Synthesis and biological evaluation of 3,4-dihydro-1H-[1,4] oxazepino [6,5,4-hi] indol-1-ones and 4,6-dihydrooxepino [5,4,3-cd] indol-1(3H)-ones as Mycobacterium tuberculosis inhibitors

Champciaux, Bastien; Raynaud, Clément; Viljoen, Albertus; Chene, Loïc; Thibonnet, Jérôme; Vincent, Stéphane P.; Kremer, Laurent; Thiery, Emilie

Published in:
Bioorganic & medicinal chemistry

DOI:
10.1016/j.bmc.2021.116248

Publication date:
2021

Document Version
Publisher's PDF, also known as Version of record

Bioorg. Med. Chem. 43 (2021) 116248

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis and biological evaluation of 3,4-dihydro-1*H*-[1,4] oxazepino [6,5,4-*hi*] indol-1-ones and 4,6-dihydrooxepino [5,4,3-*cd*] indol-1(3*H*)-ones as *Mycobacterium tuberculosis* inhibitors

Bastien Champciaux [a], Clément Raynaud [b], Albertus Viljoen [b,1], Loïc Chene [c], Jérôme Thibonnet [a], Stéphane P. Vincent [c], Laurent Kremer [b,d], Emilie Thiery [a,*]

[a] Laboratoire Synthèse et Isolement de Molécules Bioactives (SIMBA, EA 7502), Université de Tours, Faculté de Pharmacie, Parc de Grandmont, 31 Avenue Monge, 37200 Tours, France
[b] Institut de Recherche en Infectiologie de Montpellier (IRIM), CNRS UMR 9004, Université de Montpellier, 34293 Montpellier, France
[c] Department of Chemistry, University of Namur, Rue de Bruxelles 61, 5000 Namur, Belgium
[d] INSERM, IRIM, 34293 Montpellier, France

ARTICLE INFO

Keywords:
Heterocycles
Indoles
Mycobacterium tuberculosis
Inhibitor

ABSTRACT

This study focuses on the synthesis of 1,7- and 3,4-indole-fused lactones *via* a simple and efficient reaction sequence. The functionalization of these "oxazepino-indole" and "oxepino-indole" tricycles is carried out by palladium catalysed C—C coupling, nucleophilic substitution or 1,3-dipolar cycloaddition. The evaluation of their activity against *Mycobacterium tuberculosis* shows that the "oxazepino-indole" structure is a new inhibitor of *M. tuberculosis* growth *in vitro*.

1. Introduction

Due to their multiple biological properties, heterocycles have a central place in medicinal chemistry. Amongst all, the indole is one of the most important and attractive heterocycles, often reported as privileged scaffolds for the development of new therapeutic agents. The synthesis of polycyclic indole derivatives creates a broad structural diversity by varying the cyclic junction and the nature of the fused rings. Indoles and their fused derivatives exhibit many interesting pharmacological properties, including anti-inflammatory, antitubercular, antidiabetic, anti-HIV or anticonvulsant (Figure 1).[1] We have been particularly interested in indole-fused lactones since the combination of these two pharmacophores should offer scaffolds of interest in medicinal chemistry. Although the 2,3-indole-fused lactone structures have been known for a hundred years, new synthetic strategies to access these structures are still to be developed.[2] Noteworthy, some synthetic 1,2-indole-fused lactones[3] have been reported as anticancer,[4] anti-inflammatory[5] and anti-tuberculosis[6] agents.

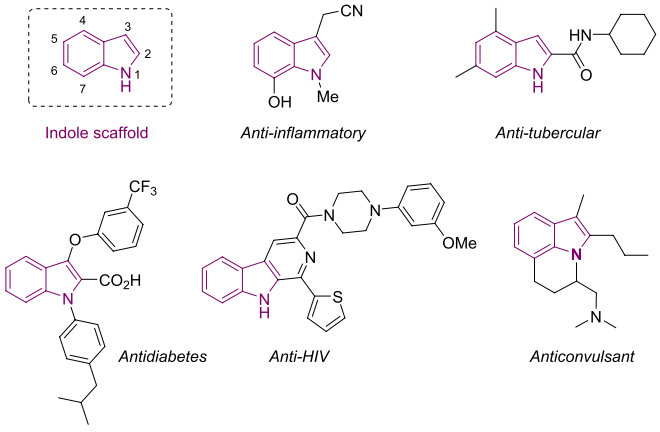


Fig. 1. Representative indole-containing bioactive scaffolds.

* Corresponding author.
E-mail address: emilie.thiery@univ-tours.fr (E. Thiery).
[1] Louvain Institute of Biomolecular Science and Technology, UCLouvain, Croix du Sud, 4-5, bte L7.07.07, B-1348 Louvain-la-Neuve, Belgium.

https://doi.org/10.1016/j.bmc.2021.116248
Received 1 April 2021; Received in revised form 13 May 2021; Accepted 28 May 2021
Available online 7 June 2021

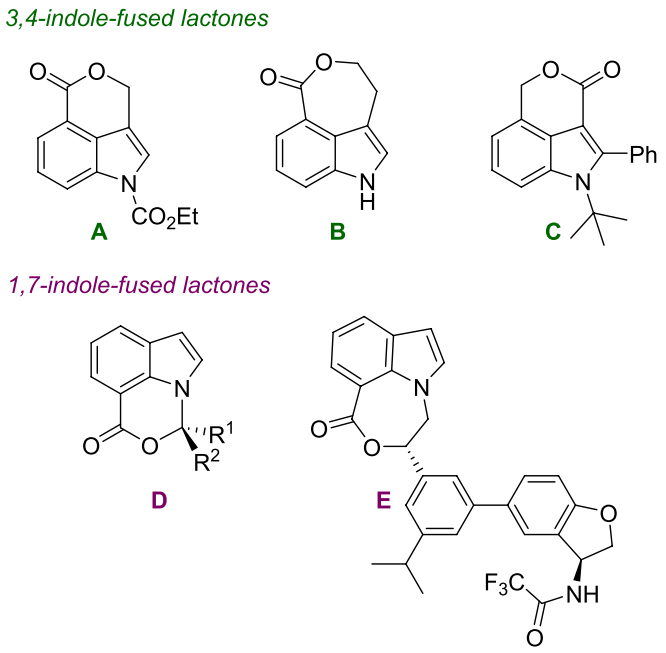


Fig. 2. 3,4- and 1,7-indole-fused lactones described in literature.

To the best of our knowledge, 3,4- and 1,7-indole-fused lactones have rarely been described in the literature. The first 3,4-indole-fused lactone was described in 1994 (Figure 2, **A**).[7] It results from the palladium catalysed carbonylation of a (4-iodo-1*H*-indol-3-yl) methanol under high pressure. In 2010, the 7-membered lactone **B** was obtained as an undesired product during the total synthesis of (–) – Aurantioclavin (Figure 2).[8] In 2019, a compound of similar structure was described as a degradation product of Rucaparib.[9] Finally, 3,4-indole fused lactone **C** was prepared through cascade carbopalladation and C—H amination (Figure 2).[10] 1,7-Indole-fused lactones have only recently been reported in the literature. In 2019, the addition of a carbene catalyst to indole aldehyde was shown to lead to the formation of chiral oxazinoindoles **D** (Figure 2).[11] In 2020, the 7-membered lactone **E** was observed during the synthesis of *N*-substituted indole as factor XIa inhibitors.[12]

Our previous work has enabled us to discover the anti-mycobacterial potential of "oxazino-indoles" (Figure 3).[6] Tuberculosis (TB), one of the world's deadliest infectious diseases, responsible for the death of 1.8 million people each year, is a global priority for research and development today.[13] The emergence of resistant strains of *Mycobacterium tuberculosis* (*Mt*) makes treatments ineffective and leads to the use of a combination of several antibiotics. The development of new molecular structures is thus necessary to provide new therapeutic options for the treatment of the disease.[14] We thus focused our efforts on the synthesis and functionalization of 1,7 and 3,4 indole-fused lactones, which are poorly described in the literature (Figure 3) and report their *in vitro* anti-tubercular activities.

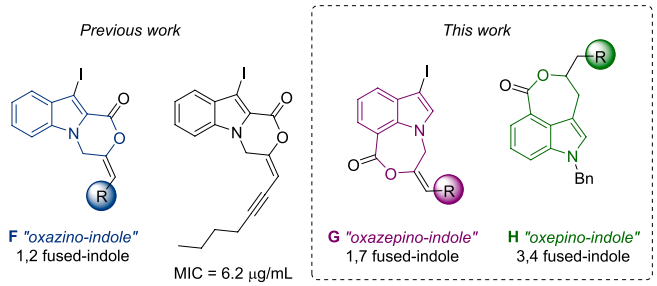
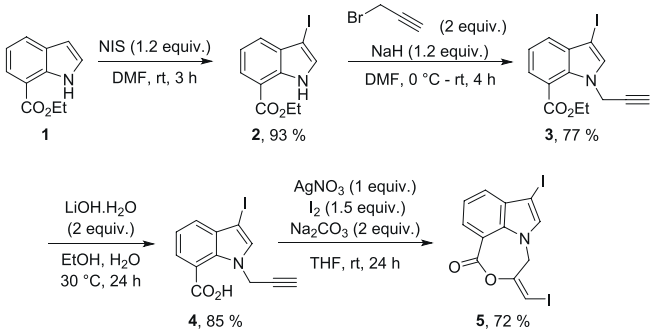


Fig. 3. Fused tricyclic indoles.

2. Results and discussion

2.1. Synthesis of "oxazepino-indole" G

Based on the work previously developed in our laboratory,[3] a synthetic route for obtaining the 1–7 junction indole tricycles has been considered from commercial methyl indole-1*H*-7-carboxylate **1** (Scheme 1). The iodination/propargylation/saponification reaction sequence generates compound **4** in good yields. According to a known protocol,[15] the 7-*exo-trig* iodocyclization of compound **4** is performed in the presence of diiodine, silver nitrate and sodium carbonate in tetrahydrofuran. Iodolactonization is regio and stereoselective, and only leads to *E* configured oxepino-indole **5**, whose structure was confirmed by X-ray analysis (Figure 4, Supporting Information).



Scheme 1. Synthesis of oxazepino-indole **5.**

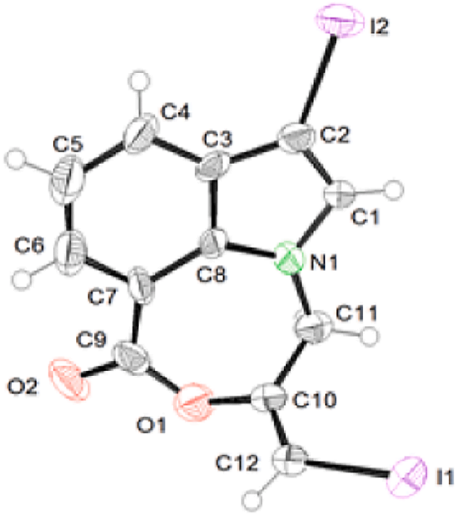
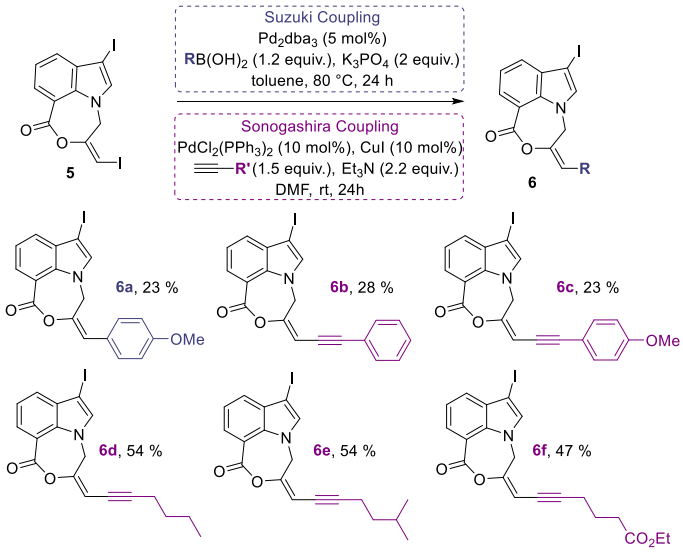


Fig. 4. X-ray structure of oxazepino-indole **5.**

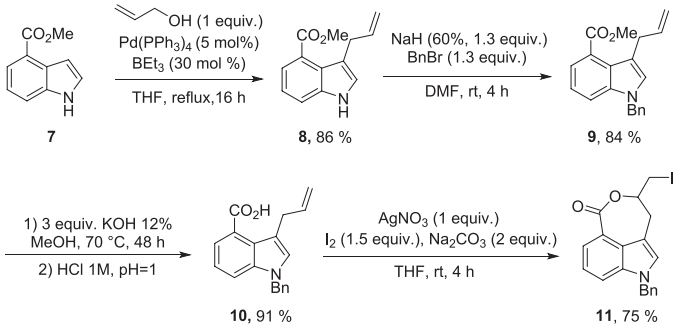
Compound **5** was then engaged in C—C coupling reactions (Scheme 2). Under standard Suzuki-Miyaura or Sonogashira reaction conditions, compound **5** leads to coupling products **6a** or **6b-f**, respectively, with modest yields. The reaction is regioselective since only the vinyl iodine is functionnalized. The low yields are mainly due to the delicate purification of the **6a-f** tricyclic compounds.



Scheme 2. Functionalization of oxazepino-indole **5** by C—C coupling.

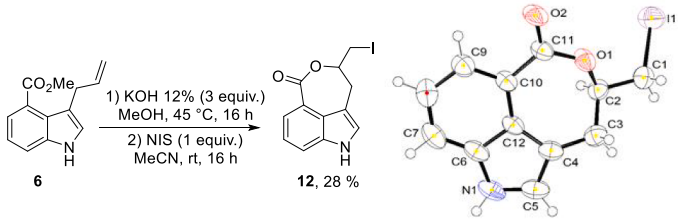
2.2. Synthesis of "oxepino-indole" H

A few studies reported in the literature describe the synthesis of "oxepino-indole" structure **H** (Figure 3) but do not provide access to simple functionalization of the lactone for pharmacomodulation.[7,8] This explains why an alternative synthetic route was considered to benefit, after cyclization, from an easily modulated position (Scheme 3). According to a procedure described in the literature,[16] the allylation in position C-3 of methyl 1*H*-indole-4-carboxylate **7** is carried out in the presence of palladium (0) and triethylborane. The reaction is chemoselective and the expected side-product of *N*-alkylation is observed in negligible amounts. Then, compound **8** is *N*-benzylated in the presence of sodium hydride and allyl bromide in dimethylformamide. Saponification of compound **9** leads to carboxylic acid **10** with a very high yield. Then, the regioselective 7-*exo-tet* iodolactonization of compound **10** conducts only to the oxepino-indole **11**.



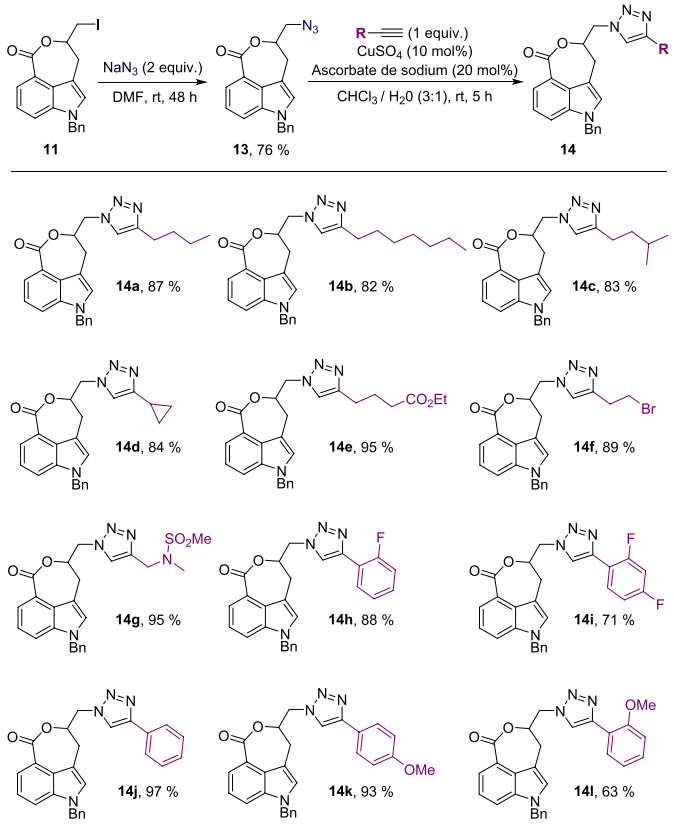
Scheme 3. Synthesis of "oxepino-indole" **11**.

A one-pot saponification/iodocyclization sequence was carried out from compound **6** (Scheme 4). The tricycle **12** was obtained with a yield of 28%. The "oxepino-indole" structure was confirmed by X-ray analysis (Scheme 4, Supporting Information).



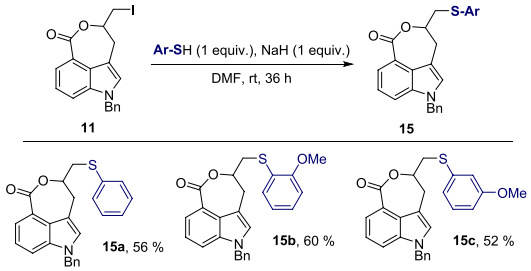
Scheme 4. Synthesis of compound **12** and X-ray structure of its enantiomer *R*.

In order to achieve various functionalizations, compound **11** was then engaged in nucleophilic substitution reactions. The introduction of an azide made it possible to obtain compound **13** in order to prepare triazoles *via* a 1,3-dipolar cycloaddition (Scheme 5). Thus compound **13**, in the presence of copper sulfate, sodium ascorbate and various aliphatic or aryl alkynes, allowed the synthesis of 12 compounds **14a-l** with good yields of 63 to 97%. The structure of the triazole was then confirmed by X-ray diffraction analysis of compound **14j** (See Supporting Information).



Scheme 5. Synthesis of compounds **14**: azidation and 1,3-dipolar cycloaddition of compound **11**.

Finally, the nucleophilc substitution of compound **11** by an aromatic thiol led to the preparation of compounds **15** with good yields (Scheme 6).



Scheme 6. Synthesis of compounds **15**: nucleophilic substitution of compound **11.**

2.3. Antitubercular activity

The anti-tuberculosis activity of the "oxazepino-indole" compounds **5**–**6** and of the racemic mixtures of the "oxepino-indole" **14**–**15** was then tested by determining the minimum inhibitory concentration (MIC) against M. tuberculosis mc26230 (Table 1). All compounds of the "oxazepino-indole" series, except compound **6a**, display MICs below or equal to 1.6 μg/mL, thus highlighting their potent anti-mycobacterial activity (entries 1–7). On the other hand, only halogenated compounds **11** and **14f** of the "oxepino-indole" series show an anti-tubercular activity (entries 8 and 14).

Based on our previous work,[6] one of the potential targets of these indole tricycles is UDP-galactopyranose mutase (UGM), involved in the biosynthesis of the *M. tuberculosis* cell wall.[17] The dissociation constants (K_d's) of the best anti-mycobacterial indoles for UGM were determined using a known fluorescence polarization assay.[18] However, only compounds **5** and **6c** exhibited a measurable K_d and only showed a moderate affinity for *Mt*-UGM (K_d = 138.2 ± 1.7 μM and 72.9 ± 1.8 μM, respectively). These affinities for *Mt*-UGM do not account for the powerful antimycobacterial activities (MICs) measured for molecule **5** and **6a-f** whose biological targets within *Mt* remain to be identified.

Table 1
MIC values of "oxazepino-indole" and "oxepino-indole" compounds.

Entry	Compound	MIC[a][μg/mL]
1	**5**	1.6
2	**6a**	>100
3	**6b**	0.4
4	**6c**	0.2
5	**6d**	0.4
6	**6e**	0.2
7	**6f**	0.4
8	**11**	12.5
9	**14a**	>100
10	**14b**	>100
11	**14c**	>100
12	**14d**	>100
13	**14e**	>100
14	**14f**	25
15	**14 g**	>100
16	**14 h**	>100
17	**14i**	>100
18	**14j**	>100
19	**14 k**	>100
20	**14 l**	>100
21	**15a**	>100
22	**15b**	>100
23	**15c**	>100

[a] The concentrations tested varied over a discrete 2-fold range. MIC determinations were performed in duplicate on three independent experiments, with zero variation between experiments.

3. Conclusion

Using a simple and efficient method, we have synthesized new fused-indoles whose anti-mycobacterial potential has been evaluated against *M. tuberculosis*. Our synthetic strategy was also designed to provide access to libraries of these poorly studied scaffolds by 1,3-dipolar cycloaddition of nucleophilic substitution using aromatic thiols. The biological investigation of this new series of indole derivatives shows that 3,4-dihydro-1*H*-[1,4] oxazepino [6,5,4-*hi*] indol-1-ones **6b-f** exhibited potent anti-tubercular activity. The *Mtb* primary target(s) of these compounds needs to be investigated in future studies.

4. Experimental section

4.1. Chemistry

4.1.1. General methods

All reactions were carried out under argon atmosphere in dried glassware. Dry solvents and catalysts were purchased from Sigma-Aldrich®. NMR spectra were recorded on a Bruker® Avance 300 (300 MHz) NMR spectrometer, using $CDCl_3$ as solvent. Data, reported using $CHCl_3$ (δ_H = 7.26 ppm) as internal reference, were as follows (in order): chemical shift (δ in ppm relative to $CHCl_3$), multiplicity (s, d, t, q, quint, m, br for singlet, doublet, triplet, quartet, quintuplet, multiplet, broad) and coupling constants (*J* in Hz). **^{13}C NMR** was recorded at 75 MHz on the same instrument, using the $CDCl_3$ solvent peak at (δ_C = 77.16 ppm) as reference. ^{19}F NMR was recorded at 282 MHz on the same instrument. HRMS was obtained with a LCMS-IT-TOF mass Perkin-Elmer Spectrum One spectrophotometer. Melting points were uncorrected. IR spectra were recorded on a Perkin-Elmer Spectrum One spectrophotometer. Reactions were monitored by TLC with Merck® Silica gel 60 F254. Purifications by flash chromatography were carried out using Merck® Geduran® Si 60 silica gel (40–63 μm).

4.1.2. Synthesis of the oxazepino[6,5,4-hi]indol-1-one serie

4.1.2.1. Ethyl 3-iodo-1H-indole-7-carboxylate (2). In a round-bottomed flask, ethyl 1*H*-indole-7-carboxylate **1** (1.89 g, 10 mmol, 1 equiv.) was dissolved in DMF (12 mL). NIS (3.38 g, 15 mmol, 1.5 equiv.) was added and the mixture was stirred at room temperature for 3 h, hydrolyzed with an aqueous solution of $Na_2S_2O_3$ (10%, 40 mL). The resulting mixture was stirred for 30 min and the aqueous phase was then extracted with EtOAc (3 × 30 mL). The organic phases were washed with an aqueous saturated solution of NH_4Cl (20 mL), brine (20 mL), dried over anhydrous $MgSO_4$, filtered and solvents were evaporated under vacuum. The residue was purified by column chromatography on a silica gel (petroleum ether/EtOAc = 90:10) to afford the compound **2**. $C_{11}H_{10}INO_2$, MW = 315.11 g/mol, yield = 93%, beige solid, mp = 137–139 °C. **IR** (ATR) ν = 3290, 2984, 1683, 1616, 1570, 1507 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 10.03 (s, 1H), 7.95 (dd, *J* = 7.5 Hz, 0.6 Hz, 1H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.40 (d, *J* = 2.6 Hz, 1H), 7.24 (t, 1H, *J* = 7.6 Hz, 1H), 4.45 (q, *J* = 7.2 Hz, 2H), 1.45 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 166.9 (C), 135.9 (C), 131.0 (C), 129.7 (CH), 126.7 (CH), 125.4 (CH), 120.0 (CH), 113.4 (C), 61.1 (CH_2), 57.5 (C), 14.6 (CH_3). **HRMS** (ESI) calcd. for $C_{11}H_{11}INO_2$ $[M+H]^+$: 315.98290; found: 315.98215.

4.1.2.2. Ethyl 3-iodo-1-(prop-2-yn-1-yl)-1H-indole-7-carboxylate (3). In a round-bottomed flask, ethyl 3-iodo-1*H*-indole-7-carboxylate **2** (2.52 g, 8 mmol, 1 equiv.) was dissolved in DMF (15 mL) under argon and cooled to 0 °C. Sodium hydride (60% in oil, 480 mg, 12 mmol, 1.5 equiv.) was

added portionwise and the resulting mixture was stirred for 30 min. Propargyl bromide (0.90 mL, 12 mmol, 1.5 equiv.) was added dropwise. The solution was stirred overnight, then hydrolyzed with an aqueous saturated solution of NH_4Cl (20 mL) at 0 °C and extracted with AcOEt (3 × 40 mL). The organic phases were washed with an aqueous saturated solution of NH_4Cl (20 mL), a saturated solution of NaCl (2 × 20 mL), dried over anhydrous $MgSO_4$, filtered and solvents were evaporated under vacuum. The residue was purified by column chromatography on a silica gel (petroleum ether/EtOAc = 95:5) to afford the expected compound. $C_{14}H_{12}INO_2$, MW = 353.16 g/mol, yield = 77%, beige solid, mp = 66–68 °C. **IR** (ATR) ν = 3286, 1704, 1271, 1138 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.80 (dd, J = 7.5 Hz, 1.2 Hz, 1H), 7.64 (dd, J = 7.8 Hz, 1.2 Hz, 1H), 7.35 (s, 1H), 7.24 (t, J = 7.8 Hz, 1H), 5.20 (d, J = 2.7 Hz, 2H), 4.45 (q, J = 7.2 Hz, 2H), 2.34 (t, J = 2.7 Hz, 1H), 1.45 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 167.2 (C), 134.7 (CH), 133.4 (C), 133.0 (C), 126.6 (CH), 126.2 (CH), 120.2 (CH), 117.4 (C), 78.1 (C), 74.4 (CH), 61.6 (CH_2), 57.8 (C), 39.9 (CH_2), 14.6 (CH_3). **HRMS** (ESI) calcd. for $C_{14}H_{13}INO_2$ $[M+H]^+$: 353.99855; found: 353.99836.

4.1.2.3. 3-iodo-1-(prop-2-yn-1-yl)-1H-indole-7-carboxylic acid (4). In a round bottom flask, an aqueous solution of lithium hydroxide (3 M, 4 mL, 12 mmol, 2 equiv.) was added to a solution of compound **3** (2.12 g, 6 mmol, 1 equiv.) in ethanol (8 mL). The mixture was stirred overnight at 30 °C, cooled at 0 °C and acidified with an aqueous solution of hydrochloric acid 1 M to obtain pH = 1. The formed precipitate was filtered on a Büchner flask, washed with water a few times and dried in an oven (100 °C) overnight to afford compound **4**. $C_{12}H_8INO_2$, MW = 325.11 g/mol, yield = 84%, beige solid, mp = 188–190 °C. **IR** (ATR) ν = 3298, 3108, 2981, 2664, 1674, 1576, 1517, 1438, 1272 cm^{-1}. **^{1}H NMR** (300 MHz, CD_3OD) δ = 11. 4 (s, 1H), 7.75 (dd, J = 7.5 Hz, 0.8 Hz, 1H), 7.69 (dd, J = 8.0 Hz, 0.8 Hz, 1H), 7.44 (br s, 1H), 7.25 (t, J = 7.8 Hz, 1H), 4.68 (dt, J = 9.2 Hz, 5.1 Hz, 1H), 3.64 (d, J = 5.2 Hz, 2H), 3.29 (d, J = 16.1 Hz, 1H), 3.14 (ddd, J = 16.1 Hz, 9.1 Hz, 1.3 Hz, 1H).**^{13}C NMR** (75 MHz, CD_3OD) δ = 167.7 (C), 136.5 (C), 125.0 (C), 124.8 (CH), 124.6 (CH), 121.1 (CH), 119.4 (C), 117.1 (CH), 110.4 (C), 78.8 (CH), 32.6 (CH_2), 10.4 (CH_2). **HRMS** (ESI) calcd. for $C_{12}H_9INO_2$ $[M+H]^+$: 325.96725; found: 325.96691.

4.1.2.4. (E)-7-iodo-3-(iodomethylene)-3,4-dihydro-1H-[1,4]oxazepino [6,5,4-hi]indol-1-one (5). In a round bottom flask, potassium carbonate (1.38 g, 10 mmol, 2 equiv.), iodine (1.90 g, 7.5 mmol, 1.5 equiv.), and silver nitrate (849 mg, 5 mmol, 1 equiv.) were successively added to compound **4** (1.63 g, 5 mmol, 1 equiv.) in solution in THF (25 mL) under Argon. The reaction mixture was stirred for 24 h at room temperature, cooled at 0 °C and hydrolyzed with an aqueous solution of $Na_2S_2O_3$ (5%, 30 mL). The resulting mixture was stirred for 15 min and filtered through a pad of Celite® with EtOAc. The filtrate was then extracted with EtOAc (4 × 25 mL). The organic phases were washed with brine (2 × 30 mL), dried over anhydrous $MgSO_4$, filtered and solvents were evaporated under vacuum to afford compound **5**. $C_{12}H_7I_2NO_2$, MW = 451.00, yield = 70%, white solid, mp = 202–204 °C. **IR** (ATR) ν = 3140, 3054, 2923, 1717, 1628, 1600, 1575, 1510, 1451, 1265 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.14 (dd, J = 7.5 Hz, 0.9 Hz, 1H), 7.75 (dd, J = 8.1 Hz, 1.2 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.32 (s, 1H), 6.58 (s, 1H), 5.23 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 163.2 (C), 147.9 (C), 132.9 (C), 132.2 (C), 132.2 (CH), 130.7 (CH), 128.6 (CH), 121.1 (CH), 111.9 (C), 73.6 (CH), 57.7 (C), 51.2 (CH_2) ppm. HRMS (ESI) calcd. for $C_{12}H_8I_2NO_2$ $[M+H]^+$: 451.86389; found: 451.86307.

4.1.2.5. (E)-7-iodo-3-(4-methoxybenzylidene)-3,4-dihydro-1H-[1,4]oxazepino[6,5,4-hi]indol-1-one (6a). A Schlenk tube was loaded with **5** (0.3 mmol, 135 mg, 1 equiv.), tris(dibenzylideneacetone)dipalladium (0.015 mmol, 14 mg, 5 mol%), (4-methoxyphenyl)boronic acid (0.36 mmol, 55 mg, 1.2 equiv.) and potassium phosphate (0.6 mmol, 127 mg, 2 equiv.), submitted to vacuum for 10 min and filled with argon. Then toluene (3 mL) was introduced and the mixture was stirred at 80 °C for 24 h. After cooling, the reaction mixture was diluted with water (10 mL) and extracted with AcOEt (3 × 10 mL). The organic phases were washed with an aqueous saturated solution of NaCl (15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on a silica gel with petroleum ether/EtOAc as eluent to afford the compound **6a**. $C_{19}H_{14}INO_3$, MW = 431.23 g/mol, yield = 37%, beige solid, mp = 133–135 °C. **IR** (ATR) ν = 3103, 2955, 2929, 28960, 1716, 1644, 1602, 1576, 1508, 1453, 1387, 1290, 1147, 1085, 1005, 768, 736. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.18 (dd, J = 7.8 Hz, 1.2 Hz, 1H), 7.74 (dd, J = 7.8 Hz, 1.2 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.30 (s, 1H), 6.93 (d, J = 8.9 Hz, 2H), 6.88 (d, J = 8.9 Hz, 2H), 5.02 (s, 2H), 3.81 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 165.3 (C), 159.8 (C), 141.9 (C), 133.2 (C), 132.1 (C), 131.0 (CH), 130.7 (CH), 130.1 (2CH), 128.2 (CH), 125.5 (C), 123.4 (CH), 121.0 (CH), 114.4 (2CH), 112.9 (C), 57.9 (C), 55.5 (CH_3), 49.1 (CH_2). **HRMS** (ESI) calcd. for $C_{19}H_{15}INO_3$ $[M+H]^+$: 432.00911; found: 432.00893.

4.1.2.6. General procedure for the Sonogashira coupling. A Schlenk tube was loaded with **5** (0.3 mmol, 135 mg, 1 equiv.), bis(triphenylphosphine)palladium(II) dichloride (0.03 mmol, 21 mg, 10 mol%), copper iodide (0.03 mmol, 5.7 mg, 10 mol%.), submitted to vacuum for 10 min and filled with argon. Then DMF (5 mL), triethylamine (0.66 mmol, 92 µl, 2.2 equiv.) and alkyne (0.45 mmol, 1.5 equiv.) were introduced and the mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with an aqueous saturated solution of NH_4Cl (10 mL) and the resulting was filtered through a pad of Celite® with EtOAc. The aqueous phase was extracted with AcOEt (3 × 10 mL). The organic phases were washed with aqueous saturated solution of NaCl (2 × 15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with petroleum ether/ EtOAc as eluent to afford the expected compound.

4.1.2.7. (E)-7-iodo-3-(3-phenylprop-2-yn-1-ylidene)-3,4-dihydro-1H-[1,4]oxazepino[6,5,4-hi]indol-1-one (6b). $C_{20}H_{12}INO_2$, MW = 425.23 g/mol, yield = 28%, yellow solid, mp = 145–147 °C. **IR** (ATR) ν = 3098, 2927, 2207, 1732, 1637, 1573, 1508, 1488, 1450, 1388, 1295, 1238, 1188, 1152, 1079, 998, 752, 731, 679. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.16 (dd, J = 7.8 Hz, 0.9 Hz, 1H), 7.75 (dd, J = 7.8 Hz, 0.9 Hz, 1H), 7.46–7.42 (m, 2H), 7.39–7.36 (m, 3H), 7.34 (t, J = 7.8 Hz, 1H), 7.30 (s, 1H), 5.22 (s, 1H), 5.22 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 163.8 (C), 151.8 (C), 133.0 (C), 132.2 (C), 132.0 (CH), 131.6 (2CH), 130.6 (CH), 129.3 (CH), 128.7 (2CH), 128.4 (CH), 122.3 (C), 121.0 (CH), 112.1 (C), 104.0 (CH), 97.5 (C), 82.0 (C), 57.7 (C), 48.8 (CH_2). **HRMS** (ESI) calcd. for $C_{20}H_{13}INO_2$ $[M+H]^+$: 425.99855; found: 425.99766.

4.1.2.8. (E)-7-iodo-3-(3-(4-methoxyphenyl)prop-2-yn-1-ylidene)-3,4-dihydro-1H-[1,4]oxazepino[6,5,4-hi]indol-1-one (6c). $C_{21}H_{14}INO_3$, MW = 455.25 g/mol, yield = 28%, yellow solid, mp = 167–169 °C. **IR** (ATR) ν = 3100, 2959, 2930, 2915, 2834, 2200, 11716, 1642, 1600, 1506, 1450, 1391, 1289, 1246, 1186, 1153, 1106, 1084, 998, 836, 733. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.15 (dd, J = 7.7 Hz, 1.0 Hz, 1H), 7.74 (dd, J = 7.8 Hz, 1.0 Hz, 1H), 7.37 (d, J = 8.7 Hz, 2H), 7.33 (t, J = 7.8 Hz, 1H), 7.30 (s, 1H), 6.88 (d, J = 8.7 Hz, 2H), 5.98 (s, 1H), 5.20 (s, 2H), 3.84 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 163.9 (C), 160.4 (c), 151.2 (C), 133.2 (2CH), 133.1 (C), 132.2 (C), 132.1 (CH), 130.6 (CH), 128.4 (CH), 121.0 (CH), 114.4 (2CH), 112.2 (C), 104.3 (CH), 97.8 (C), 80.8 (C), 57.6 (C), 55.5 (CH_3), 48.9 (CH_2).**HRMS** (ESI) calcd. for $C_{21}H_{15}INO_3$ $[M+H]^+$: 456.00911; found: 456.00847.

4.1.2.9. (E)-3-(hept-2-yn-1-ylidene)-7-iodo-3,4-dihydro-1H-[1,4]oxazepino[6,5,4-hi]indol-1-one (6d). $C_{18}H_{16}INO_2$, MW = 405.24 g/mol, yield = 47%, yellow solid, mp = 100–102 °C, yield 47%. **IR** (ATR) ν = 3103, 2954, 2929, 2220, 1721, 1644, 1577, 1508, 1452, 1386, 1289, 1147,

1103, 1005, 735. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.13 (dd, J = 7.8 Hz, 0.9 Hz, 1H), 7.72 (dd, J = 8.1 Hz, 0.9 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 7.25 (s, 1H), 5.75 (d, J = 2.1 Hz, 2H), 5.11 (s, 2H), 2.36 (td, J = 6.9 Hz, 2.4 Hz, 2H), 1.56–1.38 (m, 4H), 0.95 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 164.1 (C), 151.2 (C), 133.0 (C), 132.1 (CH, C), 130.5 (CH), 128.3 (CH), 120.9 (CH), 112.2 (C), 104.7 (CH), 99.5 (C), 73.5 (C), 57.4 (C), 48.7 (CH_2), 30.6 (CH_2), 22.1 (CH_2), 19.4 (CH_2), 13.7 (CH_3). **HRMS** (ESI) calcd. for $C_{18}H_{17}INO_2$ $[M+H]^+$: 406.02985; found: 406.02911.

4.1.2.10. (E)-7-iodo-3-(6-methylhept-2-yn-1-ylidene)-3,4-dihydro-1H-[1,4]oxazepino[6,5,4-hi]indol-1-one (6e). $C_{19}H_{18}INO_2$, MW = 419.26 g/mol, yield = 54%, yellow solid, mp = 104–106 °C. **IR** (ATR) ν = 3118, 3105, 2955, 2926, 2864, 2219, 1721, 1638, 1578, 1509, 1453, 1391, 1300, 1230, 1191, 1149, 1084, 1056, 1004, 737. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.14 (dd, J = 7.5 Hz, 0.6 Hz, 1H), 7.72 (dd, J = 7.8 Hz, 0.9 Hz, 1H), 7.32 (t, J = 7.8 Hz, 1H), 7.24 (s, 1H), 5.75 (t, J = 2.4 Hz, 1H), 5.11 (s, 2H), 2.37 (td, J = 7.5 Hz, 2.4 Hz, 2H), 1.68 (sept, J = 6.9 Hz, 2H), 1.43 (q, J = 7.2 Hz, 2H), 0.94 (s, 3H), 0.92 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 164.1 (C), 151.2 (C), 133.0 (C), 132.1 (CH, C), 130.5 (CH), 128.3 (CH), 120.9 (CH), 112.2 (C), 104.6 (CH), 99.5 (C), 73.4 (C), 57.4 (C), 48.7 (CH_2), 37.4 (CH_2), 27.4 (CH), 22.3 ($2CH_3$), 17.7 (CH_3). **HRMS** (ESI) calcd. for $C_{19}H_{19}INO_2$ $[M+H]^+$: 420.04550; found: 420.04473.

4.1.2.11. Ethyl (E)-7-(7-iodo-1-oxo-1H-[1,4]oxazepino[6,5,4-hi]indol-3(4H)-ylidene)hept-5-ynoate (6f). $C_{20}H_{18}INO_4$, MW = 463.27 g/mol, yield = 54%, yellow solid, mp = 111–113 °C. **IR** (ATR) ν = 3109, 2982, 2937, 2218, 1710, 1579, 1511, 1437, 1391, 1300, 1234, 1194, 1147, 1086, 1007, 740. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.11 (dd, J = 7.8 Hz, 0.9 Hz, 1H), 7.70 (dd, J = 7.8 Hz, 0.9 Hz, 1H), 7.33 (s, 1H), 7.30 (t, J = 7.8 Hz, 1H), 5.73 (t, J = 2.1 Hz, 1H), 5.11 (s, 2H), 4.16 (q, J = 7.2 Hz, 2H), 2.46–2.40 (m, 4H), 1.87 (quint, J = 6.9 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 173.0 (C), 164.0 (C), 151.5 (C), 132.9 (C), 132.2 (C), 132.1 (CH), 130.4 (CH), 128.3 (CH), 120.9 (CH), 112.1 (C), 104.2 (CH), 97.8 (C), 74.3 (C), 60.7 (CH_2), 57.4 (C), 48.6 (CH_2), 33.2 (CH_2), 23.7 (CH_2), 19.1 (CH_2), 14.4 (CH_3). **HRMS** (ESI) calcd. for $C_{20}H_{19}INO_4$ $[M+H]^+$: 464.03533; found: 464.03482.

4.1.3. Synthesis of the oxépino[5,4,3-cd]indolone serie

4.1.3.1. Methyl-3-allyl-1H-indole-4-carboxylate (8).[16]. In a Schlenk tube under argon, triethyl boron (1 M in THF, 2.55 mL, 2.55 mmol, 30 mol%) and allyl alcohol (0.58 mL, 8.5 mmol, 1 equiv.) were added dropwise to a solution of methyl 1*H*-indole-4-carboxylate **7** (1.49 g, 8.5 mmol, 1 equiv.) and tetrakis(triphenylphosphine)palladium(0) (491 mg, 0,43 mmol, 5 mol%) in anhydrous THF (35 mL). The resulting mixture was stirred for 16 h at 70 °C, cooled at room temperature, diluted with EtOAc (100 mL) and hydrolyzed with aqueous saturated solution of $NaHCO_3$ (50 mL). The aqueous phase was extracted with EtOAc (2 × 40 mL). The organic phases were washed with aqueous saturated solution of $NaHCO_3$ (50 mL), brine (2 × 50 mL), dried over anhydrous $MgSO_4$, filtered and solvents were evaporated under vacuum. The residue was purified by column chromatography on silica gel with petroleum ether/EtOAc as eluent to afford compound **8**. $C_{13}H_{13}NO_2$, MW = 215.25 g/mol, yield = 85%, pale yellow oil. **IR** (ATR) ν = 3357, 2949, 1695, 1435, 1344, 1270, 1194, 1178, 1141, 1042, 1.022, 997. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.28 (brs, 1H), 7.61 (dd, J = 7.4 Hz, 1.0 Hz, 1H), 7.50 (dd, J = 8.1 Hz, 0.9 Hz, 1H), 7.19 (t, J = 7.7 Hz, 1H), 7.11 (m, 1H), 6.04 (ddt, J = 16.6 Hz, 10.4 Hz, 6.2 Hz, 1H), 5.04–4.96 (m, 2H), 3.95 (s, 3H), 3.66 (dq, J = 6.2 Hz, 1.5 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 169.3 (C═O), 138.1 (CH), 137.9 (C), 125.2 (CH), 124.4 (C), 124.4 (C), 122.5 (CH), 121.0 (CH), 115.4 (CH), 115.2 (C), 115.0 (CH_2), 52.1 (CH_3), 31.8 (CH_2). **HRMS** (ESI) calcd. for $C_{13}H_{14}NO_2$ $[M+H]^+$: 216.10191; found: 216.10155.

4.1.3.2. Methyl-3-allyl-1-benzyl-1H-indole-4-carboxylate (9). In a round bottom flask, the substrate **8** (1.08 g, 5 mmol, 1 equiv.) was dissolved in anhydrous DMF (10 mL) under argon and cooled to 0 °C. Sodium hydride (60% in oil, 249 mg, 6.5 mmol, 1.3 equiv.) was added portionwise and the resulting mixture was stirred for 30 min. Benzyl bromide (0.77 mL, 6.5 mmol, 1.3 equiv.) was added dropwise. The solution was stirred for 3 h, then hydrolyzed with an aqueous saturated solution of NH_4Cl (20 mL) at 0 °C and extracted with AcOEt (3 × 30 mL). The organic phases were washed with an aqueous saturated solution of NH_4Cl (20 mL), a saturated solution of NaCl (2 × 20 mL), dried over anhydrous $MgSO_4$, filtered and solvents were evaporated under vacuum. The residue was purified by column chromatography on a silica gel (petroleum ether/EtOAc) to afford the expected compound. $C_{20}H_{19}NO_2$, MW = 305.38 g/mol, yield = 84%, pale yellow oil. **IR** (ATR) ν = 2947, 1715, 1436, 1265, 1194, 1172, 1146, 1046, 910. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.59 (dd, J = 7.4 Hz, 0.9 Hz, 1H), 7.41 (dd, J = 8.3 Hz, 0.9 Hz, 1H), 7.31–7.26 (m, 3H), 7.16 (t, J = 7.7 Hz, 1H), 7.09–7.06 (m, 3H), 6.04 (ddt, J = 18.0 Hz, 9.2 Hz, 6.2 Hz, 1H), 5.31 (s, 2H), 5.03 (m, 1H), 4.99 (m, 1H), 3.95 (s, 3H), 3.67 (dd, J = 6.2 Hz, 0.9 Hz, 2H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ = 169.0 (C═O), 138.1 (CH), 138.0 (C), 137.3 (C), 129.4 (CH), 128.8 (2CH),127.7 (CH), 126.7 (2CH),125.0 (C), 124.7 (C), 122.2 (CH), 120.7 (CH), 114.9 (CH_2), 114.2 (C), 113.7 (CH), 52.0 (CH_3), 50.0 (CH_2), 31.7 (CH_2). **HRMS** (ESI) calcd. for $C_{20}H_{20}NO_2$ $[M+H]^+$: 306.14886; found: 306.14831.

4.1.3.3. 3-Allyl-1-benzyl-1H-indole-4-carboxylic acid (10). In a round bottom flask equipped with a reflux condenser, an aqueous solution of potassium hydroxide (2.5 M, 9.6 mL, 24 mmol, 3 equiv.) was added to a solution of compound **9** (2.44 g, 8 mmol, 1 equiv.) in methanol (15 mL). The mixture was stirred for 2 days at 70 °C, cooled at 0 °C and acidified with an aqueous solution of hydrochloric acid 1 M to obtain pH = 1. The formed precipitate was filtered on a Büchner flask, washed with water a few times and dried in an oven (100 °C) overnight to afford compound **10**. $C_{19}H_{17}NO_2$, MW = 291.35 g/mol, yield = 91%, white solid, mp = 160–162 °C. **IR** (ATR) ν = 2918, 2601, 1673, 1454, 1435, 1349, 1268, 1202, 1155. **^{1}H NMR** (300 MHz, MeOD-*d4*) δ = 7.80 (dd, J = 7.6 Hz, 1.0 Hz, 1H), 7.47 (dd, J = 8.2 Hz, 0.9 Hz, 1H), 7.34–7.27 (m, 3H), 7.20 (t, J = 7.7 Hz, 1H), 7.11 (s,1H), 7.10–7.07 (m, 2H), 6.08 (ddt, J = 17.7 Hz, 9.5 Hz, 6.2 Hz, 1H), 5.34 (s, 2H), 5.05 (m, 1H), 5.01 (m, 1H), 3.77 (dd, J = 6.2 Hz, 0.8 Hz, 2H).**^{13}C NMR** (75 MHz, MeOD-*d4*) δ = 173.7 (C═O), 138.5 (CH), 138.3 (C), 137.3 (C), 130.0 (CH), 129.0 (2CH),127.9 (CH), 126.7 (2CH),125.6 (C), 123.6 (CH), 123.4 (C), 120.8 (CH), 115.1 (CH_2), 114.8 (CH), 114.7 (C), 50.2 (CH_2), 32.1 (CH_2). **HRMS** (ESI) calcd. for $C_{19}H_{18}NO_2$ $[M+H]^+$: 292.13321; found: 292.13260.

4.1.3.4. 6-Benzyl-3-(iodomethyl)-4,6-dihydrooxepino[5,4,3-cd]indol-1(3H)-one (11). In a round bottom flask, potassium carbonate (1.48 g, 14 mmol, 2 equiv.), iodine (2.66 g, 10.5 mmol, 1.5 equiv.), and silver nitrate (1.19 g, 7 mmol, 1 equiv.) were successively added to compound **33** (2.04 g, 7 mmol, 1 equiv.) in solution in THF (35 mL) under Argon. The reaction mixture was stirred for 4 h at room temperature, cooled at 0 °C and hydrolyzed with an aqueous solution of $Na_2S_2O_3$ (5%, 30 mL). The resulting mixture was stirred for 15 min and filtered through a pad of Celite® with EtOAc. The filtrate was then extracted with EtOAc (4 × 30 mL). The organic phases were washed with brine (2 × 30 mL), dried over anhydrous $MgSO_4$, filtered and solvents were evaporated under vacuum to afford compound **11**. $C_{19}H_{16}INO_2$, MW = 417.25 g/mol, yield = 75%, pale yellow solid, mp = 152–154 °C. **IR** (ATR) ν = 1676, 1455, 1436, 1273, 1166, 1130, 1062, 1009. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.00 (dd, J = 7.6 Hz, 0.8 Hz, 1H), 7.51 (dd, J = 8.2 Hz, 0.8 Hz, 1H), 7.36–7.27 (m, 4H), 7.13–7.10 (m, 2H), 7.09 (s,1H), 5.33 (s, 2H), 4.83 (dddd, J = 8.9 Hz, 6.7 Hz, 5.5 Hz, 1.1 Hz, 1H), 3.59 (dd, J = 10.4 Hz, 5.5 Hz, 1H), 3.48 (dd, J = 10.4 Hz, 6.8 Hz, 1H), 3.43 (d, J = 15.9 Hz, 1H), 3.30 (ddd, J = 16.2 Hz, 8.9 Hz, 1.4 Hz, 1H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ = 168.1 (C═O), 136.9 (C), 136.8 (C), 129.1 (2CH), 128.1 (CH), 127.2

(CH), 127.0 (2CH), 126.4 (C), 126.2 (CH), 122.1 (CH), 120.6 (C), 115.3 (CH), 111.2 (C), 79.7 (CH), 50.4 (CH_2), 32.5 (CH_2), 7.0 (CH_2). **HRMS** (ESI) calcd. for $C_{19}H_{17}INO_2$ [M+H]+: 418.02985; found: 418.02927.

4.1.3.5. 3-(Iodomethyl)-4,6-dihydrooxepino[5,4,3-cd]indol-1(3H)-one (12). In a round bottom flask, an aqueous solution of potassium hydroxide (2.5 M, 2.0 mL, 5 mmol, 3 equiv.) was added to a solution of compound **10** (350 mg, 1.63 mmol, 1 equiv.) in methanol (4 mL). The mixture was stirred overnight at 45 °C and solvents were evaporated under vacuum. The residue was diluted in anhydrous DMF (4 mL) and *N*-iodosuccinimide (915 mg, 4.07 mmol, 2.5 equiv.) was added. The mixture was stirred for 1 h at room temperature, hydrolyzed with an aqueous saturated solution of $Na_2S_2O_3$ (10 mL), diluted with water (10 mL) and stirred for an additional 30 min. The aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with an aqueous saturated solution of NH_4Cl (20 mL), brine (20 mL), dried over anhydrous $MgSO_4$, filtered and solvents were evaporated under vacuum. The residue was purified by column chromatography on a silica gel (DMC/EtOAc/MeOH) to afford compound **12**. $C_{12}H_{10}INO_2$, MW = 327.12 g/mol, yield = 28%, pale yellow solid, decomposition at 140 °C. **IR** (ATR) ν = 3237, 1668, 1434, 1355, 1280, 1259, 1229, 1174, 1131, 1027. **^{1}H NMR** (300 MHz, DMSO-d_6) δ = 11,42 (brs, 1H), 7.75 (dd, J = 7.5 Hz, 0.8 Hz, 1H), 7.69 (dd, J = 8.0 Hz, 0.8 Hz, 1H), 7.44 (s, 1H), 7.25 (t, J = 7.8 Hz, 1H), 4.68 (dt, J = 9.2 Hz, 5.1 Hz, 1H), 3.64 (d, J = 5.2 Hz, 2H), 3.29 (d, J = 16.1 Hz, 1H), 3.14 (ddd, J = 16.1 Hz, 9.1 Hz, 1.3 Hz, 1H), 3.49 (dd, J = 10.4 Hz, 6.8 Hz, 1H), 3.47 (d, J = 15.8 Hz, 1H), 3.31 (ddd, J = 16.2 Hz, 8.9 Hz, 1.4 Hz, 1H). **^{13}C NMR** (75 MHz, DMSO-d_6) δ = 167.6 (C═O), 136.5 (C), 125.0 (C), 124.8 (CH), 124.6 (CH), 121.1 (CH), 119.4 (C), 117.1 (CH), 110.4 (C), 78.8 (CH), 32.6 (CH_2), 10.4 (CH_2). **HRMS** (ESI) calcd. for $C_{12}H_{11}INO_2$ $[M+H]^+$: 327.98290; found: 327.98325.

4.1.3.6. 3-(Azidomethyl)-6-benzyl-4,6-dihydrooxepino[5,4,3-cd]indol-1(3H)-one (13). In a round bottom flask, sodium azide (585 mg, 9 mmol, 2 equiv.) was added to compound **11** (1.88 g, 4.5 mmol, 1 equiv.) in solution in anhydrous DMF (15 mL) under argon. The mixture was stirred for 2 days at room temperature, diluted with water and extracted with EtOAc (3 × 30 mL). The organic phases were washed with brine (2 × 20 mL), dried over anhydrous $MgSO_4$, filtered and solvents were evaporated under vacuum. The residue was purified by column chromatography on a silica gel with PE/EtOAc (90:10 to 70:30) as eluent to afford compound **13**. $C_{19}H_{16}N_4O_2$, MW = 332.13 g/mol, yield = 76%, white solid, mp = 147–149 °C. **IR** (ATR) ν = 2096, 1690, 1440, 1355, 1263, 1246, 1170, 1138, 1118, 1072. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.03 (dd, J = 7.6 Hz, 0.7 Hz, 1H), 7.53 (dd, J = 8.2 Hz, 0.7 Hz, 1H), 7.37–7.31 (m, 4H), 7.15–7.12 (m, 2H), 7.09 (s, 1H), 5.35 (s, 2H), 4.86 (m, 1H), 3.78 (dd, J = 12.7 Hz, 6.3 Hz, 1H), 3.58 (dd, J = 12.7 Hz, 5.4 Hz, 1H), 3.27 (ddd, J = 16.3 Hz, 9.0 Hz, 1.4 Hz, 1H), 3.17 (dd, J = 16.2 Hz, 1.1 Hz, 1H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ = 168.4 (C═O), 136.9 (C), 136.8 (C), 129.1 (2CH), 128.2 (CH), 127.1 (CH), 127.0 (2CH), 126.4 (C), 126.3 (CH), 122.2 (CH), 120.6 (C), 115.3 (CH), 111.7 (C), 79.0 (CH), 54.6 (CH_2), 50.4 (CH_2), 30.3 (CH_2). **HRMS** (ESI) calcd. for $C_{19}H_{17}N_4O_2$ $[M+H]^+$: 333.13460; found: 333.13392.

4.1.3.7. General procedure for [1–3] dipolar cycloaddition. In a round bottom flask, alkyne (0.3 mmol, 1 equiv.) was added to compound **11** in solution in $H_2O/CHCl_3$ (3:1, 7.5 mL:2.5 mL) at 0 °C. Then sodium ascorbate (12 mg, 0.06 mmol, 20 mol%) and $CuSO_4{\cdot}5H_2O$ (7.5 mg, 0.03 mmol, 10 mol%) were added. The resulting mixture was stirred for 5 h at room temperature. Solvents were evaporated under vacuum and the residue was dissolved in water (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic phases were washed with water (15 mL), brine (2 × 15 mL), dried over anhydrous $MgSO_4$, filtered and solvents were evaporated under vacuum. The residue was purified by column chromatography on a silica gel with (DCM/MeOH) as eluent to afford compound **14**.

4.1.3.8. 6-Benzyl-3-((4-butyl-1H-1,2,3-triazol-1-yl)methyl)-4,6-dihydrooxepino[5,4,3-cd]indol-1(3H)-one (14a). $C_{25}H_{26}N_4O_2$, MW = 414.51 g/mol, yield = 87%, white solid, mp = 129–131 °C. **IR** (ATR) ν = 2923, 1687, 1683, 1453, 1438, 1352, 1326, 1260, 1136, 1051. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.96 (d, J = 7.6 Hz, 1H), 7.70 (brs, 1H), 7.50 (d, J = 8.1 Hz, 1H), 7.34–7.24 (m, 4H), 7.08 (dd, J = 7.7 Hz, 2.3 Hz, 2H), 7.06 (s, 1H), 5.31 (s, 2H), 5.08 (m, 1H), 4.79 (dd, J = 14.6 Hz, 3.9 Hz, 1H), 4.72 (dd, J = 14.4 Hz, 6.2 Hz, 1H), 3.21 (d, J = 16.2 Hz, 1H), 3.04 (ddd, J = 16.2 Hz, 9.6 Hz, 1H), 2.73 (t, J = 7.2 Hz, 2H), 1.68 (quint, J = 7.0 Hz, 2H), 1.39 (sext, J = 7.4 Hz, 2H), 0.94 (t, J = 7.4 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ = 168.3 (C═O), 137.0 (C), 136.7 (C), 129.1 (2CH), 128.2 (CH), 127.4 (CH), 126.9 (2CH), 126.4 (CH), 126.3 (C), 122.2 (CH), 120.2 (C), 115.6 (CH), 111.2 (C), 78.9 (CH), 54.3 (CH_2), 50.4 (CH_2), 31.6 (CH_2), 30.2 (CH_2), 25.5 (CH_2), 22.5 (CH_2), 13.9 (CH_3). **HRMS** (ESI) calcd. for $C_{25}H_{27}N_4O_2$ $[M+H]^+$:415.21285; found: 415.21272.

4.1.3.9. 6-Benzyl-3-((4-heptyl-1H-1,2,3-triazol-1-yl)methyl)-4,6-dihydrooxepino[5,4,3-cd]indol-1(3H)-one (14b). $C_{28}H_{32}N_4O_2$, MW = 456.59 g/mol, yield = 82%, clear paste. **IR** (ATR) ν = 2922, 1700, 1683, 1609, 1439, 1352, 1259, 1171, 1136, 1052. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.95 (dd, J = 7.8 Hz, 0.9 Hz, 1H), 7.69 (brs, 1H), 7.49 (dd, J = 8.1 Hz, 0.9 Hz, 1H), 7.33–7.22 (m, 4H), 7.11–7.05 (m, 3H), 5.30 (s, 2H), 5.06 (ddd, J = 13.2 Hz, 6.3 Hz, 4.2 Hz, 1H), 4.78 (dd, 14.4 Hz, 3.9 Hz, 1H), 4.71 (dd, J = 14.4 Hz, 6.3 Hz, 1H), 3.21 (d, J = 16.2 Hz), 3.03 (ddd, J = 16.2 Hz, 9.6 Hz, 1.5 Hz, 1H), 2.72 (t, J = 7.8 Hz, 2H), 1.69 (quint, J = 6.6 Hz, 2H), 1.33–1.26 (m, 8H), 0.86 (t, J = 6.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 168.3 (C═O), 136.9 (C), 136.7 (C), 129.1 (2CH), 128.1 (CH), 127.4 (CH), 126.9 (2CH), 126.3 (CH), 126.3 (C), 122.2 (CH), 120.2 (C), 115.5 (CH), 111.2 (C), 78.9 (CH), 54.3 (CH_2), 50.4 (CH_2), 31.9 (CH_2), 30.2 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 25.8 (CH_2), 22.7 (CH_2), 14.2 (CH_3). **HRMS** (ESI) calcd. for $C_{28}H_{33}N_4O_2$ $[M+H]^+$: 457.25980; found: 457.25904.

4.1.3.10. 6-Benzyl-3-((4-isopentyl-1H-1,2,3-triazol-1-yl)methyl)-4,6-dihydrooxepino[5,4,3-cd]indol-1(3H)-one (14c). $C_{26}H_{28}N_4O_2$, MW = 428.54 g/mol, yield = 83%, white solid, mp = 106–108 °C. **IR** (ATR) ν = 2954, 1698, 1455, 1438, 1354, 1257, 1171, 1133, 1050. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.94 (dd, J = 7.5 Hz, 0.9 Hz, 1H), 7.70 (brs, 1H), 7.48 (dd, J = 8.1 Hz, 0.9 Hz, 1H), 7.33–7.28 (m, 3H), 7.24 (t, J = 7.9 Hz, 1H), 7.08–7.04 (m, 3H), 5.29 (s, 2H), 5.06 (ddd, J = 13.5 Hz, 6 Hz, 4 Hz, 1H), 4.77 (dd, J = 14.4 Hz, 3.9 Hz, 1H), 4.70 (dd, J = 14.1 Hz, 6 Hz, 1H), 3.20 (d, J = 16.2 Hz, 1H), 3.02 (ddd, J = 16.2 Hz, 9.6 Hz, 1.5 Hz, 1H), 2.72 (t, J = 8.1 Hz, 2H), 1.62–1.56 (m, 3H), 0.93 (d, J = 6 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 168.3 (C═O), 136.9 (C), 136.7 (C), 129.0 (2CH), 128.1 (CH), 127.4 (CH), 126.9 (2CH), 126.3 (CH), 126.2 (C), 122.1 (CH), 120.2 (C), 115.5 (CH), 111.1 (C), 78.9 (CH), 54.3 (CH_2), 50.4 (CH_2), 38.5 (CH_2), 30.1 (CH_2), 27.8 (CH), 23.7 (CH_2), 22.5 ($2CH_3$). **HRMS** (ESI) calcd. for $C_{26}H_{29}N_4O_2$ $[M+H]^+$: 429.22850; found: 429.22791.

4.1.3.11. 6-Benzyl-3-((4-cyclopropyl-1H-1,2,3-triazol-1-yl)methyl)-4,6-dihydrooxepino[5,4,3-cd]indol-1(3H)-one (14d). $C_{24}H_{22}N_4O_2$, MW = 398.47 g/mol, yield = 84%, beige solid, mp = 92–94 °C.**IR** (ATR) ν = 2921, 1693, 1610, 1453, 1439, 1353, 1325, 1253, 1170, 1132, 1030. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.96 (dd, J = 7.8 Hz, 0.8 Hz, 1H), 7.66 (brs, 1H), 7.50 (dd, J = 8.1 Hz, 0.8 Hz, 1H), 7.34–7.23 (m, 4H), 7.09–7.05 (m, 3H), 5.29 (s, 2H), 5.06 (m, 1H), 4.76 (dd, J = 14.3 Hz, 3.8 Hz, 1H), 4.68 (dd, J = 14.3 Hz, 6.3 Hz, 1H), 3.20 (d, J = 16.2 Hz, 1H), 3.05 (ddd, J = 16.2 Hz, 9.7 Hz, 1.1 Hz, 1H), 1.97 (tt, J = 8.4 Hz, 5.1 Hz, 1H), 0.99–0.84 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 168.3 (C═O), 136.9 (C), 136.7 (C), 129.1 (2CH), 128.2 (CH), 127.4 (CH), 127.4 (2CH), 126.9 (CH), 126.4 (C), 122.2 (CH), 120.2 (C), 115.6 (CH), 113.7 (CH), 111.1 (C), 78.9 (CH), 54.6 (CH_2), 50.4 (CH_2), 30.2 (CH_2), 8.0 ($2CH_2$), 6.8 (CH).

HRMS (ESI) calcd. for $C_{24}H_{23}N_4O_2$ $[M+H]^+$:399.18155; found: 399.18104.

4.1.3.12. Ethyl 4-(1-((6-benzyl-1-oxo-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-3-yl)methyl)-1H-1,2,3-triazol-4-yl)butanoate (14e). $C_{27}H_{28}N_4O_4$, MW = 472.53 g/mol, yield = 95%, yellow oil. **IR** (ATR). ν = 3136, 3030, 2934, 2872, 1696, 1610, 1454, 1439, 1254, 1170, 1132, 1053, 732. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.94 (d, J = 7.5 Hz, 1H), 7.72 (s, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.32–7.21 (m, 3H), 7.24 (t, J = 8.0 Hz, 1H), 7.08–7.05 (m, 3H), 5.29 (s, 2H), 5.06 (m, 1H), 4.76 (dd, J = 14.3 Hz, 3.8 Hz, 1H), 4.70 (dd, J = 14.3 Hz, 6.2 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.20 (d, J = 16.3 Hz, 1H), 3.03 (dd, J = 16.2 Hz, 9.6 Hz, 1H), 2.77 (t, J = 7.4 Hz, 2H), 2.36 (t, J = 7.4 Hz, 2H), 2.02 (quint, J = 7.4 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 173.3 (C═O), 168.2 (C═O), 147.6 (C), 136.8 (C), 136.7 (C), 129.0 (2CH), 128.1 (CH), 127.4 (CH), 126.8 (2CH), 126.3 (CH), 126.2 (C), 122.7 (CH), 122.1 (CH), 120.1 (C), 115.5 (CH), 111.0 (C), 78.8 (CH), 60.4 (CH_2), 54.2 (CH_2), 50.3 (CH_2), 33.7 (CH_2), 30.1 (CH_2), 25.0 (CH_2), 24.7 (CH_2), 14.3 (CH_3). **HRMS** (ESI) calcd. for $C_{27}H_{29}N_4O_4$ $[M+H]^+$: 473.21833; found: 473.21766.

4.1.3.13. 6-Benzyl-3-((4-(2-bromoethyl)-1H-1,2,3-triazol-1-yl)methyl)-4,6-dihydrooxepino[5,4,3-cd]indol-1(3H)-one (14f). $C_{23}H_{20}N_4O_2Br$, MW = 465.35 g/mol, yield = 89%, white solid, mp = 71–73 °C. **IR** (ATR) ν = 2924, 1694, 1610, 1454, 1438, 1354, 1255, 1170, 1132, 1050. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.97 (dd, J = 7.6 Hz, 0.8 Hz, 1H), 7.86 (s, 1H), 7.50 (dd, J = 8.2 Hz, 0.8 Hz, 1H), 7.33–7.24 (m, 4H), 7.10–7.06 (m, 3H), 5.31 (s, 2H), 5.09 (m, 1H), 4.81 (dd, J = 14.3 Hz, 3.8 Hz, 1H), 4.74 (dd, J = 14.3 Hz, 6.4 Hz, 1H), 3.67 (t, J = 6.8 Hz, 2H), 3.32 (t, J = 6.8 Hz, 2H), 3.22 (d, J = 16.1 Hz, 1H), 3.061 (ddd, J = 16.3 Hz, 9.7 Hz, 1.4 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 168.2 (C═O), 145.3 (C), 137.0 (C), 136.7 (C), 129.1 (2CH), 128.2 (CH), 127.4 (CH), 126.9 (2CH), 126.4 (CH), 126.3 (C), 123.5 (CH), 122.2 (CH), 120.2 (C), 115.6 (CH), 111.1 (C), 78.8 (CH), 54.3 (CH_2), 50.4 (CH_2), 31.4 (CH_2), 30.2 (CH_2), 29.6 (CH_2). **HRMS** (ESI) calcd. for $C_{23}H_{21}^{79}BrN_4O_2$ $[M+H]^+$:465.09207; found: 465.09147.

4.1.3.14. N-((1-((6-benzyl-1-oxo-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-3-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-N-methylmethanesulfonamide (14g). $C_{24}H_{25}N_5O_4S$, MW = 479.56 g/mol, yield = 95%, white solid, mp = 139–141 °C. **IR** (ATR) ν = 2930, 1694, 1610, 1455, 1439, 1354, 1322, 1255, 1133, 1052. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.98 (s, 1H), 7.95 (dd, J = 7.5 Hz, 0.7 Hz, 1H), 7.50 (dd, J = 8.1 Hz, 0.7 Hz, 1H), 7.35–7.21 (m, 4H), 7.10–7.07 (m, 3H), 5.28 (s, 2H), 5.09 (m, 1H), 4.82 (dd, J = 14.1 Hz, 3.5 Hz, 1H), 4.72 (dd, J = 14.3 Hz, 7.0 Hz, 1H), 4.51 (s, 2H), 3.24 (d, J = 16.1 Hz, 1H), 3.09 (ddd, J = 16.2 Hz, 9.6 Hz, 1.2 Hz, 1H), 2.88 (s, 3H), 2.84 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 168.0 (C═O), 143.2 (C), 137.0 (C), 136.7 (C), 129.1 (2CH), 128.2 (CH), 127.4 (CH), 126.9 (2CH), 126.5 (CH), 126.2 (C), 124.8 (CH), 122.3 (CH), 120.1 (C), 115.7 (CH), 110.9 (C), 78.6 (CH), 54.4 (CH_2), 50.4 (CH_2), 44.9 (CH_2), 37.5 (CH_3), 34.7 (CH_3), 30.3 (CH_2). **HRMS** (ESI) calcd. for $C_{24}H_{26}N_5O_4S$ $[M+H]^+$:480.17000; found: 480.16944.

4.1.3.15. 6-Benzyl-3-((4-(2-fluorophenyl)-1H-1,2,3-triazol-1-yl)methyl)-4,6-dihydrooxepino[5,4,3-cd]indol-1(3H)-one (14 h). $C_{27}H_{21}FN_4O_2$, MW = 452.49 g/mol, yield = 88%, beige solid, mp = 166–168 °C. **IR** (ATR) ν = 1691, 1611, 1486, 1452, 1436, 1353, 1327, 1171, 1133, 1071, 1028. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.33 (d, J = 3.6 Hz, 1H), 8.29 (td, J = 7.4 Hz, 1.9 Hz, 1H), 7.99 (dd, J = 7.6 Hz, 0.8 Hz, 1H), 7.52 (dd, J = 8.2 Hz, 0.8 Hz, 1H), 7.37–7.23 (m, 6H), 7.17 (ddd, J = 10.9 Hz, 8.1 Hz, 1.3 Hz, 1H), 7.12–7.07 (m, 3H), 5.33 (s, 2H), 5.19 (m, 1H), 4.90 (dd, J = 14.3 Hz, 4.7 Hz, 1H), 4.85 (dd, J = 14.3 Hz, 6.0 Hz, 1H), 3.26 (d, J = 15.8 Hz, 1H), 3.15 (ddd, J = 16.3 Hz, 9.5 Hz, 1.4 Hz, 1H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ = -114.0. **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 168.2 (C), 159.5 (d, J = 247.3 Hz, C-F), 141.7 (d, J = 2.4 Hz, C), 136.9 (C), 136.7 (C), 129.6 (d, J = 8.4 Hz, CH), 129.1 (2CH), 128.2 (CH), 128.0 (d, J = 3.3 Hz, CH), 127.4 (CH), 126.9 (2CH), 126.5 (CH), 126.3 (C), 124.7 (d, J = 3.0 Hz, CH), 124.4 (d, J = 12.4 Hz, CH), 122.3 (CH), 120.2 (C), 118.6 (d, J = 13.1 Hz, C), 115.9 (d, J = 21.5 Hz, CH),115.6 (CH), 111.1 (C), 78.7 (CH), 54.4 (CH_2), 50.4 (CH_2), 30.3 (CH_2). **HRMS** (ESI) calcd. for $C_{27}H_{22}FN_4O_2$ $[M+H]^+$:453.17213; found: 453.17157.

4.1.3.16. 6-Benzyl-3-((4-(2,4-difluorophenyl)-1H-1,2,3-triazol-1-yl)methyl)-4,6-dihydrooxepino[5,4,3-cd]indol-1(3H)-one (14i). $C_{27}H_{20}F_2N_4O_2$, MW = 470.48 g/mol, yield = 71%, beige solid, mp = 181–183 °C.**IR** (ATR) ν = 2322, 1696, 1613, 1562, 1493, 1455, 1353, 1263, 1171, 1136, 1068. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.27 (d, J = 3.4 Hz, 1H), 8.24 (td, J = 8.6 Hz, 6.6 Hz, 1H), 7.96 (dd, J = 7.6 Hz, 0.7 Hz, 1H), 7.50 (dd, J = 8.2 Hz, 0.7 Hz, 1H),7.33–7.23 (m, 4H), 7.10–7.06 (m, 3H), 6.98 (ddd, J = 8.2 Hz, 7.5 Hz, 2.5 Hz, 1H), 6.90 (td, J = 8.9 Hz, 2.5 Hz, 1H), 5.30 (s, 2H), 5.15 (m, 1H), 4.87 (dd, J = 14.3 Hz, 4.3 Hz, 1H), 4.81 (dd, J = 14.3 Hz, 6.2 Hz, 1H), 3.26 (d, J = 16.0 Hz, 1H), 3.12 (ddd, J = 16.2 Hz, 9.5 Hz, 1.3 Hz, 1H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ = -110.10, −110.11.**^{13}C NMR** (75 MHz, $CDCl_3$) δ = 168.1 (C), 162.7 (dd, J = 248.8 Hz, J = 12.3 Hz, C-F), 159.5 (dd, J = 250.0 Hz, 12.0 Hz, C-F), 141.0 (dd, J = 1.7 Hz, 1.0 Hz, C), 136.9 (C), 136.7 (C), 129.1 (2CH), 128.9 (dd, J = 9.1 Hz, 5.5 Hz, CH), 128.2 (CH), 127.4 (CH), 126.9 (2CH), 126.4 (CH), 126.3 (C), 123.9 (dd, J = 10.9 Hz, 2.3 Hz, CH), 122.3 (CH), 120.2 (C), 115.6 (CH), 115.1 (dd, J = 10.8 Hz, 6.0 Hz, C), 112.1 (dd, J = 20.3 Hz, 4.7 Hz, CH), 111.0 (C), 104.3 (t, J = 25.5 Hz, CH), 78.7 (CH), 54.4 (CH_2), 50.4 (CH_2), 30.3 (CH_2). **HRMS** (ESI) calcd. for $C_{27}H_{21}F_2N_4O_2$ $[M+H]^+$:471.16271; found: 471.16202.

4.1.3.17. 6-Benzyl-3-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)-4,6-dihydrooxepino[5,4,3-cd]indol-1(3H)-one (14j). $C_{27}H_{22}N_4O_2$, MW = 434.50 g/mol, yield = 97%, white solid, mp = 160–162 °C. **IR** (ATR) ν = 3029, 1695, 1610, 1454, 1439, 1353, 1252, 1170, 1132, 1057. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.22 (s, 1H), 7.96 (dd, J = 7.6 Hz, 0.8 Hz, 1H), 7.86 (m, 2H), 7.50 (dd, J = 8.2 Hz, 0.8 Hz, 1H), 7.43 (m, 2H), 7.36–7.23 (m, 5H), 7.07 (m, 3H), 5.30 (s, 2H), 5.13 (m, 1H), 4.87 (dd, J = 14.3 Hz, 3.4 Hz, 1H), 4.78 (dd, J = 14.3 Hz, 6.3 Hz, 1H), 3.25 (d, J = 16.2 Hz, 1H), 3.09 (ddd, J = 16.3 Hz, 9.7 Hz, 1.2 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 168.2 (C═O), 148.3 (C), 136.9 (C), 136.7 (C), 130.6 (C), 129.1 (2CH), 129.0 (2CH), 128.3 (CH), 128.2 (CH), 127.4 (CH), 126.9 (2CH), 126.4 (CH), 126.3 (C), 126.0 (2CH), 122.2 (CH), 121.3(CH), 120.1 (C), 115.6 (CH), 111.0 (C), 78.8 (CH), 54.4 (CH_2), 50.4 (CH_2), 30.2 (CH_2). **HRMS** (ESI) calcd. for $C_{27}H_{23}N_4O_2$ $[M+H]^+$:435.18155; found: 435.18145.

4.1.3.18. 6-Benzyl-3-((4-(4-methoxyphenyl)-1H-1,2,3-triazol-1-yl)methyl)-4,6-dihydrooxepino[5,4,3-cd]indol-1(3H)-one (14 k). $C_{28}H_{24}N_4O_3$, MW = 464.53 g/mol, yield = 93%, beige solid, mp = 194–196 °C . **IR** (ATR) ν = 2926, 2323, 1697, 1610, 1497, 1454, 1439, 1353, 1247, 1171, 1132, 1064, 1027. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.12 (s, 1H), 7.96 (dd, J = 7.6 Hz, 0.8 Hz, 1H), 7.79 (dt, J = 8.9 Hz, 2.1 Hz, 2H), 7.49 (dd, J = 8.2 Hz, 0.8 Hz, 1H), 7.34–7.23 (m, 4H), 7.09–7.05 (m, 3H), 6.96 (dt, J = 8.9 Hz, 2.1 Hz, 2H), 5.29 (s, 2H), 5.13 (m, 1H), 4.85 (dd, J = 14.3 Hz, 3.9 Hz, 1H), 4.78 (dd, J = 14.3 Hz, 6.2 Hz, 1H), 3.84 (s, 3H), 3.25 (d, J = 16.1 Hz, 1H), 3.09 (ddd, J = 16.3 Hz, 9.7 Hz, 1.4 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 168.3 (C═O), 159.8 (C), 148.1 (C), 136.9 (C), 136.7 (C), 129.1 (2CH), 128.2 (CH), 127.4 (CH), 127.3 (2CH), 126.9 (2CH), 126.5 (CH), 126.3 (C), 123.2 (C), 122.2 (CH), 120.6 (CH), 120.1 (C), 115.6 (CH), 114.4 (2CH), 111.1 (C), 78.9 (CH), 55.5 (CH_3), 54.5 (CH_2), 50.4 (CH_2), 30.2 (CH_2). **HRMS** (ESI) calcd. for $C_{28}H_{25}N_4O_3$ $[M+H]^+$:465.19212; found: 465.19164.

*4.1.3.19. **6**-Benzyl-3-((4-(2-methoxyphenyl)-1H-1,2,3-triazol-1-yl)methyl)-4,6-dihydrooxepino[5,4,3-cd]indol-1(3H)-one (14 l).* $C_{28}H_{24}N_4O_3$, MW = 464.53 g/mol, yield = 63%, beige solid, mp = 174–176 °C. **IR** (ATR) ν = 2939, 1695, 1609, 1489, 1439, 1354, 1247, 1171, 1132, 1067, 1025. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.43 (s, 1H), 8.32 (dd, J = 7.7 Hz, 1.6 Hz, 1H), 7.97 (d, J = 7.5 Hz, 1H), 7.49 (d, J =

8.4 Hz, 1H), 7.34–7.23 (m, 5H), 7.10–7.05 (m, 4H), 6.99 (d, $J = 8.3$ Hz, 2H), 5.30 (s, 2H), 5.15 (dt, $J = 9.9$ Hz, 5.3 Hz, 1H), 4.87 (dd, $J = 14.3$ Hz, 4.5 Hz, 1H), 4.81 (dd, $J = 14.3$ Hz, 6.2 Hz, 1H), 3.98 (s, 3H), 3.25 (d, $J = 16.1$ Hz, 1H), 3.13 (dd, $J = 16.2$ Hz, 9.4 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) $\delta = 168.3$ (C═O), 156.0 (C), 143.6 (C), 136.9 (C), 136.7 (C), 129.2 (CH), 129.1 (2CH), 128.2 (CH), 127.8 (CH), 127.5 (CH), 126.9 (2CH), 126.4 (CH), 126.3 (C), 124.5 (CH), 122.2 (CH), 121.1 (CH), 120.2 (C), 119.3 (C), 115.5 (CH), 111.2 (C), 111.0 (CH), 78.9 (CH), 55.6 (CH_3), 54.3 (CH_2), 50.4 (CH_2), 30.3 (CH_2). **HRMS** (ESI) calcd. for $C_{28}H_{25}N_4O_3$ $[M+H]^+$:465.19212; found: 465.19154.

4.1.3.20. General procedure for nucleophilic substitution. In a round bottom flask, the thiophenol (0.24 mmol, 1 equiv.) was dissolved in anhydrous DMF (1.2 mL) under argon and cooled to 0 °C. Sodium hydride (60% in oil, 9.6 mg, 0.24 mmol, 1 equiv.) was added and the resulting mixture was stirred for 30 min. The substrate **11** (100 mg, 0.24 mmol, 1 equiv.) in solution in anhydrous DMF (1.2 mL) was added dropwise. The solution was stirred for 36 h at room temperature, then hydrolyzed with an aqueous saturated solution of NH_4Cl (10 mL) and extracted with AcOEt (3 × 10 mL). The organic phases were washed with water (10 mL), brine (10 mL), dried over anhydrous $MgSO_4$, filtered and solvents were evaporated under vacuum. The residue was purified by column chromatography on a silica gel with (DCM/MeOH) as eluent to afford compound **15**.

4.1.3.21. 6-Benzyl-3-((phenylthio)methyl)-4,6-dihydrooxepino[5,4,3-cd] indol-1(3H)-one (15a). $C_{25}H_{21}NO_2S$, MW = 399.51 g/mol, yield = 56%, clear paste. **IR** (ATR) $\nu = 3061, 3029, 3921, 1688, 1609, 1582, 1480, 1453, 1437, 1352, 1257, 1132, 1061, 114, 733, 690$. **^{1}H NMR** (300 MHz, $CDCl_3$) $\delta = 7.99$ (dd, $J = 7.5$ Hz, 0.6 Hz, 1H), 7.48 (dd, $J = 8.2$ Hz, 0.6 Hz, 1H), 7.38–7.23 (m, 8H), 7.20–7.10 (m, 3H), 7.06 (s, 1H), 5.31 (s, 2H), 4.80 (td, $J = 8.6$ Hz, 5.2 Hz, 1H), 3.54 (dd, $J = 13.9$ Hz, 5.1 Hz, 1H), 3.46 (d, $J = 16.2$ Hz, 1H), 3.21 (dd, $J = 13.8$ Hz, 8.4 Hz, 1H), 3.19 (ddd, $J = 16.3$ Hz, 9.1 HZ, 1.3 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) $\delta = 168.8$ (C═O), 136.9 (C), 136.8 (C), 135.3 (C), 129.7 (2CH), 129.2 (2CH), 129.0 (2CH), 128.1 (CH), 127.2 (CH), 127.0 (2CH), 126.7 (CH), 126.5 (C), 126.1 (CH), 122.0 (CH), 120.8 (C), 115.2 (CH), 112.0 (C), 79.5 (CH), 50.3 (CH_2), 38.7 (CH_2), 31.3 (CH_2). **HRMS** (ESI) calcd. for $C_{25}H_{22}NO_2S$ $[M+H]^+$:400.13658; found: 400.13611.

4.1.3.22. 6-Benzyl-3-(((2-methoxyphenyl)thio)methyl)-4,6-dihydrooxepino[5,4,3-cd]indol-1(3H)-one (15b). $C_{26}H_{23}NO_2S$, MW = 429.53 g/mol, yield = 60%, white solid, mp = 66–68 °C. **IR** (ATR) $\nu = 3063, 3003, 2917, 2834, 1687, 1608, 1576, 1452, 1433, 1351, 1242, 1131, 1061, 1014, 738, 699$. **^{1}H NMR** (300 MHz, $CDCl_3$) $\delta = 7.96$ (dd, $J = 7.6$ Hz, 0.7 Hz, 1H), 7.48 (dd, $J = 8.2$ Hz, 0.7 Hz, 1H), 7.34–7.22 (m, 5H), 7.20 (td, $J = 8.1$ Hz, 1.6 Hz, 1H), 7.12–7.09 (m, 2H), 7.05 (s, 1H), 6.87 (td, $J = 7.5$ Hz, 1.1 Hz, 1H), 6.82 (dd, $J = 8.2$ Hz, 0.9 Hz, 1H), 5.31 (s, 2H), 4.78 (td, $J = 8.6$ Hz, 4.8 Hz, 1H), 3.81 (s, 3H), 3.54 (d, $J = 16.2$ Hz, 1H), 3.50 (dd, $J = 13.7$ Hz, 4.7 Hz, 1H), 3.18 (ddd, $J = 16.2$ Hz, 9.3 HZ, 1.3 Hz, 1H), 3.15 (dd, $J = 13.7$ Hz, 9.1 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) $\delta = 168.9$ (C═O), 158.1 (C), 136.9 (2C), 131.2 (CH), 129.1 (2CH), 128.4 (CH), 128.1 (CH), 127.2 (CH), 127.0 (2CH), 126.6 (C), 126.1 (CH), 122.8 (C), 122.0 (CH), 121.3 (CH), 120.9 (C), 115.1 (CH), 112.2 (C), 111.0 (CH), 79.7 (CH), 55.9 (CH_3), 50.3 (CH_2), 37.2 (CH_2), 31.2 (CH_2). **HRMS** (ESI) calcd. for $C_{26}H_{24}NO_2S$ $[M+H]^+$:430.14714; found: 430.14689.

4.1.3.23. 6-Benzyl-3-(((3-methoxyphenyl)thio)methyl)-4,6-dihydrooxepino[5,4,3-cd]indol-1(3H)-one (15c). $C_{26}H_{23}NO_2S$, MW = 429.53 g/mol, yield = 52%, yellow paste. **IR** (ATR) $\nu = 3061, 3019, 2921, 1688, 1609, 1582, 1480, 1453, 1437, 1352, 1257, 1168, 1132, 1061, 1014, 734, 691$. **^{1}H NMR** (300 MHz, $CDCl_3$) $\delta = 7.98$ (dd, $J = 7.6$ Hz, 0.8 Hz, 1H), 7.48 (dd, $J = 8.2$ Hz, 0.7 Hz, 1H), 7.33–7.23 (m, 4H), 7.17 (t, $J = 8.0$ Hz, 1H), 7.14–7.09 (m, 2H), 7.05 (s, 1H), 6.95–6.90 (m, 2H), 6.71 (ddd, $J = 8.2$ Hz, 2.5 Hz, 0.8 Hz, 1H), 5.30 (s, 2H), 4.81 (td, $J = 8.4$ Hz, 5.3 Hz, 1H), 3.76 (s, 3H), 3.53 (dd, $J = 13.9$ Hz, 5.2 Hz, 1H), 3.44 (d, $J = 16.2$ Hz, 1H), 3.21 (dd, $J = 13.9$ Hz, 8.3 Hz, 1H), 3.19 (ddd, $J = 16.2$ Hz, 9.2 HZ, 1.3 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) $\delta = 168.8$ (C═O), 160.0 (C), 136.9 (C), 136.8 (C), 136.6 (C), 130.1 (CH), 129.0 (2CH), 128.1 (CH), 127.2 (CH), 127.0 (2CH), 126.5 (C), 126.1 (CH), 122.0 (CH), 121.7 (CH), 120.8 (C), 115.2 (CH), 115.0 (CH), 112.5 (CH), 112.0 (C), 79.4 (CH), 55.4 (CH3), 50.3 (CH2), 38.5 (CH2), 31.3 (CH2). **HRMS** (ESI) calcd. for $C_{26}H_{24}NO_2S$ $[M+H]^+$:430.14714; found: 430.14671.

4.2. In vitro anti-tubercular activity

Antitubercular evaluations were performed against the pantothenate-auxotrophic *Mt* mc^{2}6230 strain[19] cultured in Middlebrook 7H9 broth supplemented with oleic acid-albumin-dextrose-catalase enrichment (OADC) and 109 μM pantothenic acid (complete 7H9 medium) at 37 °C without agitation. MIC determination was done using the broth dilution method. Briefly, a log-phase ($OD_{600} \sim 1$) culture was diluted to an $OD_{600} = 0.05$ in complete 7H9 medium and deposited in all the wells of a 96-well microtiter plate (for the first row 200 μl/well, for all other rows 100 μl/well). The tested compounds were then directly added (2 μl per well of a 10 mg/ml stock solution) to the first row wells. Serial 2-fold dilutions were then done starting from the first row. As a measure to minimize evaporation of media, plates were wrapped in plastic, placed in a 37 °C incubator and observed after 7 days. Control wells included a control for the vehicle that compounds were dissolved in (DMSO), in which bacterial growth was not inhibited (as for untreated wells) and wells containing a drug with known antitubercular activity (INH), in which bacterial growth was inhibited at ~30 ng/ml in line with the reported MIC of this drug.[20] The MIC was defined as the lowest concentration of compound at which no visible bacterial growth (change in turbidity) was observed.

4.3. Mt UGM inhibitory activity

UGM preparation: A vector construct (pET-29b) containing the gene encoding for UGM from Mt was provided by Prof. Laura L. Kiessling. The overexpression and UGM purification followed our previously published procedure.[21]

FP assay; The assay described by Kiessling *et al.* was strictly followed, including the synthesis of the fluorescent probe (UDP-fluorescein).[18] To determine the binding affinity of UDP-fluorescein towards *Mt* UGM, serial dilutions of dialyzed UGM (final concentration: 1×10^{-5} to 10 μM) were incubated with 18 nM of the fluorescent probe in 50 mM sodium phosphate buffer, pH 7.0 at room temperature. Final volumes were 30 μl in 384 well black microtiter plates and the measurements were realized in triplicate. Fluorescence polarization was analyzed using a DTX880 Multimode Detector Beckman-Coulter device ($\lambda_{excitation}$ = 485 nm,$\lambda_{emission}$ = 535 nm).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We acknowledge the French Ministry for Research and Innovation for the financial support and Dr. Frédéric Montigny (Analysis Department, Tours University) for HRMS. This study was supported by the Fondation pour la Recherche Médicale (grant DEQ20150331719 to L. K.), the Association Gregory Lemarchal and Vaincre la Mucoviscidose (grant RIF20180502320 to C.R.).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmc.2021.116248.

References

1 Thanikachalam PV, Maurya RK, Garg V, Monga V. *Eur J Med Chem*. 2019;180:562–612.
2 (a) Wang H, Zhou Z-X, Kurmoo M, Liu Y-J, Zeng M-H. *Org Lett*. 2019;21:2847–2850; (b) Xu S, Takamatsu K, Hirano K, Miura M. *Chem Eur J*. 2019;25:9400–9404; (c) Selvaraj K, Debnath S, Kumara Swamy KCK. *Org Lett*. 2019;21:5447–5451; (d) Cheng J, Sun J, Yan J, et al. *J Org Chem*. 2017;82:13342–13347; (e) Suresh RR, Swamy KCK. *J Org Chem*. 2012;77:6959–6969; (f) Inack Ngi S, Guilloteau V, Abarbri M, Thibonnet J. *J Org Chem*. 2011;76:8347–8354.
3 (a) Mayooufi A, Romdhani-Younes M, Carcenac Y, Thibonnet J. *Synth Commun*. 2019;49:2168–2179; (b) Hammoud S, Anselmi E, Cherry K, Kizirian J-C, Thibonnet J. *Eur J Org Chem*. 2018:6314–6327; (c) Taskaya S, Menges N, Balci M. *Beilstein J Org Chem*. 2015;11:897–905; (d)Vandavasi JK, W.-P. Hu W-P, Senadi GC, Boominathan SSK, Chen H-Y, Wang J-J. Eur. J. Org. Chem. 2014:6219–6226. (e) Puteya A, Fourneta G, Lozachb O, Perrina L, Meijer L, Joseph B. *Eur J Med Chem*. 2014;83:617–629.
4 Ayral-Kaloustian S, Zhang N, Venkatesan AM, Mansour TS, Nguyen TH, Anderson JT. U. S. Pat. Appl. Publ. 2009, US 20090192147 A1.
5 (a) Zimmerman WT. PCT Int. Appl. 1991, WO 9110668 A1. (b) Zimmerman WT. U. S. 1994, US 5356862 A.
6 Maaliki C, Fu J, Villaume S, et al. *Bioorg Med Chem*. 2020;28, 115579.
7 Tidwell JH, Peat AJ, Buchwald SL. *J Org Chem*. 1994;59:7164–7168.
8 Brak K, Ellman JA. *Org Lett*. 2010;12:2004–2007.
9 Palakeeti B, Ramesh T, Reddy KV, Konakanchi R, Rao PN, Gobi KV. *Chromatographia*. 2019;82:591–604.
10 Cheng C, Zuo X, Tu D, Wan B, Zhang Y. *Org Lett*. 2020;22:4985–4989.
11 Yang X, Luo G, Zhou L, Liu B, Zhang , Gao H, Jin Z, Chi YR. ACS Catal. 2019:9:10971–10976.
12 Lorthiois E, et al. *J Med Chem*. 2020;63:8088–8113.
13 "Antibacterial agents in clinical development. An analysis of the antibacterial clinical development pipeline, including tuberculosis", September 2017, World Health Organization.
14 Koul A, Arnoult E, Lounis N, Guillemont J, Andries K. *Nature*. 2011;469:483–490.
15 Zhang X, Zhou Y, Wang H, et al. *Adv Synth Catal*. 2011;353:1429–1437.
16 Kimura M, Futamata M, Mukai R, Am TYJ. *Chem Soc*. 2005;127:4592–4593.
17 (a) Konyariková Z, Savková K, Kozmon S, Mikušová K. Antibiotics 2020;9:20. (b) Richards MR, Lowary TL. ChemBioChem 2009;10:1920–1938. (c) Eppe G, El Bkassiny S, Vincent SP, "Galactofuranose Biosynthesis: Discovery, Mechanisms and Therapeutic Relevance". Editors: J. Jimenés-Barbeo, F.J. Cañada, S. Martin-Santamaria. Publisher: RSC. In Carbohydrates in Drug Design and Discovery, 2015; Volume 43:209–241.
18 Carlson EE, May JF, Kiessling LL. *Chem Biol*. 2006;13:825–837.
19 Sambandamurthy VK, Derrick SC, Hsu T, et al. *Vaccine*. 2006;24:6309–6320.
20 Kremer L, Douglas JD, Baulard AR, et al. *J Biol Chem*. 2000;275:16857–16864.
21 (a) Villaume SA, Fu J, N'Go I, et al. *Chem Eur J*. 2017:10423–10429; (b) Fu J, Fu H, Dieu M, et al. *Chem Commun*. 2017;53:10632–10635.