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Short communication

Synthesis and antitubercular activity of new mefloquine-oxazolidine derivatives

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ABSTRACT

In this work, we report the synthesis and the antitubercular evaluation of 16 new mefloquine derivatives, formed from reactions between mefloquine and benzaldehydes, with the activity expressed as the minimum inhibitory concentration (MIC) in μM. The compounds were non-cytotoxic and exhibited an important activity (12.6 μM). The appreciable activity of these compounds can be considered an important finding for the rational design of new leads for anti-TB compounds.

1. Introduction

Since 1993, tuberculosis (TB) has been considered a global health emergency by the World Health Organization (WHO). According to statistics, one-third of the world's population is currently infected with the TB bacillus, each year, 8 million people worldwide develop active TB and about 1.7 million people die [1]. Moreover, the emergence of multi-drug resistant TB (MDR-TB) and extensive drug resistant TB (XDR-TB) become one of the biggest challenges in the treatment of this disease, creating an urgent need to develop new therapeutics [2–9].

Quinoline derivatives have been reported to exhibit substantial anti-mycobacterial activities and can be considered a promising area for the discovery of new anti-TB agents [10–18]. The most important example is the diarylquinoline TMC207 (ex R207910), which was developed by Johnson & Johnson Pharmaceutical Research & Development. This substance possesses a new mechanism of action based on the attack on the enzyme adenosine triphosphate (ATP) synthase, which is the energy source for the bacterium. Due to the promising perspectives against tuberculosis, TMC207 is currently in phase 2 clinical trials [19].

The quinoline derivative, mefloquine (MFL), which has been used for a long time as an antimalarial, has recently received considerable attention as an anti-mycobacterial drug. This substance has been found to possess substantial activities against Gram-positive bacteria [20] and *Mycobacterium* species [21–24]. MFL is active against *Mycobacterium avium* resistant to macrolides, quinolones and rifamycins, and displays a MIC range of 21.1–42.1 μM against *M. avium* [21] and *Mycobacterium tuberculosis* [22,23]. In *in vivo* assays, this substance was active against *M. avium* at a concentration of 20 mg/kg [21], and presented a synergistic activity with ethambutol [21,24], a first-line anti-TB drug and moxifloxacin, a fluoroquinolone actually in phase III study against *M. tuberculosis* [25]. Moreover, in the recent literature several mefloquine derivatives displaying modest to excellent actives against tuberculosis have been described [26–30].

The procariotic target of MFL was found to be the *c* subunit of the cytoplasmatic membrane sector F_0 of the enzyme F_0F_1 ATPase in *Streptococcus pneumoniae* [31]. In a study with *M. tuberculosis*, Martín-Galiano and co-workers [22] showed that exposure of the bacteria to MFL at a 4× MIC concentration lead to upregulation of

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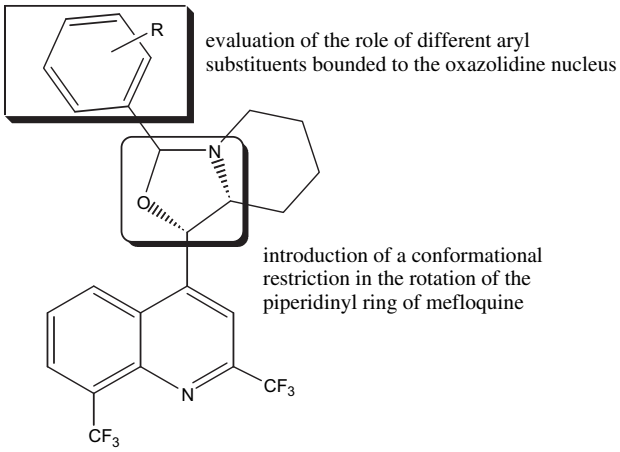


Scheme 1. Design of mefloquine derivatives.

the expression of gene coding membrane proteins, suggesting that the target for mefloquine in *M. tuberculosis* is in the cell wall. However, there are no data in the literature showing molecular interactions of mefloquine with its target. The aims of the present work are to evaluate (i) the introduction of conformational restriction in the rotation of the piperidinyl ring of mefloquine, by the construction of an oxazolidine ring on reaction with a substituted benzaldehyde, and (ii) the activities of different substituents in the phenyl ring (Scheme 1). Conformational restriction of flexible drugs has proved a very useful strategy in medicinal chemistry, helping to determine drug receptor steric requirements and in the identification of new structures with greater efficacy and selectivity.

2. Results and discussion

2.1. Chemistry

The preparation of mefloquine derivatives **1a**–**p** is summarized in Scheme 2. The compounds were obtained from the reaction of mefloquine with the respective substituted benzaldehyde in toluene, utilizing a Dean–Stark apparatus. Ring formation to give the oxazolidine system does not occur at either of the chiral centres in the racemic *erythro* mefloquine reagent and hence these stereochemistries are preserved in the products. Two new chiral centres atom are generated from the benzaldehyde carbonyl group and the piperidinyl nitrogen in the product, which is formed as a racemate.

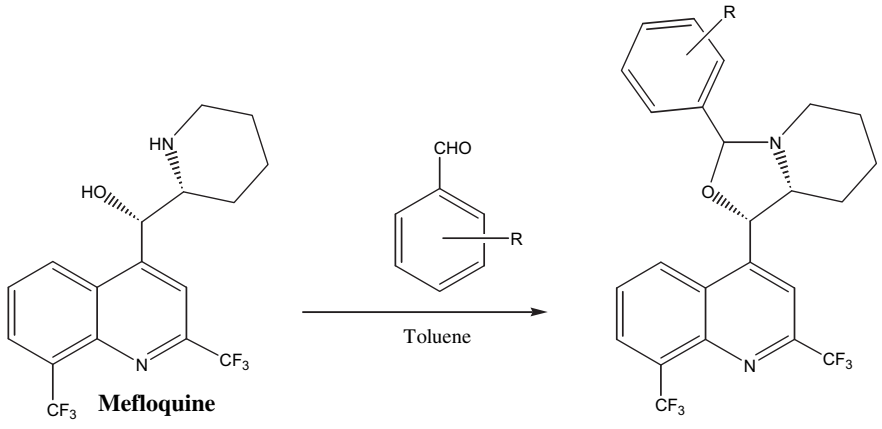
The formation of the oxazolidenyl ring was confirmed by the ^{1}H NMR spectra of the synthesized compounds, which showed a characteristic singlet at 5.53–4.85 ppm, corresponding to $H_{11'}$. The assignment of all hydrogen signals was carried using COSY experiments. In the IR spectra, characteristic signals at 1310-1306 cm^{-1} were observed for the C–O axial deformation and at 1214-1089 cm^{-1} for the C–F axial deformation. Usually, more than one signal was observed for the CF_3 group as a result of the presence of rotational isomers.

The structure of **1p** was confirmed by X-ray crystallography [32–34]: monoclinic non-chiral space group, P21/n, was assigned. The non-chiral space group indicates that both enantiomers of **1p** are present in the single crystal examined. The chiral centres at C9, C10, C17 and N2 are (*R**), (*S**), (*S**) and (*R**), respectively. Fig. 1 shows the atom arrangements in the (*R*), (*S*), (*S*), (*R*)-enantiomer. The bond angles and bond lengths are all in the expected regions. The piperidinyl ring has a near perfect chair conformation, while the five membered 1,3-oxazolidine ring has an envelope shape with flap at the nitrogen atom. The angle between the plane of the quinoline moiety and (a) the plane of the phenyl ring is 38.50° and (b) with the best plane through the piperidinyl and oxazolidenyl rings is 82.16°. The only intermolecular interactions are weak C–H···F intermolecular hydrogen bonds, π···π and C–H···π interactions.

2.2. Antimycobacterial activity

The antimycobacterial activities of all synthesized compounds, **1**, were assessed against *M. tuberculosis* ATCC 27294 [35] using the micro plate Alamar Blue assay (MABA) [36] (Table 1). This methodology is nontoxic, uses a thermally stable reagent and shows good correlation with proportional and BACTEC radiometric methods [37,38]. In each case, a racemic mixture of 1 was used.

Compound **1j** displayed the greatest activity, with a MIC of 12.6 μM, 2.6 times greater than that of mefloquine (MIC = 33 μM) and thus has an activity comparable with that of the first line tuberculostatic agent, ethambutol (MIC = 15.9 μM). Other compounds **1g**, **1h**, **1i**, **1k**, **1l** and **1p** exhibited antimycobacterial activities slightly greater than that of mefloquine, at 25.8, 25.9, 25.9, 25.2, 25.2 and 26.8 μM, respectively. These results show that the introduction of the oxazolidine nucleus in mefloquine structure can improve the activity against *M. tuberculosis*. While the activities are substantially



R = H, NO_2, OCH_3, OH, F, Cl, Br

Scheme 2. Synthesis of mefloquine derivatives. Mefloquine reagent used was the racemic erythro, 9-(*R**), 10-(*S**)-form, and stereochemistry of the product formed at C9, C10, C17 and N2 (*R**), (*S**), (*S**),(*R**), respectively. Only the (*R*),(*S*)-reagent and (*R*),(*S*),(*S*),(*R*)-product are shown.

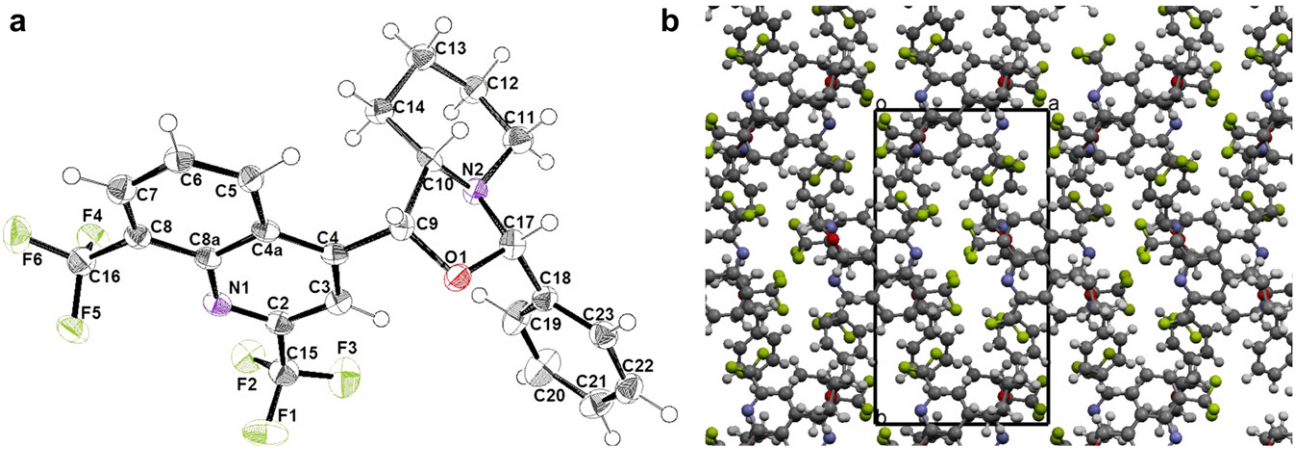


Fig. 1. (a) Atom arrangements and numbering scheme in **1p** and (b) packing arrangement.

dependent on the substituent in the aromatic ring bounded to C-17 of the oxazolidenyl nucleus, the Hammett constant (σ) of the substituent does not show a linear correlation with the biological activity. However, compounds having hydroxyl or methoxyl substituents, which are both electron releasing groups and substituents capable of forming strong hydrogen bonds, as in (**1h**–**1l**), are generally active. In contrast, with one exception, compounds having nitro or halo substituents (electron withdrawing groups, and, at best, only capable of forming weak hydrogen bonds), as in (**1a**–**1f** and **1m**–**1o**), are inactive. The exception is compound **1g**, with a fluorine atom in the *para* position: of interest, a *p*-fluoro group has the least electron withdrawing effect of *p*-F, *m*-F and *o*-F groups. Also active is the parent compound, **1p**.

2.3. Cell viability assay

The cellular viability in the presence and absence of test compounds was determined by Mosmans's MTT (3-(4,5-demethylthylthiazol-2-yl)-2,5-dimethyl tetrazolium bromide; Merck) microcultured tetrazolium assay [39,40] at three different concentrations, 50, 25 and 12.5 μM. The results were expressed as percentage cell viability (Table 2). This table shows that, all active compounds were not cytotoxic to the host cells, being less toxic than mefloquine in their respective active concentrations. Compound **1j** is the most active (12.5 μM), and compound **1l**, with a MIC of 25.2 μM showed 100% of cell viability in all concentrations.

3. Conclusion

We have synthesized a series of new mefloquine derivatives, having restricted rotation of the piperidinyl ring. The reaction between the racemic mefloquine reagent and the aldehyde produces both stereoisomers of the product oxazolidine, as indicated by the findings of the X-ray crystallographic study on **1p**. The *in vitro* micro plate Alamar Blue assay showed that **1g**, **1h**, **1i**, **1k**, **1l** and **1p** were slightly more active than mefloquine whereas, compound **1j** displayed the greatest activity, with a MIC 2.6 times greater than mefloquine and comparable with the first line tuberculostatic agent ethambutol. The substituent in the aromatic ring has an important role in the biological activity and, generally, compounds having electron-releasing groups, such as hydroxyl and methoxyl groups are active. These compounds are also not cytotoxic to host cells at the concentrations effective in inhibiting *M.*

Table 1
Antimycobacterial activities, melting points and yields of mefloquine derivatives **1a**–**p**.

Entry	Substituents					Yield (%)	Mp (°C)	MIC[a] (μM)
	R^1	R^2	R^3	R^4	R^5			
1a	Cl	H	H	H	H	65	148	>250
1b	H	Cl	H	H	H	70	223	>250
1c	H	H	Cl	H	H	70	181	>250
1d	H	Br	H	H	H	75	147	>250
1e	H	H	Br	H	H	82	175	>250
1f	F	H	H	H	H	74	147	>250
1g	H	H	F	H	H	67	155	25.8
1h	OH	H	H	H	H	78	154	25.9
1i	H	H	OH	H	H	77	205	25.9
1j	OMe	H	H	H	H	63	152	12.6
1k	H	OMe	H	H	H	76	128	25.2
1l	H	H	OMe	H	H	81	179	25.2
1m	NO_2	H	H	H	H	64	148	>250
1n	H	NO_2	H	H	H	68	178	>250
1o	H	H	NO_2	H	H	65	231	>250
1p	H	H	H	H	H	83	130	26.8
Mefloquine	–					–	–	33.0
Ethambutol	–					–	–	15.9

[a] Minimum inhibitory concentration.

Table 2
Data of cytotoxic effects of tested compounds on murine macrophages cells 18 h after the treatment.

Compound	% Cell viability/doses (μM)		
	50	25	12.5
1a	100	100	100
1b	90	100	100
1c	100	100	100
1d	85	85	100
1e	100	100	100
1f	100	100	100
1g	82	84	93
1h	85	85	100
1i	80	80	100
1j	100	100	100
1k	80	80	100
1l	100	100	100
1m	100	100	100
1n	100	100	100
1o	100	100	100
1p	95	96	100
Mefloquine	76	77	81

tuberculosis. More information regarding SAR and QSAR are currently under way in our laboratory.

4. Experimental

4.1. General procedures

Melting points were determined on a Buchi apparatus and are uncorrected. Infrared spectra were recorded on a Thermo Nicolet Nexus 670 spectrometer as potassium bromide pellets and frequencies are expressed in cm^{-1}. Mass spectra (ESI assay insolution of ammonium chloride) were recorded on Micromass ZQ Waters mass spectrometer. NMR spectra were recorded on a Bruker Avance 400 operating at 400.00 MHz (^1H) and 100.0 MHz (^{13}C) and Bruker Avance 500 spectrometer operating at 500.00 MHz (^1H) and 125.0 MHz (^{13}C), in deuterated acetone. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane and J-coupling in Hertz (Hz). Proton and carbon spectra were typically obtained at room temperature. For TLC plates coated with silica gel were run in ethyl acetate/hexane mixture and spots were developed in ultraviolet ($\lambda = 254$ nm).

4.2. Synthesis of the mefloquine derivatives **1a**–**p**

A toluene solution (5 ml) containing 0.3 g (0.8 mmol) of mefloquine and 0.96 mmol of the respective benzaldehyde was heated under reflux overnight while the removal of water was carried out with a Dean–Stark apparatus. Thereafter, the solvent was evaporated under reduced pressure and the resultant semisolid was triturated with cold ethanol, in order to produce a solid, which was filtered to yield the pure product.

4.2.1. 4-[3-(2-Chlorophenyl)hexahydro[1,3]oxazolo[3,4-a]pyridin-1-yl]-2,8-dimethylquinoline (**1a**)

^1H NMR [500.00 MHz (FIDRES ± 0.12 Hz), $(CH_3)_2CO$-d_6] δ: 8.68 (1H; d; $J = 7.0$ Hz; H_5 or H_7); 8.35 (1H; d; $J = 5.8$ Hz; H_5 or H_7); 8.03-7.95 (3H; m; H_3 and $H_{3''}$,$H_{4''}$,$H_{5''}$ or $H_{6''}$); 7.60-7.52 (3H; m; H_6 and $H_{3''}$,$H_{4''}$,$H_{5''}$ or $H_{6''}$); 6.35 (1H; d; $J = 6.6$ Hz; $H_{1'}$); 5.42 (1H; s; $H_{11'}$); 3.29 (1H; dddd; $J = 8.6$, 6.3 and 1.9 Hz; $H_{2'}$); 2.89 (1H; d; $J = 9.0$ Hz; $H_{7'}$ or $H_{8'}$); 2.17 (1H; ddd; $J = 10.5$, 9.0 and 1.9 Hz; $H_{7'}$ or $H_{8'}$); 1.72-1.56 (3H; m; $H_{3'}$ or $H_{4'}$, $H_{9'}$ and $H_{10'}$); 1.42-1.27 (2H; m; $H_{5'}$ and $H_{6'}$); 0.39 (1H; dddd; $J = 12.9$, 9.8 and 3.1 Hz; $H_{3'}$ or $H_{4'}$) ppm.

^{13}C NMR (125.0 MHz DMSO-d_6) δ: 151.0; 147.5; 147.3; 143.0; 137.2; 135.6; 134.2; 133.8; 130.8; 130.2; 129.3; 128.9; 128.8; 127.5; 127.4; 127.2; 116.4; 92.6; 76.8; 65.9; 47.8; 26.8; 23.9; 23.4 ppm.

LC/MS: m/z [M + H] = 501.

IR ν_{max} (cm^{-1}; KBr pellets): 1307 (C–O); 1186, 1157, 1111 (C–F).

4.2.2. 4-[3-(3-Chlorophenyl)hexahydro[1,3]oxazolo[3,4-a]pyridin-1-yl]-2,8-dimethylquinoline (**1b**)

^1H NMR [500.00 MHz (FIDRES ± 0.12 Hz), $(CH_3)_2CO$-d_6] δ: 8.68 (1H; d; $J = 8.6$ Hz; H_5 or H_7); 8.36 (1H; d; $J = 7.2$ Hz; H_5 or H_7); 8.09 (1H; s; H_3); 7.97 (1H; t; $J = 7.9$ Hz; H_6); 7.78-7.67 (4H; m; $H_{2''}$, $H_{4''}$, $H_{5''}$ and $H_{6''}$); 6.32 (1H; d; $J = 8.0$ Hz; $H_{1'}$); 4.85 (1H; s; $H_{11'}$); 3.23 (1H; dddd; $J = 10.8$, 8.0 and 2.1 Hz; $H_{2'}$); 2.82 (1H; sl; $H_{7'}$ or $H_{8'}$); 2.05 (1H; ddd; $J = 6.6$, 4.4 and 2.2 Hz $H_{7'}$ or $H_{8'}$); 1.69-1.53 (3H; m; $H_{3'}$ or $H_{4'}$, $H_{9'}$ and $H_{10'}$); 1.39-1.22 (2H; m; $H_{5'}$ and $H_{6'}$); 0.44-0.32 (1H; dddd; $J = 15.3$, 12.0 and 3.6 Hz; $H_{3'}$ or $H_{4'}$) ppm.

^{13}C NMR (125.0 MHz DMSO-d_6) δ: 152.1; 148.5; 144.1; 137.0; 135.9; 131.2; 130.4; 129.9; 129.8; 129.1; 128.4; 126.1; 123.7; 123.5; 121.3; 117.2; 97.0; 77.6; 67.1; 48.4; 48.7; 27.9; 25.0; 24.4 ppm.

LC/MS: m/z [M + H] = 501.

IR ν_{max} (cm^{-1}; KBr pellets): 1310 (C–O); 1148, 1109 (C–F).

4.2.3. 4-[3-(4-Chlorophenyl)hexahydro[1,3]oxazolo[3,4-a]pyridin-1-yl]-2,8-dimethylquinoline (**1c**)

^1H NMR [500.00 MHz (FIDRES ± 0.12 Hz), $(CH_3)_2CO$-d_6] δ: 8.68 (1H; d; $J = 8.6$ Hz; H_5 or H_7); 8.35 (1H; d; $J = 7.2$ Hz; H_5 or H_7); 8.10 (1H; s; H_3); 7.96 (1H; t; $J = 7.9$ Hz; H_6); 7.77 (2H; dd; $J = 8.4$ and 1.7 Hz $H_{2''}$ and $H_{6''}$); 7.59 (2H; dd; $J = 8.4$ and 1.7 Hz; $H_{3''}$ and $H_{5''}$); 6.31 (1H; d; $J = 8.0$ Hz; $H_{1'}$); 4.98 (1H; s; $H_{11'}$); 3.23 (1H; dddd; $J = 10.8$,8.0 and 2.1 Hz; $H_{2'}$); 2.82 (1H; m; $H_{7'}$ or $H_{8'}$); 2.13 (1H; ddd; $J = 13.7$, 11.3 and 2.7 Hz $H_{7'}$ or $H_{8'}$); 1.67-1.55 (3H; m; $H_{3'}$ or $H_{4'}$, $H_{9'}$ and $H_{10'}$); 1.37-1.23 (2H; m; $H_{5'}$ and $H_{6'}$); 0.39 (1H; dddd; $J = 15.8$, 12.2 and 3.8 Hz; $H_{3'}$ or $H_{4'}$) ppm.

^{13}C NMR (125.0 MHz DMSO-d_6) δ: 151.9; 148.4; 144.0; 137.0; 135.8; 131.1; 130.2; 129.8; 129.7; 128.4; 128.3; 126.2; 123.9; 123.5; 117.2; 96.9; 77.4; 67.1; 48.4; 27.7; 24.8; 24.3 ppm.

LC/MS: m/z [M + H] = 501.

IR ν_{max} (cm^{-1}; KBr pellets): 1308 (C–O); 1212, 1189, 1148, 1109 (C–F).

4.2.4. 4-[3-(3-Bromophenyl)hexahydro[1,3]oxazolo[3,4-a]pyridin-1-yl]-2,8-dimethylquinoline (**1d**)

^1H NMR [500.00 MHz (FIDRES ± 0.12 Hz), $(CH_3)_2CO$-d_6] δ: 8.68 (1H; d; $J = 8.3$ Hz; H_5 or H_7); 8.36 (1H; d; $J = 7.3$ Hz; H_5 or H_7); 8.11 (1H; s; H_3); 7.98-7.94 (2H; m; H_6 and $H_{2''}$) 7.74-7.70 (2H; m; $H_{4''}$ and $H_{6''}$); 7.52 (1H; t; $J = 7.8$ Hz; $H_{5''}$); 6.32 (1H; d; $J = 7.8$ Hz; $H_{1'}$); 4.97 (1H; s; $H_{11'}$); 3.23 (1H; dddd; $J = 10.7$, 7.8 and 1.9 Hz; $H_{2'}$); 2.79 (1H; sl; $H_{7'}$ or $H_{8'}$); 2.16-2.12 (1H; m; $H_{7'}$ or $H_{8'}$); 1.67-1.55 (3H; m; $H_{3'}$ or $H_{4'}$, $H_{9'}$ and $H_{10'}$); 1.34-1.27 (2H; m; $H_{5'}$ and $H_{6'}$); 0.40 (1H; dddd; $J = 12.5$, 9.7 and 3.1 Hz; $H_{3'}$ or $H_{4'}$) ppm.

^{13}C NMR (125.0 MHz DMSO-d_6) δ: 151.9; 148.5; 148.2; 144.0; 140.8; 133.5; 132.1; 131.7; 130.3; 130.2; 130.1; 129.1; 128.5; 128.4; 128.3; 123.3; 117.13; 96.8; 77.5; 67.0; 48.4; 27.7; 24.8; 24.2 ppm.

LC/MS: m/z [M + H] = 546.

IR ν_{max} (cm^{-1}; KBr pellets): 1308 (C–O); 1185, 1136, 1110 (C–F).

4.2.5. 4-[3-(4-bromophenyl)hexahydro[1,3]oxazolo[3,4-a]pyridin-1-yl]-2,8-dimethylquinoline (**1e**)

^1H NMR [500.00 MHz (FIDRES ± 0.12 Hz), $(CH_3)_2CO$-d_6] δ: 8.67 (1H; d; $J = 8.3$ Hz; H_5 or H_7); 8.35 (1H; d; $J = 7.3$ Hz; H_5 or H_7); 8.09 (1H; s; H_3); 7.95 (1H; t; $J = 7.8$ Hz; H_6); 7.75 (2H; d; $J = 8.3$ Hz; $H_{2''}$ and $H_{6''}$); 7.71 (2H; t; $J = 8.3$ Hz; $H_{3''}$ and $H_{5''}$) 6.30 (1H; d; $J = 8.3$ Hz; $H_{1'}$); 4.96 (1H; s; $H_{11'}$); 3.24-3.20 (1H; m; $H_{2'}$); 2.84 (1H; sl; $H_{7'}$ or $H_{8'}$); 2.12 (1H; ddd; $J = 10.8$, 9.3 and 1.5 Hz; $H_{7'}$ or $H_{8'}$); 1.66-1.54 (3H; m; $H_{3'}$ or $H_{4'}$, $H_{9'}$ and $H_{10'}$); 1.33-1.26 (2H; m; $H_{5'}$ and $H_{6'}$); 0.42-0.35 (1H; m; $H_{3'}$ or $H_{4'}$) ppm.

^{13}C NMR (125.0 MHz DMSO-d_6) δ: 151.0; 147.3; 141.1; 136.5; 131.9; 130.5; 129.4; 129.3; 128.9; 127.5; 127.4; 123.1; 116.3; 96.1; 76.5; 66.2; 47.5; 26.9; 23.9; 23.4 ppm.

LC/MS: m/z [M + H] = 546.

IR ν_{max} (cm^{-1}; KBr pellets): 1307 (C–O); 1189, 1148, 1109 (C–F).

4.2.6. 4-[3-(2-Fluoro)hexahydro[1,3]oxazolo[3,4-a]pyridin-1-yl]-2,8-dimethylquinoline (**1f**)

^1H NMR [500.00 MHz (FIDRES ± 0.12 Hz), $(CH_3)_2CO$-d_6] δ: 8.70 (1H; d; $J = 8.8$ Hz; H_5 or H_7); 8.36 (1H; d; $J = 7.3$ Hz; H_5 or H_7); 8.04 (1H; s; H_3); 8.02-7.92 (2H; m; H_6 and $H_{3''}$ or $H_{6''}$); 7.61-7.55 (1H; m; $H_{3''}$ or $H_{6''}$); 7.45 (1H; t; $J = 7.3$ Hz; $H_{4''}$ or $H_{5''}$); 7.29 (1H; t; $J = 9.7$ Hz; $H_{4''}$ or $H_{5''}$); 6.35 (1H; d; $J = 7.8$ Hz; $H_{1'}$); 5.34 (1H; s; $H_{11'}$); 3.26 (1H; dddd; $J = 10.7$, 8.3 and 2.4 Hz; $H_{2'}$); 2.86 (1H; d; $J = 16.6$ Hz; $H_{7'}$ or $H_{8'}$); 2.19-2.13 (1H; m; $H_{7'}$ or $H_{8'}$); 1.70-1.56 (3H; m; $H_{3'}$ or $H_{4'}$, $H_{9'}$ and $H_{10'}$); 1.37-1.28 (2H; m; $H_{5'}$ and $H_{6'}$); 0.38 (1H; dddd; $J = 15.1$, 11.7 and 3.4 Hz; $H_{3'}$ or $H_{4'}$) ppm.

^{13}C NMR (125.0 MHz DMSO-d_6) δ: 164.5; 162.6; 151.9; 148.4; 143.9; 132.3; 132.2; 130.2; 129.8; 129.6; 129.5; 128.4; 125.9; 125.7; 117.3; 116.9; 116.7; 90.6; 77.6; 66.9; 48.6; 27.7; 24.8; 24.2 ppm.

LC/MS: m/z [M + H] = 485.

IR ν_{max} (cm^{-1}; KBr pellets): 1308 (C–O); 1188, 1148, 1111 (C–F).

*4.2.7. 4-[3-(4-Fluoro)hexahydro[1,3]oxazolo[3,4-a]pyridin-1-yl]-2,8-dimethylquinoline (**1g**)*

^{1}H NMR [500.00 MHz (FIDRES ± 0.12 Hz), $(CH_3)_2CO$-d_6] δ: 8.69 (1H; d; J = 8.8 Hz; H_5 or H_7); 8.36 (1H; d; J = 7.3 Hz; H_5 or H_7); 8.11 (1H; s; H_3); 7.96 (1H; t; J = 7.8 Hz; H_6); 7.82-7.79 (2H; m; $H_{2''}$ and $H_{6''}$); 7.35-7.31 (2H; m; $H_{2''}$ and $H_{6''}$); 6.30 (1H; d; J = 7.8 Hz; $H_{1'}$); 4.98 (1H; s; $H_{11'}$); 3.22 (1H; dddd; J = 10.7, 8.3 and 1.9 Hz; $H_{2'}$); 2.82 (1H; d; J = 10.7 Hz; $H_{7'}$ or $H_{8'}$); 2.16-2.03 (1H; m; $H_{7'}$ or $H_{8'}$); 1.67-1.54 (3H; m; $H_{3'}$ or $H_{4'}$, $H_{9'}$ and $H_{10'}$); 1.33-1.25 (2H; m; $H_{5'}$ and $H_{6'}$); 0.38 (1H; dddd; J = 15.1, 11.7 and 3.4 Hz; $H_{3'}$ or $H_{4'}$) ppm.

^{13}C NMR (125.0 MHz DMSO-d_6) δ: 165.3; 163.4; 152.0; 148.2; 143.9; 134.3; 134.2; 131.5; 131.4; 130.2; 129.8; 128.3; 117.2; 116.5; 116.3; 96.9; 77.3; 67.0; 48.4; 27.7; 24.8; 24.3 ppm.

LC/MS: m/z [M + H] = 485.

IR ν_{max} (cm^{-1}; KBr pellets): 1308 (C—O); 1224, 1157, 1116 (C—F).

*4.2.8. 2-[1-(2,8-Dimethylquinolin-4-yl)hexahydro[1,3]oxazolo[3,4-a]pyridin-3-yl]phenol (**1h**)*

^{1}H NMR [500.00 MHz (FIDRES ± 0.12 Hz), $(CH_3)_2CO$-d_6] δ: 8.64 (1H; d; J = 8.8 Hz; H_5 or H_7); 8.36 (1H; d; J = 7.3 Hz; H_5 or H_7); 8.32 (1H; s; H_3); 7.96 (1H; t; J = 7.8 Hz; H_6); 7.39-7.35 (2H; m; $H_{3''}$, $H_{4''}$, $H_{5''}$ or $H_{6''}$); 6.96-6.92 (2H; m; $H_{3''}$, $H_{4''}$, $H_{5''}$ or $H_{6''}$); 6.37 (1H; d; J = 8.3 Hz; $H_{1'}$); 5.22 (1H; s; $H_{11'}$); 3.37 (1H; m; $H_{2'}$); 2.95 (1H; d; J = 10.7 Hz; $H_{7'}$ or $H_{8'}$); 2.32-2.28 (1H; m; $H_{7'}$ or $H_{8'}$); 1.74-1.67 (3H; m; $H_{3'}$ or $H_{4'}$, $H_{9'}$ and $H_{10'}$); 1.38-1.33 (2H; m; $H_{5'}$ and $H_{6'}$); 0.49 (1H; dddd; J = 15.6, 12.2 and 3.4 Hz; $H_{3'}$ or $H_{4'}$) ppm.

^{13}C NMR (125.0 MHz DMSO-d_6) δ: 159.0; 150.9; 148.8; 144.0; 132.2; 131.9; 130.3; 130.2; 129.3; 128.5; 128.1; 125.9; 123.7; 123.5; 120.2; 117.7; 116.5; 97.8; 76.7; 67.2; 48.5; 27.9; 24.9; 24.2 ppm.

LC/MS: m/z [M + H] = 483.

IR ν_{max} (cm^{-1}; KBr pellets): 1309 (C—O); 1180, 1153, 1114 (C—F).

*4.2.9. 4-[1-(2,8-Dimethylquinolin-4-yl)hexahydro[1,3]oxazolo[3,4-a]pyridin-3-yl]phenol (**1i**)*

^{1}H NMR [500.00 MHz (FIDRES ± 0.12 Hz), $(CH_3)_2CO$-d_6] δ: 8.67 (1H; d; J = 7.0 Hz; H_5 or H_7); 8.34 (1H; d; J = 5.5 Hz; H_5 or H_7); 8.23 (1H; s; H_3); 7.95 (1H; t; J = 6.3 Hz; H_6); 7.58 (2H; d; J = 6.6 Hz; $H_{2''}$ and $H_{6''}$); 7.00 (2H; d; J = 6.6 Hz; $H_{3''}$ and $H_{5''}$); 6.24 (1H; d; J = 6.3 Hz; $H_{1'}$); 4.88 (1H; s; $H_{11'}$); 3.31-3.13 (1H; m; $H_{2'}$); 2.82 (1H; d; J = 8.6 Hz; $H_{7'}$ or $H_{8'}$); 2.07-2.03 (1H; m; $H_{7'}$ or $H_{8'}$); 1.64-1.52 (3H; m; $H_{3'}$ or $H_{4'}$, $H_{9'}$ and $H_{10'}$); 1.31-1.26 (2H; m; $H_{5'}$ and $H_{6'}$); 0.38-0.34 (1H; m; $H_{3'}$ or $H_{4'}$) ppm.

^{13}C NMR (125.0 MHz DMSO-d_6) δ: 159.6; 152.5; 148.5; 144.0; 130.9; 130.2; 129.4; 129.1; 128.9; 128.5; 128.4; 126.0; 123.8; 117.5; 116.5 97.9; 77.1; 67.1; 48.6; 27.9; 24.9; 24.5 ppm.

LC/MS: m/z [M + H] = 483.

IR ν_{max} (cm^{-1}; KBr pellets): 1306 (C—O); 1190, 1154, 1140 (C—F).

*4.2.10. 4-[3-(2-Methoxyphenyl)hexahydro[1,3]oxazolo[3,4-a]pyridin-1-yl]-2,8-dimethylquinoline (**1j**)*

^{1}H NMR [500.00 MHz (FIDRES ± 0.12 Hz), $(CH_3)_2CO$-d_6] δ: 8.68 (1H; d; J = 7.0 Hz; H_5 or H_7); 8.34 (1H; d; J = 5.8 Hz; H_5 or H_7); 8.11 (1H; s; H_3); 7.95 (1H; t; J = 6.2 Hz; H_6); 7.88 (1H; d; J = 5.9 Hz; $H_{3''}$, $H_{4''}$, $H_{5''}$ or $H_{6''}$); 7.47 (1H; t; J = 5.5 Hz; $H_{3''}$, $H_{4''}$, $H_{5''}$ or $H_{6''}$); 7.17-7.13 (2H; m; $H_{3''}$, $H_{4''}$, $H_{5''}$ or $H_{6''}$); 6.27 (1H; d; J = 6.2 Hz; $H_{1'}$); 5.41 (1H; s; $H_{11'}$); 3.91 (3H; s; OCH_3) 3.21-3.17 (1H; m; $H_{2'}$); 2.86 (1H; d; J = 9.0 Hz; $H_{7'}$ or $H_{8'}$); 2.09-2.05 (1H; m; $H_{7'}$ or $H_{8'}$); 1.67-1.53 (3H; m; $H_{3'}$ or $H_{4'}$, $H_{9'}$ and $H_{10'}$); 1.34-1.26 (2H; m; $H_{5'}$ and $H_{6'}$); 0.35 (1H; dddd; J = 16.0, 6.7 and 2.7 Hz; $H_{3'}$ or $H_{4'}$) ppm.

^{13}C NMR (125.0 MHz DMSO-d_6) δ: 160.5; 152.5; 148.6; 143.9; 131.5; 130.2; 130.1; 129.8; 128.8; 128.5; 128.3; 125.7; 123.8; 121.5; 117.7; 112.4; 91.3; 77.3; 67,1; 56.0; 48.9; 27.9; 24.9; 24.4 ppm.

LC/MS: m/z [M + H] = 497.

IR ν_{max} (cm^{-1}; KBr pellets): 1309 (C—O); 1189, 1137, 1111 (C—F).

*4.2.11. 4-[3-(3-Methoxyphenyl)hexahydro[1,3]oxazolo[3,4-a]pyridin-1-yl]-2,8-dimethylquinoline (**1k**)*

^{1}H NMR [500.00 MHz (FIDRES ± 0.12 Hz), $(CH_3)_2CO$-d_6] δ: 8.68 (1H; d; J = 8.6 Hz; H_5 or H_7); 8.35 (1H; d; J = 7.2 Hz; H_5 or H_7); 8.21 (1H; s; H_3); 7.96 (1H; t; J = 7.9 Hz; H_6); 7.45 (1H; J = 7.7 Hz; $H_{5''}$); 7.32-7.30 (2H; m; $H_{2''}$ and $H_{6''}$); 7.08-7.05 (1H; m; $H_{4''}$) 6.29 (1H; d; J = 8.0 Hz; $H_{1'}$); 4.93 (1H; s; $H_{11'}$); 3.89 (3H; s; OCH_3); 3.20 (1H; dddd; J = 10.8, 8.1 and 2.2 Hz; $H_{2'}$); 2.86 (1H; d; J = 10.7 Hz; $H_{7'}$ or $H_{8'}$); 2.11 (1H; ddd; J = 13.6, 11.4 and 2.8 Hz; $H_{7'}$ or $H_{8'}$); 1.66-1.54 (3H; m; $H_{3'}$ or $H_{4'}$, $H_{9'}$ and $H_{10'}$); 1.37-1.23 (2H; m; $H_{5'}$ and $H_{6'}$); 0.39 (1H; dddd; J = 15.6, 11.6 and 3.7 Hz; $H_{3'}$ or $H_{4'}$) ppm.

^{13}C NMR (125.0 MHz DMSO-d_6) δ: 161.2; 152.2; 148.4; 144.0; 139.6; 130.6; 130.2; 129.7; 128.4; 128.3; 126.2; 123.9; 123.5; 121.6; 117.4; 116.1; 114.5; 97.8; 77.2; 67.1; 55.5; 48.5; 27.8; 24.9; 24.4 ppm.

LC/MS: m/z [M + H] = 497.

IR ν_{max} (cm^{-1}; KBr pellets): 1307 (C—O); 1213, 1190, 1144, 1112 (C—F).

*4.2.12. 4-[3-(4-Methoxyphenyl)hexahydro[1,3]oxazolo[3,4-a]pyridin-1-yl]-2,8-dimethylquinoline (**1l**)*

^{1}H NMR [500.00 MHz (FIDRES ± 0.12 Hz), $(CH_3)_2CO$-d_6] δ: 8.67 (1H; d; J = 8.5 Hz; H_5 or H_7); 8.35 (1H; d; J = 7.1 Hz; H_5 or H_7); 8.21 (1H; s; H_3); 7.95 (1H; t; J = 8.1 Hz; H_6); 7.67 (2H; dd; J = 8.8 and 1.8 Hz; $H_{2''}$ and $H_{6''}$); 7.09 (2H; dd; J = 8.8 and 1.8 Hz; $H_{3''}$ and $H_{5''}$); 6.26 (1H; d; J = 8.1 Hz; $H_{1'}$); 4.91 (1H; s; $H_{11'}$); 3.88 (3H; s; OCH_3); 3.17 (1H; dddd; J = 13.4,10.9, 8.1 and 2.0 Hz; $H_{2'}$); 2.79 (1H; sl; $H_{71'}$ or $H_{8'}$); 2.05 (1H; ddd; J = 6.3, 4.3 and 2.3 Hz; $H_{7'}$ or $H_{8'}$); 1.64-1.53 (3H; m; $H_{3'}$ or $H_{4'}$, $H_{9'}$ and $H_{10'}$); 1.29-1.26 (2H; m; $H_{5'}$ and $H_{6'}$); 0.37 (1H; dddd; J = 15.3, 11.6 and 3.5; $H_{3'}$ or $H_{4'}$) ppm.

^{13}C NMR (125.0 MHz DMSO-d_6) δ: 161.9; 152.4; 144.1; 130.8; 130.3; 130.0; 129.8; 128.5; 128.4; 126.3; 124.0; 123.6; 117.5; 115.0; 97.8; 77.1; 67.2; 55.8; 48.6; 27.9; 24.9; 24.5 ppm.

LC/MS: m/z [M + H] = 497.

IR ν_{max} (cm^{-1}; KBr pellets): 1308 (C—O); 1188, 1145, 1108 (C—F).

*4.2.13. 2,8-Dimethyl-4-[3-(2-nitrophenyl)hexahydro[1,3]oxazolo[3,4-a]pyridin-1-yl]quinoline (**1m**)*

^{1}H NMR [500.00 MHz (FIDRES ± 0.12 Hz), $(CH_3)_2CO$-d_6] δ: 8.67 (1H; d; J = 6.8 Hz; H_5 or H_7); 8.35 (1H; d; J = 5.7 Hz; H_5 or H_7); 8,27 (1H; dd; J = 6.1 and 0.6 Hz; $H_{3''}$ or $H_{6''}$); 8,10 (1H; dd; J = 6.3 and 0.5 Hz; $H_{3''}$ or $H_{6''}$); 7.99-7.95 (2H; m; H_3 and $H_{4''}$ or $H_{5''}$); 7.82-7.79 (2H; m; H_6 and $H_{4''}$ or $H_{5''}$); 6.36 (1H; d; J = 6.3 Hz; $H_{1'}$); 5.53 (1H; s; $H_{11'}$); 3.32 (1H; dddd; J = 8.6, 6.3 and 1.8 Hz; $H_{2'}$); 2.95 (1H; d; J = 8.7 Hz; $H_{7'}$ or $H_{8'}$); 2.22 (1H; ddd; J = 10.9, 9.0 and 1.9 Hz; $H_{7'}$ or $H_{8'}$); 1.73-1.58 (3H; m; $H_{3'}$ or $H_{4'}$, $H_{9'}$ and $H_{10'}$); 1.44-1.30 (2H; m; $H_{5'}$ and $H_{6'}$); 0.40 (1H; dddd; J = 12.8, 9.8 and 3.1 Hz; $H_{3'}$ or $H_{4'}$) ppm.

^{13}C NMR (125.0 MHz DMSO-d_6) δ: 151.3; 150.8; 147.4; 143.0; 133.5; 130.9; 130.6; 129.4; 129.0; 128.9; 128.6; 128.4; 127.5; 127.4; 124.9; 124.8; 116.1; 90.8; 77.1; 65.9; 48.0; 26.9; 23.8; 23.3 ppm.

LC/MS: m/z [M + H] = 512.

IR ν_{max} (cm^{-1}; KBr pellets): 1309 (C—O); 1214, 1183, 1153, 1112 (C—F).

*4.2.14. 2,8-Dimethyl-4-[3-(3-nitrophenyl)hexahydro[1,3]oxazolo[3,4-a]pyridin-1-yl]quinoline (**1n**)*

^{1}H NMR [500.00 MHz (FIDRES ± 0.12 Hz), $(CH_3)_2CO$-d_6] δ: 8.70 (1H; d; J = 8.5 Hz; H_5 or H_7); 8.62 (1H; t; J = 1.8 Hz; $H_{2''}$); 8.42 (1H; dddd; J = 3.4, 2.4 and 1.0 Hz; $H_{4''}$); 8.37 (1H; d; J = 7.2 Hz; H_5 or H_7); 8.20 (1H; d; J = 7.6 Hz; $H_{6''}$); 8.03 (1H; s; H_3); 7.98 (1H; t; J = 7.9 Hz; H_6); 7.89 (1H; t; J = 7.9 Hz; $H_{5''}$); 6.38 (1H; d; J = 8.0 Hz; $H_{1'}$); 5.16 (1H; s; $H_{11'}$); 3.31 (1H; dddd; J = 10.9, 8.1 and 2.3 Hz; $H_{2'}$); 2.85 (1H; dd; J = 10.7 and 2.9 Hz; $H_{7'}$ or $H_{8'}$); 2.22 (1H; ddd; J = 11.4, 10.8 and 2.7 Hz; $H_{7'}$ or $H_{8'}$); 1.71-1.57 (3H; m; $H_{3'}$ or $H_{4'}$, $H_{9'}$ and $H_{10'}$); 1.38-1.28 (2H; m; $H_{5'}$ and $H_{6'}$); 0.43 (1H; dddd; J = 15.3, 11.9 and 3.6 Hz; $H_{3'}$ or $H_{4'}$) ppm.

^{13}C NMR (125.0 MHz DMSO-d_6) δ: 151.7; 149.9; 148.5; 144.1; 140.5; 135.8; 131.4; 131.3; 130.3; 129.8; 129.4; 129.1; 128.5; 128.3; 125.4; 123.9; 116.9; 96.3; 77.7; 67.1; 48.4; 27.7; 24.8; 24.4 ppm.

LC/MS: m/z [M + H] = 512.

IR ν_{max} (cm^{-1}; KBr pellets): 1307 (C–O); 1212, 1185, 1144, 1109 (C–F).

4.2.15. 2,8-Dimethyl-4-[3-(4-nitrophenyl)hexahydro[1,3]oxazolo [3,4-a]pyridin-1-yl]quinoline (**1o**)

^{1}H NMR [500.00 MHz (FIDRES ± 0.12 Hz), $(CH_3)_2CO$-d_6] δ: 8.70 (1H; d; J = 8.5 Hz; H_5 or H_7); 8.44 (2H; d; J = 8.7 Hz; $H_{3''}$ and $H_{5''}$); 8.36 (1H; d; J = 7.2 Hz; H_5 or H_7); 8.05 (2H; d; J = 8.7 Hz; $H_{2''}$ and $H_{6''}$); 8.03 (1H; s; H_3); 7.97 (1H; t; J = 7.9 Hz; H_6); 6.37 (1H; d; J = 8.1 Hz; $H_{1'}$); 5.14 (1H; s; $H_{11'}$); 3.30 (1H; dddd; J = 13.7, 10.8, 8.1 and 2.3 Hz; $H_{2'}$); 2.82 (1H; sl; $H_{7'}$ or $H_{8'}$); 2.21 (1H; ddd; J = 13.6, 11.2 and 2.5 Hz; $H_{7'}$ or $H_{8'}$); 1.69-1.57 (3H; m; $H_{3'}$ or $H_{4'}$, $H_{9'}$ and $H_{10'}$); 1.41-1.27 (2H; m; $H_{5'}$ and $H_{6'}$); 0.43 (1H; dddd; J = 15.8, 12.2 and 3.9 Hz; $H_{3'}$ or $H_{4'}$) ppm.

^{13}C NMR (125.0 MHz DMSO-d_6) δ: 151.6; 149.9; 148.3; 145.0; 144.0; 130.6; 130.3; 129.8; 128.5; 128.3; 125.9; 124.8; 123.7; 121.5; 117.0; 96.3; 77.8; 67.1; 48.5; 27.7; 24.8; 24.2 ppm.

LC/MS: m/z [M + H] = 512.

IR ν_{max} (cm^{-1}; KBr pellets): 1308 (C–O); 1213, 1181, 1153, 1132, 1106 (C–F).

4.2.16. 2,8-Dimethyl-4-(3-phenylhexahydro[1,3]oxazolo[3,4-a] pyridin-1-yl)quinoline (**1p**)

^{1}H NMR [500.00 MHz (FIDRES ± 0.12 Hz), $(CH_3)_2CO$-d_6] δ: 8.68 (1H; d; J = 8.8 Hz; H_5 or H_7); 8.34 (1H; d; J = 7.3 Hz; H_5 or H_7); 8.20 (1H; s; H_3); 7.95 (1H; t; J = 7.8 Hz; H_6); 7.76-7.74 (2H; m; $H_{2''}$,$H_{3''}$, $H_{4''}$, $H_{5''}$ or $H_{6''}$); 7.56-7.50 (3H; m; $H_{2''}$, $H_{3''}$, $H_{4''}$, $H_{5''}$ or $H_{6''}$); 6.29 (1H; d; J = 7.8 Hz; $H_{1'}$); 4.96 (1H; s; $H_{11'}$); 3.20 (1H; dddd; J = 10.7, 8.3, 2.4 Hz; $H_{2'}$); 2.84-2.80 (1H; m; $H_{7'}$ or $H_{8'}$); 2.12-2.08 (1H; m; $H_{7'}$ or $H_{8'}$); 1.66-1.53 (3H; m; $H_{3'}$ or $H_{4'}$, $H_{9'}$ and $H_{10'}$); 1.36-1.23 (2H; m; $H_{5'}$ and $H_{6'}$); 0.39 (1H; dddd; J = 15.6, 12.2 and 3.9 Hz; $H_{3'}$ or $H_{4'}$) ppm.

^{13}C NMR (125.0 MHz DMSO-d_6) δ: 152.2; 148.2; 143.9; 138.0; 130.5; 130.2; 129.7; 129.6; 129.4; 129.3; 129.0; 128.4; 128.3; 125.9; 117.4; 97.9; 77.3; 67.1; 48.4; 27.7; 24.8; 24.3 ppm.

LC/MS: m/z [M + H] = 467.

IR ν_{max} (cm^{-1}; KBr pellets): 1306 (C–O); 1183, 1142, 1109, 1089 (C–F).

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