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Synthesis of Oxazino[4,3-*a*]indoles and Biological Applications

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Summary

This review brings together the various pathways to the oxazino[4,3-*a*]indole motif over the last decades. Representative examples showing the scope of these processes will illustrate the synthetic pathways and the biological activity of the synthesized oxazinoindoles will be mentioned wherever possible.

Keywords: Oxazinoindole, Cyclization, Lactonization, Catalysis, Heterocycle, Biological activity.

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1. Introduction

The 3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indole ring commonly referred to as oxazino[4,3-*a*]indole or oxazinoindole is a tricyclic system resulting from the fusion of an indole and a morpholine in which the nitrogen atom and the C2 atom of the indole are linked by a six-membered oxygenated ring (Figure 1).

Figure 1. Oxazino[4,3-*a*]indoles and derivatives **A**, **B** and **C**.

This class of heterocycle has received particular attention in recent years within the scientific community because the oxazinoindole core is present in a variety of synthetic compounds having biological activities (Figure 2). Especially, oxazino[4,3-*a*]indole **1a** of type **A** is known to possess potential antidepressant activity[1] whereas oxazinoindoles **2a** and **2b** exhibit potent anti-tumor properties.[2,3] In the lactone series of type **B**, oxazinoindolone **3** was found as a potent anti-cancer agent[4] and compound **4** displayed anti-inflammatory activities.[5] Among the polycyclic compounds incorporating the oxazinoindole unit (series **C**), it has been shown that oxazinocarbazole **5**, in which a morpholine nucleus is fused to a carbazole, acts as a 5-HT₆ receptor antagonist at a very low concentration.[6]

Figure 2. Selection of biologically active oxazino[4,3-*a*]indoles.

We wish to present herein a compilation of existing methods used to prepare (substituted)-oxazinoindoles **A**, oxazinoindolones **B**, and some polycyclic rings containing the oxazinoindole moiety of type **C**. It therefore seemed useful to identify the different pathways to this heterocyclic motif, which is an oxygenated analogue of the pyridoindole nucleus with a variety of activities.[7] A selection of representative examples will be depicted for each protocol and the properties of biologically active oxazinoindoles will be also mentioned. Concerning the synthesis of oxazinoindoles of

type A, this part will be divided in three sections including recent methodologies used to prepare this tricyclic system having (i) an unsubstituted C-ring (section 2.1), (ii) a (poly)substituted C-ring having only Csp³ atoms on the morpholino-ring (section 2.2) and (iii) various substituted C-rings having both Csp³ and Csp² carbons (section 2.3). Section 2.1 dedicated to the synthesis of this motive will deal with accesses to this heterocyclic system by creating the C-ring and then the B-ring. In the two next sections, we will see successively the syntheses of substituted-oxazinoindoles A (which were only prepared by creating the morpholine C-ring), where the substituted C-ring carries only Csp³ (section 2.2) or also Csp² hybrid carbons (C=O, C=C, section 2.3). The second part dedicated to oxazinoindolones of type B will be devoted to the syntheses of (substituted)-heterocycles which has only been created by cyclization reactions forming the lactone C-ring. Finally, the last part will deal with the synthesis of polycyclic systems containing the oxazinoindole unit, very often from appropriately substituted carbazoles. The bonds formed during the different synthetic processes presented will be highlighted in bold in the reaction schemes.

2. Synthesis of substituted-oxazino[4,3-*a*]indoles A

2.1 Oxazinoindoles having an unsubstituted C-ring (R² = R³ = R⁴ = H)

In 2011, Chen and Xiao developed the synthesis of unsubstituted oxazinoindoles **6** from (1*H*-indol-2-yl)methanol substrates **7** and diphenyl vinylsulfonium triflate salts **8** (Scheme 1).[8]

Scheme 1. Synthesis and representative examples of oxazinoindoles **6** using diphenyl vinylsulfonium triflate **8**.

The reaction proceeded *via* a conjugated addition of the nitrogen anion of the indole to the sulfonium salt. After a proton shift, the resulting oxygen anion reacted by S_N2 on the methylene close to the sulfonium to give **6** and diphenylsulfide. It is of note that the reaction tolerated well electron-withdrawing and electron-donating groups on the C5 and C7 positions of indoles **7**. Moreover, it was showed that a C3-substituted indole can be used in this reaction easy to implement as well as an indole bearing a secondary alcohol function. To show the synthetic utility of this process, the authors prepared anti-tumour agent **2b**, depicted in Fig. 2, from the corresponding indole and the sulfonium salt with an excellent yield of 77%. Recently, in our group, we observed that replacing KOH by NaH as the base and CH₂Cl₂ by fluorobenzene as the solvent increased the efficiency of this process, since the Michael-addition of **7c** on diphenyl vinylsulfonium triflate followed by subsequent O-cyclization reaction produced **6c** in only 30 minutes with a 92 % yield (*vs* 10 h, 76% for **6c** using KOH and CH₂Cl₂). Further a Pd-coupling reaction on the bromine atom of **6c** was performed to give rapid access to compound **6d** which displayed a nanomolar level of toxicity on human colon carcinoma HCT116 cancer cells.[9] Very recently, Chen and Xiao reported the synthesis of *ortho*-substituted anilines by a copper-catalyzed three component reaction of aryne precursors, terminal alkynes, and electrophilic aminating reagent.[10] As a possible application of this process, the authors transformed the generated *ortho*-alkynyl aniline **9** into 3-aroil oxazino[4,3-*a*]indole **10** by forming the B-ring of the heterocycle, using an intramolecular Cu(I)-catalyzed oxidative reaction (Scheme 2).

Scheme 2. Synthesis of oxazinoindole **10** from the cyclization of **9**.

This cyclization reaction suggests that it would be certainly possible to prepare a series of variously substituted oxazinoindoles from morpholine derivatives of type **9** *via* this elegant transformation involving a radical mechanism.[11]

The construction of the B-ring of the oxazinoindole system was also proposed by Akiyama in a paper dedicated to the synthesis of *N*-fused indoles (Scheme 3).[12] The reaction proceeds *via* a fluorine-substituted carbenoid *I* formed in the presence of NbCl_5 and NaAlH_4 [13] which undergoes insertion into the C-H σ bond close to the nitrogen atom. A subsequent dehydrofluorination of intermediate *II* occurs to give a mixture of **12** and indoline which can be oxidized using 8 mol% of ruthenium zirconium phosphate under an oxygen atmosphere. This process is very elegant for preparing tricyclic systems of different sizes and is tolerant with various groups or atoms ($\text{X} = \text{CH}_2, \text{O}, \text{S}, \text{N-Me}$). However, the trifluoromethylated reagents successively lose their 3 fluorine atoms in this process, which could be considered as a critical point.

Scheme 3. Synthesis of oxazinoindole **12** from the cyclization of **11**.

2.2. Oxazinoindoles having a substituted C-ring

Five years after the work of Chen and Xiao, Bagnoli proposed a similar process to prepare substituted oxazinoindoles **13** from (1*H*-indol-2-yl)methanol substrates **7** by replacing the sulfonium salts with vinyl selenones **14** as Michael acceptors[14] (Scheme 4).

Scheme 4. Synthesis and representative examples of oxazinoindoles **13** using vinyl selenones **14**.

The process starts with an oxa-Michael type reaction in basic medium, and, after a proton transfer, the nitrogen anion eliminates the phenylselenenyl group during the formation of the C-ring of the oxazinoindole system. It should be noted that 18-crown-6 is very useful in this reaction because it prevents the formation of unwanted isomers.

Scheme 5. Synthesis and representative examples of oxazinoindoles **1** from 3-alkylindole-1-ethanols.

The first paper describing the synthesis and biological properties of oxazinoindoles was published in 1975 by Humber (Scheme 5).^[1] In hot benzene in the presence of a catalytic amount of PTSA, 3-methyl- and 3-ethylindole-1-ethanols reacted with various β -ketoesters to give, after saponification, the oxazino[4,3-*a*]indole-1-alcanoic acids with fair to good yields. After amidification followed by reduction or reduction followed by amination, a series of twenty-three C1-disubstituted-oxazinoindoles **1** were synthesized and evaluated as antidepressive agents under their salt forms. Prevention of reserpine-induced ptosis was estimated and the percentage of mice in which ptosis was prevented was recorded and ED_{50} were determined for most active compounds. Thus, compounds **1a**, **1b** and **1c** were identified as the most active oxazinoindoles in this series, with oxazinoindole **1a** proving to be 9-fold more active than amitriptyline taken as the reference molecule.

To combat neuronal damage induced by the aggregation of the peptide A β 25-35, implicated in Alzheimer's disease, Zhang and Guo synthesized in 2016 chiral oxazinoindoles **16** and **17** from optically active secondary alcohols of type **15** (Scheme 6).^[15]

Scheme 6. Synthesis and representative examples of oxazinoindoles **13** using vinyl selenones **14**.

The intermolecular oxa-Pictet-Spengler reaction between alcohols of type **15**, readily obtained from chiral epoxypropanes, and (hetero)aromatic aldehydes in the presence of $BF_3 \cdot Et_2O$ furnished a (1/1) diastereoisomeric mixture

of oxazinoindoles **16** and **17**, easily separable by column chromatography. Each enantiomer was then separately tested for its neuroprotective properties by preventing neurological disorders caused by the Ab₂₅₋₃₅ peptide in SH-SY5Y neuroblastoma cell lines. The more bioactive oxazinoindoles depicted in Scheme 6, were found to be as neuroprotective as epigallocatechin gallate (EGCG) taken as a reference. It should be noted that the level of neuroprotective activity seems to be closely related to the absolute configuration of carbon atoms C1 and C3. While these results are very promising in term of neuroprotective activity, it is regrettable that no experimental protocol is detailed both chemically and biologically in this letter. It is interesting to note that Gorai reported that it is possible to prepare this type of C1- and C3-disubstituted-oxazinoindoles in a racemic fashion and with a modest diastereoisomeric ratio by using the Pictet-Spengler reaction from skatole, epoxides and aldehydes or ketones in the presence of BF₃·Et₂O and MgSO₄ in a one-pot process.[16]

A few years earlier, Gharpure showed that the diastereoselectivity of the oxa-Pictet-Spengler reaction could be significantly improved by using indoles **18** bearing an *N*-tethered vinylogous carbonate moiety (Scheme 7).[17] Gharpure explained the *cis*-orientation of C1 and C3 substituents because of the preference of the R¹ substituent and the

Scheme 7. Synthesis and representative examples of oxazinoindoles **19** using vinyl indoles **18**.

bulkier (CH₂CO₂Et)-group to occupy a pseudo-equatorial orientation in the transition state to avoid 1,3-diaxial interactions. It was also showed that a *one-pot* tandem oxa-Pictet-Spengler cyclization/Friedel-Crafts acylation on C3 was possible to furnish a variety of tri-substituted oxazinoindoles with high yields, excellent diastereoselectivity and a good functional group tolerance which makes this process extremely attractive.

Scheidt, also proposed in 2013 a tandem isomerization/oxa-Pictet-Spengler strategy to prepare C1-substituted oxazinoindoles **21** from allyl ethers **20**[18] (Scheme 8).

Scheme 8. Synthesis and representative examples of oxazinoindoles **21** using allyl ethers **20**.

It was found that the iridium catalyst [IrH₂(THF)₂(PPh₂Me)₂][19] was the more efficient catalyst to convert the allyl ether to a (*E*)-vinyl ether substituent. After the isomerization reaction, the oxa-Pictet-Spengler cyclization reaction was studied with a variety of Brønsted- and Lewis-acids and Bi(OTf)₃ has proven to be the more effective catalyst to

achieve the Prins-type cyclization. To prepare a substrate as **21c**, it is preferable to add successively the iridium catalyst and then Bi(OTf)₃, whereas this is not necessary with easier substrates having a terminal double bond while, in this case, the catalysts can be added simultaneously to the reaction medium. An enantioselective version of the Pictet-Spengler cyclization was proposed to prepare **21a** with an average e.e. = 80:20 by replacing Bi(OTf)₃ by a chiral phosphoric acid[18] making this process the first enantioselective access to C1-substituted oxazinoindoles.

In a program dedicated to the discovery of Sphingosine-1-Phosphate receptor subtype 1 (S1P₁) modulators that have proven effective in the treatment of autoimmune diseases, Jones has prepared a series of C1-, C8- and C10-substituted oxazinoindoles **24**[20] (Scheme 9). The oxazolinoindole core of the platform **23** was created according to an oxo-Michael cyclization of indole **22** in a modest yield of 33%. In four steps, **23** was transformed into a series of eight oxazinoindoles **24** as potent modulators of the S1P₁ receptor. Human S1P1 EC₅₀ values for oxazinoindoles **24** were determined in a homogeneous time resolved fluorescence (HTRF) cyclase assay. All tri-substituted oxazinoindoles **24** tested exhibited an impressive activity against S1P₁, and particularly **24a-c** having EC₅₀ values in the sub-nanomolar range.

Scheme 9. Synthesis and representative examples of S1P₁ modulators **24**.

It was also found that an enantiomer of **24b** (absolute configuration of C1 not determined), obtained after chiral chromatography was evaluated in β -arrestin and had an EC₅₀ value of 0.83 nM. Moreover, this potent S1P₁ agonist was also observed to be orally bioavailable in rat as a suspension in 0.5% methylcellulose in water and has an acceptable half-life of 3.4 h in rat, which makes this molecule promising for other biological evaluations.

In 2013, Bandini reported an efficient synthesis of a wide range of poly-substituted oxazinoindoles **26** from a double heterocyclization of aniline diols **25** under gold-catalysis[21] (Scheme 10).

Scheme 10. Synthesis and representative examples of oxazinoindoles **26** using aniline diols **25**.

The reaction proceeds according to a first 5-*endo-dig* hydroamination reaction catalyzed by the gold(I)-catalyst which is then re-used for a second cyclizing alkoxylation leading to a variety of variously substituted oxazinoindoles **26** with good to excellent yields. Functional groups were well tolerated as (alkyl, aryl, esters, CN and halogens). This process

has also been successfully used to synthesize more complex heterocycles systems such as oxazepinoindoles and oxazinocarbazoles. As it can be seen in Scheme 10, oxazinoindole **1 AY-23,673** which has an anti-depressant activity[1] was prepared in a good yield of 71% illustrating the synthetic utility of this process.

The same year, Bandini also prepared C3-vinyl-oxazinoindoles **28** using an unprecedented enantioselective gold-catalyzed cascade sequence from the cyclization of aniline diols of type **27**[22] (Scheme 11). The process starts as above with a gold-catalyzed 5-*endo-dig* hydroamination in the presence of the C2-symmetric chiral biposphine ligand (S)-DTBM-segphos. After the protodeauration step, an alkoxyauration of the C=C occurs according to a 6-*exo-trig* process to give, after an *anti*-elimination of [Au]-OH, the desired oxazinoindoles **28**. It is interesting to note that when the reaction was carried out in a coordinating solvent as dioxane, an oxazocino[4,3-*a*]indole (eight membered-ring) was exclusively formed. In toluene, a series of 3-vinyl-oxazolinoindoles was rapidly prepared in mild conditions by creating successively a C-N and a C-O bond with good yields and excellent enantiomeric excess. Absolute configuration of oxazinoindoles **28** was unambiguously determined to be (S), as the DTBM-segphos ligand, by X-ray analysis of **28c**.

Scheme 11. Synthesis and representative examples of oxazinoindoles **28** using aniline diols **27**.

2.3. Oxazinoindoles having an ethylene double-bond on C-ring

Abbiati reported the efficient and easy to implement synthesis of twelve oxazinoindoles **30** having a C3 = C4 ethylene-bond from the domino/cyclization of δ -alkynylaldehydes **29** in the presence of alkoxides[23] (Scheme 12).

Scheme 12. Synthesis of oxazinoindoles **30** from the cyclization of δ -alkynylaldehydes **29** in the presence of alkoxides. After addition of the alkoxide to aldehyde, the resulting transient hemiacetal anion attacks the triple bond (or possibly its allenic form) according to a 6-*exo-dig* mode with no formation of a seven-membered ring. After protonation by the solvent and isomerization, oxazinoindoles **30** are formed with moderate to good yields. The authors showed that primary and secondary alcohols were well tolerated as well as electron-poor aromatic-rings linked on the triple-bond of

29. On the contrary, terminal alkynes and electron-rich aromatic nuclei led to the expected oxazinoindoles **30** with modest yields (33-50%).

Scheme 13. Synthesis and representative examples of oxazinoindoles **32** from the hydroxyalcoxylation of alkynes **31**.

A very close approach to oxazinoindoles of type **32** was proposed later by Chen and Wang from the hydroxyalcoxylation of terminal and internal alkynes **31**[24] (Scheme 13). A variety of electrophiles, Lewis-acids and bases were tested with a model substrate and best conditions were found by using K_2CO_3 in hot DMF. Under these relatively mild conditions, it was showed that both electron-donating and electron-withdrawing groups were well tolerated whatever their position on the indole and on the aromatic ring linked to the triple bond. Finally, it has been verified by flame atomic absorption spectroscopy that traces of metals, possibly present in K_2CO_3 , are in no way involved in this cyclization reaction.

Sha described in 2014 a rhodium(III)-catalyzed C2 olefination reaction of various indoles by using *ortho*-phenolic OH as directing groups allowing the insertion of the catalyst into the C2-H bond.[25] Thus, a library of indoles, carrying both a phenol on the nitrogen atom and on C2 various Michael acceptors, were rapidly prepared with efficiency, functional group tolerance and low loading of the Rh-catalyst. To show the synthetic interest of such indoles, compound **33** reacted with triethylamine to give oxazinoindole **34** with an excellent yield of 94% by a hetero-Michael process (Scheme 14).

Scheme 14. Synthesis of oxazinoindole **34** from the cyclization of **33**.

To our knowledge, there is only one example of oxazinoindole having an exocyclic double bond at C1. In a study devoted to the synthesis of (+)-conolidine, an alkaloid isolated from *Tabernaemontana divaricata*,[26] Fujii and Ohno studied the gold(I)-catalyzed double cyclization reaction of conjugated diynes **35**[27] (Scheme 15).

Scheme 15. Synthesis of oxazinoindoles **36** from the gold-catalyzed double cyclization of diynes **35**.

In a previous work, the authors had demonstrated that seven-membered rings, resulting from an initial 5-*endo-dig* *N*-cyclization followed by a 7-*endo-dig* *O*-annulation predominated when anilines having no-substituent on the ethanol chain reacted with IPrAuCl/AgOTf.[28] To improve the **36/37** ratio, it has been shown that the introduction of a bulky group, close to the nitrogen atom, improved the formation of the desired oxazolinoindole of type **36**, which however, remains in the minority (**36a/37a** = 29/71). The additional introduction of a phenyl bulky group close to the alcohol function (R = Ph), makes it possible to significantly orient the second *O*-cyclization reaction to give mainly oxazinoindole **36b**. Finally, it has been shown that an acid (R = O) in place of the alcohol function, leads majority to the oxazinoindol-3-one skeleton but with a low yield (<35%).

The last example of this section concerns the synthesis of oxazinoindoles **39**[29] having various aromatic rings on C1, a -CO₂Me function on C3 and a C=O on C4 (Scheme 16). A variety of Lewis acids as Sc(OTf)₃, Cu(OTf)₂, In(OTf)₃, Yb(OTf)₃ and others were evaluated in this process and Sc(OTf)₃ has proven to be the most effective of the Lewis-acids tested on a model substrate.

Scheme 16. Synthesis and representative examples of oxazinoindoles **39** obtained from a selective oxiranes **38** ring-opening followed by Friedel-Crafts cyclization.

From a mechanistic point of view, highly functionalized oxiranes of type **38** undergo highly chemoselective carbon-carbon cleavage in the presence of Sc(OTf)₃ which is followed by a Friedel-Crafts cyclization to create the new C-C bond of the oxazolinoindole skeleton. It was found that electron-poor aromatic rings were more cooperative in this tandem reaction than their electron-rich aromatic congeners which worked well with more catalyst loading and higher temperatures (80 °C). It was not mentioned which was the major diastereoisomer and whether it could be isolated by silica gel chromatography.

3. Synthesis of oxazino[3,4-*a*]indolones **B**

The first synthesis of an oxazino[3,4-*a*]indolone **41** (type B) was proposed by Coppola in a program dedicated to the synthesis of novel hypoglycemic agents, analogs of Fluvastatin (Scheme 17).[30]

Scheme 17. Synthesis of oxazinoindolone **41**.

Oxazinoindolone **41** was obtained in two steps after a B_2H_6 reduction of the acid-function of **40** followed by a lactonization of the alcohol intermediate in the presence of a catalytic amount of *para*-toluenesulfonic acid (PTSA). The intrinsic structure of oxazinoindol-3-ones of type B suggests that the lactonization reaction is perfectly adapted to access this type of skeleton. Thus, in a program devoted to the synthesis of cyclin-dependant kinase (CDKs) inhibitors, Joseph used the halolactonisation reaction of *N*-allyl indoles **42** to prepare a variety of oxazinoindolones **43**[31,32] (Scheme 18). It was observed that the iodination at the C3 position (when unoccupied) of the indole and the 6-*endo-trig* iodolactonisation occurred at the same time, that require to use an excess of the electrophilic agent to avoid mixtures. As it can be seen with oxazinoindol-1-ones **43**, the presence of halogen atoms (I, Br) on C10 should make it possible to introduce various substituents on this position by means of appropriate coupling reactions. Finally, oxazinoindolones **43** were rapidly transformed into tetrahydro[1,4]-diazepino[1,2-*a*]indol-1-ones which showed interesting cyclin-dependent kinases (CDKs) inhibitory properties.[33] In this work, the authors showed that *N*-iodosuccinimide (NIS) in 2,6-lutidine was preferred as I_2 as electrophilic agent because the reaction takes place at a lower temperature of -20 °C (vs 70 °C using I_2).

Scheme 18. Synthesis of oxazinoindolones **43**.

Recently, Thibonnet reported that, when using 2 equivalents of I_2 at rt as electrophile, NaH (2 eq) as base and $AgNO_3$ (0.5 eq) as additive, the iodolactonization reaction was definitively improved leading to the expected lactones **43** after only 2 hours of reaction with nearly quantitative yields.[34]

Scheme 19. Synthesis and biological evaluation of oxazinoindolones **45** and **46**.

In a study dedicated to the synthesis and evaluation of tricyclic heterocycles as oxazolidinones as potential inhibitors of *Mycobacterium tuberculosis* UDP-galactopyranose mutase (*Mt* UGM), an enzyme involved in the biosynthesis of the galactan moiety of the cell wall, Thiery prepared various oxazinoindolones **45** from the iodolactonization of *N*-propargylindoles **44**[35,36] (Scheme 19). It was demonstrated that the iodolactonization was very effective with electron-rich and electron-poor substituents on indoles and tolerated alkyl and aromatic substituents on the alkyne triple bond ($R^1 = \text{Me, Ph}$). Interestingly, this reaction which is efficient at a gram-scale and which is applicable to the synthesis of 7-membered lactones, worked with a total stereoselectivity as only more stable (*E*)-isomers **45** were obtained. Sonogashira, Stille and Suzuki Pd-couplings were successfully achieved on the more reactive exocyclic vinyl iodide of **45** to give mainly or totally the mono-coupling adducts. Thus, the Sonogashira reaction with hex-1-yne gave enynes **46** with yields ranging from 48 to 85%. The *Mt* UGM inhibition for compounds **45** and **46** was evaluated and revealed that compounds **46a-c**, as well as vinyl iodide **45a**, displayed at a concentration of 1 mM, a satisfactory inhibition level, comparable to the best heterocyclic *Mt* UGM inhibitors reported in literature. [37,38,39]

The lactonization of *N*-propargyl indole-2-carboxylic acids **47** was studied by Balci in 2015 using AuCl_3 as the activating agent of the alkyne triple bond[40] (Scheme 20).

Scheme 20. Synthesis of oxazinoindolones **48** from gold(III)-catalyzed 6-*exo-dig* cyclization of **47**.

In this study, it was demonstrated that AuCl_3 and AgOTf were very efficient catalysts to promote the lactonization with high yields (92 to 99%). The reaction was efficient with indoles **47** and with their homologue's pyrrole-2-carboxylic acids.

The last example forming the oxazinoindol-3-one unit by O-C bond creation was described by Krasavin in a study dedicated to the cyclodehydration of dicarboxylic acids with oxalyl chloride[41] (Scheme 21).

Scheme 21. Synthesis of anhydride **50** from the cyclodehydration of indole **49**.

It was reported that the cyclodehydration of a variety of dicarboxylic acids including indole **49** was more efficient in hot toluene rather than in DCM, chlorobenzene and 1,2-dichloroethane and that a catalytic amount of DMF accelerated the process.[42]

After identifying the methods for accessing the oxazinoindolone motif by creating a C-O bond, we will now report intramolecular Michael addition reactions giving access of oxazolidinones by forming a C-N bond. In a study dedicated to the synthesis of benzylbutyrolactones, the group of You reported a single example of oxazolidinone formation as an illustration of the intramolecular aza-Michael addition process used for the formation of butyrolactones[43] (Scheme 22).

Scheme 22. Synthesis of oxazinoindolone **52** from intramolecular aza-Michael reaction.

At the same period, Bandini and Miscione proposed an enantioselective access to this type of oxazolidinones using an optically active *N*-benzyl-ammoniumcinchonidium salt **54** catalyst for the creating the ring C of oxazolidinone **55**[44] (Scheme 23). Mechanistic explanations were proposed to explain the stereoselectivity of this intramolecular aza-Michael addition for which the formation of an ion pair between the catalyst and the indolate intermediate would certainly to be at the origin of a good stereo-differentiation. For comparison, *N*-benzylamides, where a nitrogen atom replaces the oxygen atom of **53** and therefore have stronger interactions with catalyst **54** were transformed into the corresponding pyrazinoindolinones with better enantiomeric excesses ranging from 75 to 98%.

Scheme 23. Synthesis of optically active oxazinoindolone **55** from an intramolecular aza-Michael reaction under asymmetric phase-transfer catalysis.

4. Synthesis of polycyclic systems C containing oxazinoindole nucleus.

In this last section dedicated to the synthesis of complicated heterocycles containing an oxazinoindole nucleus, we will focus our attention with the syntheses using as starting materials carbazoles and carbazole-derivatives. Thus, we will examine some methods linking the nitrogen atom of the carbazole nucleus to its aromatic nucleus by creating a morpholine type additional ring.

Van Vranken reported an efficient enantioselective palladium-catalyzed synthesis of α -(*N*-carbazolyl)- α -arylesters of type **56a** from the insertion of carbenes into the N-H bond of unsubstituted carbazoles.[45] Thus formed, *N*-substituted carbazole **56a** was next transformed in three steps (DIBAL-H reduction of the ester, mesylation of the resulting alcohol **56b** and thermal dealkylating cyclization) into 1,2-dihydro-[1,4]oxazino[2,3,4-*j,k*]carbazole **57** (Scheme 24). This rapid access of the core of 5-HT6 receptor antagonist **5** (Figure 2) shows the interest of this process as it avoids a late-stage Fischer indolization to build the oxazinoindole skeleton.[6]

Scheme 24. Three-steps synthesis of oxazinoindole **57**.

Their analogues oxazinoindoles **59** compounds having a C=O on C1 in place of a benzene ring were synthesized by mixing **58** with ethyl bromoacetate in the presence of K_2CO_3 [46] (Scheme 25).

Scheme 25. Synthesis and representative examples of oxazinocarbazole **59**.

The solvent played an important role in this reaction as in acetone, oxazinocarbazoles **59** were obtained in a two-steps “one pot” manner with average yields, whereas in DMF, it was reported that the cyclization occurred between the OH and the aldehyde function to give a benzofuran derivative.[47] A possible mechanism evoked an initial attack of the phenolate on the BrCH_2 -group followed by a *N*-cyclization reaction on the ester.

It was also reported by the same group that 9*H*-carbazol-1-ol substrates **60** reacted as nucleophilic clamps with oxalyl chloride in acidic media to give the corresponding [1,4]oxazio[2,3,4-*j,k*]carbazole-1,2-diones **61** with good yields[48] (Scheme 26).

Scheme 26. Synthesis and representative examples of [1,4]oxazio[2,3,4-*j,k*]carbazole-1,2-diones **61**.

Westwood showed, in a study dedicated to the oxidative cleavage of oxazinocarbazoles **63**, that such compounds were obtained from the reduction and internal cyclization of *N*-substituted tetrahydro-1*H*-carbazol-1-one derivatives **62**[49] (Scheme 27).

Scheme 27. Two-steps one-pot synthesis oxazinocarbazoles **63** from keto-derivatives **62**.

Ketones **62** which were obtained in four steps from cyclanones ($n = 0-3$), were reduced by NaBH_4 to give the expected oxazinocarbazoles **63** after a $\text{S}_{\text{N}}2$ cyclization reaction. The reduction-cyclization process was successfully applied to oxazinocarbazoles analogues containing a seven- or an eight-membered ring but failed with five-membered rings. A

chiral version was also proposed using the Corey-Bakshi-Shibata catalyst[50] allowing an asymmetric reduction of the ketone, the resulting alcohol (e.e. = 98%) cyclizing in a second step in the presence of *t*BuOK at rt.

Another example of a lactonization process giving access to oxazinoindolone **65** was reported by Kuckländer from the internal cyclization of keto-acid **64** followed by dehydration of the resulting tertiary alcohol[51] (Scheme 28).

Scheme 28. Cyclization and dehydration of ketone **64** in acetic anhydride.

The last example of this section dealing with the construction of tetracycles containing the oxazinoindole nucleus (Scheme 29) was described by Bandini[21] in a study concerning the synthesis of polycyclic fused indoles by gold(I)-catalyzed reaction, previously described in Scheme 10. Even if the synthesis of diol **66** is relatively tedious, the three-consecutive gold-assisted ring-closing events (first hydroamination followed by (i) an alkoxylation reaction (ii) a hydroindoylation and (iii) a final protodeauration) constitute a very elegant process to prepare oxazinocarbazole **67** in a "one-pot" manner.

Scheme 29. Hydroamination/alkoxylation/hydroindoylation process producing **67**.

The final example of this review concerns the synthesis of complicated pentacyclic and hexacyclic systems containing the oxazinoindole core. To this end, Padwa studied the bimolecular [3+2] cycloadditions of α -diazamide compound **68** with a variety of dipolarophiles under Rh(II) catalysis[52] (Scheme 30).

Scheme 30. Dipolar cycloaddition of **68** with dipolarophiles and cycloaddition of **70** under Rh(II)-catalysis.

In the presence of Rh₂(OAc)₄, heating α -diazocompound **68** generates a rhodacarbenoid which undergoes a cyclization with the neighboring amide function. A subsequent cycloaddition of the intermediate thus formed with various

dipolarophiles leads to pentacyclic derivatives **69** according to a [3+2] cycloaddition. Using this intramolecular dipolar-cycloaddition, England and Padwa also synthesized the hexacyclic derivative **71** from **70** with an excellent yield of 95% and a total diastereoselectivity.[53] This oxa-hexacyclic compound **71** was then transformed in six steps into ($\pm$)-3*H*-epivincamine, an alkaloid which exhibits strong vasodilatation activity.[54]

5. Conclusion

In this review, we have seen that there are a wide variety of methods for accessing to the oxazinoindolic skeleton. The presence of an oxygen atom in this tricyclic heterocycle makes its synthesis simpler (hetero-Michael, alkyne hydroalkoxylation, lactonization,...) than the one of pyridoindole, its carbonaceous counterpart.[7] This simplicity of synthesis should encourage chemists to develop new ways of accessing this motif that are compatible with environmental requirements and mainly catalytic accesses. Indeed, the oxazinoindole motive is of major interest in medicinal chemistry since it is found in many compounds with significant biological activity and, in heterocyclic chemistry since it can be used as a synthetic intermediate in the construction of complex polycyclic systems. The numerous and recent publications concerning heterocyclic systems incorporating an indole ring such as pyridoindoles, oxazinoindoles or pyrazinoindoles[55] show unambiguously that modern access to these heterocycles is sought from a synthetic point of view but also from a therapeutic point of view as shown by the very numerous applications.

Conflict of Interest

The authors declare no conflict of interest.

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