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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

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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

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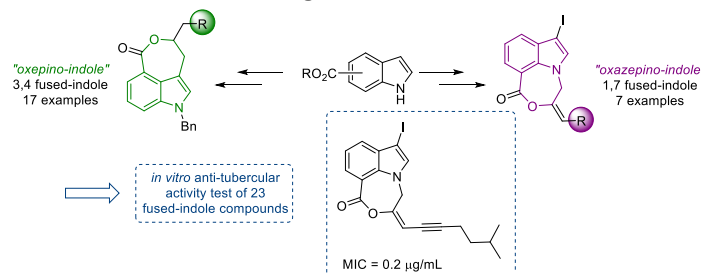
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Abstract

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 palladocatalyzed 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 lactones³ have been reported as anticancer,⁴ anti-inflammatory⁵ and anti-tuberculosis⁶ agents.

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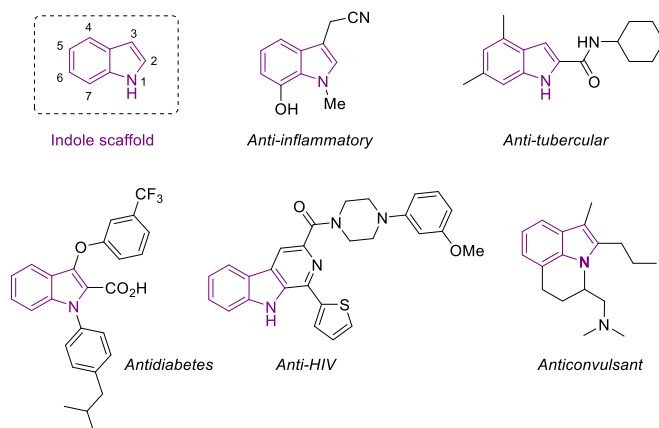


Figure 1. Representative indole-containing bioactive scaffolds.

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

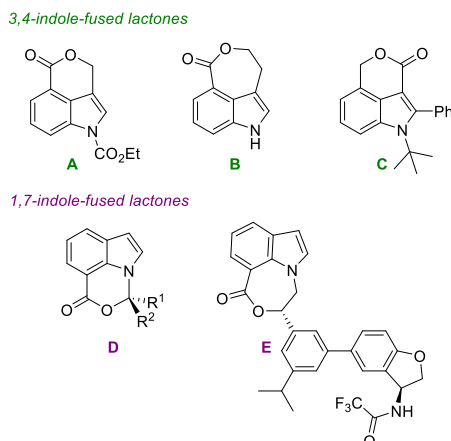


Figure 2. 3,4- and 1,7-indole-fused lactones described in literature.

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.

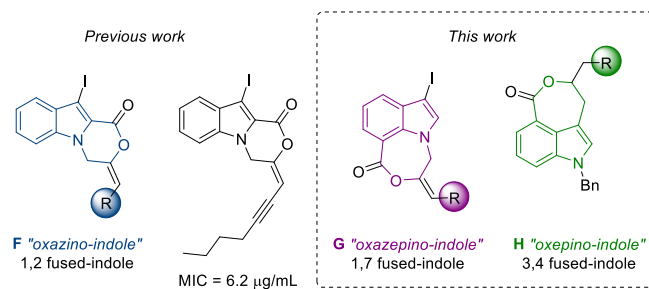
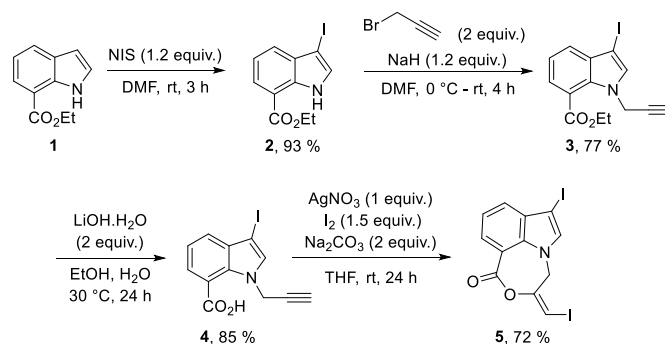


Figure 3. Fused tricyclic indoles.

2. Results and discussion

2.1. Synthesis of "oxazepino-indole" **G**

Based on the work previously developed in our laboratory,^{3b} 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**

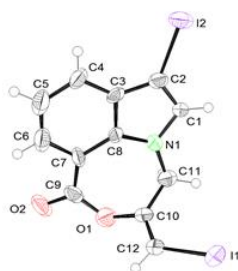
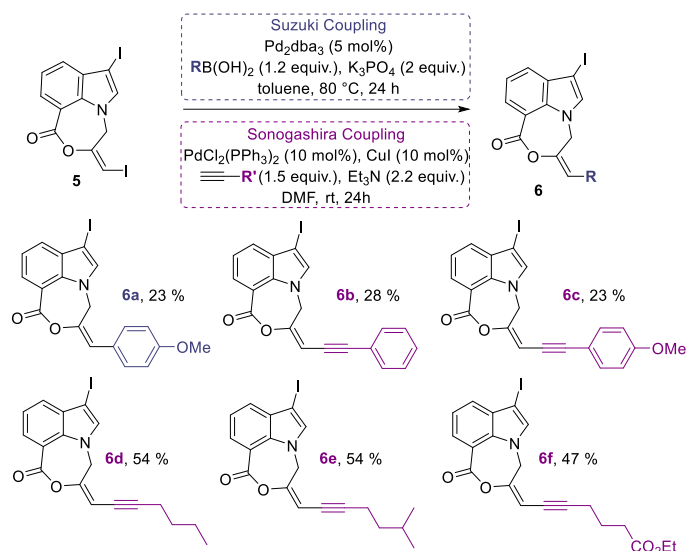


Figure 4. X-ray structure of oxazepino-indole **5**.

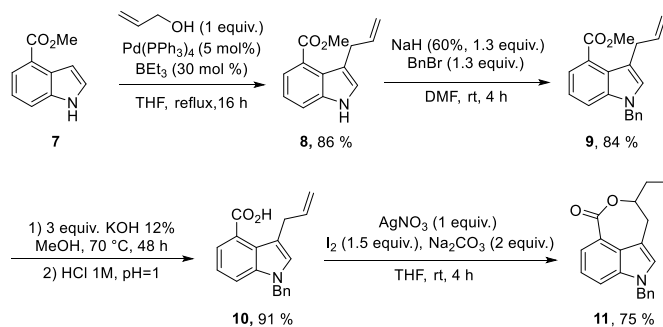
Compound **5** was then engaged in C-C coupling reactions (Scheme 2). Under standard Suzuki or Sonogashira reaction conditions, compound **5** leads to coupling products **6a** or **6b-f**, respectively, with modest yields. The reaction is regioselective at the vinyl iodine level. The low yields are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



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

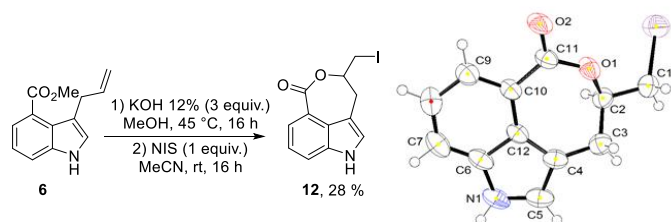
2.2. Synthesis of "oxepino-indole" **H**

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**.



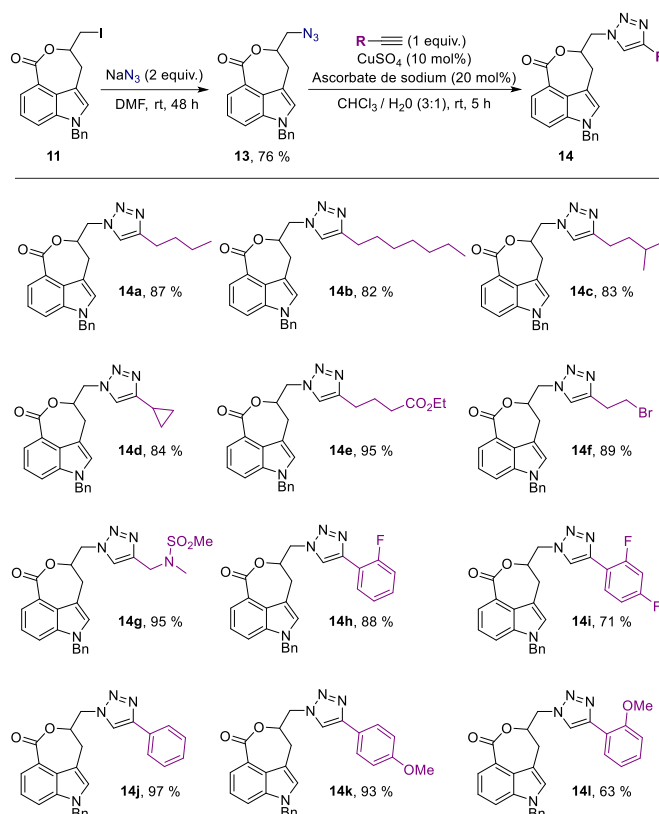
Scheme 3. Synthesis of "oxepino-indole" **11**.

A monotopic 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).



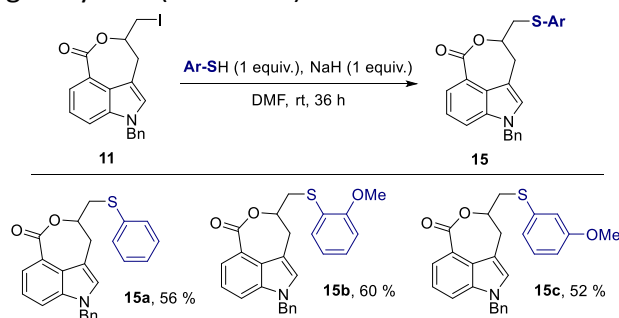
Scheme 4. Synthesis of compound **12** and X-ray structure of its enantiomer **R**.

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 nucleophilic 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 $\mu\text{g/mL}$, 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).

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

Entry	Compound	MIC ^[a] [$\mu\text{g/mL}$]
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	14g	>100
16	14h	>100
17	14i	>100
18	14j	>100
19	14k	>100
20	14l	>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.

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 ($K_d = 138.2 \pm 1.7 \mu\text{M}$ and $72.9 \pm 1.8 \mu\text{M}$, 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.

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 understudied 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 CDCl₃ as solvent. Data, reported using CHCl₃ ($\delta_{\text{H}} = 7.26$ ppm) as internal reference, were as follows (in order): chemical shift (δ in ppm relative to CHCl₃), multiplicity (s, d, t, q, quint, m, br for singlet, doublet, triplet, quartet, quintuplet, multiplet, broad) and coupling constants (J in Hz). ¹³C NMR was recorded at 75 MHz on the same instrument, using the CDCl₃ solvent peak at ($\delta_{\text{C}} = 77.16$ ppm) as reference. ¹⁹F 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

Ethyl 3-iodo-1*H*-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 hours, hydrolyzed with an aqueous solution of Na₂S₂O₃ (10 %, 40 mL). The resulting mixture was stirred for 30 minutes and the aqueous phase was then extracted with EtOAc (3 x 30 mL). The organic phases were washed with an aqueous saturated solution of NH₄Cl (20 mL), brine (20 mL), dried over anhydrous MgSO₄, 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**. C₁₁H₁₀INO₂, MW= 315.11 g/mol, yield= 93 %, beige solid, mp= 137-139 °C. IR (ATR) $\nu = 3290, 2984, 1683, 1616, 1570, 1507$ cm⁻¹. ¹H NMR (300 MHz, CDCl₃) $\delta = 10.03$ (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). ¹³C NMR (75 MHz, CDCl₃) $\delta = 166.9$ (C), 135.9 (C), 131.0 (C), 129.7 (CH), 126.7 (CH), 125.4 (CH), 120.0 (CH), 113.4 (C), 61.1 (CH₂), 57.5 (C), 14.6 (CH₃). HRMS (ESI) calcd. for C₁₁H₁₁INO₂ [M+H]⁺: 315.98290; found: 315.98215.

Ethyl 3-iodo-1-(prop-2-yn-1-yl)-1*H*-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 minutes. 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 NH₄Cl (20 mL) at 0°C and extracted with AcOEt (3 x 40 mL). The organic phases were washed with an aqueous saturated solution of NH₄Cl (20 mL), a saturated solution of NaCl (2 x 20 mL), dried over anhydrous MgSO₄, 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. C₁₄H₁₂INO₂, MW= 353.16 g/mol, yield= 77 %, beige solid, mp= 66-68°C. IR (ATR) $\nu = 3286, 1704, 1271, 1138$ cm⁻¹. ¹H NMR (300 MHz, CDCl₃) $\delta = 7.80$ (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 $\text{C}_{14}\text{H}_{13}\text{INO}_2$ [$\text{M}+\text{H}$] $^+$: 353.99855; found: 353.99836.

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 1M 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**. $\text{C}_{12}\text{H}_8\text{INO}_2$, 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} . ^1H 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 $\text{C}_{12}\text{H}_9\text{INO}_2$ [$\text{M}+\text{H}$] $^+$: 325.96725; found: 325.96691.

(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 hours at room temperature, cooled at 0°C and hydrolyzed with an aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ (5 %, 30 mL). The resulting mixture was stirred for 15 minutes and filtered through a pad of Celite® with EtOAc. The filtrate was then extracted with EtOAc (4 x 25 mL). The organic phases were washed with brine (2 x 30 mL), dried over anhydrous MgSO_4 , filtered and solvents were evaporated under vacuum to afford compound **5**. $\text{C}_{12}\text{H}_7\text{I}_2\text{NO}_2$, 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} . ^1H 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 $\text{C}_{12}\text{H}_8\text{I}_2\text{NO}_2$ [$\text{M}+\text{H}$] $^+$: 451.86389; found: 451.86307.

(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 minutes and filled with argon. Then toluene (3 mL) was introduced and the mixture was stirred at 80°C for 24 hours. After cooling, the reaction mixture was diluted with water (10 mL) and extracted with AcOEt (3 x 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**. $\text{C}_{19}\text{H}_{14}\text{INO}_3$, 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. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 (CH₃), 49.1 (CH₂). HRMS (ESI) calcd. for C₁₉H₁₅INO₃ [M+H]⁺: 432.00911; found: 432.00893.

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 minutes 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 hours. The reaction mixture was diluted with an aqueous saturated solution of NH₄Cl (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 MgSO₄, 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.

(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). C₂₀H₁₂INO₂, 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. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 (CH₂). HRMS (ESI) calcd. for C₂₀H₁₃INO₂ [M+H]⁺: 425.99855; found: 425.99766.

(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). C₂₁H₁₄INO₃, 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. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 (CH₃), 48.9 (CH₂). HRMS (ESI) calcd. for C₂₁H₁₅INO₃ [M+H]⁺: 456.00911; found: 456.00847.

(E)-3-(hept-2-yn-1-ylidene)-7-iodo-3,4-dihydro-1H-[1,4]oxazepino[6,5,4-*hi*]indol-1-one (6d). C₁₈H₁₆INO₂, 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. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 (CH₂), 30.6 (CH₂), 22.1 (CH₂), 19.4 (CH₂), 13.7 (CH₃). **HRMS** (ESI) calcd. for C₁₈H₁₇INO₂ [M+H]⁺: 406.02985; found: 406.02911.

(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). C₁₉H₁₈INO₂, 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. **¹H NMR** (300 MHz, CDCl₃) 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). **¹³C NMR** (75 MHz, CDCl₃) 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 (CH₂), 37.4 (CH₂), 27.4 (CH), 22.3 (2CH₃), 17.7 (CH₃). **HRMS** (ESI) calcd. for C₁₉H₁₉INO₂ [M+H]⁺: 420.04550; found: 420.04473.

Ethyl (E)-7-(7-iodo-1-oxo-1H-[1,4]oxazepino[6,5,4-hi]indol-3(4H)-ylidene)hept-5-ynoate (6f). C₂₀H₁₈INO₄, 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. **¹H NMR** (300 MHz, CDCl₃) 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). **¹³C NMR** (75 MHz, CDCl₃) 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 (CH₂), 57.4 (C), 48.6 (CH₂), 33.2 (CH₂), 23.7 (CH₂), 19.1 (CH₂), 14.4 (CH₃). **HRMS** (ESI) calcd. for C₂₀H₁₉INO₄ [M+H]⁺: 464.03533; found: 464.03482.

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

Methyl-3-allyl-1H-indole-4-carboxylate (8).¹⁶ In a Schlenk tube under argon, triethyl boron (1M 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 1H-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 hours at 70°C, cooled at room temperature, diluted with EtOAc (100 mL) and hydrolyzed with aqueous saturated solution of NaHCO₃ (50 mL). The aqueous phase was extracted with EtOAc (2 x 40 mL). The organic phases were washed with aqueous saturated solution of NaHCO₃ (50 mL), brine (2 x 50 mL), dried over anhydrous MgSO₄, 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**. C₁₃H₁₃NO₂, 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. **¹H NMR** (300 MHz, CDCl₃) 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). **¹³C NMR** (75 MHz, CDCl₃) 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 (CH₂), 52.1 (CH₃), 31.8 (CH₂). **HRMS** (ESI) calcd. for C₁₃H₁₄NO₂ [M+H]⁺: 216.10191; found: 216.10155.

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 minutes. Benzyl bromide (0.77 mL, 6.5 mmol, 1.3 equiv.) was added dropwise. The solution was stirred for 3 hours, then hydrolyzed with an aqueous saturated solution of NH_4Cl (20 mL) at 0°C and extracted with AcOEt (3 x 30 mL). The organic phases were washed with an aqueous saturated solution of NH_4Cl (20 mL), a saturated solution of NaCl (2 x 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. $\text{C}_{20}\text{H}_{19}\text{NO}_2$, MW= 305.38 g/mol, yield= 84 %, pale yellow oil. **IR** (ATR) ν = 2947, 1715, 1436, 1265, 1194, 1172, 1146, 1046, 910. **^1H 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 $\text{C}_{20}\text{H}_{20}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 306.14886; found: 306.14831.

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 1M 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**. $\text{C}_{19}\text{H}_{17}\text{NO}_2$, MW= 291.35 g/mol, yield= 91 %, white solid, mp= $160\text{-}162^\circ\text{C}$. **IR** (ATR) ν = 2918, 2601, 1673, 1454, 1435, 1349, 1268, 1202, 1155. **^1H NMR** (300 MHz, $\text{MeOD-}d_4$) 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, $\text{MeOD-}d_4$) 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 $\text{C}_{19}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 292.13321; found: 292.13260.

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 hours at room temperature, cooled at 0°C and hydrolyzed with an aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ (5 %, 30 mL). The resulting mixture was stirred for 15 minutes and filtered through a pad of Celite[®] with EtOAc. The filtrate was then extracted with EtOAc (4 x 30 mL). The organic phases were washed with brine (2 x 30 mL), dried over anhydrous MgSO_4 , filtered and solvents were evaporated under vacuum to afford compound **11**. $\text{C}_{19}\text{H}_{16}\text{INO}_2$, MW= 417.25 g/mol, yield= 75 %, pale yellow solid, mp= $152\text{-}154^\circ\text{C}$. **IR** (ATR) ν = 1676, 1455, 1436, 1273, 1166, 1130, 1062, 1009. **^1H 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 (CH₂), 32.5 (CH₂), 7.0 (CH₂). **HRMS** (ESI) calcd. for C₁₉H₁₇INO₂ [M+H]⁺: 418.02985; found: 418.02927.

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 hour at room temperature, hydrolyzed with an aqueous saturated solution of Na₂S₂O₃ (10 mL), diluted with water (10 mL) and stirred for an additional 30 minutes. The aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with an aqueous saturated solution of NH₄Cl (20 mL), brine (20 mL), dried over anhydrous MgSO₄, 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**. C₁₂H₁₀INO₂, 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. **¹H 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). **¹³C 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 (CH₂), 10.4 (CH₂). **HRMS** (ESI) calcd. for C₁₂H₁₁INO₂ [M+H]⁺: 327.98290; found: 327.98325.

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 x 30 mL). The organic phases were washed with brine (2 x 20 mL), dried over anhydrous MgSO₄, 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**. C₁₉H₁₆N₄O₂, 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. **¹H NMR** (300 MHz, CDCl₃) 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). **¹³C NMR** (75 MHz, CDCl₃) 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 (CH₂), 50.4 (CH₂), 30.3 (CH₂). **HRMS** (ESI) calcd. for C₁₉H₁₇N₄O₂ [M+H]⁺: 333.13460; found: 333.13392.

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 H₂O/CHCl₃ (3:1, 7.5 mL:2.5 mL) at 0°C. Then sodium ascorbate (12 mg, 0.06 mmol, 20 mol%) and CuSO₄·5H₂O (7.5 mg, 0.03 mmol, 10 mol%) were added. The resulting mixture was stirred for 5 hours at room temperature. Solvents were evaporated under vacuum and the residue was dissolved in water (15 mL) and extracted with CH₂Cl₂ (3 x 15 mL). The organic phases were washed with water (15 mL), brine (2 x 15 mL), dried over anhydrous MgSO₄, 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**.

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). C₂₅H₂₆N₄O₂, 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. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 (CH₂), 50.4 (CH₂), 31.6 (CH₂), 30.2 (CH₂), 25.5 (CH₂), 22.5 (CH₂), 13.9 (CH₃). HRMS (ESI) calcd. for C₂₅H₂₇N₄O₂ [M+H]⁺:415.21285; found: 415.21272.

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). C₂₈H₃₂N₄O₂, MW= 456.59 g/mol, yield= 82 %, clear paste. IR (ATR) ν = 2922, 1700, 1683, 1609, 1439, 1352, 1259, 1171, 1136, 1052. ¹H NMR (300 MHz, CDCl₃) 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*= 6.6Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) 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 (CH₂), 50.4 (CH₂), 31.9 (CH₂), 30.2 (CH₂), 29.5 (CH₂), 29.3 (CH₂), 29.1 (CH₂), 25.8 (CH₂), 22.7 (CH₂), 14.2 (CH₃). HRMS (ESI) calcd. for C₂₈H₃₃N₄O₂ [M+H]⁺: 457.25980; found: 457.25904.

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). C₂₆H₂₈N₄O₂, 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. ¹H NMR (300 MHz, CDCl₃) 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*= 7.9Hz, 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). ¹³C NMR (75 MHz, CDCl₃) 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 (CH₂), 50.4 (CH₂), 38.5 (CH₂), 30.1 (CH₂), 27.8 (CH), 23.7 (CH₂), 22.5 (2CH₃). HRMS (ESI) calcd. for C₂₆H₂₉N₄O₂ [M+H]⁺: 429.22850; found: 429.22791.

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). C₂₄H₂₂N₄O₂, 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. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 (CH₂), 50.4 (CH₂), 30.2 (CH₂), 8.0 (2CH₂), 6.8 (CH). **HRMS** (ESI) calcd. for C₂₄H₂₃N₄O₂ [M+H]⁺:399.18155; found: 399.18104.

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). C₂₇H₂₈N₄O₄, 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. **¹H NMR** (300 MHz, CDCl₃) 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). **¹³C NMR** (75 MHz, CDCl₃) 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 (CH₂), 54.2 (CH₂), 50.3 (CH₂), 33.7 (CH₂), 30.1 (CH₂), 25.0 (CH₂), 24.7 (CH₂), 14.3 (CH₃). **HRMS** (ESI) calcd. for C₂₇H₂₉N₄O₄ [M+H]⁺: 473.21833; found: 473.21766.

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). C₂₃H₂₀N₄O₂Br, 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. **¹H NMR** (300 MHz, CDCl₃) 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). **¹³C NMR** (75 MHz, CDCl₃) 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 (CH₂), 50.4 (CH₂), 31.4 (CH₂), 30.2 (CH₂), 29.6 (CH₂). **HRMS** (ESI) calcd. for C₂₃H₂₁⁷⁹BrN₄O₂ [M+H]⁺:465.09207; found: 465.09147.

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). C₂₄H₂₅N₅O₄S, 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. **¹H NMR** (300 MHz, CDCl₃) 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). **¹³C NMR** (75 MHz, CDCl₃) 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 (CH₂), 50.4 (CH₂), 44.9 (CH₂), 37.5 (CH₃), 34.7 (CH₃), 30.3 (CH₂). **HRMS** (ESI) calcd. for C₂₄H₂₆N₅O₄S [M+H]⁺:480.17000; found: 480.16944.

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 (14h). C₂₇H₂₁FN₄O₂, 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. **¹H NMR** (300 MHz, CDCl₃) 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, 1 H), 3.26 (d, $J = 15.8$ Hz, 1 H), 3.15 (ddd, $J = 16.3$ Hz, 9.5 Hz, 1.4 Hz, 1 H). **^{19}F NMR** (282 MHz, CDCl_3) $\delta = -114.0$. **^{13}C NMR** (75 MHz, CDCl_3) $\delta = 168.2$ (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 $\text{C}_{27}\text{H}_{22}\text{FN}_4\text{O}_2$ $[\text{M}+\text{H}]^+$: 453.17213 ; found: 453.17157 .

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). $\text{C}_{27}\text{H}_{20}\text{F}_2\text{N}_4\text{O}_2$, MW = 470.48 g/mol, yield = 71% , beige solid, mp = $181-183$ °C. **IR** (ATR) $\nu = 2322, 1696, 1613, 1562, 1493, 1455, 1353, 1263, 1171, 1136, 1068$. **^1H NMR** (300 MHz, CDCl_3) $\delta = 8.27$ (d, $J = 3.4$ Hz, 1 H), 8.24 (td, $J = 8.6$ Hz, 6.6 Hz, 1 H), 7.96 (dd, $J = 7.6$ Hz, 0.7 Hz, 1 H), 7.50 (dd, $J = 8.2$ Hz, 0.7 Hz, 1 H), $7.33-7.23$ (m, 4 H), $7.10-7.06$ (m, 3 H), 6.98 (ddd, $J = 8.2$ Hz, 7.5 Hz, 2.5 Hz, 1 H), 6.90 (td, $J = 8.9$ Hz, 2.5 Hz, 1 H), 5.30 (s, 2 H), 5.15 (m, 1 H), 4.87 (dd, $J = 14.3$ Hz, 4.3 Hz, 1 H), 4.81 (dd, $J = 14.3$ Hz, 6.2 Hz, 1 H), 3.26 (d, $J = 16.0$ Hz, 1 H), 3.12 (ddd, $J = 16.2$ Hz, 9.5 Hz, 1.3 Hz, 1 H). **^{19}F NMR** (282 MHz, CDCl_3) $\delta = -110.10, -110.11$. **^{13}C NMR** (75 MHz, CDCl_3) $\delta = 168.1$ (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 $\text{C}_{27}\text{H}_{21}\text{F}_2\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$: 471.16271 ; found: 471.16202 .

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): $\text{C}_{27}\text{H}_{22}\text{N}_4\text{O}_2$, MW = 434.50 g/mol, yield = 97% , white solid, mp = $160-162$ °C. **IR** (ATR) $\nu = 3029, 1695, 1610, 1454, 1439, 1353, 1252, 1170, 1132, 1057$. **^1H NMR** (300 MHz, CDCl_3) $\delta = 8.22$ (s, 1 H), 7.96 (dd, $J = 7.6$ Hz, 0.8 Hz, 1 H), 7.86 (m, 2 H), 7.50 (dd, $J = 8.2$ Hz, 0.8 Hz, 1 H), 7.43 (m, 2 H), $7.36-7.23$ (m, 5 H), 7.07 (m, 3 H), 5.30 (s, 2 H), 5.13 (m, 1 H), 4.87 (dd, $J = 14.3$ Hz, 3.4 Hz, 1 H), 4.78 (dd, $J = 14.3$ Hz, 6.3 Hz, 1 H), 3.25 (d, $J = 16.2$ Hz, 1 H), 3.09 (ddd, $J = 16.3$ Hz, 9.7 Hz, 1.2 Hz, 1 H). **^{13}C NMR** (75 MHz, CDCl_3) $\delta = 168.2$ (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 $\text{C}_{27}\text{H}_{23}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$: 435.18155 ; found: 435.18145 .

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 (14k). $\text{C}_{28}\text{H}_{24}\text{N}_4\text{O}_3$, MW = 464.53 g/mol, yield = 93% , beige solid, mp = $194-196$ °C. **IR** (ATR) $\nu = 2926, 2323, 1697, 1610, 1497, 1454, 1439, 1353, 1247, 1171, 1132, 1064, 1027$. **^1H NMR** (300 MHz, CDCl_3) $\delta = 8.12$ (s, 1 H), 7.96 (dd, $J = 7.6$ Hz, 0.8 Hz, 1 H), 7.79 (dt, $J = 8.9$ Hz, 2.1 Hz, 2 H), 7.49 (dd, $J = 8.2$ Hz, 0.8 Hz, 1 H), $7.34-7.23$ (m, 4 H), $7.09-7.05$ (m, 3 H), 6.96 (dt, $J = 8.9$ Hz, 2.1 Hz, 2 H), 5.29 (s, 2 H), 5.13 (m, 1 H), 4.85 (dd, $J = 14.3$ Hz, 3.9 Hz, 1 H), 4.78 (dd, $J = 14.3$ Hz, 6.2 Hz, 1 H), 3.84 (s, 3 H), 3.25 (d, $J = 16.1$ Hz, 1 H), 3.09 (ddd, $J = 16.3$ Hz, 9.7 Hz, 1.4 Hz, 1 H). **^{13}C NMR** (75 MHz, CDCl_3) $\delta = 168.3$ (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 $\text{C}_{28}\text{H}_{25}\text{N}_4\text{O}_3$ $[\text{M}+\text{H}]^+$: 465.19212 ; found: 465.19164 .

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 (14l). C₂₈H₂₄N₄O₃, 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. **¹H NMR** (300 MHz, CDCl₃) 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). **¹³C NMR** (75 MHz, CDCl₃) δ = 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 (CH₃), 54.3 (CH₂), 50.4 (CH₂), 30.3 (CH₂). **HRMS** (ESI) calcd. for C₂₈H₂₅N₄O₃ [M+H]⁺:465.19212; found: 465.19154.

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 minutes. 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 hours at room temperature, then hydrolyzed with an aqueous saturated solution of NH₄Cl (10 mL) and extracted with AcOEt (3 x 10 mL). The organic phases were washed with water (10 mL), brine (10 mL), dried over anhydrous MgSO₄, 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**.

6-Benzyl-3-((phenylthio)methyl)-4,6-dihydrooxepino[5,4,3-cd]indol-1(3H)-one (15a). C₂₅H₂₁NO₂S, MW= 399.51 g/mol, yield= 56 %, clear paste. **IR** (ATR) ν = 3061, 3029, 3921, 1688, 1609, 1582, 1480, 1453, 1437, 1352, 1257, 1132, 1061, 114, 733, 690. **¹H NMR** (300 MHz, CDCl₃) δ = 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). **¹³C NMR** (75 MHz, CDCl₃) δ = 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 (CH₂), 38.7 (CH₂), 31.3 (CH₂). **HRMS** (ESI) calcd. for C₂₅H₂₂NO₂S [M+H]⁺:400.13658; found: 400.13611.

6-Benzyl-3-(((2-methoxyphenyl)thio)methyl)-4,6-dihydrooxepino[5,4,3-cd]indol-1(3H)-one (15b). C₂₆H₂₃NO₂S, MW= 429.53 g/mol, yield= 60 %, white solid, mp= 66-68°C. **IR** (ATR) ν = 3063, 3003, 2917, 2834, 1687, 1608, 1576, 1452, 1433, 1351, 1242, 1131, 1061, 1014, 738, 699. **¹H NMR** (300 MHz, CDCl₃) δ = 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). **¹³C NMR** (75 MHz, CDCl₃) δ = 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 (CH₃), 50.3 (CH₂), 37.2 (CH₂), 31.2 (CH₂). **HRMS** (ESI) calcd. for C₂₆H₂₄NO₂S [M+H]⁺:430.14714; found: 430.14689.

6-Benzyl-3-(((3-methoxyphenyl)thio)methyl)-4,6-dihydrooxepino[5,4,3-cd]indol-1(3H)-one (15c). C₂₆H₂₃NO₂S, MW= 429.53 g/mol, yield= 52 %, yellow paste. IR (ATR) ν = 3061, 3019, 2921, 1688, 1609, 1582, 1480, 1453, 1437, 1352, 1257, 1168, 1132, 1061, 1014, 734, 691. ¹H NMR (300 MHz, CDCl₃) δ = 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). ¹³C NMR (75 MHz, CDCl₃) δ = 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 C₂₆H₂₄NO₂S [M+H]⁺:430.14714; found: 430.14671.

4.2. *In vitro* anti-tubercular activity

Antitubercular evaluations were performed against the pantothenate-auxotrophic *Mt* mc²6230 strain¹⁹ cultured in Middlebrook 7H9 broth supplemented with oleic acid-albumin-dextrose-catalase enrichment (OADC) and 109 μ M pantothenic acid (complete 7H9 medium) at 37°C without agitation. MIC determination was done using the broth dilution method. Briefly, a log-phase (OD₆₀₀ ~ 1) culture was diluted to an OD₆₀₀ = 0.05 in complete 7H9 medium and deposited in all the wells of a 96-well microtiter plate (for the first row 200 μ l/well, for all other rows 100 μ l/well). The tested compounds were then directly added (2 μ l 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).²² To determine the binding affinity of UDP-fluorescein towards *Mt* UGM, serial dilutions of dialyzed UGM (final concentration: 1x10⁻⁵ to 10 μ M) 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 μ l 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 ($\lambda_{\text{excitation}}$ = 485 nm, $\lambda_{\text{emission}}$ = 535 nm).

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Supplementary Material

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