Tetrahedron Letters 50 (2009) 3872–3876

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Palladium-catalyzed C–C coupling: efficient preparation of new 5-thio-β-D-xylopyranosides as oral venous antithrombotic drugs

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ARTICLE INFO

Article history:
Received 12 January 2009
Revised 8 April 2009
Accepted 14 April 2009
Available online 17 April 2009

Keywords:
5-Thioxylopyranosides
Antithrombotic
Glycosaminoglycan
Suzuki
Stille
Coupling reactions

ABSTRACT

First examples of a Suzuki and Stille cross-coupling reaction to prepare derivatives of pyridinyl 5-thio-β-D-xylopyranosides are described. Some of these compounds are orally active in an animal model of venous thrombosis.

Thromboembolic disorders are a major cause of morbidity and mortality in industrialized countries. The prophylaxis of these disorders is largely managed by intravenous heparin therapy or by oral warfarin therapy. The drawbacks of heparin therapy are the mode of administration and the high hemorrhagic risk. The drawbacks of warfarin therapy are the delay of their action, the risk in bleeding and the interactions with numerous drugs representing serious problems.

In our search for new orally active antithrombotic drugs without such serious side effects, we developed a lead-finding program based on the hypothesis that β-D-xylopyranosides might be effective antithrombotic drugs[1–4] since they induce the biosynthesis of glycosaminoglycans in cell culture, as demonstrated by Okayama,[5] Schwarz,[6] and others. We previously reported[2–4] that 5-thio-β-D-xylopyranosides were more potent than their 5-oxo analogs and therefore we focused on the former. Within these series, Odiparcil (Chart 1) was evaluated in clinical trials in patients[7] for the prevention of venous thromboembolism (VTE), particularly following orthopedic surgery (e.g., knee or hip arthroplasty) with some preliminary proof of principle.

Our plans focused on the elucidation of structural analogs of Odiparcil. Previously[1–4] we investigated aromatic aglycons and studied heteroaromatic moieties. Particularly, pyridine derivatives were assessed since these new chemical entities could induce (i) improved pharmacokinetic profiles, with much better solubility properties and (ii) improved activity with novel interactions between the target and the nitrogen atom. This led us to prepare 5-thio-β-D-xylopyranosides containing pyridine moieties and led to the discovery of lead compound **1** (Chart 1) which shows prom-

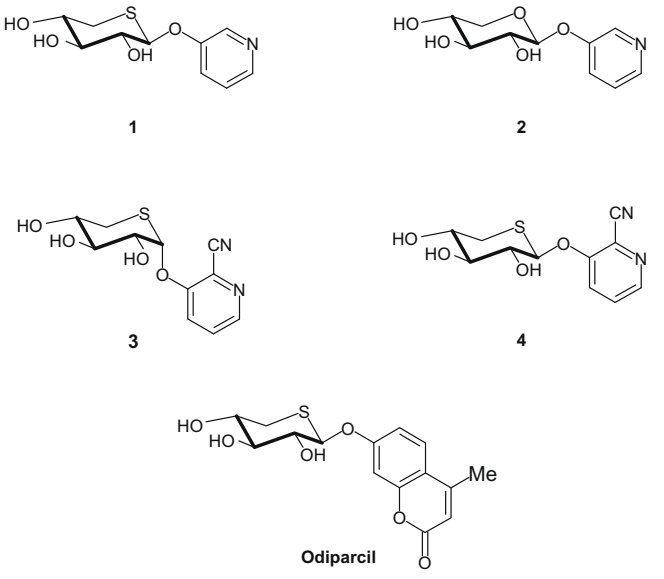

Chart 1.

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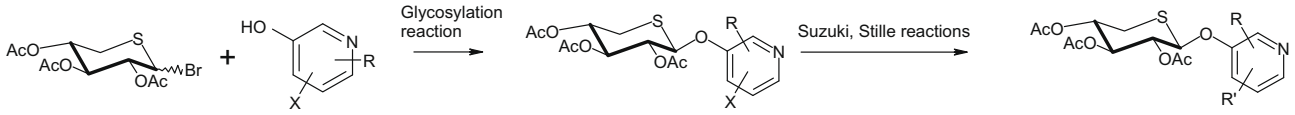
doi:10.1016/j.tetlet.2009.04.050

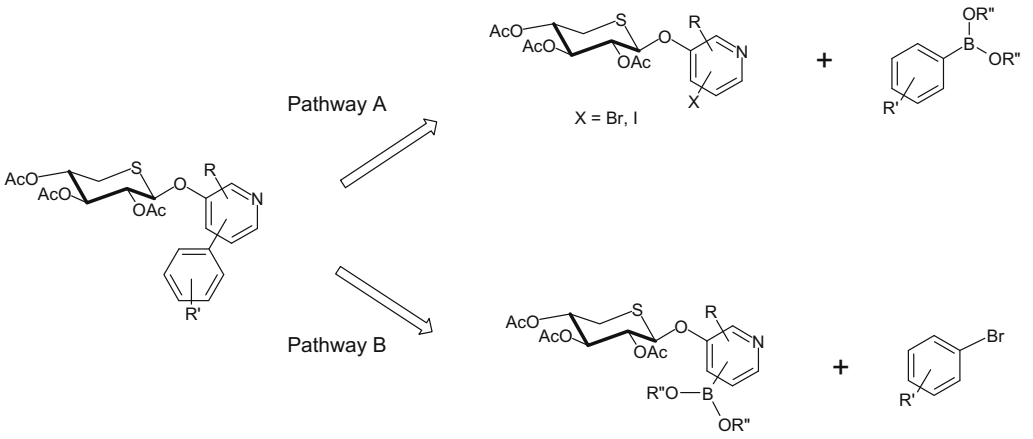
ising pharmacological profile.[8] We first determined the influence of the heteroatom of the osidic ring and the influence of the anomeric configuration by synthesizing the 5-oxo analog of compound **1 (2)** and the α-analog **3** of another active compound (**4**[8]). As previously observed with other aglycon series[2–4], compounds **2**[9] and **3**[10] are inactive. Therefore we focused our syntheses on 5-thio-β-D-xylopyranosides.

We first investigated compounds with small substituents such as halogens, cyano, nitro, alkyl, or trifluoromethyl groups[8] on the pyridine ring. The preparation of such derivatives was relatively straightforward using several commercially available aglycons but biological results were rather disappointing. We therefore decided to switch our synthetic efforts to bicyclic aglycons or to acylated pyridines in order to explore the targeted binding site. Therefore, a robust synthetic protocol was needed in order to prepare numerous xylopyranosides for the structure–activity relationship studies.

In this type of chemistry the critical step is the glycosylation step between the glycosyl donor and the pyridinol. As a strict β-configuration of the glycosidic bond is required for the biological activity[2], the chromatographic separation of both the α and β epimers, generated during the reaction, represents a serious limitation to the method. Thus, we developed chemical synthetic routes based on Suzuki and Stille coupling reactions (Scheme 1) which had never been reported for 5-thiosugars. As illustrated below, this chemistry allowed for parallel synthesis, thereby resulting in increased efficiency. Using the Suzuki and Stille coupling reactions, we have prepared a large number of novel compounds that avoid the glycosylation reaction for each compound (Scheme 1). This type of strategy has been utilized to prepare several nucleosides[11–13] and pyranosides.[14,15] Because of the high affinity of palladium for sulfur and of the vulnerability of acetate-protecting groups for basic conditions, it was not clear whether the Suzuki and Stille cross-coupling reactions could be applied to these protected thioglycosides.

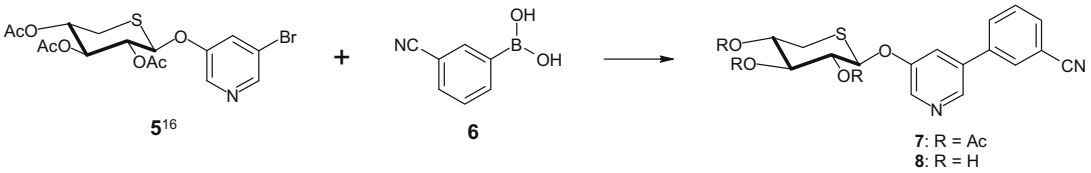


Scheme 1. General pathway.



Scheme 2. Suzuki cross-coupling reactions.

Table 1
Suzuki cross-coupling reactions: search for optimal base and catalyst



5[16] **6** **7**: R = Ac **8**: R = H

Entry	Boronic acid derivative (equiv)	Base	Catalyst	Solvent	Time[a] (min)	Yield[b] (%)
1	1.2	CsF (2 equiv)	PS-PPh_3-Pd[c] (0.05 equiv)	DME[d]/CH_3OH	30	48
2	1.2	MP-Carbonate[c] (2 equiv)	PS-PPh_3-Pd (0.05 equiv)	DME/CH_3OH	30	39
3	1.2	PL-HCO_3 MR-Resin[e] (2 equiv)	PS-PPh_3-Pd (0.05 equiv)	DME/CH_3OH	30	14
4	2	Na_2CO_3 (1.5 equiv)	Pd(dppf)Cl_2·CH_2Cl_2 (0.1 equiv)	DME/H_2O	20	65
5	2	Cs_2CO_3 (2 equiv)	PS-PPh_3-Pd (0.05 equiv)	DME/CH_3OH	30	57[f]

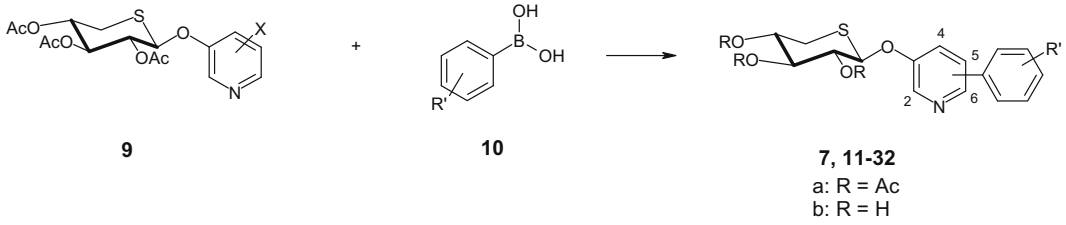
[a] All the experiments have been performed under microwave heating at 120 °C.
[b] Yield in isolated **7**.
[c] Commercially available at Argonaut Technologies.
[d] Dimethoxyethane.
[e] Commercially available at Polymer Laboratories.
[f] Yield in isolated **8**.

Our first target was to obtain xylopyranosides with pyridine rings substituted by aryl[16] and heteroaryl groups.[17] Glycosylations were performed according to classical methods.[8,16,17] Two synthetic pathways were studied (Scheme 2), the boronic moiety being attached to the phenyl ring (pathway A) or to the pyridinyl xylopyranoside (pathway B).

In a first series of reactions (pathway A), we used a pyridinyl xylopyranoside bearing a halide substituent which was combined with a series of phenyl boronic acid derivatives. Various conditions were studied using different catalysts and different bases (Table 1) and microwave heating. The best results were obtained with $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ as a catalyst and Na_2CO_3 as a base.[18] Using Cs_2CO_3 as a base, DME/MeOH as solvents (Table 1, entry 5), we surprisingly obtained the unprotected xylopyranosides directly. Having demonstrated the synthetic utility of the Suzuki coupling to provide different substituents on the pyridine ring, we turned our attention to the preparation of various xylopyranosides[16] (Table 2). This led us to study numerous xylopyranosides in biological assays and structure–activity relationship studies.

In order to increase the diversity of our library of 5-thio-xylopyranosides we also explored pathway B, starting from aryl halides (Scheme 3). The new challenge was to synthesize boron derivatives from 5-thio-xylopyranosides. To our knowledge, these types of compounds have never been reported. All the experiments were

Table 2
Examples of Suzuki cross-coupling reactions of thioxylosides (pathway A)

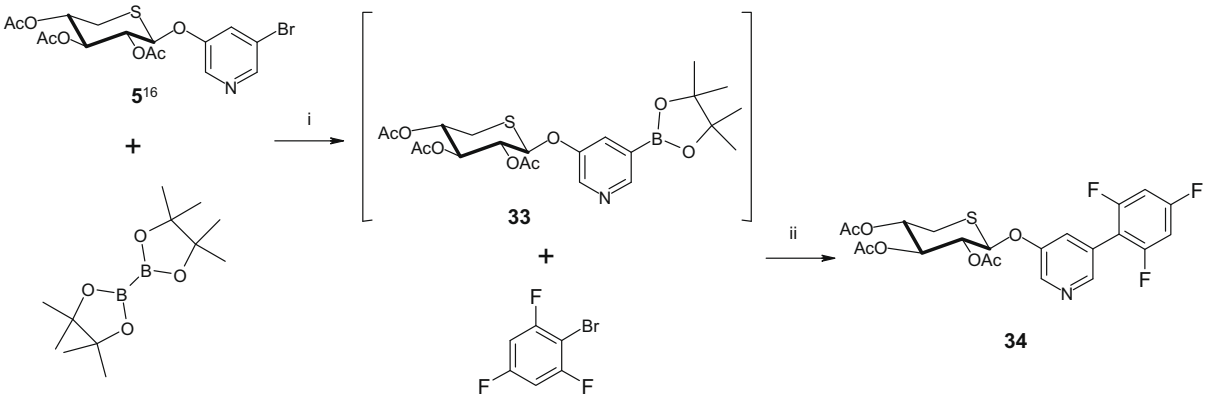


9 **10** **7, 11-32**

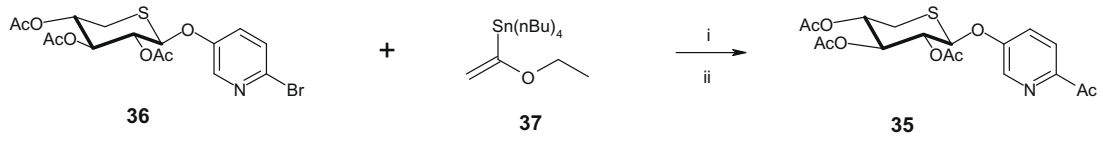
a: R = Ac
b: R = H

Entry	X	Aryl position	R'	Product	Yield (%)
1	Br	2	4-F	**11a**[19]	64
2	Br	2	4-OMe	**12b**[20]	65
3	I	4	4-F	**13a**[21]	47
4[a]	Br	4	4-OMe	**14a**[22]	29
5	Br	5	4-F	**15b**[23]	41
6[a]	Br	5	4-OMe	**16a**[24]	80
7	Br	5	2,4-diF	**17a**[25]	87
8	Br	5	2-Cl, 4-F	**18a**[26]	81
9	Br	5	3-CN, 4-F	**19a**[27]	66
10	Br	5	3-F, 4-CN	**20a**[28]	65
11	Br	5	3-CN	**7a**[29]	59
12	Br	5	3-OMe	**21a**[30]	77
13	Br	5	4-O*i*Pr	**22a**[31]	55
14	Br	5	3,4-diOMe	**23a**[32]	73
15	Br	5	3,5-diMe, 4-OMe	**24a**[33]	52
16	Br	5	3-Cl, 4-OMe	**25a**[34]	66
17	Br	5	4-F, 2-OMe	**26a**[35]	92
18	Br	5	3-F-4-O*i*Pr	**27a**[36]	82
19	Br	5	2,6-diF, 4-OMe	**28a**[37]	30
20	Br	5	3-Me, 4-F	**29a**[38]	48
21	Br	5	2-Me, 4-F	**30a**[39]	72
22	Br	6	4-F	**31b**[40]	46
23[a]	Br	6	4-OMe	**32a**[41]	28

Experimental conditions: $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$, Na_2CO_3, DME/H_2O, under microwave heating at 120 °C for 20 min.
[a] The used base is MP-carbonate.

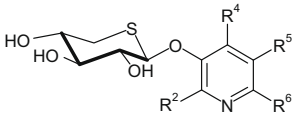


Scheme 3. Example of Suzuki cross-coupling reactions (Pathway B). Reagents and conditions: (i) $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$, KOAc, DME, 150 °C, 1 h, μwaves; (ii) $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$, Na_2CO_3, DME, 120 °C, 30 min, μwaves; Overall yield: 40%.



Scheme 4. Stille cross-coupling reaction. Reagents and conditions: (i) $PdCl_2(PPh_3)_2$/CuI/AcN/reflux, 1 h; (ii) HCl, 1 h; Overall yield: 68%.

Table 3
Some antithrombotic activities



Product	R^2	R^4	R^5	R^6	Activity[a] (%)
38[44]	H	H	H	Ac	55
39[45]	4-F Ph	H	H	H	40
40[46]	H	4-F Ph	H	H	38
15b[23]	H	H	4-F Ph	H	99
31b[40]	H	H	H	4-F Ph	61
12b[20]	4-OMe Ph	H	H	H	28
41[47]	H	4-OMe Ph	H	H	28
42[48]	H	H	4-OMe Ph	H	100
43[49]	H	H	H	4-OMe Ph	61

[a] Dosage = 6 mg/kg.

performed under microwave heating. The best results were obtained with Pd(dppf)Cl_2·CH_2Cl_2 as a catalyst and KOAc as a base for the formation of the boron derivatives, and using Pd(dppf)Cl_2·CH_2Cl_2 as a catalyst, and Na_2CO_3 as a base, for the coupling step (Scheme 3).

As we had also planned to generate 5-thio-xylopyranosides of acyl-substituted pyridinols (e.g., **35:** Scheme 4)[16] the possibility of obtaining them by using Koenigs–Knorr glycosidations was explored. Unfortunately, this was not successful (very low yields) in all but in a few cases (moderate yield). However, we found that **36**[16] could undergo a Stille cross coupling with **37** producing the desired compound **35** and giving a 68% yield (Scheme 4).

In all cases the final step was a deacetylation reaction (using MeONa/MeOH or NH_3/MeOH) that generates the corresponding non-protected 5-thio-xylopyranosides which were evaluated for their biological properties.

The 5-thio-xylopyranosides novel chemical entities described were screened using an antithrombotic model (see Wessler[42,43]) performed in the rat. Factor Xa is the thrombogenic agent. The activity is expressed as the percentage of decrease of the thrombus weight between control and treated animals. The compounds were administered orally 2 h prior to the induction of thrombosis with Factor Xa. Selected results are shown in Table 3.

Due to the fact that these results (Table 3) are obtained after oral administration, it is difficult to establish truly meaningful structure–activity relationships. At this moment, we can, however, conclude that (i) in the acetyl series, the 2-position seemed to be favorable, (ii) in phenyl-substituted derivatives, the substituents of the phenyl ring modulated the in vivo activity, (iii) in these latter series, the position of the phenyl ring on the pyridine moiety is important. Extensive biological experiments, in particular using the galactosyltransferase[50] (enzyme involved in the biosynthesis of glycosaminoglycans: β4Gal-T7; EC 2.4.1.133), are ongoing.

These data demonstrate for the first time that palladium-catalyzed reactions like Suzuki and Stille coupling reactions can be performed on 5-thiosugars. This divergent strategy allows us to generate large library of compounds in a short time. Many of the new compounds prepared could not be obtained through glycosylation of the substituted pyridinols. Preliminary bioassays showed that some of our new 5-thio-β-D-xylopyranosides possess antithrombotic efficacy and should be more fully investigated in preclinical studies.

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9. Compound **2** was obtained in 93% yield by deacetylation (MeONa, MeOH) of the corresponding 2,3,4-tri-*O*-acetyl-β-D-xylopyranoside. The latter compound was obtained in 65% yield by glycosylation starting from 2,3,4-tri-*O*-acetyl β-D-xylopyranosyl bromide and 3-pyridinol, using Ag_2O as promoter and acetonitrile as solvent. Compound **2**: Mp = 203–206 °C; $[\alpha]_D^{23}$ −32 (*c* 0.5, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.15–3.45 (m, 4H), 3.75 (dd, 1H), 4.96 (d, *J* = 6.6 Hz, 1H), 5.09 (d, 1H), 5.15 (d, 1H), 5.42 (d, 1H), 7.33 (dd, *J* = 4.6 Hz, 8.3 Hz, 1H), 7.44 (m, 1H), 8.23 (dd, *J* = 1.3 Hz, 4.6 Hz, 1H), 8.32 (d, *J* = 2.8 Hz, 1H).
10. Compound **3** was obtained in 52% yield by deacetylation (MeONa, MeOH) of the corresponding 2,3,4-tri-*O*-acetyl-β-D-xylopyranoside. The latter compound was obtained in 2% yield (after flash chromatography on silica gel) by glycosylation starting from 2,3,4-tri-*O*-acetyl β-D-xylopyranosyl bromide and 2-cyano-3-pyridinol using zinc chloride and silver imidazolate as promoters and toluene and acetonitrile as solvents. Compound **3**: Mp = 180–181 °C; $[\alpha]_D^{20}$ 310 (*c* 0.3, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.46 (ddd, *J* = 13.3 Hz, 4.0 Hz, 1.4 Hz, 1H), 2.63 (dd, *J* = 13.3 Hz, 10.8 Hz, 1H), 3.45–3.67 (m, 2H), 3.72 (m, 1H), 5.11 (d, *J* = 4.3 Hz, 1H), 5.30 (d, *J* = 4.0 Hz, 1H), 5.49 (d, *J* = 5.0 Hz, 1H), 5.82 (dd, *J* = 1.3 Hz, 3.1 Hz, 1H), 7.73 (dd, *J* = 4.5 Hz, 8.8 Hz, 1H), 7.98 (dd, *J* = 1.1 Hz, 8.8 Hz, 1H), 8.36 (dd, *J* = 1.1 Hz, 4.5 Hz, 1H).
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18. *General procedure*: To a solution of a halogeno derivative in DME were added 1.5 equiv of aqueous sodium carbonate, 0.1 equiv of Pd(dppf)Cl_2·CH_2Cl_2 and 2 equiv of boronic acid derivative. The mixture was heated for 20 min under microwave heating at 120 °C, then cooled, diluted with water, and extracted by ethyl acetate. The organic phase is washed with an aqueous solution of sodium carbonate and water until neutral pH, dried over magnesium sulfate, and concentrated under vacuum. The crude material is purified by chromatography.
19. Mp = 147–151 °C; $[\alpha]_D^{27}$ −91 (*c* 0.3, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.82 (s, 3H), 1.97 (s, 3H), 2.00 (s, 3H), 2.91 (dd, *J* = 4.8 Hz, 13.5 Hz, 1H), 3.03 (dd, *J* = 10.6 Hz, 13.5 Hz, 1H), 4.96 (ddd, *J* = 4.8 Hz, 9.5 Hz, 10.6 Hz, 1H), 5.21 (t, *J* = 9.5 Hz, 1H), 5.34 (dd, *J* = 8.8 Hz, 9.5 Hz, 1H), 5.91 (d, *J* = 8.8 Hz, 1H), 7.21 (t, *J* = 8.8 Hz, 2H), 7.46 (dd, *J* = 8.4 Hz, 4.4 Hz, 1H), 7.73–7.86 (m, 3H), 8.37 (dd, *J* = 1.2 Hz, 4.4 Hz, 1H).
20. Mp = 137 °C; $[\alpha]_D^{33}$ −79 (*c* 0.2, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.52–2.70 (m, 2H), 3.14 (td, *J* = 8.8 Hz, 4.5 Hz 1H), 3.48 (m, 1H), 3.62 (td, *J* = 8.5 Hz, 4.9 Hz, 1H), 3.81 (s, 3H), 5.13 (d, *J* = 4.5 Hz 1H), 5.19 (d, *J* = 4.1 Hz, 1H), 5.38 (d, *J* = 8.5 Hz, 1H), 5.55 (d, *J* = 4.9 Hz, 1H), 6.98 (d, *J* = 9.1 Hz, 2H), 7.31

(dd, J = 4.4 Hz, 8.5 Hz, 1H), 7.80 (dd, J = 1.1 Hz, 8.5 Hz, 1H), 7.99 (d, J = 9.1 Hz, 2H), 8.26 (dd, J = 1.1 Hz, 4.4 Hz, 1H).

21. Mp = 110 °C; $[\alpha]_D^{30}$ −49 (c 0.3, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ ppm 1.83 (s, 3H), 1.96 (s, 3H), 1.99 (s, 3H), 2.89 (dd, J = 4.7 Hz, 13.4 Hz, 1H), 3.04 (dd, J = 10.4 Hz, 13.4 Hz, 1H), 4.93 (ddd, J = 4.7 Hz, 9.5 Hz, 10.4 Hz, 1H), 5.18 (t, J = 9.5 Hz, 1H), 5.26 (dd, J = 8.8 Hz, 9.5 Hz, 1H), 5.94 (d, J = 8.8 Hz, 1H), 7.26 (t, J = 8.8 Hz, 2H), 7.41 (d, J = 4.9 Hz, 1H), 7.52 (dd, J = 4.9 Hz, 4.7 Hz, 2H), 8.36(d, J = 4.7 Hz, 1H), 8.71 (s, 1H).
22. Mp = 193 °C; $[\alpha]_D^{30}$ −92 (c 0.3, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.84 (s, 3H), 1.97 (s, 3H), 1.99 (s, 3H), 2.88 (dd, 1H), 3.03 (dd, 1H), 3.81 (s, 3H), 4.93 (td, 1H), 5.19 (t, 1H), 5.29 (t, 1H), 5.94 (d, J = 8.8 Hz, 1H), 6.98 (d, J = 9.1 Hz, 2H), 7.39 (d, J = 4.8 Hz, 1H), 7.45 (d, J = 9.1 Hz, 2H), 8.32 (d, J = 4.8 Hz, 1H), 8.68 (s, 1H) .
23. Mp = 208–209 °C; $[\alpha]_D^{25}$ −84 (c 0.1, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.59 (dd, J = 13.4 Hz, 4.8 Hz, 1H), 2.69 (dd,, J = 13.4 Hz, 10.4 Hz, 1H), 3.14 (td, J = 8.8 Hz, 4.5 Hz, 1H), 3.49 (m, 1H), 3.61 (td, J = 8.8 Hz, 4.8 Hz, 1H), 5.05 (d, J = 4.5 Hz, 1H), 5.16 (d,, J = 4.5 Hz, 1H), 5.46 (d, J = 8.8 Hz, 1H), 5.56 (d, J = 4.8 Hz, 1H), 7.35 (t, J = 9.2 Hz, 2H), 7.76–7.87 (m, 3H), 8.36 (d, J = 2.9 Hz, 1H), 8.52 (d, J = 2.2 Hz, 1H).
24. Mp = 156 °C; $[\alpha]_D^{25}$ −11 (c 0.4, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.97 (s, 3H), 2.01 (s, 6H), 2.95 (dd, J = 13.3 Hz, 4.8 Hz, 1H), 3.05 (dd, J = 13.3 Hz, 10.4 Hz, 1H), 3.82 (s, 3H), 5.00 (td, J = 8.9 Hz, 4.8 Hz, 1H), 5.24 (t, J = 8.9 Hz, 1H), 5.37 (t, J = 8.9 Hz, 1H), 6.05 (d, J = 8.9 Hz, 1H), 7.08 (d, J = 8.8 Hz, 2H), 7.71 (d, J = 8.8 Hz, 2H), 7.74 (m, 1H), 8.29 (s, 1H), 8.58 (s, 1H).
25. Mp = 121 °C; $[\alpha]_D^{27}$ −9 (c 0.3, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.97 (s, 3H), 2.01 (s, 6H), 2.94 (dd, J = 5.1 Hz, 13.5 Hz, 1H), 3.03 (dd, J = 10.2 Hz, 13.5 Hz, 1H), 4.99 (ddd, J = 5.1 Hz, 9.5 Hz, 10.2 Hz, 1H), 5.22 (t, J = 9.5 Hz, 1H), 5.36 (dd, J = 8.8 Hz, 9.5 Hz, 1H), 6.01 (d, J = 8.8 Hz, 1H), 7.27 (tdd, J = 0.8 Hz, 2.6 Hz, 8.4 Hz, 1H), 7.46 (ddd, J = 2.6 Hz, 9.2 Hz, 11.0 Hz, 1H), 7.66–7.74 (m, 2H), 8.40 (d, J = 2.9 Hz, 1H), 8.45 (t, J = 1.8 Hz, 1H).
26. Mp = 115 °C; $[\alpha]_D^{27}$ −11 (c 0.4, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.97 (s, 3H), 2.00 (s, 6H), 2.93 (dd, J = 4.8 Hz, 13.5 Hz, 1H), 3.02 (dd, J = 10.6 Hz, 13.5 Hz, 1H), 4.99 (ddd, J = 4.8 Hz, 9.5 Hz, 10.6 Hz, 1H), 5.22 (t, J = 9.5 Hz, 1H), 5.36 (dd, J = 8.8 Hz, 9.5 Hz, 1H), 5.98 (d, J = 8.8 Hz, 1H), 7.39 (td, J = 2.6 Hz, 8.4 Hz, 1H), 7.58 (dd, J = 6.2 Hz, 8.8 Hz, 1H), 7.61–7.66 (m, 2H), 8.33(d, J = 2.6 Hz, 1H), 8.40 (t, J = 2.9 Hz, 1H).
27. Mp = 176–180 °C; $[\alpha]_D^{32}$ −13 (c 0.1, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ ppm 1.97 (s, 3H), 2.01 (s, 6H), 3.00 (m, 2H), 5.01 (ddd, J = 4.4 Hz, 9.3 Hz, 10.4 Hz, 1H), 5.22 (t, J = 9.3 Hz, 1H), 5.36 (dd, J = 9.1 Hz, 9.3 Hz, 1H), 6.05 (d, J = 9.1 Hz, 1H), 7.69 (t, J = 9.0 Hz, 1H), 7.87 (dd, J = 1.9 Hz, 2.7 Hz, 1H), 8.20 (ddd, J = 2.5 Hz, 5.2 Hz, 9.1 Hz, 1H), 8.38 (dd, J = 2.4 Hz, 6.3 Hz, 1H), 8.45 (d, J = 2.7 Hz, 1H), 8.67 (d, J = 1.9 Hz, 1H).
28. Mp = 223 °C; $[\alpha]_D^{26}$ −2 (c 0.2, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ ppm 1.97 (s, 3H), 2.02 (s, 6H), 3.01 (m, 2H), 5.02 (ddd, J = 5.1 Hz, 9.3 Hz, 10.4 Hz, 1H), 5.22 (t, J = 9.3 Hz, 1H), 5.39 (dd, J = 8.8 Hz, 9.3 Hz, 1H), 6.08 (d, J = 8.8 Hz, 1H), 7.87 (dd, J = 1.7 Hz, 8.2 Hz, 1H), 7.93 (t, J = 2.3 Hz, 1H), 8.01–8.12 (m, 2H), 8.46 (d, J = 2.7 Hz, 1H), 8.74 (d, J = 1.9 Hz, 1H).
29. Mp = 129–132 °C; $[\alpha]_D^{30}$ −21 (c 0.1, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.98 (s, 3H), 2.01 (s, 6H), 3.00 (m, 2H), 5.01 (ddd, J = 5.1 Hz, 9.5 Hz, 10.3 Hz, 1H), 5.22 (t, J = 9.5 Hz, 1H), 5.39 (dd, J = 8.8 Hz, 9.5 Hz, 1H), 6.07 (d, J = 8.8 Hz, 1H), 7.73 (t, J = 7.9 Hz, 1H), 7.89 (dd, J = 0.8 Hz, 2.6 Hz, 1H), 7.92 (dt, J = 1.5 Hz, 7.7 Hz, 1H), 8.12 (ddd, J = 0.8 Hz, 1.8 Hz, 7.8 Hz, 1H) 8.28 (t, J = 1.8 Hz, 1H), 8.42 (d, J = 2.9 Hz, 1H), 8.69 (d, J = 1.8 Hz, 1H).
30. Mp = 112–115 °C; $[\alpha]_D^{32}$ 1 (c 0.1, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ ppm 1.97 (s, 3H), 2.01 (s, 6H), 2.95 (dd, J = 4.9 Hz, 13.4 Hz, 1H), 3.04 (dd, J = 10.4 Hz, 13.4 Hz, 1H), 3.84 (s, 3H), 5.00 (ddd, J = 4.9 Hz, 9.6 Hz, 10.4 Hz, 1H), 5.24 (t, J = 9.6 Hz, 1H), 5.37 (dd, J = 8.8 Hz, 9.6 Hz, 1H), 6.06 (d, J = 8.8 Hz, 1H), 7.03 (ddd, J = 1.1 Hz, 2.5 Hz, 8.2 Hz, 1H), 7.27–7.36 (m, 2H), 7.44 (t, J = 8.0 Hz, 1H), 7.79 (dd, J = 1.9 Hz, 2.7 Hz, 1H), 8.34 (d, J = 2.7 Hz, 1H), 8.61 (d, J = 1.7 Hz, 1H).
31. Mp = 135 °C; $[\alpha]_D^{31}$ −3 (c 0.3, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ ppm 1.28 (s, 3H), 1.31 (s, 3H), 1.97 (s, 3H), 2.01 (s, 6H), 2.94 (dd, J = 4.7 Hz, 13.2 Hz, 1H), 3.04 (dd, J = 10.4 Hz, 13.2 Hz, 1H), 4.70 (m, J = 6.0 Hz, 1H), 5.00 (ddd, J = 4.7 Hz, 9.4 Hz, 10.4 Hz, 1H), 5.24 (t, J = 9.4 Hz, 1H), 5.37 (dd, J = 9.1 Hz, 9.4 Hz, 1H), 6.05 (d, J = 9.1 Hz, 1H), 7.05 (d, J = 8.8 Hz, 2H), 7.68 (d, J = 8.8 Hz, 2H), 7.74 (dd, J = 1.9 Hz, 2.7 Hz, 1H), 8.27 (d, J = 2.7 Hz, 1H), 8.56 (d, J = 1.9 Hz, 1H).
32. Mp = 145 °C; $[\alpha]_D^{32}$ −8 (c 0.3, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ ppm 1.97 (s, 3H), 2.01 (s, 6H), 2.94 (dd, J = 4.9 Hz, 13.4 Hz, 1H), 3.03 (dd, J = 10.4 Hz, 13.4 Hz, 1H), 3.81 (s, 3H), 3.86 (s, 3H), 5.00 (ddd, J = 4.9 Hz, 9.4 Hz, 10.4 Hz, 1H), 5.22 (t, J = 9.4 Hz, 1H), 5.37 (dd, J = 8.8 Hz, 9.4 Hz, 1H), 6.05 (d, J = 8.8 Hz, 1H), 7.08 (d, J = 8.8 Hz, 1H), 7.29 (dd, J = 2.2 Hz, 8.0 Hz, 1H), 7.30 (s, 1H), 7.73 (dd, J = 1.9 Hz, 2.7 Hz, 1H), 8.31 (d, J = 2.5 Hz, 1H), 8.61 (d, J = 1.6 Hz, 1H).
33. Mp = 146 °C; $[\alpha]_D^{29}$ 0 (c 0.2, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ ppm 1.97 (s, 3H), 2.01 (s, 6H), 2.30 (s, 6H), 2.94 (dd, J = 4.7 Hz, 13.4 Hz, 1H), 3.04 (dd, J = 10.2 Hz, 13.4 Hz, 1H), 3.70 (s, 3H), 5.00 (ddd, J = 4.7 Hz, 9.6 Hz, 10.2 Hz, 1H), 5.25 (t, J = 9.6 Hz, 1H), 5.37 (dd, J = 8.8 Hz, 9.6 Hz, 1H), 6.05 (d, J = 8.8 Hz, 1H), 7.42 (s, 2H), 7.71 (dd, J = 1.9 Hz, 2.7 Hz, 1H), 8.30 (d, J = 2.7 Hz, 1H), 8.55 (d, J = 1.9 Hz, 1H).
34. Mp = 155 °C; $[\alpha]_D^{32}$ −7 (c 0.3, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.97 (s, 3H), 2.01 (s, 6H), 2.96 (dd, J = 4.7 Hz, 13.5 Hz, 1H), 3.03 (dd, J = 10.2 Hz, 13.5 Hz, 1H), 3.92 (s, 3H), 5.01 (ddd, J = 4.7 Hz, 9.5 Hz, 10.2 Hz, 1H), 5.23 (t, J = 9.5 Hz, 1H), 5.37 (dd, J = 8.8 Hz, 9.5 Hz, 1H), 6.07 (d, J = 8.8 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.74 (dd, J = 2.2 Hz, 8.4 Hz, 1H), 7.78 (dd, J = 2.2 Hz, 2.6 Hz, 1H), 7.87 (d, J = 2.6 Hz, 1H), 8.31 (d, J = 2.6 Hz, 1H), 8.60 (d, J = 1.8 Hz, 1H).
35. Mp = 121 °C; $[\alpha]_D^{27}$ −11 (c 0.2, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.97 (s, 3H), 2.00 (s, 6H), 2.92 (dd, J = 4.4 Hz, 13.2 Hz, 1H), 3.03 (dd, J = 10.3 Hz, 13.2 Hz, 1H), 3.82 (s, 3H), 4.99 (ddd, J = 4.7 Hz, 9.5 Hz, 10.3 Hz, 1H), 5.23 (t, J = 9.5 Hz, 1H), 5.35 (dd, J = 8.8 Hz, 9.5 Hz, 1H), 5.94 (d, J = 8.8 Hz, 1H), 6.91 (td, J = 2.6 Hz, 8.4 Hz, 1H), 7.09 (dd, J = 2.6 Hz, 11.7 Hz, 1H), 7.42 (dd, J = 6.6 Hz, 8.4 Hz, 1H), 7.60 (dd, J = 1.8 Hz, 2.9 Hz, 1H), 8.30 (d, J = 2.9 Hz, 1H), 8.37 (d, J = 1.8 Hz, 1H).
36. Mp = 65 °C; $[\alpha]_D^{29}$ 3 (c 0.2, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ ppm 1.31 (s, 3H), 1.33 (s, 3H), 1.97 (s, 3H), 2.01 (s, 6H), 2.96 (dd, J = 4.9 Hz, 13.4 Hz, 1H), 3.03 (dd, J = 10.2 Hz, 13.4 Hz, 1H), 4.72 (m, J = 6.0 Hz, 1H), 5.01 (ddd, J = 4.9 Hz, 9.3 Hz, 10.2 Hz, 1H), 5.23 (t, J = 9.3 Hz, 1H), 5.37 (dd, J = 8.8 Hz, 9.3 Hz, 1H), 6.05 (d, J = 8.8 Hz, 1H), 7.30 (t, J = 8.8 Hz, 1H), 7.54 (dt, J = 8.5 Hz, 1.1 Hz 1H), 7.68 (dd, J = 2.2 Hz, 12.6 Hz, 1H), 7.78 (t, J = 2.2 Hz, 1H), 8.31 (d, J = 2.5 Hz, 1H), 8.60 (d, J = 1.9 Hz, 1H).
37. Mp = 62 °C; $[\alpha]_D^{30}$ −4 (c 0.2, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.96 (s, 3H), 2.00 (s, 6H), 2.94 (dd, J = 5.1 Hz, 13.4 Hz, 1H), 3.02 (dd, J = 10.6 Hz, 13.4 Hz, 1H), 3.85 (s, 3H), 4.99 (ddd, J = 5.1 Hz, 9.5 Hz, 10.6 Hz, 1H), 5.22 (t, J = 9.5 Hz, 1H), 5.35 (dd, J = 8.8 Hz, 9.5 Hz, 1H), 5.98 (d, J = 8.8 Hz, 1H), 6.94 (d, J = 10.2 Hz, 2H), 7.60–7.63 (m, 1H), 8.33 (d, J = 1.5 Hz, 1H), 8.39 (d, J = 2.6 Hz, 1H).
38. Mp = 161 °C; $[\alpha]_D^{33}$ −16 (c 0.3, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6) δ ppm 1.97 (s, 3H), 2.01 (s, 6H), 2.33 (d, J = 1.9 Hz, 3H), 2.95 (dd, J = 4.9 Hz, 13.4 Hz, 1H), 3.04 (dd, J = 10.1 Hz, 13.4 Hz, 1H), 5.01 (ddd, J = 4.9 Hz, 9.6 Hz, 10.1 Hz, 1H), 5.23 (t, J = 9.6 Hz, 1H), 5.37 (dd, J = 8.8 Hz, 9.6 Hz, 1H), 6.05 (d, J = 8.8 Hz, 1H), 7.28 (dd, J = 8.6 Hz, 9.5 Hz, 1H), 7.57–7.66 (m, 1H), 7.70 (dd, J = 1.6 Hz, 7.4 Hz, 1H), 7.76 (dd, J = 1.9 Hz, 2.7 Hz, 1H), 8.34 (d, J = 2.7 Hz, 1H), 8.58 (d, J = 1.9 Hz, 1H).
39. Mp = 120 °C; $[\alpha]_D^{34}$ −20 (c 0.3, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.96 (s, 3H), 2.00 (s, 6H), 2.26 (s, 3H), 2.93 (dd, J = 5.1 Hz, 13.4 Hz, 1H), 3.02 (dd, J = 10.3 Hz, 13.4 Hz, 1H), 4.99 (ddd, J = 5.1 Hz, 9.5 Hz, 10.3 Hz, 1H), 5.21 (t, J = 9.5 Hz, 1H), 5.36 (dd, J = 9.2 Hz, 9.5 Hz, 1H), 5.97 (d, J = 9.2 Hz, 1H), 7.15 (td, J = 3.3 Hz, 8.4 Hz, 1H), 7.23 (dd, J = 2.6 Hz, 10.2 Hz, 1H), 7.32 (dd, J = 5.9 Hz, 8.4 Hz, 1H), 7.54 (dd, J = 1.8 Hz, 2.9 Hz, 1H), 8.25 (d, J = 1.5 Hz, 1H), 8.34 (d, J = 2.9 Hz, 1H).
40. Mp = 180–183 °C; $[\alpha]_D^{30}$ −50 (c 0.1, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.54–2.74 (m, 2H), 3.14 (t, J = 8.5 Hz, 1H), 3.50 (td, J = 8.5 Hz, 5.2 Hz, 1H), 3.60 (t, J = 8.5 Hz, 1H), 4.8–5.8 (broad, 3H), 5.32 (d, J = 8.5 Hz, 1H), 7.29 (t, J = 9.1 Hz, 2H), 7.66 (dd, J = 3.0 Hz, 8.9 Hz, 1H), 7.92 (d, J = 8.9 Hz, 1H), 8.07 (dd, J = 5.8 Hz, 9.1 Hz, 2H) 8.45 (d, J = 3.0 Hz, 1H).
41. Mp = 208 °C; $[\alpha]_D^{29}$ 12 (c 0.3, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.98 (s, 3H), 2.01 (s, 6H), 2.94 (dd, J = 4.8 Hz, 13.5 Hz, 1H), 3.04 (dd, J = 10.6 Hz, 13.5 Hz, 1H), 3.81 (s, 3H), 5.00 (ddd, J = 4.8 Hz, 9.5 Hz, 10.6 Hz, 1H), 5.25 (t, J = 9.5 Hz, 1H), 5.35 (dd, J = 8.8 Hz, 9.5 Hz, 1H), 5.92 (d, J = 8.8 Hz, 1H), 7.02 (d, J = 9.1 Hz, 2H), 7.57 (dd, J = 2.9 Hz, 8.8 Hz, 1H), 7.90 (d, J = 8.8 Hz, 1 H), 7.97 (d, J = 9.1 Hz, 2 H), 8.38 (d, J = 2.9 Hz, 1H).

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44. Mp = 178–179 °C; $[\alpha]_D^{24}$ −76 (c 0.1, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.55–2.75 (m, 2H), 2.59 (s, 3H), 3.14 (t, J = 8.8 Hz, 1H), 3.49 (m, 1H), 3.61 (t, J = 8.8 Hz, 1H), 5.09 (s, 1H), 5.18 (s, 1H), 5.42 (d, J = 8.8 Hz, 1H), 5.60 (s, 1H), 7.73 (dd, J = 2.7 Hz, 8.8 Hz, 1H), 7.97 (d, J = 8.8 Hz, 1H), 8.47 (d, 2.7 Hz, 1H).
45. Mp = 107–113 °C; $[\alpha]_D^{28}$ −56 (c 0.1, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.52–2.70 (m, 2H), 3.15 (td, 1H), 3.48 (m, 1H), 3.61 (td, 1H), 5.11 (d, 1H), 5.17 (d, 1H), 5.39 (d, J = 8.4 Hz, 1H), 5.56 (d, 1H), 7.24 (t, J = 9.2 Hz, 2H), 7.38 (dd, J = 4.4 Hz, 8.8 Hz, 1H), 7.85 (dd, J = 1.5 Hz, 8.8 Hz, 1H), 8.06 (dd, J = 5.9 Hz, 9.2 Hz, 2H), 8.30 (dd, J = 1.5 Hz, 4.4 Hz, 1H).
46. Mp = 219 °C; $[\alpha]_D^{30}$ −70 (c 0.3, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.55 (dd, J = 13.5 Hz, 4.6 Hz, 1H), 2.65 (dd, J = 13.5 Hz, 10.2 Hz, 1H), 3.13 (td, J = 8.6 Hz, 4.6 Hz, 1H), 3.45 (m, 1H), 3.54 (td, J = 8.6 Hz, 5.3 Hz, 1H), 5.08 (d, J = 4.6 Hz, 1H), 5.14 (d, J = 4.5 Hz, 1H), 5.46 (d, J = 8.6 Hz, 1H), 5.53 (d, J = 5.3 Hz, 1H), 7.28 (t, J = 8.8 Hz, 2H), 7.39 (d, J = 4.9 Hz, 1H), 7.76 (dd, J = 5.5 Hz, 8.8 Hz, 2H), 8.30 (d, J = 4.9 Hz, 1H), 8.72 (s, 1H).
47. Mp = 228 °C; $[\alpha]_D^{30}$ −80 (c 0.5, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.55 (dd, J = 4.9 Hz, 13.5 Hz, 1H) 2.64 (dd, J = 10.2 Hz, 13.5 Hz, 1H), 3.13 (td, J = 8.8 Hz, 4.7 Hz, 1H), 3.45 (m, 1H), 3.55 (td, J = 8.5 Hz, 4.9 Hz, 1H), 3.81 (s, 3H) 5.06 (d, J = 4.7 Hz 1H), 5.13 (d, J = 4.4 Hz, 1H), 5.44 (d, J = 8.8 Hz, 1H), 5.48 (d, J = 4.9 Hz, 1H), 7.01(d, J = 9.1 Hz, 2H), 7.36 (d, J = 4.9 Hz, 1H), 7.68 (d, J = 9.1 Hz, 2H), 8.25 (d, J = 4.9 Hz, 1H), 8.67 (s, 1H).
48. Mp = 216 °C; $[\alpha]_D^{20}$ −91 (c 0.1, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.58 (dd, J = 13.4 Hz, 4.5 Hz, 1H), 2.70 (dd, J = 13.4 Hz, 10.0 Hz, 1H), 3.14 (td, J = 8.5 Hz, 4.5 Hz, 1H), 3.50 (m, 1H), 3.60 (td, J = 8.5 Hz, 4.5 Hz, 1H), 3.82 (s, 3H), 5.04 (d, J = 4.5 Hz, 1H), 5.15 (d, J = 4.5 Hz, 1H), 5.44 (d, J = 8.5 Hz, 1H), 5.55 (d, J = 4.5 Hz, 1H), 7.07 (d, J = 9.1 Hz, 2H), 7.70 (d, J = 9.1 Hz, 2H), 7.77 (dd, J = 1.9 Hz, 2.5 Hz, 1H), 8.31 (d, J = 2.5 Hz, 1H), 8.50 (d, J = 1.9 Hz, 1H).
49. Mp = 164 °C; $[\alpha]_D^{29}$ −37 (c 0.2, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.55–2.72 (m, 2H), 3.13 (t, J = 8.7 Hz, 1H), 3.49 (m, 1H), 3.60 (t, J = 8.7 Hz, 1H), 3.81 (s, 3H), 4.6–5.9 (broad, 3 H), 5.29 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 8.8 Hz, 2H), 7.61 (dd, J = 2.9 Hz, 8.8 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.97 (d, J = 8.8 Hz, 2H), 8.41 (d, J = 2.9 Hz, 1H).

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