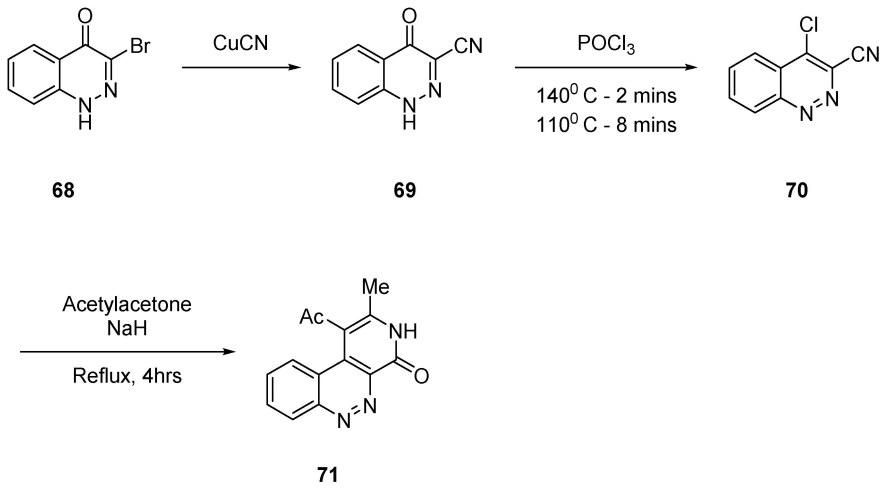
In an early study, formazan **65** was oxidized to a tetrazolium salt **66**, which upon irradiation with an ultraviolet high pressure immersion lamp PL 313 at 25° cyclized to the fused tetrazolium salt **67**. The reduction in the latter gave the parent pyridocinnoline **57** (R = H) [42] (Scheme 15).



Scheme 15. Synthesis of pyridocinnoline by reduction in tetrazolium salt.

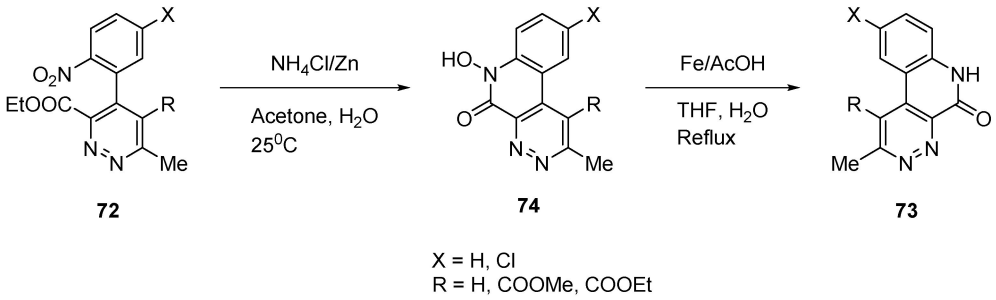
2.2.3. Benzo Fused Tricyclic Derivatives Starting from Cinnolines, Pyridazines or Tetrazines

Moreover, 3-Bromocinnoline-4-one **68** could be substituted with copper cyanide to the nitrile **69**, and the latter was chlorinated to 4-chloro-3-cyanocinnoline **70**. Nucleophilic aromatic substitution of **70** with acetylacetone, and base-catalysed hydrolysis to the amide and ring closure then gave the pyridocinnolinone **71** in a 38% yield [43] (Scheme 16).



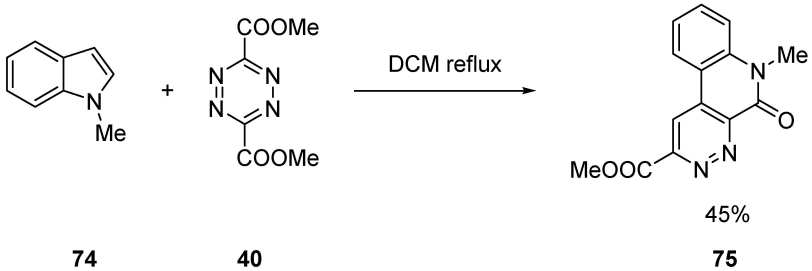
Scheme 16. Benzofused tricyclic derivatives from cinnolines.

Reductive cyclization of 4-(2-nitrophenyl) -pyridazine-3-carboxylate esters **72** with iron in acetic acid gave the lactams **73**. However, when the reduction was carried out with zinc and ammonium chloride, the hydroxamic acid derivative **74** was isolated. (Scheme 17). The inhibition of soybean 5-lipoxygenase was tested for the latter compounds and found to be only weak [44,45].



Scheme 17. Reductive cyclization leading to pyridazoquinolinones.

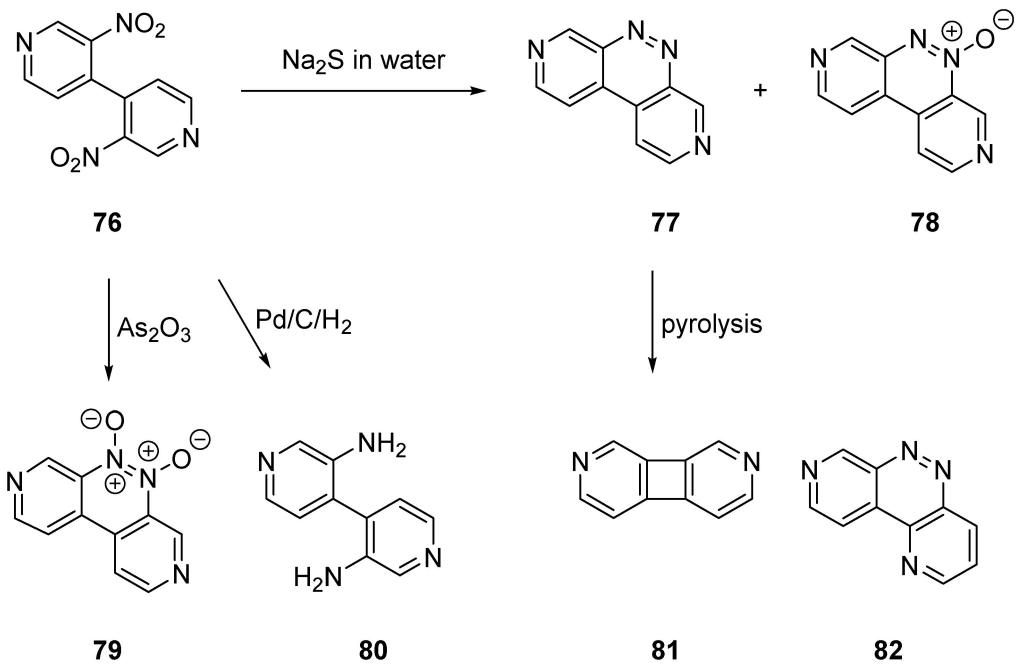
Inverse Diels-Alder reaction of N-methylindole **74** with 1,2,4,5-tetrazine-3,6-d-carboxylate **40** in dichloromethane at reflux gave after nitrogen extrusion a ring opening/ring closure sequence, giving another entry into pyridazoquinolones **75**. [46] (Scheme 18). The reaction was also carried out on 2,2′-bis-N-methylindolyl, affording protein kinase C inhibitors [47].



Scheme 18. Inverse Diels-Alder reaction leading to pyridazoquinolinones.

2.2.4. Heterocycle Fused Tricyclic Derivatives

Reduction of 2,2′-dinitro-4,4′-bipyridyl **76** with sodium sulfide initially led to a 3:1 mixture of bispyridopyridazine **77** (59% yield) and its *N*-oxide **78**. The latter could be deoxygenated with iron at 250 °C. [48] The reduction with sodium sulfide could be optimized later to give 89% of only **77**. Reduction of **76** with arsenious oxide gave the *N*, *N*′-oxide **79**, whereas the Pd/C catalyzed hydrogenation gave the diamine **80** [49]. The bispyridopyridazine **77** was used in these and many subsequent studies for the synthesis of 2,7-diazabiphenylene **81** in a 57% yield [50] by extrusion of nitrogen under different vacuum pyrolysis conditions. The bispyridopyridazine **77** can also be prepared from diamine **80** by diazotation in a 38% yield [51]. The reaction sequence in Scheme 19 was also used to prepared unsymmetrically fused bispyridopyridazine **82** by reductive cyclization of the corresponding ortho, ortho′-dinitro-2,4′-bipyridine [52].



Scheme 19. Synthesis of Bispyridopyridazines.

Widman-Stoermer type cyclization of 3-pyridyldiazonium salts involving the electrophilic substitution of electron rich five membered rings placed at the 4-position, similar to Scheme 12, was carried out successfully, affording different pyridopyridazines fused with thiophens (**83**, 85% yield and **84**, 72% yield), pyrroles (**85**, 77% yield) and furans (**86**, 76% yield) [53,54] (Figure 3).

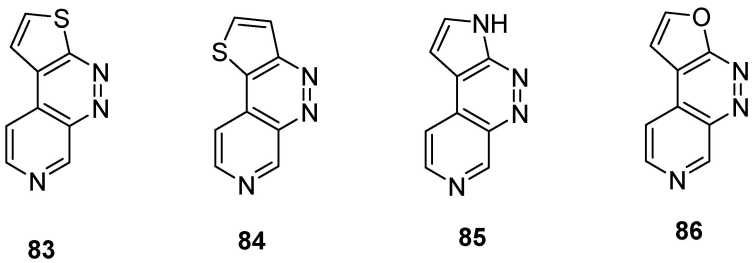
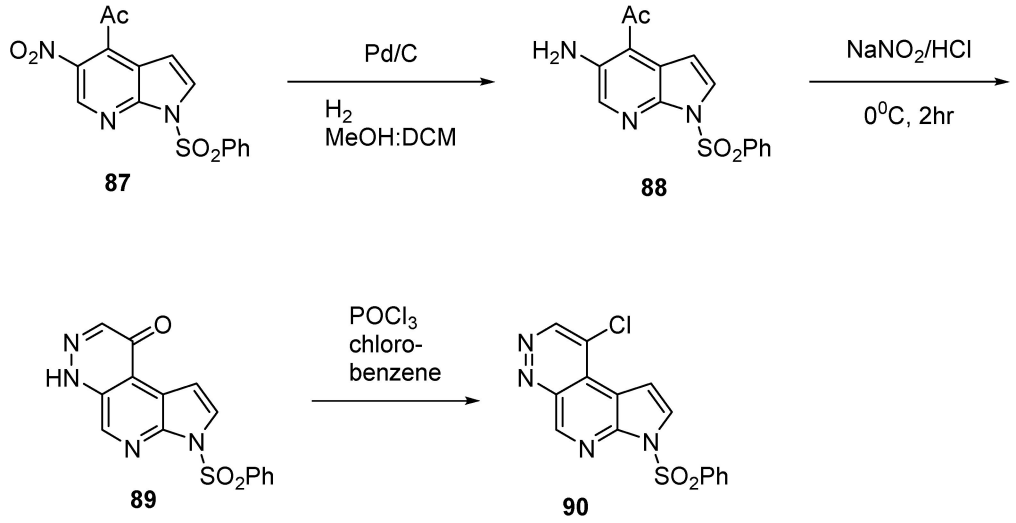


Figure 3. Pyridopyridazines fused with five-membered rings.

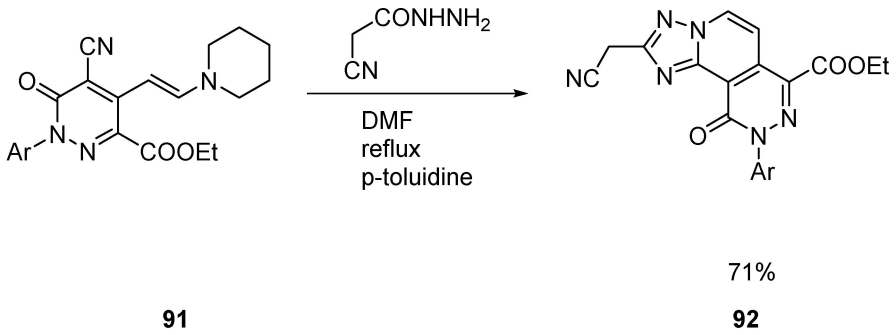
An isomeric pyrrolo fused pyridopyridazine **89** was prepared by reducing 5-nitro-4-acetyl-8-azaindole **87** and applying the Borsche cinnoline reaction on the obtained amine **88** after nitrosation and cyclization. Chlorination of 88 with phosphoryl chloride in chloroben-

zene gave the building clock **90**, that was used in a study of treatment of diseases that are mediated by JAK activity [55] (Scheme 20).



Scheme 20. Pyrrolo fused pyridopyridazine.

A 1,2,4-triazolo fused pyridopyridazine has been reported. The enamine **91**, prepared from **29** (Ar = 4-Me-phenyl) by condensation with triethyl orthoformate and piperidine, was condensed with 2-cyanoacetohydrazide by heating at reflux in dimethyl formamide solution, to afford tricyclic **92** in a 71% yield [28] (Scheme 21).

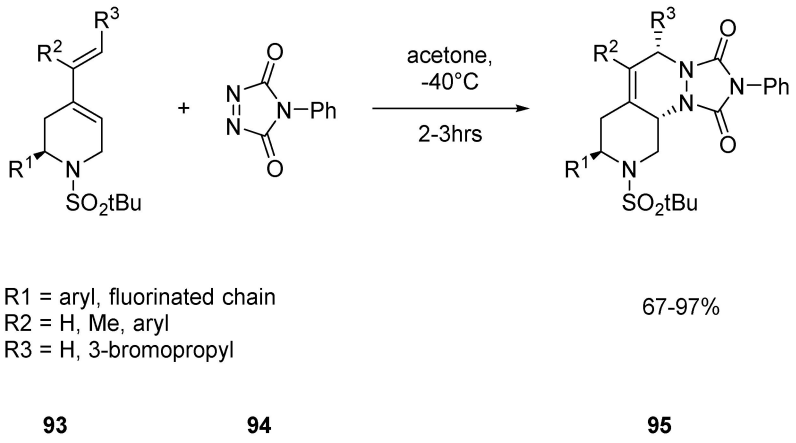


91 **92**

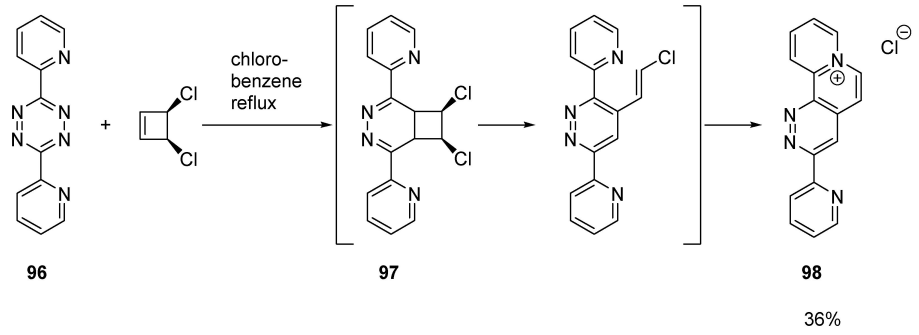
Scheme 21. 1,2,4-Triazolo fused pyridopyridazine.

An interesting diastereoselective synthesis of partially reduced triazoledione fused pyridopyridazines **95** was reported by Diels-Alder cycloaddition of 4-vinyl-1,2,5,6-tetrahydropyridine dienes **93** with *N*-phenyl-1,2,4-triazoledione dienophile **94**. The reactions proceeded within a few hours at low temperature with good to excellent chemical yields (7 examples, 67–97%) and very good diastereoselectivities (>20:1) [56] (Scheme 22).

A special case of a pyridine fused pyridopyridazine salt **98**, called the 8a-azonia-3,4-diazaphenanthrene cation by the authors, was available in a 36% yield as the only product obtained after hetero- Diels-Alder cycloaddition of 3,6-(2-pyridyl)-1,2,4,5-tetrazine **96** with *cis*-3,4-dichlorocyclobutene. The expected product **97** was not isolated, but under the reaction circumstances it is probable that ring opening of cyclobutyl/ring closure involving pyridine nitrogen occurs, finally affording **98**. The structure of the salt **98** was proven unambiguously by single crystal X-ray crystallographic analysis [57] (Scheme 23).



Scheme 22. Triazolo fused (reduced)pyridopyridazines by Diels-Alder reaction.



Scheme 23. Pyridine fused pyridopyridazine salt.

2.3. Polycyclic Derivatives

Pentacyclic analogs **99** or their N-oxide analogs could be prepared from bis(nitroquinolines) similarly to the chemistry in Scheme 19 [48]. Thermolysis of **99** led to the condensed derivative **100** [49]. In a series of publications, thebaine or other morphinanediene derivatives were combined in a room temperature Diels-Alder reaction with diazodicarboxylate, triazole dione or other cyclic diazo dienophiles, to afford diverse complex polycyclic derivatives **101** that strictly speaking contain a reduced pyridopyridazine but are somewhat out of the scope of this review. A β-face attack of the dienophile occurs in the case of the natural products containing a furan ring, whereas the derivatives with opened furan favor α-attack [58–61]. No biological properties seem to have been reported for these compounds (Figure 4).

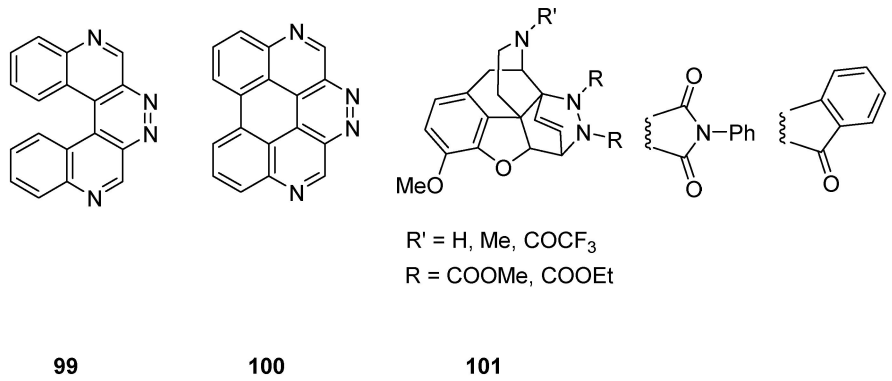


Figure 4. Different polycyclic pyridopyridazine derivatives.

3. Conclusions

The pyrido[3,4-*c*]pyridazines and their fused derivatives remain rare chemicals and the reports that have appeared so far are widely scattered, with often only a few examples given in low or only fair yield without any follow-up studies to widen the scope. Therefore, applications of this scaffold as biologically active compounds have been limited. To make further advances and to realize the recognized potential of this moiety in medical chemistry, more attention should be given in the future to apply new advances in organic synthesis, including transition metal catalyzed reactions, as well as organocatalytic, photocatalytic and electrocatalytic processes. We hope to meet this challenge in following reports of our laboratories; it was also our aim to have stimulated further research by our colleagues in the field of heterocyclic and medicinal chemistry.

Author Contributions: Conceptualization, W.D.; writing—original draft preparation, **W.D. and T.O.A.P.**; writing—review and editing, W.D. and F.d.S.E.; funding acquisition, W.D. and F.d.S.E. All authors have read and agreed to the published version of the manuscript.

Funding: The authors would like to acknowledge FAPESP/FWO for a bilateral grant (grant nr#2018/10966-3), São Paulo Research Foundation (FAPESP) and FWO. Furthermore, FWO is thanked for the grant W000620N.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: TOAP would like to acknowledge TWAS-CNPq (163813/2018-3) for a PhD fellowship.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Walsh, C.T. Nature loves nitrogen heterocycles. *Tetrahedron Lett.* **2015**, *56*, 3075–3081. [CrossRef]
2. Vitaku, E.; Smith, D.T.; Njardarson, J.T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257–10274. [CrossRef] [PubMed]
3. Pitt, W.R.; Parry, D.M.; Perry, B.G.; Groom, C.R. Heteroaromatic Rings of the Future. *J. Med. Chem.* **2009**, *52*, 2952–2963. [CrossRef] [PubMed]
4. Wojcicka, A.; Nowicka-Zuchowska, A. Synthesis and Biological Activity of Pyridopyridazine Derivatives: A Mini Review. *Mini-Rev. Org. Chem.* **2018**, *16*, 3–11. [CrossRef]
5. Thorimbert, S.; Botuha, C.; Passador, K. 'Heteroaromatic Rings of the Future': Exploration of Unconquered Chemical Space. *Synthesis* **2019**, *51*, 384–398. [CrossRef]
6. Leach, A.G.; Kidley, N.J. Quantitatively Interpreted Enhanced Inhibition of Cytochrome P450s by Heteroaromatic Rings Containing Nitrogen. *J. Chem. Inf. Model.* **2011**, *51*, 1048–1063. [CrossRef]
7. Graton, J.; le Questel, J.Y.; Maxwell, P.; Popelier, P. Hydrogen-Bond Accepting Properties of New Heteroaromatic Ring Chemical Motifs: A Theoretical Study. *J. Chem. Inf. Model.* **2016**, *56*, 322–334. [CrossRef]
8. Yamamoto, Y.; Shinkai, I. (Eds.) Product Class 18: Pyridopyridazines. In *Science of Synthesis, 16: Category 2, Hetarenes and Related Ring Systems*; Thieme: New York, NY, USA, 2004. [CrossRef]
9. Ibrahim, M.A.; Elmenoufy, A.H.; Elagawany, M.; Ghoneim, M.M.; Moawad, A. "Pyridopyridazine": A Versatile Nucleus in Pharmaceutical Field. *J. Biosci. Med.* **2015**, *3*, 59–66. [CrossRef]
10. Atkinson, C.M.; Biddle, B.N. Triazaphenanthrenes. Part VI. Further observations on the Widman-Stoermer and Borsche reactions. *J. Chem. Soc. C* **1966**, 2053–2060. [CrossRef]
11. Stockmann, V.; Primpke, S.; Fiksdahl, A. 7-Azacinnolin-4(1H)-one preparation and NMR studies of tautomery. *J. Heterocycl. Chem.* **2011**, *48*, 737–741. [CrossRef]
12. Bundy, G.L. *Heterocycle Carboxamides as Antiviral Agents (WO 02/04444)*; World Intellectual Property Organisation: Geneva, Switzerland, 2002.
13. Kochhar, M.M. 8-chloro-4-hydroxy-3-methyl-pyrido[3,4-*c*]pyridazine. *J. Heterocycl. Chem.* **1969**, *6*, 977–978. [CrossRef]
14. Jones, G.; Rafferty, P. A synthesis of annulated pyridazines by cycloaddition of azodicarboxylates to vinylpyridines. *Tetrahedron Lett.* **1978**, *19*, 2731–2734. [CrossRef]
15. Jones, G.; Rafferty, P. The synthesis of annulated pyridazines by cycloaddition of azodicarboxylates to vinyl heterocycles. *Tetrahedron* **1979**, *35*, 2027–2033. [CrossRef]
16. Gao, Y. *Piperazinyl Oxoalkyl Tetrahydroisoquinolines and Related Analogues (WO 2007/106349)*; World Intellectual Property Organization: Geneva, Switzerland, 2007.

17. Zhao, L.; Jin, L.; Jin, Y. *5,6,7,8-Tetrahydro-2H-Pyridineo [3,4-c] Pyridine Synthesis Method of Azine-3-Ketones (CN 102924452 A)*; State Intellectual Property Office of the People's Republic of China: Beijing, China, 2013.
18. Ashton, W.T.; Caldwell, C.G.; Duffy, J.L.; Mathvink, R.J.; Wang, L.; Weber, A. *3-Amino-4-Phenylbutanoic Acid Derivatives as Dipeptidyl Peptidase Inhibitors for the Treatment or Prevention of Diabetes (WO 2004/069162)*; World Intellectual Property Organization: Geneva, Switzerland, 2004.
19. Wan, H.; Geng, M.; Yu Cheng, C. *A Class of Compounds with Kinase Inhibitory Activity, Preparation Method and Uses (201610383073.2)*; State Intellectual Property Office of the People's Republic of China: Beijing, China, 2016.
20. Szabo, G.; Potor, A. *Naphthyridine and Pyrido[3,4-c]pyridazine Derivatives as GABAa α5 Receptor Modulators (WO 2021/191838)*; World Intellectual Property Organization: Geneva, Switzerland, 2021.
21. Lange, U.; Ochse, M.; van der Kam, E.; van Bergeijk, J.; Turner, S.; Oellien, F.; Walleser, P.; Amberg, W.; Hornberger, W.; Geneste, H.; et al. *Fused Heterocyclic Compounds as SlP Modulators (US 2017/0057966)*; United States Patent Application Publication: Ludwigshafen, Denmark, 2017.
22. Al-Mousawi, S.M.; Abdelhamid, I.A.; Moustafa, M.S. Alkylazinylcarbonitriles as building blocks in organic synthesis: Synthesis of 3-amino-7-arylhyrazonothieno-7H-[3,4-*c*]-pyridine-4,6-diones and pyrido-[3,4-*c*]-pyridazine-5-carbonitrile. *Arkivoc* **2007**, *2007*, 213–221. [CrossRef]
23. Barsy, M.A. Studies on Polyfunctionalised Heteroaromatics: Synthesis of Several New Cinnoline and Pyrido[3,4-*c*]pyridazine Derivatives. *J. Chin. Chem. Soc.* **2000**, *47*, 951–955. [CrossRef]
24. El Rady, E.A.; Barsy, M.A. A Convenient and Facile Synthesis of Pyridine, Pyridazine, Pyrimido[4,5-*c*]pyridazine, Pyrido[3,4-*c*]pyridazine, 1,6-Naphthyridine and Phthalazine Derivatives. *ChemInform* **2006**, *37*, 243–248. [CrossRef]
25. Elnaghi, M.H.; Hassan, M.E.; Elmaghraby, M.A.; Abdul Aziz, M.A. Studies on alkylheteroaromatics: A novel synthesis of pyrido[3,4-c]pyridazine derivatives. *Sci. Technol. Bull.* **1992**, *13*, 45–50.
26. Al-Awadhi, H.; Al-Omran, F.; HElnagdi, M.; Infantes, L.; Foces-Foces, C.; Jagerovic, N.; Elguero, J. New synthetic approaches to condensed pyridazinones: Alkylpyridazinyl carbonitriles as building blocks for the synthesis of condensed pyridazinones. *Tetrahedron* **1995**, *51*, 12745–12762. [CrossRef]
27. Laihia, K.; Kolehmainen, E.; Wegelius, E.; Miltsov, S.; Nikiforov, V.; Karavan, V. NMR Spectroscopic and X-ray Structural Characterization of Two Diaryl Derivatives of (4-Cyano-6-methyl-3,8-dioxo-2,3,5,6,7,8-hexahydropyrido[3,4-*c*] Pyridazin-6-yl)hydrazono-acetic acid Ethyl Ester. *Heterocycl. Commun.* **2004**, *10*, 35–42. [CrossRef]
28. Darwish, E.S.; Abdelrahman, M.A.; Salaheldin, A.M. Enamines in Heterocyclic Synthesis: A Novel Simple and Efficient Route to Condensed Pyridazines. *Z. Für Nat. B* **2011**, *66*, 597–602. [CrossRef]
29. Erian, A.W.; Elkholy, Y.M.; Al-arab, E.E.; Elnagdf, M.H. Polyfunctionally Substituted Heterocycles: Synthesis of New Polyfunctionally Substituted Phthalazines, Pyrido[3,4-*c*]pyridazines and Pyrazolo[3,4-*c*]pyridazines. *Phosphorus Sulfur Silicon Relat. Elem.* **1997**, *122*, 133–141. [CrossRef]
30. Manhi, F.M.; Zayed, S.E.; Ali, F.A.; Elnagdi, M.H. Studies with Polyfunctionally Substituted Heterocycles: Novel Syntheses of Pyrido[4,3-*d*]pyridazines and of Pyrido[3,4-*d*]pyridazines. *Collect. Czechoslov. Chem. Commun.* **1992**, *57*, 1770–1774. [CrossRef]
31. Elghandour, A.H.H.; Hussein, A.H.M.; Elnagdi, M.H.; Harb, A.F.A.; Metwally, S.A.M. Polyfunctionally Substituted Heterocycles: Synthesis of new polyfunctionally substituted phthalazines, thieno[3,4-*d*]pyridazines and pyrido [3,4-*c*]pyridazines. *J. Fur Prakt. Chem. Chem.-Ztg.* **1992**, *334*, 723–726. [CrossRef]
32. Hussein, A.M.; Atalla, A.A.; El-dean, A.M.K. Novel Synthesis of Pyridopyridazine, Pyrrolopyridazine and Some Pyridazine Derivatives. *Pol. J. Chem.* **1995**, *69*, 1642.
33. Hao, X. *Cinnolines as Inhibitors of HPK 1 (WO 2021/004535)*; World Intellectual Property Organization: Geneva, Switzerland, 2021.
34. Berger, U.; Dannhardt, G.; Obergrusberger, R. Diels-Alder-Reaktionen mit cyclischen Iminen, 3. Mitt. Cycloaddition von Iminen an Tetrazine. *Arch. Pharm.* **1982**, *315*, 428–437. [CrossRef]
35. Atkinson, C.M.; Mattocks, A.R. 733. Triazaphenanthrenes. Part II. Derivatives of 10-phenyl- 1:2:9-triazaphenanthrene. *J. Chem. Soc.* **1957**, 3722–3726. [CrossRef]
36. Atkinson, C.M.; Mattocks, A.R. 320. Triazaphenanthrenes. Part V. The site of quaternisation in some triazaphenanthrene methiodides. *J. Chem. Soc.* **1962**, 1671–1678. [CrossRef]
37. Cajipe, G.J.B.; Landen, G.; Semler, B.; Moore, H.W. Reaction of aminoquinones and related vinylogous amides with nitrous acid. Synthesis and chemistry of cyclic diazo ketones. *J. Org. Chem.* **1975**, *40*, 3874–3878. [CrossRef]
38. Proshchenkova, V.; Shuvalov, V.Y.; Glyzdinskaya, L.V.; Fisyuk, A.S.; Chernenko, S.A.; Khvostov, M.V.; Tolstikova, T.G.; Vorontsova, M.; Sagitullina, G.P. Synthesis of 4-Ethoxycarbonyl(cyano)-β-Carbolines via Thermolysis of 4-Aryl-3(5)-Azidopyridine Derivatives and the Study of their Optical and Hypoglycemic Properties. *Chem. Heterocycl. Compd.* **2021**, *57*, 187–198. [CrossRef]
39. Barton, J.; Walker, R. Synthesis of the monoazabiphenylenes. *Tetrahedron Lett.* **1975**, *16*, 569–572. [CrossRef]
40. Iqbal, J.; Gupta, A.; Husain, A. Photochemistry of phenazopyridine hydrochloride. *Pharmazie* **2006**, *61*, 747–750. [PubMed]
41. Al-Awadi, N.A.; Ibrahim, Y.A.; Elnagdi, M.; Adam, A.Y.; John, E. Gas-phase pyrolysis of arylazonicotinates and nicotinonitriles: Routes towards new aminopyridine and pyrido[3,4-*c*]cinnoline derivatives. *J. Anal. Appl. Pyrolysis* **2017**, *124*, 602–609. [CrossRef]
42. Jerchel, D.; Fischer, H. 2.3-Azadiphenylen-tetrazoliumsalze und Triazaphenanthrene. *Chem. Ber.* **1956**, *89*, 563–570. [CrossRef]
43. Ames, D.E.; Byrne, C.J.A. Cinnolines. Part XVII. Reactions of 4-chlorocinnoline-3-carbonitrile and preparation of 2,3-dihydro-3-imino-1H-pyrazolo[4,3-*c*]cinnolines. *J. Chem. Soc. Perkin Trans. 1* **1976**, *6*, 592. [CrossRef]
44. Goerlitzer, K.; Behrje, H. Furo-, Pyrrolo- and Pyridazino(3,4-*c*)quinolines. *Pharmazie* **1996**, *51*, 528–534. [CrossRef]

45. Goerlitzer, K.; Fabian, J.; Jones, P.G.; Frohberg, P.; Drutkowski, G. Pyridazino[3,4-*c*]quinolines and Pyridazino[4,5-*c*]quinolines—Synthesis and Investigation of Lipoxygenase Inhibition. *Pharmazie* **2002**, *57*, 362–371. [CrossRef]
46. Seitz, G.; Kämpchen, T. Inverse" Diels-Alder-Additionen, 4. Mitt.: π-Elektronenreiche, benzokondensierte Heteroaromaten als „inverse" Dienophile. *Arch. Der Pharm.* **1976**, *309*, 679–681. [CrossRef]
47. Pindur, U.; Kim, Y.S.; Schollmeyer, D. Cyclization Reactions of 2,2′-Bis-N-methylindolyl to Potential Protein Kinase C Inhibitors. *Heterocycles* **1994**, *38*, 2267. [CrossRef]
48. MacBride, J.A.H. Synthesis of 2,7-diazabiphenylene by thermal extrusion of nitrogen from 2,7,9,10-tetra-azaphenanthrene. *J. Chem. Soc. Chem. Commun.* **1974**, *9*, 359b. [CrossRef]
49. Kanoktanaporn, S.; MacBride, J.A.H. Preparation of ring-fused pyridazines by reduction of 3,3′-dinitro-4,4′-bipyridyl and 3,3′-dinitro-4,4′-biquinolyl. *J. Chem. Soc. Perkin Trans. 1* **1978**, 1126–1131. [CrossRef]
50. Kanoktanaporn, S.; MacBride, J.A.A.; King, T.J. Biphenylenes and Heterocyclic Analogs of Biphenylene. Part II. Preparation of f 2,7-Diazabiphenylene, its Quaternary Salts, and an Unstable Angular Dibenzo-derivative; X-ray Crystal Structure of 2-Allyl-2-azonia-7-azabiphenylene bromi. *J. Chem. Res. Synop.* **1980**, *11*, 2911–2940. [CrossRef]
51. Kaczmarek, U. Bipyridines. XIX. Synthesis of some novel 2,7,9,10-Tetraazaphenanthrene derivatives. *J. Fuer Prakt. Chem.* **1987**, *329*, 592–598. [CrossRef]
52. MacBride, J.; Wright, P.H.; Wakefield, B.J. Synthesis of 1.6-Diazabiphenylene by Flash Vacuum Pyrolysis of 2,5,9,10-tetra-azaphenanthrene; NMR Evidence for Rehybridisation in Biphenylenes. *Tetrahedron Lett.* **1981**, *22*, 4545–4548. [CrossRef]
53. Stockmann, V.; Fiksdahl, A. Preparation of new pyrido[3,4-*b*]thienopyrroles and pyrido[4,3-*e*]thienopyridazines. *Tetrahedron* **2008**, *64*, 7626–7632. [CrossRef]
54. Stockmann, V.; Eriksen, K.L.; Fiksdahl, A. Preparation of novel pyridine-fused tris-heterocycles; pyrido[4,3-*e*]pyrrolo-/pyrido[4,3-*e*]furano[2,3-*c*]pyridazines and pyrido[3,4-*b*]pyrrolo[3,2-*d*]pyrrole. *Tetrahedron* **2008**, *64*, 11180–11184. [CrossRef]
55. Barawkar, D.; Bende, T.; Zahler, R.; Bandyopadhyay, A.; Sarangthem, R.S.; Doshi, J.; Waman, Y.; Jadhav, R.; Singh, U.P. *Substituted Fused Tricyclic Compounds, Compositions and Medicinal Applications Thereof (WO 2012/127506)*; World Intellectual Property Organization: Geneva, Switzerland, 2012.
56. Llobat, A.; Escorihuela, J.; Sedgwick, D.M.; Rodenes, M.; Román, R.; Soloshonok, V.A.; Han, J.; Medio-Simón, M.; Fustero, S. The Ruthenium-Catalyzed Domino Cross Enyne Metathesis/Ring-Closing Metathesis in the Synthesis of Enantioenriched Nitrogen-Containing Heterocycles. *Eur. J. Org. Chem.* **2020**, 4193–4207. [CrossRef]
57. Elix, J.A.; Sterns, M.; Wilson, W.S.; Warrener, R.N. Preparation and X-ray structure of the 8a-azonia-3,4-diazaphenanthrene cation. *J. Chem. Soc. D Chem. Commun.* **1971**, *9*, 426b. [CrossRef]
58. Merz, H.; Pook, K.H. Reaktionen des thebains mit azodicarbonsäureestern. *Tetrahedron* **1970**, *26*, 1727–1741. [CrossRef]
59. Giger, R.; Rubinstein, R.; Ginsburg, D. Synthesis and reactions of the Diels-Alder adduct of thebaine with 4-phenyl-1,2,4-triazoline-3,5-dione. *Tetrahedron* **1973**, *29*, 2387–2391. [CrossRef]
60. Marton, J.; Szabó, Z.; Csorvássy, I.; Simon, C.; Hosztafi, S.; Makleit, S. Reaction of morphinan-6,8-dienes with azadienophiles. *Tetrahedron* **1996**, *52*, 2449–2464. [CrossRef]
61. Csutoras, C.; Berenyi, S.; Czako, B.; Makleit, S. Syntheses and transformations of novel nitrogen and sulfur containing morphinanedienes. *Mon. Fur Chem. Chem. Mon.* **1997**, *128*, 1267–1273. [CrossRef]