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Synthesis of spirobenzoxazine frameworks from biomass-derived chloromethylfurfural *via* a key intramolecular aza-Piancatelli reaction.

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Abstract

The synthesis of original tricyclic compounds featuring both 3,4-dihydro-*2H*-benzo[b][1,4] oxazine and cyclopentenone cores was addressed. Starting from the biobased 5-chloromethylfurfural, a robust 3-step sequence to key aryl furylcarbinol substrates supported a diastereoselective intramolecular aza Piancatelli reaction, effective under both Lewis and Brønsted catalysis. A scope of thirteen diversely substituted spirobenzoxazines was achieved and some limits could be also drawn. Seventeen diastereomerically defined spirocyclic molecules were overall isolated. All the synthesized compounds were characterized by NMR analysis. The structure and relative stereochemistry of spirocycles were confirmed by single-crystal X-ray diffraction (XRD) studies. An extension to analogous compound featuring a quinoxaline

moiety could also be initiated. Preliminary evaluations of biological activities were also performed.

Keywords

spiro-heterocyclic scaffolds, biomass-derived chemical platform, multi-step synthesis, intramolecular aza-Piancatelli reaction

Introduction

The development of novel strategies to synthesize functional compounds featuring a 1,4-benzoxazine nucleus is highly driven by its structural properties [1-3] and expected biological activities [4]. 2-Unsubstituted 3-oxo 2*H*-1,4-benzoxazin-3(4*H*)-ones such as bemoradan [5], fluconazole analogs [6] or olodaterol, developed and marketed as Striverdi Respimat® by Boehringer Ingelheim, proved to be vasodilatator, antifungal, or agonist of some β2 adrenergic human receptors used for the treatment of chronic obstructive pulmonary disease (COPD) respectively (Figure 1) [7]. Ofloxacin or the enantiomerically pure levofloxacin are ones of the representative compounds displaying antibiotic activity [8]. 2,3-Dihydro-1,4-benzoxazine compounds were shown to be effective inhibitors of angiogenesis [9,10] and a series of 3,4-diarylated compounds like **1** also recently showed promising anti-cancer activity (IC_{50} 7.86-16.2 µM against 5 cancer cell lines) [11]. Spirocyclic compounds have also been attracting high synthetic interest given their intrinsic structural properties and a wide range of applications. Comprising organic compounds in which, two or more saturated rings, share one (most frequently) or more atoms [12], spirocycles are widely targeted for their inherent higher saturation and significant three-dimensional characteristics, compared to flat heterocyclic compounds, making them widely used in the fields of

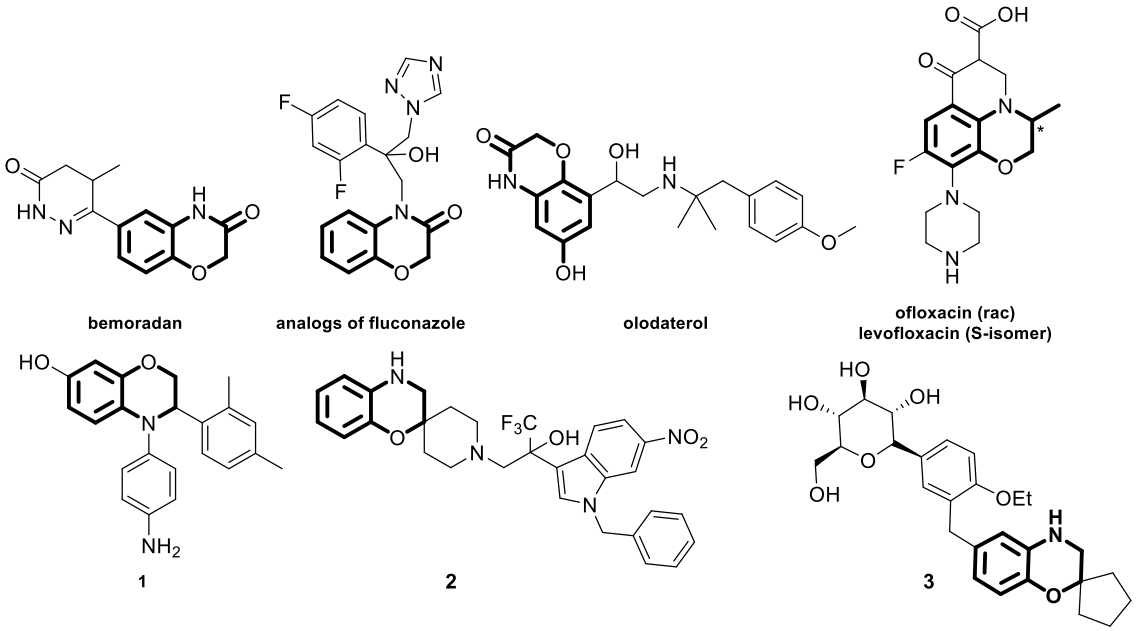
synthetic chemistry [13], materials chemistry[14], supramolecular chemistry and drug discovery [15-18].

Combining the incorporation of a benzoxazine moiety into a spirocyclic structure might lead to the discovery of unknown active compounds. Indeed, both compounds **2** and **3**, featuring a spirocyclic junction in the position 2 of dihydro-1,4-benzoxazines were patented for anti-inflammatory and anti-diabetic activities respectively [19,20]. Fused 2-substituted 1,4-dihydrobenzoxazines and oxindoles were already prepared [21] and synthesis of spirobenzoxazines featuring a motif indane [22,23], indene [24,25] or maleimide [26] after annulation of ketimine and nitroolefin, chalcone or alkyne mainly relied on Rh(III)-catalyzed C-H functionalization/annulation on 1,4-benzoxazines cores. Concomitant benzoxazine ring-closing with formation of the spirocyclic center was also described [27-29] albeit more rarely in the alpha position to the nitrogen [30]. Tandem reactions efficiently combined a cyclopentenone resulting from a Piancatelli reaction and benzoxazine or thioazine respectively: they were catalyzed by $La(OTf)_3$ or $In(OTf)_3$ [31] or more recently by tripentafluorophenyl borane [32], albeit leading to a two-atom junction (Scheme 1A).

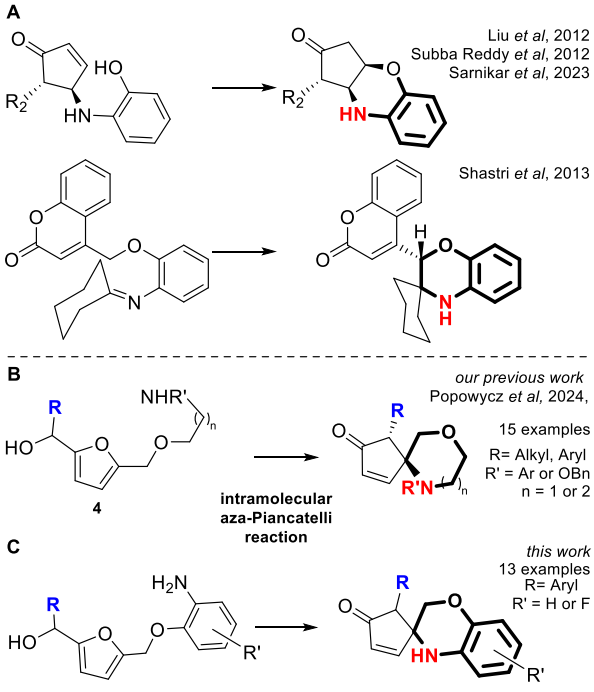
We recently developed the access to original azaspirocycles performing an intramolecular diastereoselective aza-Piancatelli reaction onto furylcarbinol precursors **4** prepared from biobased furan compounds like 5-hydroxymethylfurfural **HMF** [33]. As mentioned above, a few spirobenzoxazines, particularly featuring an aza-junction or a fused cyclopentenone (Scheme 1A) were described. Herein, we propose a new strategy using an intramolecular aza-Piancatelli reaction at the end of a multi-step sequence (Scheme 1B) to build both cycles in one step. Beyond access to novel aza-spirocycles, with benzoxazine-fused-cyclopentenone scaffolds, an interesting diversity might be explored by variation of the substituents on the α-position of ketone, by

modulation of the furylcarbinol substituent (R) or the substituents on aromatic rings (R').

Figure 1: Representative compounds with benzoxazine nucleus



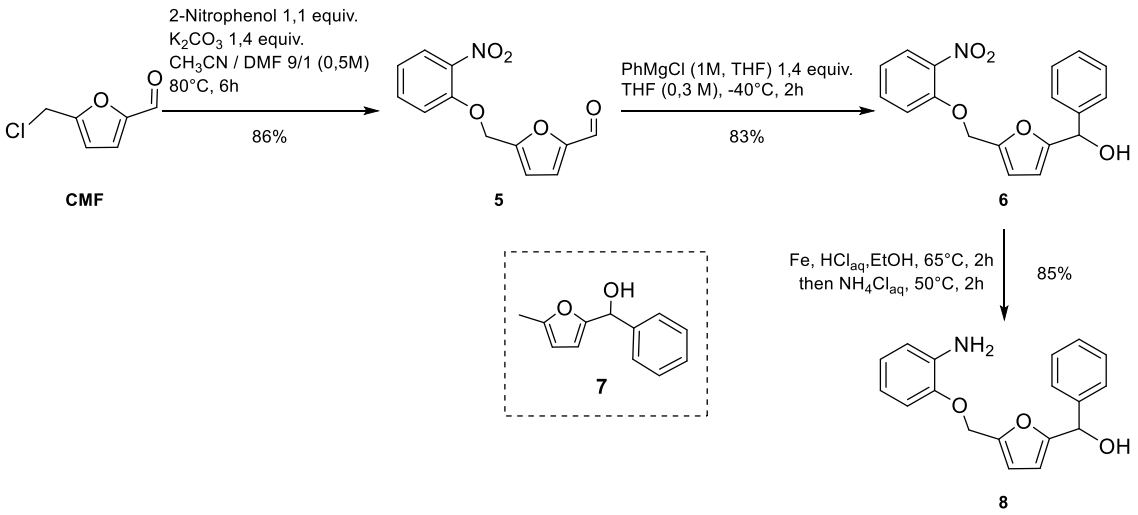
Scheme 1: A) Known strategies towards spirobenzoxazines with an alpha aza-junction; B) Our previous work on the synthesis of azaspirocycles from HMF; C) Our novel strategy towards spirobenzoxazines



Results and Discussion

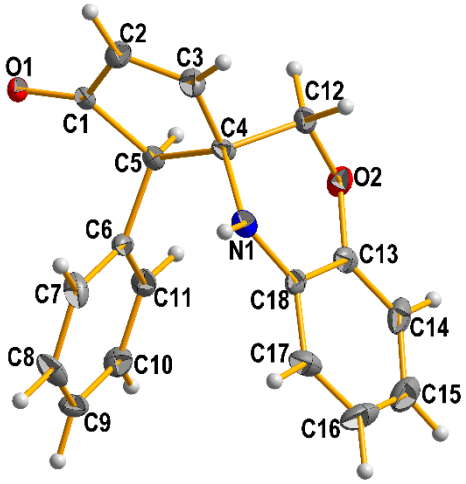
From our previous studies, we anticipated that the insertion of an orthophenylene linker between the hydroxymethyl furan core and the nucleophilic aniline might favor spirocyclisation (Scheme 1B). Access to furylcarbinols featuring an orthophenoxy aniline was required to engage into an intramolecular aza-Piancatelli reaction. A new synthetic sequence started from biobased chloromethylfurfural (**CMF**), easily prepared from **HMF** [34,35] was investigated. Coupling ortho-nitrophenol to **CMF** in the presence of potassium carbonate [36,37] then adding phenylmagnesium chloride (1M in THF) at -40°C onto aldehyde **5** led to the nitroarene **6** with 71% yield over two steps. When the reduction of the nitro group with hydrazine hydrate was carried out in ethanol at room temperature rather than 60°C, pseudo benzylic cleavage, leading to isolation of side-product **7** could be circumvented, the model furylcarbinol **8** could be obtained with 75% yield [39]. An even improved 85% yield could be eventually reached under milder conditions using activated iron in ethanol [40] (Scheme 2).

Scheme 2: Synthetic sequence towards the model substrate furylcarbinol **8**



The model furylcarbinol **8** could then be submitted to an intramolecular aza-Piancatelli reaction (Table 1). Using catalytic $Dy(OTf)_3$ (5 mol%) as suggested by Read de Alaniz [41] in nitromethane [42], a mixture of diastereomers **9** in a ratio 4/1 was first obtained with 49% isolated yield (entry 1). After recrystallization of the minor compound **9'**, X-ray analysis confirmed the relative *cis* configuration of the nitrogen (Figure 2) and the phenyl substituent in agreement with an expected *trans*-diastereoselectivity of this process [42].

Figure 2: ORTEP Diagram of the aza-Piancatelli minor product **9'** from X-ray analysis**,** CCDC 2454517



Once this proof of concept validated, a screening of the conditions was performed, varying the nature and the loading of the catalyst, the temperature, the solvent and the reaction time to study the influence on yield and diastereoselectivity (see complementary set of conditions in supporting information). With a combination of Ca(II) salt and tetrabutylammonium hexafluorophosphate (5 mol%) as previously reported system [43], similar results were obtained whether using commercial or lab-made $Ca(NTf_2)_2$ (entries 2, 3) [44,45]. With the Brønsted acid *p*-TSA (entry 4) [46],

slightly better yield and diastereoselectivity were both observed, as with *N*-trifluoromethylphosphoramidate [47] albeit in 4h (entry 5). Increasing loading charge to 10 mol% had positive impact (entry 6) but better results were obtained by running the reaction in acetonitrile in the presence of 5 mol % of $Dy(OTf)_3$ (entry 7). Complete conversion could also be obtained in less than 1h, both with $Dy(OTf)_3$ or *p*-TSA with very good yields and repeatable diastereoselectivities (entries 7-8). In the presence of other lanthanides salts or previously described active catalysts such as boronic acids [48], conversion remained incomplete or lower yields were measured (entry 9 and supporting information). In acidic HFIP used as solvent [49], the conversion was effective at room temperature albeit requiring more than 5 hours to be complete providing the mixture of diastereomers in a range of 50-67% but with a surprising inversion of diastereoselectivity (entries 10-13). In the absence of specific computational studies, we may only make the hypothesis that in HFIP, particular hydrogen bonds might stabilize one conformation of the pentadienyl cation over another accounting for a conrotatory torquoselectivity in favor of the *cis* diastereomer **9'** (Table 1) [50,51]. The stability of these original spirocycles was confirmed by NMR both after one month at room temperature or six months at 4°C.

To target molecular diversity, we first explored the reactivity of various furylcarbinols with a range of substituents (Scheme 3). The spirocyclisation of each of arylfurylcarbinols **8a-l** (Table 2), obtained similarly to **8** (see Supporting information for details), was carried out under the two best sets of conditions identified by the previous optimization. Globally fair good, isolated yields for compounds **9a-g** were obtained in a range of 55-70% featuring electron-donating or electron-withdrawing groups. Slightly better results were obtained for conditions A ($Dy(OTf)_3$, 5 mol%) compared to conditions B (*p*-TSA, 5 mol%) while these latter ones led to comparable or better measured diastereoselectivities. Unfortunately, unsatisfying outcomes did not allow

proper characterization of products from alkylfurylcarbinols. As expected *para*-trifluoromethylphenyl furylcarbinol **8h** showed a lower reactivity requiring 24 hours at 110°C in a sealed tube.

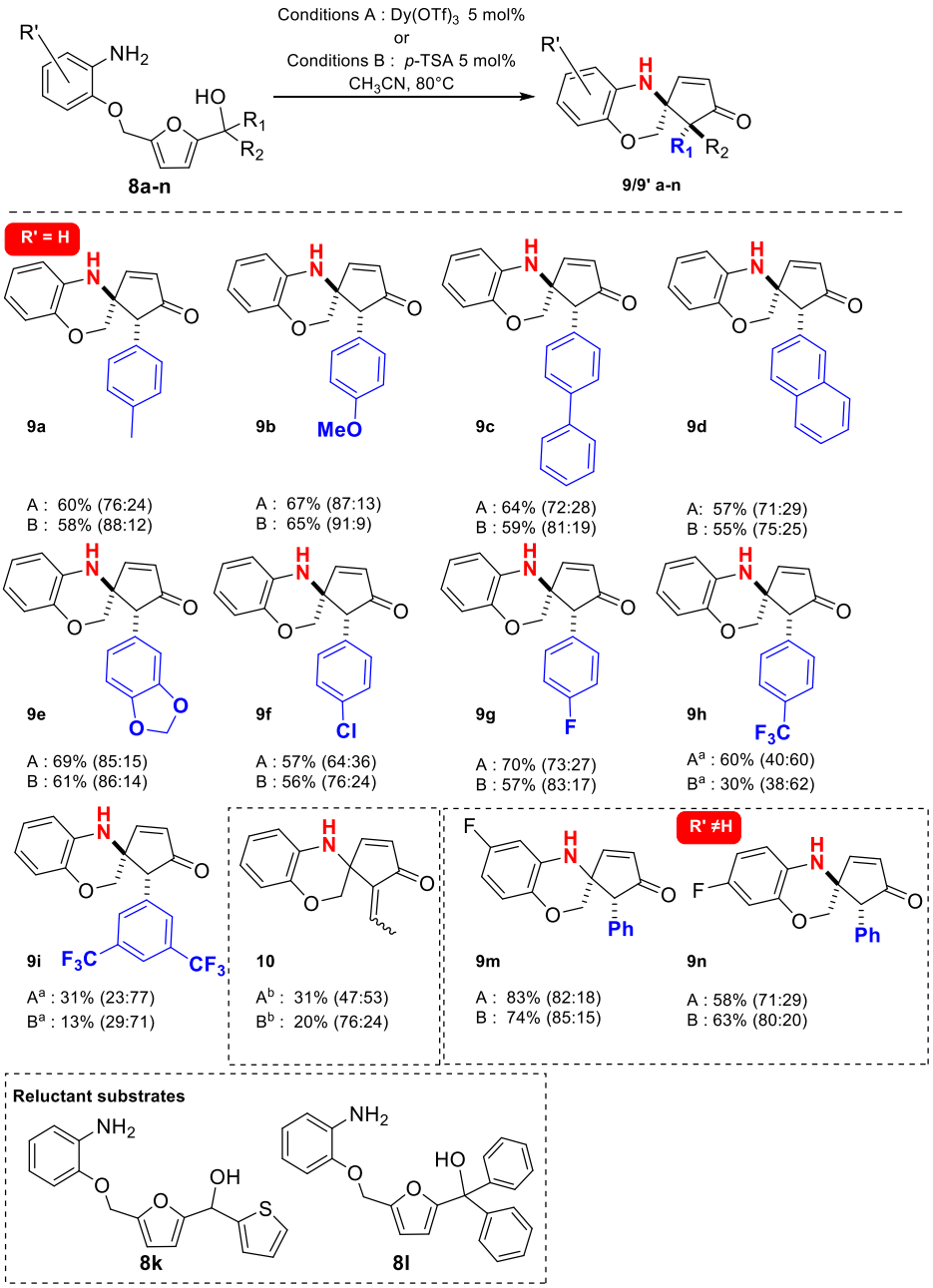
Table 1: Optimization of the conditions for the aza-Piancatelli reaction[a].

Entry	Cat (mol%)	Solvent	Temp. (°C)	Time (h)	Yield[b] (dr[c])
1	$Dy(OTf)_3$ (5)	CH_3NO_2	80	0.5	49% (80/20)
2	$Ca(NTf_2)_2$ (5)[d], nBu_4NPF_6 (5)	CH_3NO_2	100	0.5	53% (72/28)
3	$Ca(NTf_2)_2$ (5)[e], nBu_4NPF_6 (5l%)	CH_3NO_2	100	0.5	50% (71/29)
4	*p*-TSA (5)	CH_3NO_2	80	0.5	57% (87/13)
5	*N*Tf -phosphoramidate (10)	DCE	80	4	54% (85/15)
6	$Dy(OTf)_3$ (10)	CH_3NO_2	80	0.5	66% (75/25)
7	**$Dy(OTf)_3$ (5)**	**CH_3CN**	**80**	**0.5**	**82% (71/29)**
8	***p*-TSA (5)**	**CH_3CN**	**80**	**0.5**	**77% (81/19)**
9	$Sc(OTf)_3$ (5)	CH_3CN	80	0.5	65% (76/24)
10	$Dy(OTf)_3$ (5)	HFIP	r.t	24	57% (28/72)
11	$Ca(NTf_2)_2$ (5)[d], nBu_4NPF_6 (5)	HFIP	r.t	5	67% (36/64)
12	$Ca(NTf_2)_2$ (5)[e], nBu_4NPF_6 (5)	HFIP	r.t	5	55% (29/71)
13	*p*-TSA (5)	HFIP	r.t	5	50% (30/70)

[a] Conditions: **8** (about 0.34 mmol), and catalyst in the corresponding solvent (0.03M) at 80°C for the indicated time; [b] Isolated yield; [c] dr in all cases determined by ^1H NMR in $CDCl_3$ at 298K analysis of the crude material. See supporting information for a more complete table with the dr determination of the isolated mixture of both diastereomers;

[d] Commercial $Ca(NTf_2)_2$; [e] Lab-made $Ca(NTf_2)_2$

Scheme 3: Substrate scope towards diversely substituted spirobenzoxazines-cyclopentenones*



*for clarity only *trans* diastereomer is drawn; isolated yields of the mixture of diastereomers are given for both conditions (see Table 1); (diastereomeric ratio is indicated)

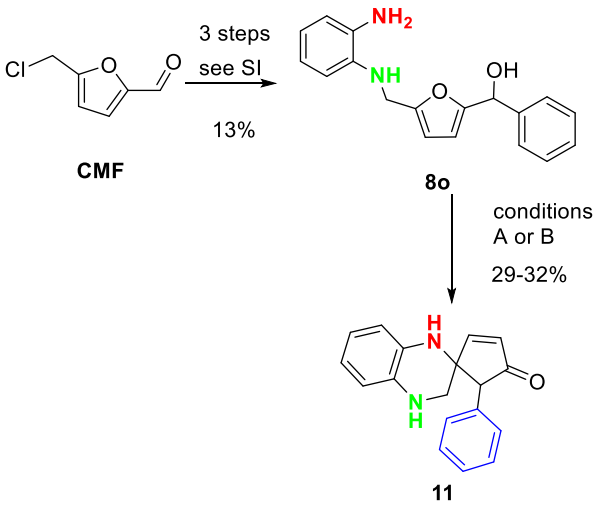
[a] 110°C in a sealed tube for 24h

[b] 80°C for 24h in a round-bottom flask

An unexplained slight inversion of stereoselectivity was noticed whether with Lewis or Brønsted catalysis in favor of **9'h**. Not surprisingly, *bis*-3,5-trifluoromethylphenyl furylcarbinol **8i** only reacted partially even after 24h leading to degradation and only very poor yields of the expected compounds **9i** but again with an inverted unexplained diastereomeric ratio in favor of **9'i**. Vinylfurylcarbinol **8j** was reacted for 24h at 80°C to convert the mixture towards diastereomeric spirocyclic compounds **10** with an ethylidene-2-cyclopentenone moiety after isomerization albeit with low yields. Regarding thienyl furylcarbinol **8k** or tertiary diphenyl furylcarbinol **8l**, both identified conditions led to poor conversion even after several hours in refluxing CH_3CN. To further expand the substrate scope, we also investigated the introduction of substituents on the benzoxazine moiety starting from other substituted nitrophenols. Ovofloxacin structure and synthesis inspired us to access compounds **9m** and **9n** issued from 4-fluoro-2-nitrophenol and from 5-fluoro-2-nitrophenol respectively [52]. Under both identified conditions, better results were obtained for the fluorine atom in *meta* than in *para* position of the benzoxazine nitrogen atom (**9m** *vs* **9n** : 83% *vs* 58% and 74% *vs* 63%). Further modification might be offered by potential fluorine substitution to expand this series of compounds.

Moreover, starting a sequence from the *ortho*-nitroaniline, the synthesis of a spiroquinoxaline, analogous to spirobenzoxazine **9**, featuring two endocyclic nitrogen atoms was addressed. Quinoxalines, like benzoxazines, represent an important class of compounds serving as core structure of various natural products. Once the furylcarbinol **8o** prepared (Scheme 4), intramolecular aza-Piancatelli led to the unknown spiroquinoxalines **11** and **11'**. Albeit not optimized, thorough details for the synthesis sequence as well as structural characterizations of separated diastereomers are given in the supporting information.

Scheme 4: Extension to a spiroquinoxaline framework



Conclusion

Starting from biobased platform chloromethylfurfural, functionalized aryl furyl carbinols with an amino phenoxyl lateral chain were prepared through a robust 3-step sequence. An intramolecular aza-Piancatelli reaction could lead to original spirocyclic structures incorporating fused cyclopentenones and dihydro-1,4-benzoxazines under Lewis or Brønsted acid catalysis. With some introduced chemical diversity, and the isolation of pure diastereomerically defined molecules, an implementation to chemical libraries is currently being prepared for a complementary screening of biological activities. Preliminary results from an evaluation of the cytotoxicity of isolated **9** and **9'** on five human cancer cells indeed revealed a decrease in cells viability superior to 50% at 10 µM [53].

Supporting Information

The data supporting this article have been included as part of the Supplementary Information. Experimental procedures, characterization data, copies of NMR ^{1}H and

$^{13}C\{1H]$ spectra for 56 compounds **5** to **11'** and X-ray cif file are provided. Crystallographic data for **9'** has been deposited at the CCDC under 2454517.

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