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Graphical abstract

New series of monoamidoxime derivatives displaying versatile antiparasitic activity.

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32
 IC_{50} *Ld* = **9.16** μ M
 IC_{50} *Pf* > 10 μ M

Ld = *Leishmania donovani*
Pf = *Plasmodium falciparum*

36
 IC_{50} *Ld* = 22.10 μ M
 IC_{50} *Pf* = **2.76** μ M

40
 IC_{50} *Ld* > 50 μ M
 IC_{50} *Pf* = **4.17** μ M

New series of monoamidoxime derivatives displaying versatile antiparasitic activity.

Clémence Tabélé^a, Anita Cohen^b, Christophe Curti^a, Ahlem Bouhlef^a, Sébastien Hutter^b, Vincent Remusat^a, Nicolas Primas^a, Thierry Terme^a, Nadine Azas^b, Patrice Vanelle^{a,*}.

^a Aix-Marseille Université, CNRS, ICR, UMR 7273, Laboratoire de Pharmaco-Chimie Radicalaire, Faculté de Pharmacie, 27 Boulevard Jean Moulin – CS30064, 13385 Marseille cedex 05, France

^b Aix Marseille Université, IRD, IRBA, Université de Montpellier 1, IP-TPT UMR MD 3, Infections Parasitaires, Transmission, Pharmacologie et Thérapeutique, Faculté de Pharmacie, 27 Boulevard Jean Moulin – CS30064, 13385 Marseille cedex 05, France

ABSTRACT

Following the promising antileishmanial results previously obtained in monoamidoxime series, a new series of derivatives was synthesized using manganese(III) acetate, Wittig reactions and Suzuki-Miyaura cross coupling reactions. Pharmacomodulation in R¹, R² or R³ substituents on the amidoxime structure is shown to influence antiprotozoan activity *in vitro*: a monosubstituted phenyl group in R₁ (**32-35**) led to an activity against *Leishmania donovani* promastigotes (**32**, IC₅₀ = 9.16 μM), whereas a polysubstituted group (**36-37**) led to an activity against *Plasmodium falciparum* (**36**, IC₅₀ = 2.76 μM). Modulating chemical substituents in R² and R³ only influenced the antiplasmodial activity *in vitro*. This suggests that the amidoxime scaffold has properties that could make it a promising new antiparasitic pharmacophore.

Highlights:

- Synthesis of amidoxime derivatives with valuable antiparasitic activities
- Radical synthesis of monoamidoxime derivatives mediated by manganese(III) acetate
- Pharmacomodulations carried out through Suzuki-Miyaura cross-coupling reactions
- Cytotoxicity evaluated on mouse J774A.1 macrophages and human HepG2
- Activity tested on *Leishmania donovani* promastigotes (strain MHOM/IN/00/DEVI)

Keywords:

Amidoximes

Dihydrofuran

Manganese(III) acetate

Palladium-catalyzed coupling reactions

Pharmacomodulation

Cytotoxicity *in vitro*

Antiprotozoan activity *in vitro*

1. Introduction

Human visceral leishmaniasis (VL) is a major public health problem [1] mainly caused by two species of a parasite from the Trypanosomatidae family: *Leishmania donovani* and *Infantum*, flagellate protozoans. A total of 98 countries and 3 territories on 5 continents reported endemic leishmaniasis transmission, with 200 to 400,000 new cases of visceral leishmaniasis declared yearly. [2]

Currently, few antileishmanial treatments are available: pentavalent antimonials are used as first-line drugs in endemic areas (India), [3] liposomal amphotericin B is used as a first-line drug in Europe and pentamidine is also used principally for immunosuppressed patients (VL/HIV coinfection). [4] Lastly there is miltefosin, the first antileishmanial drug for oral use. [5] However, all these treatments have drawbacks, notably drug resistance and toxicity, which accounts for the prevalence of the disease. [6] There is therefore an urgent need for suitable drugs offering the following: low-cost manufacturing, single daily oral dose, innovative structure to overcome drug resistance, wide therapeutic range.

In line with our general interest in the preparation of original molecules with pharmacological properties, [7-11] our team developed the radical synthesis of mono- and diarylamidoxime derivatives mediated by manganese(III) acetate.

Manganese(III) acetate has been extensively explored during the past decades (especially oxidative free-radical cyclization), and it remains a useful tool for carbon-carbon bond formation. [12-14] Recently, it enabled 40 mono- and diamidoximes to be synthesized, showing antileishmaniasis potential with valuable antiparasitic activities. [15-16]

Findings highlighted the antileishmanial potential of monoamidoxime derivatives, which was increased by fluorine atom or trifluoromethyl groups on the β -ketosulfone moiety. This yielded 4-(5-benzyl-3-(4-fluorophenylsulfonyl)-5-methyl-4,5-dihydrofuran-2-yl)-*N'*-hydroxy-benzimidamide (Figure 1): this molecule presents good *in vitro* antileishmanial activity on *L. donovani* promastigotes, with a better selectivity index (SI = 6.37) than conventional antileishmanial drugs (pentamidine, amphotericin B). [16]

Figure 1. 4-(5-benzyl-3-(4-fluorophenylsulfonyl)-5-methyl-4,5-dihydrofuran-2-yl)-*N'*-hydroxy-benzimidamide.

Figure 2. Pharmacomodulations carried out on the dihydrofuran scaffold.

In continuation of our research program centered on the design and synthesis of original molecules with pharmacological properties, further pharmacomodulations of R^1 , R^2 and R^3 groups (Figure 2) were carried out in order to obtain new monoamidoxime derivatives with better antileishmanial activity. Monoamidoximes were obtained using a free radical mechanism mediated by manganese(III) acetate. Suzuki-Miyaura cross-coupling reactions were also carried out to further explore the pharmacological potential.

In addition, the antiparasitic activities of the amidoxime derivatives obtained were assessed both on *L. donovani* promastigotes and *P. falciparum*. To date, the molecules synthesized by our research team have exhibited good activity against *L. donovani* promastigotes, and we wanted to determine the selectivity of this action among protozoa. Thus, assessments of both antiplasmodial and antileishmanial properties were performed for the new series of amidoximes synthesized, so as to better elucidate their mechanisms of action.

2. Results and discussion

2.1 Chemistry

Synthesis of monoamidoxime derivatives required several steps as reported in Scheme 1.

Scheme 1. Monoamidoxime derivatives synthetic pathway.

Reagents and conditions: (i) NaHCO_3 , Na_2SO_3 , H_2O -ethanol (9:1), MW, 100 °C, 200 W, 1 h. (ii) $t\text{BuOK}$, ether, 45 °C, atm Ar, 13 h. (iii) Mn(OAc)_3 , Cu(OAc)_2 , AcOH , 80 °C, 200 W, 80 min. (iv) MW, 140 °C, Ar, 1.5 h, $\text{Pd(PPh}_3)_4$, K_2CO_3 , toluene-ethanol (9:1). (v) $t\text{BuOK}$, $\text{NH}_2\text{OH.HCl}$, 0 °C RT, DMSO, 18 h, Ar.

Several β -ketosulfones (**1-7**) were synthesized using a previously reported method: [17] first, an aqueous solution of sodium sulfite, sodium bicarbonate and sulfonyl chloride was heated under microwave irradiation in order to obtain the corresponding sodium sulfinates. 4-(2-Bromoacetyl)benzonitrile was reacted with previously obtained sulfinates and the reaction mixture was irradiated for 45 min in ethanolic solution under the same conditions to give corresponding sulfones in

good yields (48-85%). All these products bear an active methylene group next to the carbonyl group, which allows further manganese(III) acetate oxidative cyclizations with alkenes.

Alkenes used were either commercial or synthesized (compounds **8-11**) by Wittig reaction, from the corresponding ketone. [18-19] Methyltriphenylphosphonium bromide (MTPP) was used as the methyl group allows the formation of terminal alkenes, in order to synthesize the dihydrofuranes required. Terminal alkenes synthesis was carried out in a two-step reaction: first, MTPP was activated into phosphorus betaine by heating and using a strong base (potassium *tert*-butoxide) in diethylether. And then, ketone was added and the reaction mixture was heated for 12 h longer to obtain the corresponding alkene (**8-11**) in good yields (60-100%).

Oxidative free-radical cyclization mediated by manganese(III) acetate has been already widely developed by our team [15-16, 20-23]; thus, it was easily synthesized the desired 2,3-dihydrofuran derivatives (**12-23**) in moderate to good yields (Table 1).

The reaction can be undertaken under classical heating, however, it has been shown that microwave irradiations dramatically improve yields, decrease reaction time and side reactions occurring. [20]

Table 1. Mn(OAc)₃ assisted oxidative cyclization.

Compound	R ¹	R ²	R ³	Mn(OAc) ₃ (Equiv.)	Cu(OAc) ₂ (equiv.)	Yield (%) ^a
12	<i>o</i> -fluoro-C ₆ H ₅ -	CH ₃ -	Bz-	2.1	1	58
13	<i>m</i> -fluoro-C ₆ H ₅ -	CH ₃ -	Bz-	2.1	1	48
14	<i>o</i> -(CF ₃)-C ₆ H ₅ -	CH ₃ -	Bz-	2.1	1	21
15	<i>m</i> -(CF ₃)-C ₆ H ₅ -	CH ₃ -	Bz-	2.1	1	53
16	<i>o,o</i> -difluoro-C ₆ H ₅ -	CH ₃ -	Bz-	2.1	1	82
17	<i>o,p</i> -difluoro-C ₆ H ₅ -	CH ₃ -	Bz-	2.1	1	29
18	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ -	Ph-	2.1	1	50
19	<i>p</i> -fluoro-C ₆ H ₅ -	Ph-	Ph-	2.1	1	43
20	<i>p</i> -fluoro-C ₆ H ₅ -	Ph-	<i>p</i> -(OMe)-C ₆ H ₅ -	2.1	1	0
20	<i>p</i> -fluoro-C ₆ H ₅ -	Ph-	<i>p</i> -(OMe)-C ₆ H ₅ -	4	2	27
21	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ CH ₂ -	<i>o</i> -(OMe)-C ₆ H ₅ -	4	2	22
22	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ -	<i>p</i> -bromo-C ₆ H ₅ -	4	2	28
23	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ -	<i>p</i> -chloro-C ₆ H ₅ -	2.1	1	15

^a Yield of isolated product based on the corresponding β -ketosulfone.

Synthesis of 2,3-dihydrofuran derivatives by oxidative free-radical cyclization mediated by manganese(III) acetate led to variable outcomes with regard to yields, according to the alkene used: alkenes with methoxy group (**9-10**) hardly react under classic conditions. [24-25] We hypothesized that methoxy- group interferes with manganese acetate, therefore more equiv. of manganese(III)

acetate and copper(II) acetate were used to achieve the reaction in better yield (compound **20** was not obtained under classical conditions, and obtained with 27% yields when number of equivalent of $\text{Mn}(\text{OAc})_3$ and $\text{Cu}(\text{OAc})_2$ were doubled). Compounds **22** and **23** were also obtained with low yields, as alkenes exhibiting electron withdrawal substituents are known for their lack of reactivity. [20]

In order to establish structure-activity relationships, pharmacomodulations were done, using palladium-catalyzed coupling reactions of a molecule bearing a bromine atom were investigated according to previously described studies. [26-29] Reaction parameters were assessed using 4-[5-(4-bromophenyl)-3-(4-fluorophenylsulfonyl)-5-methyl-4,5-dihydrofuran-2-yl]benzonitrile (**22**) as the substrate of *p*-tolylbenzeneboronic acid (Table 2), in order to optimize yields.

Table 2. Assessment of reaction parameters for Suzuki-Miyaura cross-coupling reaction.

Assay N°	Base	Solvent	Temperature (°C)	Reaction time (h)	Yield (%) ^a
1	K_2CO_3	Toluene	100	24	27
2	K_2CO_3	DME	80	72	21
3	K_2CO_3	Toluene:Ethanol (9:1)	110	48	45
4	K_2CO_3	DMF	140 ^b	1	90
5	<i>t</i> BuOK	DMF	140	48	22
6	K_2CO_3	Toluene:Ethanol (9:1)	140 ^b	1.5	100

^a Yield of isolated product based on the corresponding boronic acid.

^b Reaction carried out under microwave irradiation

Good yields were achieved with polar solvents only (DMF, toluene:ethanol); likewise, microwave irradiation leads to better yields and dramatically reduces reaction time. Outcomes revealed reaction parameter of assay 6 lead to quantitative yield, thus these reaction conditions were applied for further cross-coupling reactions. A series of 8 varied functionalized molecules (**24–31**) was obtained in moderate to quantitative yields (Table 3).

Table 3. Suzuki-Miyaura cross-coupling reactions.

Compound	R ⁴	Yield (%) ^a
24		100
25		87
26		83
27		33

28		44
29		50
30		38
31		95

^a Yield of isolated product based on the corresponding boronic acid.

Excellent yields were obtained with boronic acids exhibiting electron-withdrawal substituents (compounds **24** and **31**). It is worth noting that the substituent position influences the reactivity of boronic acids: *p*-cyanophenylboronic acid showed a better reactivity (compound **25**) than *o*-cyanophenylboronic acid (compound **29**) and *m*-cyanophenylboronic acid (compound **30**). With regard to heteroarylboronic acids, furan-2-ylboronic acid well reacted (83%) whereas pyridin-4-ylboronic acid reactivity was moderate.

The reaction of cyano derivatives synthesized from both cyclization mediated by manganese(III) acetate and Suzuki-Miyaura cross-coupling reactions (**12-31**), with hydroxylamine hydrochloride and potassium *tert*-butoxide in DMSO [30] led to conversion of the cyano group into amidoximes **32-51** in moderate to excellent yields (28-100%) as reported in Table 4.

Table 4. Synthesis and structure of amidoxime derivatives 32-51.

32-51

Compound	R ¹	R ²	R ³	Yield (%) ^a
32	<i>o</i> -fluoro-C ₆ H ₅ -	CH ₃ -	Bz-	55
33	<i>m</i> -fluoro-C ₆ H ₅ -	CH ₃ -	Bz-	69
34	<i>o</i> -(CF ₃)-C ₆ H ₅ -	CH ₃ -	Bz-	48
35	<i>m</i> -(CF ₃)-C ₆ H ₅ -	CH ₃ -	Bz-	63
36	<i>o,o</i> -difluoro-C ₆ H ₅ -	CH ₃ -	Bz-	50
37	<i>o,p</i> -difluoro-C ₆ H ₅ -	CH ₃ -	Bz-	30
38	<i>p</i> -fluoro-C ₆ H ₅ -	C ₆ H ₅ -	C ₆ H ₅ -	84
39	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ -	C ₆ H ₅ -	47
40	<i>p</i> -fluoro-C ₆ H ₅ -	C ₆ H ₅ -	<i>p</i> -(OMe)-C ₆ H ₅ -	28
41	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ -	<i>p</i> -bromo-C ₆ H ₅ -	60
42	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ CH ₂ -	<i>o</i> -(OMe)-C ₆ H ₅ -	100
43	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ -	4'-methylbiphenyl-4-yl	100

44	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ -	<i>p</i> -chloro-C ₆ H ₅ -	50
45	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ -	<i>N'</i> -hydroxybiphenyl-4-carboximidamide	100
46	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ -	4-(furan-2-yl)phenyl	76
47	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ -	3'-nitrobiphenyl-4-yl	55
48	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ -	4-(pyridin-4-yl)phenyl	100
49	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ -	2'-cyanobiphenyl-4-yl	60
50	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ -	<i>N'</i> -hydroxybiphenyl-3-carboximidamide	91
51	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ -	3',4',5'-trimethoxybiphenyl-4-yl	91

^a Yield of isolated product based on the corresponding nitrile derivative.

Excellent yields were obtained for compounds **42**, **43**, **45**, **48**, **50** and **51**: electro donating groups as R³ substituents improve reactivity. This finding is supported by outcomes provided with compounds **38** and **39**: the absence of a phenyl group as R² substituent (replaced by methyl group) almost halves the reaction yield. The conversion of two cyano groups occurs for compounds **45** and **50** but not for compound **49**, due to sterically hindered derivative. Inductive effect of nitro group probably enhances a side reaction leading to nitrobenzamide derivatives [30], hence the lower yield for compound **47**.

2.2 Biology

All amidoxime derivatives synthesized (**32-51**) underwent *in vitro* biological assessment: the first step toward synthesizing compounds of therapeutic interest was determining whether these compounds presented a toxic profile or if they could offer *in vitro* selective antiparasitic properties. Consequently, a cytotoxicity evaluation was realized *via* the MTT method [31] to determine cytotoxic concentrations of 50% (CC₅₀) and using doxorubicin as a cytotoxic reference-compound. These assays were performed with respect to two complementary cell lines: mouse J774A.1 macrophages (J774A.1 CC₅₀) and human HepG2 (HepG2 CC₅₀). J774A.1 macrophages are commonly used as *in vitro* host cell models for the screening of antileishmanial drugs allowing intracellular stage amastigote *L. donovani* to develop. [16] HepG2 is a commonly used human-derived hepatocarcinoma cell line that has shown characteristics similar to those of primary hepatocytes. These cells express many of the hepatocyte-specific metabolic enzymes, thus enabling the cytotoxicity of tested product metabolites to be evaluated. Then, molecules were tested for their activity (*Ld* promastigotes IC₅₀) against promastigotes (strain MHOM/IN/00/DEVI). Two reference drug compounds, amphotericin B and pentamidine, were tested under identical conditions. All tested compounds were also assessed for their *in vitro* antiplasmodial activity against a K1 multi-resistant strain of *Plasmodium falciparum*, using the SYBR Green I fluorescence-based method. [32, 33] In order to identify compounds with significant potential, two reference drug compounds, chloroquine and doxycycline, were also tested under the same conditions. Their inhibitory concentrations 50% (*Pf*K1 IC₅₀) were then calculated, as well as their selectivity indexes (SI). For each assay, three independent experiments in duplicate were performed. Outcomes are summarized in Table 5.

Table 5. Biological evaluation of amidoxime derivatives.

Compound	Activity <i>L. donovani</i> <i>Ld</i> promastigotes	Cytotoxicity J774A.1 CC ₅₀ (μM) ^a	Antileishmanial Selectivity Index ^b	Activity <i>P.</i> <i>falciparum</i> <i>Pf</i> K1 IC ₅₀	Cytotoxicity Hep G2 CC ₅₀ (μM) ^a	Antiplasmodial Selectivity Index ^c
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	IC ₅₀ (μM) ^a			(μM) ^a		
32	9.16 (± 0.4)	29.09 (± 5.2)	3.2	> 10 ^d	61.73 (± 1.2)	< 6.2
33	13.10 (± 0.5)	28.34 (± 6.4)	2.2	7.16 (± 0.9)	59.63 (± 2.3)	8.3
34	15.45 (± 3.2)	23.48 (± 4.8)	1.5	> 10 ^d	57.47 (± 1.2)	< 5.7
35	11.89 (± 1.6)	14.52 (± 3.2)	1.2	6.54 (± 0.5)	33.43 (± 1.4)	5.1
36	22.10 (± 1.3)	26.98 (± 7.6)	1.2	2.76 (± 0.4)	91.41 (± 4.3)	33.2
37	32.50 (± 0.5)	41.52 (± 9.3)	1.3	8.21 (± 1.2)	90.62 (± 5.3)	11.0
38	15.65 (± 2.3)	10.21 (± 1.8)	0.7	3.90 (± 1.0)	19.18 (± 0.5)	4.9
39	> 50 ^d	29.69 (± 5.7)	< 0.6	> 10 ^d	68.29 (± 3.4)	< 6.8
40	> 50 ^d	11.29 (± 3.1)	< 0.2	4.17 (± 0.8)	29.42 (± 1.8)	7.0
41	10.75 (± 0.1)	10.47 (± 0.8)	1.0	> 10 ^d	19.19 (± 0.4)	< 1.9
42	12.43 (± 1.5)	9.88 (± 1.0)	0.8	7.88 (± 0.8)	27.00 (± 1.4)	3.4
43	11.83 (± 0.6)	7.91 (± 1.5)	0.7	> 10 ^d	13.70 (± 0.7)	< 1.4
44	48.39 (± 0.2)	31.53 (± 4.6)	0.7	> 10 ^d	61.38 (± 1.9)	< 6.1
45	> 50 ^d	3.94 (± 0.7)	< 0.08	4.93 (± 0.3)	15.30 (± 2.6)	3.1
46	> 25 ^d	4.56 (± 1.4)	< 0.2	> 10 ^d	7.01 (± 1.6)	< 0.7
47	14.13 (± 2.8)	11.14 (± 1.0)	0.8	5.82 (± 0.8)	> 50 ^d	> 8.6
48	27.99 (± 5.2)	6.75 (± 1.4)	0.2	3.20 (± 0.1)	30.30 (± 1.0)	9.5
49	20.98 (± 2.7)	9.29 (± 0.6)	0.4	> 10 ^d	58.29 (± 2.9)	< 5.8
50	> 50 ^d	11.00 (± 1.0)	< 0.2	4.34 (± 0.7)	19.03 (± 3.0)	4.4
51	> 25 ^d	5.22 (± 0.7)	< 0.2	5.03 (± 0.3)	> 50 ^d	> 9.9
Doxorubicin^e	-	0.01	-	-	0.02	-
Amphotericin B^f	0.15	6.91	47.1			
Pentamidine^f	5.52	0.56	0.1			
Chloroquine^g				0.50	30	60
Doxycycline^g				5.00	20	4

^a The values are means ± SD of three independent experiments.

^b Selectivity Index was calculated according to the formula : SI = (J774A.1 CC₅₀) / (*L. donovani* IC₅₀).

^c Selectivity Index was calculated according to the formula : SI = (HepG2 CC₅₀) / (K1 IC₅₀).

^d Determination of the IC₅₀ or CC₅₀ value was limited by lack of solubility in the culture medium.

^e Doxorubicin was used as a cytotoxic drug compound of reference.

^f Amphotericin B and pentamidine were used as antileishmanial drug compounds of reference.

^g Chloroquine and doxycycline were used as antiplasmodial drug compounds of reference.

The evaluation revealed that almost all the compounds are twice as toxic *in vitro* toward J774A.1 macrophages as HepG2 cells. This result suggests firstly that there is product metabolization by hepatocyte-specific metabolic enzymes in the HepG2 cell line, and secondly that these metabolites are less toxic *in vitro* than tested compounds. Several amidoximes possessing a methyl in R², a benzyl in R³ and a variously monosubstituted phenyl group in R¹ (**32-35**) showed valuable *in vitro* effects toward *L. donovani* promastigotes, the most active compound **32** exhibiting an IC₅₀ value of 9.16 μM as compared with amphotericin B (0.15 μM) and pentamidine (5.52 μM) used as antileishmanial reference drugs. Moreover, **36** and **37** exhibited the highest IC₅₀ values which suggests that polysubstitution on the phenylsulfonyl group decreases antileishmanial potential, but enhances antiplasmodial activity, notably in *para* position: **36** exhibited *PfK1* IC₅₀ of 2.76 μM as compared with chloroquine (0.50 μM) and doxycycline (5 μM). Moreover, these amidoximes (**32-37**) were not cytotoxic, neither toward murine macrophages (14.52 μM ≤ J774A.1 CC₅₀ ≤ 41.52 μM) nor toward HepG2 (33.43 μM ≤ HepG2 CC₅₀ ≤ 91.41 μM), as compared with doxorubicin used as reference drug (J774A.1 CC₅₀ = 0.01 μM, HepG2 CC₅₀ = 0.02 μM), confirming that the nature of the substituted phenyl group in R¹ plays a key role in the cytotoxicity and the antileishmanial activity of the

amidoxime scaffold when combined with a methyl in R² and a benzyl in R³. Nevertheless, these results also demonstrate that a fluorinated substituent in *para* position of the phenyl group in R¹ is still the most favorable antileishmanial pharmacophore in the amidoxime series. [16] Derivatives with different substituents in R² and R³ showed lower activities and selectivity indexes against *L. donovani* ($< 0.08 \leq \text{Antileishmanial IS} \leq 1$). However, most of these compounds exhibited encouraging *in vitro* activities against *P. falciparum*: a phenyl group in R³, whether substituted or not, led to an absence of antiplasmodial activity (**39**, **41**, **44**, **46**), whereas the addition of a phenyl group in R² (**38**, **40**), or to a lesser extent an ethyl group (**42**), gave better results. If R³ is represented by a biphenyl group substituted by a second amidoxime in *para* (**45**) or *meta* (**50**) position, the corresponding compound revealed an encouraging antiplasmodial activity, such as 4-phenylpyridine (**48**). Substitution in *para* and/or *meta* position of a phenyl group in R³ by an electron-donating (**51**) or electron-deficient (**47**) substituent had no influence on cytotoxicity and antiplasmodial activity *in vitro*, while the presence of an electron-deficient group in *ortho* position, such as cyano group (**49**), led to a loss of activity.

3. Conclusion

Our findings show, first, that free-radical cyclization mediated by manganese(III) acetate depends on alkenes (variable yields). Second, Suzuki-Miyaura cross-coupling reactions appear promising for the synthesis of varied 2,3-dihydrofurane derivatives: from a single halide substrate, several functionalized molecules can be synthesized. In conclusion, Suzuki-Miyaura cross-coupling reactions and manganese(III) mediated reactions here allowed the synthesis of a new series of amidoxime derivatives. Structure-activity and toxicity relationships indicate that modulating chemical substituents on amidoxime enables antiprotozoan activity to be selective, making this chemical scaffold a promising candidate as an antiparasitic pharmacophore. To refine these findings, studies are in progress for further pharmacomodulations: the 4-fluorophenylsulfonyl group needs to be maintained as R¹ substituent (recent findings showed a better SI for the *para*-fluorophenylsulfonyl group), and a methylene spacer in α -position of the dihydrofurane is required with regard to the R³ group.

4. Experimental

4.1 Chemistry

4.1.1 General

TLC were performed on 5 cm $\times$ 10 cm aluminium plates coated with silica gel (layer 0.2 mm) 60F₂₅₄ (Merck) in an appropriate solvent. The following adsorbent was used for flash column chromatography: silica gel 60 (Merck, particle size 0.063-0.200 nm, 70-230 mesh ASTM). Melting points were determined through capillary tubes, with a B-540 Büchi melting point apparatus. ¹H-NMR and ¹³C-NMR spectra were recorded in CDCl₃ or DMSO, with tetramethylsilane (Me₄Si) as an internal reference using a Bruker ARX 200 spectrometer operating at 200 MHz for ¹H-NMR and 50 MHz for ¹³C-NMR; spectra were carried out at the Service Interuniversitaire de RMN de la Faculté de Pharmacie de Marseille. The ¹H chemical shifts are quoted in parts per million as δ downfield from tetramethylsilane (δ 0.00) as an internal standard and the ¹³C chemical shifts were referenced to the solvent peaks: CDCl₃ (76.9 ppm) or DMSO-*d*₆ (39.6 ppm). Coupling constants (J values) are given in hertz. NMR multiplicities are abbreviated as follows: s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet) and m (a more complex multiplet or overlapping multiplets). Microwave-assisted reactions were performed in a multimode microwave oven (ETHOS Synth Lab Station, Ethos start, Milestone Inc., Rockford, IL, USA) or in a monomode microwave oven for the Suzuki-Miyaura cross-coupling reactions (Biotage Initiator Microwave oven using 10-20 mL sealed vials; temperatures were measured with an IR-sensor and reaction times given as hold times). Elemental analysis and mass spectra, run on an API-QqToF mass spectrometer, were carried out at the Spectropole de la Faculté

des Sciences site Saint-Jérôme. IR analysis were implemented spectra were carried out at the Spectropole de la Faculté des Sciences site Saint-Jérôme, using a thermo-Nicolet IR 200 spectrometer ($4000\text{--}400\text{ cm}^{-1}$) coupled with Attenuated Total Reflectance technique (Spectra-Tech Foundation Thunderdome). All commercial reagents were used without purification.

4.1.2 General preparation of β -Ketosulfones

Sodium sulfite (1.26 g, 10 mmol) and sodium bicarbonate (0.84 g, 10 mmol) were added to a solution of sulfonyl chloride (6.00 mmol) in water (15 mL). The reaction mixture was heated under reflux in a microwave oven under irradiation (500 W, $100\text{ }^{\circ}\text{C}$) for 15 min. Then, an ethanolic solution of the corresponding acetophenone (6 mmol) was added. Heating of the reaction mixture was continued for 45 min under the same conditions. After cooling, the reaction mixture was filtered and the precipitate thus formed was crystallized from isopropanol.

4.1.2.1 4-[2-(2-fluorophenylsulfonyl)acetyl]benzonitrile (1). White powder, yield 48%, m.p. $164\text{ }^{\circ}\text{C}$ (isopropanol). ^1H NMR (CDCl_3 , 200 MHz, δ ppm): 4.91 (s, 2 H, CH_2), 7.26–7.38 (m, 2 H, CH), 7.66–7.88 (m, 2 H, CH), 7.81 (d, 2 H, CH, $J = 8.2\text{ Hz}$), 8.09 (d, 2 H, CH, $J = 8.2\text{ Hz}$). ^{13}C NMR (CDCl_3 , 50 MHz, δ ppm): 62.6 (CH_2), 117.3 (d, CH, $J = 20.9\text{ Hz}$), 117.5 (C), 117.7 (C), 124.9 (d, CH, $J = 3.7\text{ Hz}$), 126.3 (d, C, $J = 13.9\text{ Hz}$), 129.7 (2 CH), 130.7 (CH), 132.7 (2 CH), 137.1 (d, CH, $J = 8.8$), 138.5 (C), 159.6 (d, C, $J = 256.1\text{ Hz}$), 186.7 (C). Anal. calcd for $\text{C}_{15}\text{H}_{10}\text{FNO}_3\text{S}$ (303.31): C, 59.40; H, 3.32; N, 4.62. Found: C, 59.38; H, 3.44; N, 4.65.

4.1.2.2 4-[2-(3-fluorophenylsulfonyl)acetyl]benzonitrile (2). White powder, yield 70%, m.p. $154\text{--}155\text{ }^{\circ}\text{C}$ (isopropanol). ^1H NMR (CDCl_3 , 200 MHz, δ ppm): 4.75 (s, 2 H, CH_2), 7.37–7.45 (m, 1 H, CH), 7.53–7.71 (m, 3 H, CH), 7.82 (d, 2 H, CH, $J = 8.5\text{ Hz}$), 8.08 (d, 2 H, CH, $J = 8.5\text{ Hz}$). ^{13}C NMR (CDCl_3 , 50 MHz, δ ppm): 63.5 (CH_2), 116.0 (d, CH $J = 24.5\text{ Hz}$), 117.5 (C), 117.7 (C), 122.0 (d, CH, $J = 21.2\text{ Hz}$), 124.4 (d, CH, $J = 3.3\text{ Hz}$), 129.7 (2 CH), 131.3 (d, CH, $J = 7.7\text{ Hz}$), 132.7 (2 CH), 138.3 (C), 140.2 (d, C, $J = 6.6\text{ Hz}$), 162.4 (d, C, $J = 253.6\text{ Hz}$), 186.7 (C). Anal. calcd for $\text{C}_{15}\text{H}_{10}\text{FNO}_3\text{S}$ (303.31): C, 59.40; H, 3.32; N, 4.62. Found: C, 59.30; H, 3.36; N, 4.60.

4.1.2.3 4-[2-[2-(trifluoromethyl)phenylsulfonyl]acetyl]benzonitrile (3). White powder, yield 71%, m.p. $148\text{--}149\text{ }^{\circ}\text{C}$ (isopropanol). ^1H NMR (CDCl_3 , 200 MHz, δ ppm): 4.90 (s, 2 H, CH_2), 7.73–7.90 (m, 4 H, CH), 7.95–7.99 (m, 1 H, CH), 8.08 (d, 2 H, CH, $J = 8.6\text{ Hz}$), 8.13–8.18 (m, 1 H, CH). ^{13}C NMR (CDCl_3 , 50 MHz, δ ppm): 63.7 (CH_2), 117.5 (C), 117.7 (C), 128.6 (q, CH, $J = 6.2\text{ Hz}$), 129.7 (2 CH), 132.6 (CH), 132.7 (2 CH + C), 133.5 (CH), 134.6 (CH), 138.5 (C), 186.8 (C). 2 (C) were not observed under these experimental conditions. Anal. calcd for $\text{C}_{16}\text{H}_{10}\text{F}_3\text{NO}_3\text{S}$ (353.32): C, 54.39; H, 2.85; N, 3.96. Found: C, 54.29; H, 2.74; N, 3.97.

4.1.2.4 4-[2-[3-(trifluoromethyl)phenylsulfonyl]acetyl]benzonitrile (4). White powder, yield 85%, m.p. $136\text{ }^{\circ}\text{C}$ (isopropanol). ^1H NMR (CDCl_3 , 200 MHz, δ ppm): 4.80 (s, 2 H, CH_2), 7.71–7.75 (m, 1 H, CH), 7.81 (d, 2 H, CH, $J = 8.5$), 7.94–7.98 (m, 1 H, CH), 8.06 (d, 2 H, CH, $J = 8.5\text{ Hz}$), 8.10–8.20 (m, 2 H, CH). ^{13}C NMR (CDCl_3 , 50 MHz, δ ppm): 63.3 (CH_2), 117.4 (C), 117.8 (C), 122.9 (q, C, $J = 273.5\text{ Hz}$), 125.8 (q, CH $J = 4.0\text{ Hz}$), 129.6 (2 CH), 130.2 (CH), 131.2 (q, CH, $J = 3.3\text{ Hz}$), 132.0 (CH), 132.1 (q, C, $J = 33.7\text{ Hz}$), 132.7 (2 CH), 138.2 (C), 139.5 (C), 186.7 (C). Anal. calcd for $\text{C}_{16}\text{H}_{10}\text{F}_3\text{NO}_3\text{S}$ (353.32): C, 54.39; H, 2.85; N, 3.96. Found: C, 54.33; H, 2.73; N, 4.05.

4.1.2.5 4-[2-(2,6-difluorophenylsulfonyl)acetyl]benzonitrile (5). White powder, yield 74%, m.p. $207\text{ }^{\circ}\text{C}$ (isopropanol). ^1H NMR (CDCl_3 , 200 MHz, δ ppm): 4.91 (s, 2 H, CH_2), 7.08 (t, 2 H, CH, $J = 8.5\text{ Hz}$), 7.58–7.73 (m, 1 H, CH), 7.82 (d, 2 H, CH, $J = 8.6\text{ Hz}$), 8.09 (d, 2 H, CH, $J = 8.6\text{ Hz}$). ^{13}C NMR (CDCl_3 , 50 MHz, δ ppm): 63.7 (CH_2), 113.5 (dd, 2 CH, $J_1 = 3.7$, $J_2 = 23.0$), 117.5 (C), 117.8 (C), 129.6 (2 CH), 132.7 (2 CH), 136.8 (CH + C), 138.4 (C), 160.3 (dd, 2 C, $J_1 = 3.7\text{ Hz}$, $J_2 = 261.6\text{ Hz}$), 186.9 (C). Anal. calcd for $\text{C}_{15}\text{H}_9\text{F}_2\text{NO}_3\text{S}$ (321.30): C, 56.07; H, 2.82; N, 4.36. Found: C, 55.48; H, 2.90; N, 4.21.

4.1.2.6 4-[2-(2,4-difluorophenylsulfonyl)acetyl]benzonitrile (6). White powder, yield 72%, m.p. 138-139 °C (isopropanol). ¹H NMR (CDCl₃, 200 MHz, δ ppm): 4.89 (s, 2 H, CH₂), 6.99-7.10 (m, 2 H, CH), 7.82 (d, 2 H, CH, *J* = 8.6 Hz), 7.86-7.95 (m, 1 H, CH), 8.08 (d, 2 H, CH, *J* = 8.6 Hz). ¹³C NMR (CDCl₃, 50 MHz, δ ppm): 62.5 (d, CH₂, *J* = 2.2 Hz), 105.9 (dd, CH, *J*₁ = 24.6 Hz, *J*₂ = 26.0 Hz), 112.6 (dd, CH, *J*₁ = 3.7 Hz, *J*₂ = 21.9 Hz), 117.4 (C), 117.8 (C), 122.7 (dd, C, *J*₁ = 4.0 Hz, *J*₂ = 14.3 Hz), 129.6 (2 CH), 132.7 (2 CH), 132.9 (m, CH), 138.3 (C), 160.6 (dd, C, *J*₁ = 13.2 Hz, *J*₂ = 259.1 Hz), 167.1 (dd, C, *J*₁ = 11.7 Hz, *J*₂ = 260.5 Hz), 186.7 (C). Anal. calcd for C₁₅H₉F₂NO₃S (321.30) : C, 56.07; H, 2.82; N, 4.36. Found: C, 55.97; H, 2.76; N, 4.39.

4.1.2.7 4-[2-(4-fluorophenylsulfonyl)acetyl]benzonitrile (7). White powder, yield 82%, m.p. 162 °C (isopropanol) (Lit.: 160-161 °C [16]). ¹H NMR (CDCl₃, 200 MHz, δ ppm): 4.75 (s, 2 H, CH₂), 7.21-7.29 (m, 2 H, CH), 7.81 (d, 2 H, CH, *J* = 8.5 Hz), 7.87-7.93 (m, 2 H, CH), 8.08 (d, 2 H, CH, *J* = 8.5 Hz). ¹³C NMR (CDCl₃, 50 MHz, δ ppm): 63.7 (CH₂), 116.8 (d, 2 CH, *J* = 23 Hz), 117.6 (C), 129.7 (2 CH), 131.6 (d, 2 CH, *J* = 9.8 Hz), 132.7 (2 CH), 134.3 (C), 138.4 (C), 163.8 (C), 168.9 (C), 187.1 (C). IR (cm⁻¹) 2231 (-CN nitrile), 1684 (-CO), 1320 (O=S=O), 1144 (O=S=O).

4.1.3 General preparation of alkenes using Wittig reaction

Methyltriphenylphosphonium bromide (4.38 g, 11.1 mmol, 1.2 equiv.) and potassium *tert*-butoxide (1.24 g, 11.1 mmol, 1.2 equiv.) were added in anhydrous diethylether (50 mL) in order to form phosphorus ylide. The bright yellow reaction mixture was heated for 60 min under inert atmosphere. Ketone (9.25 mmol, 1 equiv.) was added progressively at room temperature, as this results in an exothermic reaction. The reaction mixture was heated for 12 h under the same conditions. Then, the reaction mixture was poured into 100 mL of cold water and extracted with diethyl ether (3 × 50 mL). The organics extracts were collected and washed with saturated aqueous NaHCO₃ (3 × 50 mL) and dried (MgSO₄). Solvent was evaporated under reduced pressure and crude product was purified by column chromatography with an appropriate solvent.

4.1.3.1 1,1-diphenylethene (8). [34] Colorless oil, yield 81%. Compound purified by silica gel column chromatography eluting with petroleum ether and dichloromethane (9:1). ¹H NMR (CDCl₃, 200 MHz, δ ppm): 5.23 (s, 2 H, CH₂), 6.90-7.29 (m, 10 H, CH). ¹³C NMR (CDCl₃, 50 MHz, δ ppm): 114.2 (CH₂), 127.9 (2 CH), 128.3 (4 CH), 128.6 (4 CH), 141.6 (2C), 150.2 (C).

4.1.3.2 1-methoxy-4-(1-phenylvinyl)benzene (9). Pink powder, yield 60%, m.p. 77 °C (petroleum ether) (Lit.: 73-75 °C [35]). Compound purified by silica gel column chromatography eluting with petroleum ether and dichloromethane (8:2). ¹H NMR (CDCl₃, 200 MHz, δ ppm): 3.83 (s, 3 H, CH₃), 5.36 (d, 1 H, CH₂, *J* = 2.1 Hz), 5.40 (d, 1 H, CH₂, *J* = 2.1 Hz), 6.87 (d, 2 H, CH, *J* = 2.1 Hz), 7.24-7.35 (m, 7 H, CH). ¹³C NMR (CDCl₃, 50 MHz, δ ppm): 55.3 (CH₃), 112.9 (CH₂), 113.5 (2 CH), 127.6 (CH), 128.1 (2 CH), 128.3 (2 CH), 129.4 (2 CH), 134.0 (C), 141.8 (C), 149.5 (C), 159.3 (C).

4.1.3.3 1-(but-1-en-2-yl)-2-methoxybenzene (10). [36] Yellow oil, yield 92%. Compound purified by silica gel column chromatography eluting with petroleum ether and dichloromethane (8:2). ¹H NMR (CDCl₃, 200 MHz, δ ppm): 1.06 (t, 3 H, CH₃, *J* = 7.4 Hz), 2.53 (q, 2 H, CH₂, *J* = 7.4 Hz), 5.05 (d, 1 H, CH₂, *J* = 1.8 Hz), 5.19 (d, 1 H, CH₂, *J* = 1.9 Hz), 6.89-6.99 (m, 2 H, CH), 7.17-7.38 (m, 2 H, CH). ¹³C NMR (CDCl₃, 50 MHz, δ ppm): 12.7 (CH₃), 29.1 (CH₂), 55.3 (CH₃), 110.5 (CH), 112.7 (CH₂), 120.4 (CH), 128.2 (CH), 130.0 (CH), 132.4 (C), 150.6 (C), 156.4 (C).

4.1.3.4 1-bromo-4-(prop-1-en-2-yl)benzene (11). [37] Colorless oil, yield 100%. Compound purified by silica gel column chromatography eluting with dichloromethane. ¹H NMR (CDCl₃, 200 MHz, δ ppm): 2.14-2.17 (m, 3 H, CH₃), 5.10-5.13 (m, 1 H, CH₂), 5.37 (m, 1 H, CH₂), 7.30-7.49 (m, 4 H, CH). ¹³C NMR (CDCl₃, 50 MHz, δ ppm): 21.6 (CH₃), 113.0 (CH₂), 121.3 (C), 127.14 (2 CH), 131.2 (2 CH), 140.1 (C), 142.2 (C).

4.1.4 General procedure for Mn(OAc)₃-mediated reaction of β -Ketosulfones with alkenes

A solution of manganese(III) acetate dihydrate (6.87 mmol, 1.84 g, 2.1 equiv. or 13.74 mmol, 3.68 g, 4 equiv) and copper(II) acetate (3.27 mmol, 0.59 g, 1 equiv or 6.54 mmol, 1.18 g, 2 equiv.) in 15 mL of glacial acetic acid was heated at 80 °C under microwave irradiation for 15 min. Then the reaction mixture was cooled down and a solution of β -ketosulfone (3.27 mmol, 1 equiv.) and alkene (6.54 mmol, 2 equiv.) in acetic acid was added. The reaction mixture was heated for 45 min under the same conditions, poured into 200 mL of cold water and extracted with dichloromethane (3 $\times$ 40 mL). The organic extracts were collected and washed with saturated aqueous NaHCO₃ (3 $\times$ 40 mL) and dried (MgSO₄). Solvent was evaporated under reduced pressure and crude product was purified by column chromatography with an appropriate solvent, and the product obtained was recrystallized from the appropriate solvent.

4.1.4.1 4-[5-benzyl-3-(2-fluorophenylsulfonyl)-5-methyl-4,5-dihydrofuran-2-yl]benzonitrile (12).

White powder, yield 58%, m.p. 176 °C (isopropanol). Compound purified by silica gel column chromatography eluting with petroleum ether, dichloromethane and diethyl ether (5:4.5:0.5). ¹H NMR (CDCl₃, 200 MHz, δ ppm): 1.50 (s, 3 H, CH₃), 2.90 (d, 1 H, CH₂, *J* = 14.8 Hz), 2.94 (d, 1 H, CH₂, *J* = 13.8 Hz), 3.04 (d, 1 H, CH₂, *J* = 13.8 Hz), 3.15 (d, 1 H, CH₂, *J* = 14.8 Hz), 7.04-7.26 (m, 7 H, CH), 7.49-7.57 (m, 1 H, CH), 7.61-7.77 (m, 5 H, CH). ¹³C NMR (CDCl₃, 50 MHz, δ ppm): 26.8 (CH₃), 41.6 (d, CH₂, *J* = 1.8 Hz), 46.4 (CH₂), 89.4 (C), 111.4 (C), 114.2 (C), 117.1 (d, CH, *J* = 21.2 Hz), 118.2 (C), 124.2 (d, CH, *J* = 3.6 Hz), 127.1 (CH), 128.3 (2 CH), 129.0 (d, C, *J* = 13.5 Hz), 129.8 (CH), 130.1 (2 CH), 130.3 (2 CH), 131.4 (2 CH), 133.0 (C), 135.3 (C), 135.4 (d, CH, *J* = 8.4 Hz), 159.2 (d, C, *J* = 256.1 Hz), 161.4 (C). Anal. calcd for C₂₅H₂₀FO₃S (433.49): C, 69.27; H, 4.65; N, 3.23. Found: C, 69.09; H, 4.68; N, 3.28.

4.1.4.2 4-[5-benzyl-3-(3-fluorophenylsulfonyl)-5-methyl-4,5-dihydrofuran-2-yl]benzonitrile (13).

White powder, yield 48%, m.p. 127-128 °C (isopropanol). Compound purified by silica gel column chromatography eluting with petroleum ether, dichloromethane and diethyl ether (5:4.5:0.5). ¹H NMR (CDCl₃, 200 MHz, δ ppm): 1.52 (s, 3 H, CH₃), 2.85 (d, 1 H, CH₂, *J* = 13.9 Hz), 2.86 (d, 1 H, CH₂, *J* = 14.8 Hz), 3.02 (d, 1 H, CH₂, *J* = 13.9 Hz), 3.05 (d, 1 H, CH₂, *J* = 14.8 Hz), 7.04-7.12 (m, 2 H, CH), 7.16-7.24 (m, 4 H, CH), 7.27-7.34 (m, 2 H, CH), 7.35-7.46 (m, 1 H, CH), 7.63-7.73 (m, 4 H, CH). ¹³C NMR (CDCl₃, 50 MHz, δ ppm): 27.4 (CH₃), 41.5 (CH₂), 46.5 (CH₂), 89.2 (C), 114.1 (d, CH, *J* = 24.1 Hz), 114.4 (C), 118.1 (C), 120.2 (d, CH, *J* = 21.2 Hz), 122.5 (d, CH, *J* = 3.2 Hz), 127.1 (CH), 128.3 (2 CH), 130.0 (2 CH), 130.2 (2 CH), 130.8 (d, CH, *J* = 8.1 Hz), 131.5 (2 CH), 132.9 (C), 135.2 (C), 143.2 (d, C, *J* = 6.6 Hz), 161.0 (C), 162.3 (d, C, *J* = 252.1 Hz). 1 (C) was not observed under these experimental conditions. Anal. calcd for C₂₅H₂₀FO₃S (433.49): C, 69.27; H, 4.65; N, 3.23. Found: C, 69.30; H, 4.75; N, 3.22.

4.1.4.3 4-[5-benzyl-5-methyl-3-[2-(trifluoromethyl)phenylsulfonyl]-4,5-dihydrofuran-2-yl]benzonitrile (14).

Orange oil, yield 21%. Compound purified by silica gel column chromatography eluting with petroleum ether, dichloromethane and diethyl ether (5:4.5:0.5). ¹H NMR (CDCl₃, 200 MHz, δ ppm): 1.49 (s, 3 H, CH₃), 2.75-3.04 (m, 4 H, CH₂), 7.03-7.08 (m, 2 H, CH), 7.19-7.26 (m, 3 H, CH), 7.59-7.72 (m, 6 H, CH), 7.77-7.81 (m, 1 H, CH), 7.88-7.92 (m, 1 H, CH). ¹³C NMR (CDCl₃, 50 MHz, δ ppm): 27.0 (CH₃), 42.0 (CH₂), 46.4 (CH₂), 89.1 (C), 111.2 (C), 114.3 (C), 118.2 (C), 122.4 (q, C, *J* = 274.8 Hz), 127.1 (CH), 127.5 (q, C, *J* = 33.3 Hz), 128.3 (2 CH), 128.4 (d, CH, *J* = 6.6 Hz), 130.2 (2 CH), 130.3 (2 CH), 131.4 (2 CH), 131.8 (CH), 132.1 (CH), 133.0 (C), 133.1 (CH), 135.3 (C), 139.4 (C), 160.8 (C).

4.1.4.4 4-[5-benzyl-5-methyl-3-[3-(trifluoromethyl)phenylsulfonyl]-4,5-dihydrofuran-2-yl]benzonitrile (15).

White powder, yield 53%, m.p. 102-103 °C (isopropanol). Compound purified by silica gel column chromatography eluting with petroleum ether, dichloromethane and diethyl ether

(5:4.5:0.5). ^1H NMR (CDCl_3 , 200 MHz, δ ppm): 1.53 (s, 3 H, CH_3), 2.84 (d, 1 H, CH_2 , $J = 13.9$ Hz), 2.89 (d, 1 H, CH_2 , $J = 14.7$ Hz), 3.03 (d, 1 H, CH_2 , $J = 13.9$), 3.06 (d, 1 H, CH_2 , $J = 14.7$ Hz), 7.00–7.22 (m, 5 H, CH), 7.50–7.73 (m, 6 H, CH), 7.75–7.86 (m, 2 H, CH). ^{13}C NMR (CDCl_3 , 50 MHz, δ ppm): 27.4 (CH_3), 41.3 (CH_2), 46.4 (CH_2), 89.4 (C), 111.1 (C), 114.6 (C), 118.0 (C), 123.0 (q, C, $J = 273.0$ Hz), 123.9 (q, CH, $J = 3.3$ Hz), 127.1 (CH), 128.2 (2 CH), 129.5 (q, CH, $J = 3.3$ Hz), 129.9 (CH), 130.0 (2 CH), 130.1 (2 CH), 131.5 (2 CH), 131.6 (q, C, $J = 33.3$ Hz), 132.8 (C), 135.1 (C), 142.4 (C), 161.5 (C). 1 (CH) was not observed under these experimental conditions. Anal. calcd for $\text{C}_{26}\text{H}_{20}\text{F}_3\text{NO}_3\text{S}$ (483.50): C, 64.59; H, 4.17; N, 2.90. Found: C, 64.39; H, 4.18; N, 3.02.

4.1.4.5 4-[5-benzyl-3-(2,6-difluorophenylsulfonyl)-5-methyl-4,5-dihydrofuran-2-yl]benzonitrile

(16). Orange oil, yield 82%. Compound purified by silica gel column chromatography eluting with petroleum ether, dichloromethane and diethyl ether (5:4.5:0.5). ^1H NMR (CDCl_3 , 200 MHz, δ ppm): 1.53 (s, 3 H, CH_3), 2.96 (d, 1 H, CH_2 , $J = 13.9$ Hz), 3.00 (d, 1 H, CH_2 , $J = 14.7$ Hz), 3.06 (d, 1 H, CH_2 , $J = 13.9$ Hz), 3.36 (d, 1 H, CH_2 , $J = 14.7$ Hz), 6.69 (t, 2 H, CH, $J = 8.5$ Hz), 7.07–7.29 (m, 5 H, CH), 7.38–7.52 (m, 1 H, CH), 7.64 (d, 2 H, CH, $J = 8.5$ Hz), 7.73 (d, 2 H, CH, $J = 8.5$ Hz). ^{13}C NMR (CDCl_3 , 50 MHz, δ ppm): 26.9 (CH_3), 41.5 (CH_2), 46.5 (CH_2), 89.5 (C), 113.0 (dd, 2 CH, $J_1 = 3.7$ Hz, $J_2 = 23.4$ Hz), 113.1 (C), 114.3 (C), 118.1 (C), 127.1 (CH), 128.3 (2 CH), 130.0 (2 CH), 130.2 (2 CH), 131.5 (2 CH), 132.8 (C), 135.0 (dd, CH, $J_1 = 11.0$ Hz, $J_2 = 11.3$ Hz), 135.3 (C), 159.8 (dd, 2 C, $J_1 = 3.7$ Hz, $J_2 = 256.0$ Hz), 161.3 (C). 1 (C) was not observed under these experimental conditions.

4.1.4.6 4-[5-benzyl-3-(2,4-difluorophenylsulfonyl)-5-methyl-4,5-dihydrofuran-2-yl]benzonitrile

(17). White powder, yield 29%, m.p. 148–149 °C (isopropanol). Compound purified by silica gel column chromatography eluting with petroleum ether, dichloromethane and diethyl ether (5:4.5:0.5). ^1H NMR (CDCl_3 , 200 MHz, δ ppm): 1.52 (s, 3 H, CH_3), 2.7 (d, 1 H, CH_2 , $J = 14.8$ Hz), 2.94 (d, 1 H, CH_2 , $J = 13.9$ Hz), 3.04 (d, 1 H, CH_2 , $J = 13.9$ Hz), 3.15 (d, 1 H, CH_2 , $J = 14.8$ Hz), 6.75–6.91 (m, 2 H, CH), 7.04–7.16 (m, 2 H, CH), 7.19–7.30 (m, 4 H, CH), 7.63–7.71 (m, 4 H, CH). ^{13}C NMR (CDCl_3 , 50 MHz, δ ppm): 27.1 (CH_3), 41.5 (d, CH_2 , $J = 1.5$ Hz), 46.4 (CH_2), 89.4 (C), 105.7 (dd, CH, $J_1 = 24.9$ Hz, $J_2 = 26.0$ Hz), 111.0 (C), 111.7 (dd, CH, $J_1 = 3.7$ Hz, $J_2 = 21.9$ Hz), 114.4 (C), 118.1 (C), 125.4 (dd, C, $J_1 = 3.7$ Hz, $J_2 = 14.3$ Hz), 127.1 (CH), 128.3 (2 CH), 130.1 (2 CH), 130.3 (2 CH), 131.4 (2 CH), 131.6 (dd, CH, $J_1 = 1.1$ Hz, $J_2 = 10.6$ Hz), 132.9 (C), 135.3 (C), 160.0 (dd, C, $J_1 = 12.8$ Hz, $J_2 = 259.1$ Hz), 161.7 (C), 165.9 (dd, C, $J_1 = 11.7$ Hz, $J_2 = 258.7$ Hz). Anal. calcd for $\text{C}_{25}\text{H}_{19}\text{F}_2\text{NO}_3\text{S}$ (451.49): C, 66.51; H, 4.24; N, 3.10. Found: C, 66.54; H, 4.40; N, 3.15.

4.1.4.7 4-[3-(4-fluorophenylsulfonyl)-5-methyl-5-phenyl-4,5-dihydrofuran-2-yl]benzonitrile (18).

Yellow oil, yield 50%. Compound purified by silica gel column chromatography eluting with petroleum ether, dichloromethane and ethyl acetate (6:3.5:0.5). ^1H NMR (CDCl_3 , 200 MHz, δ ppm): 1.73 (s, 3 H, CH_3), 3.27 (d, 1 H, CH_2 , $J = 14.6$ Hz), 3.29 (d, 1 H, CH_2 , $J = 14.6$ Hz), 7.10 (t, 2 H, CH, $J = 8.6$ Hz), 7.28–7.32 (m, 5 H, CH), 7.66–7.76 (m, 4 H, CH), 7.89 (d, 2 H, CH, $J = 8.4$ Hz). ^{13}C NMR (CDCl_3 , 50 MHz, δ ppm): 28.8 (CH_3), 45.5 (CH_2), 89.4 (C), 111.8 (C), 114.3 (C), 116.3 (d, 2 CH, $J = 22.5$ Hz), 117.9 (C), 123.8 (2 CH), 127.7 (CH), 128.5 (2 CH), 129.4 (d, 2 CH, $J = 0.5$ Hz), 130.1 (2 CH), 131.4 (2 CH), 132.6 (CH), 137.0 (C), 144.1 (C), 159.9 (C), 165.1 (d, C, $J = 254.0$ Hz). HMRS (ESI): m/z calculated for $\text{C}_{24}\text{H}_{18}\text{FNO}_3\text{S}$ $[\text{M}+\text{H}]^+$: 420.1064 Found: 420.1063.

4.1.4.8 4-[3-(4-fluorophenylsulfonyl)-5,5-diphenyl-4,5-dihydrofuran-2-yl]benzonitrile (19).

White powder, yield 43%, m.p. 210 °C (isopropanol). Compound purified by silica gel column chromatography eluting with petroleum ether, dichloromethane and ethyl acetate (6:3.5:0.5). ^1H NMR (CDCl_3 , 200 MHz, δ ppm): 3.78 (s, 2 H, CH_2), 7.10 (m, 2 H, CH), 7.26–7.30 (m, 10 H, CH), 7.67–7.75 (m, 4 H, CH), 7.89 (d, 2 H, CH, $J = 8.3$ Hz). ^{13}C NMR (CDCl_3 , 50 MHz, δ ppm): 45.3 (CH_2), 92.6 (C), 112.5 (C), 114.8 (C), 116.2 (d, 2 CH, $J = 22.6$ Hz), 118.1 (C), 125.5 (4 CH), 128.2 (2 CH), 128.6 (4 CH), 129.7 (d, 2 CH, $J = 9.2$ Hz), 130.4 (2 CH), 131.7 (2 CH), 132.5 (C), 137.2 (C), 137.8 (C), 143.2 (2 C), 159.9 (C). Anal. calcd for $\text{C}_{29}\text{H}_{20}\text{FNO}_3\text{S}$ (481.11): C, 72.33; H, 4.19; N, 2.91; S, 6.66. Found: C, 72.34; H, 4.18; N, 2.84.

4.1.4.9 4-[3-(4-fluorophenylsulfonyl)-5-(4-methoxyphenyl)-5-phenyl-4,5-dihydrofuran-2-yl]benzonitrile (20). Yellow oil, yield 27%. Compound purified by silica gel column chromatography eluting with petroleum ether, dichloromethane and ethyl acetate (6:3.5:0.5). ¹H NMR (CDCl₃, 200 MHz, δ ppm): 3.69 (d, 1 H, CH₂, J = 14.9 Hz), 3.79 (s, 3 H, CH₃), 3.80 (d, 1 H, CH₂, J = 14.9 Hz), 6.80-6.85 (m, 2 H, CH), 7.06-7.19 (m, 4 H, CH), 7.24-7.34 (m, 5 H, CH), 7.66-7.75 (m, 4 H, CH), 7.86-7.90 (m, 2 H, CH). ¹³C NMR (CDCl₃, 50 MHz, δ ppm): 45.3 (CH₂), 55.3 (CH₃), 92.6 (C), 112.4 (C), 113.8 (2 CH), 114.6 (C), 116.4 (d, 2 CH, J = 22.4 Hz), 118.1 (C), 125.4 (2 CH), 127.0 (2 CH), 128.1 (CH), 128.5 (2 CH), 129.6 (d, 2 CH, J = 9.3 Hz), 130.4 (2 CH), 131.6 (2 CH), 132.5 (C), 135.1 (C), 137.2 (d, C, J = 3.5 Hz), 143.5 (C), 159.4 (C), 159.9 (C), 165.3 (d, C, J = 255.9 Hz). HRMS (ESI +) m/z calcd for C₃₀H₂₅FN₂O₅S [M+H]⁺: 544.1468. Found: 544.1541.

4.1.4.10 4-[5-ethyl-3-(4-fluorophenylsulfonyl)-5-(2-methoxyphenyl)-4,5-dihydrofuran-2-yl]benzonitrile (21). White powder, yield 22%, m.p. 160 °C (isopropanol). Compound purified by silica gel column chromatography eluting with petroleum ether, dichloromethane and ethyl acetate (6:3.5:0.5). ¹H NMR (CDCl₃, 200 MHz, δ ppm): 0.74 (t, 3 H, CH₃, J = 7.4 Hz), 2.04 (q, 2 H, CH₂, J = 7.4 Hz), 3.31 (s, 2 H, CH₂), 3.80 (s, 3 H, CH₃), 6.88-6.95 (m, 2 H, CH), 7.07-7.15 (m, 2 H, CH), 7.24-7.40 (m, 2 H, CH), 7.66-7.75 (m, 4 H, CH), 7.85-7.89 (m, 2 H, CH). ¹³C NMR (CDCl₃, 50 MHz, δ ppm): 8.0 (CH₃), 32.5 (CH₂), 43.7 (CH₂), 55.2 (CH₃), 91.7 (C), 111.1 (CH), 112.9 (C), 114.4 (C), 116.3 (d, 2 CH, J = 22.3 Hz), 118.2 (C), 120.3 (CH), 125.9 (CH), 129.0 (CH), 129.6 (d, 2 CH, J = 9.7 Hz), 130.3 (2 CH), 131.1 (C), 131.6 (2 CH), 133.2 (C), 137.5 (d, C, J = 2.8 Hz), 154.8 (C), 159.7 (C), 165.2 (d, C, J = 256.0 Hz). Anal. calcd for C₂₆H₂₂FNO₄S (463.12): C, 67.37; H, 4.78; N, 3.02. Found: C, 67.39; H, 4.70; N, 2.99.

4.1.4.11 4-[5-(4-bromophenyl)-3-(4-fluorophenylsulfonyl)-5-methyl-4,5-dihydrofuran-2-yl]benzonitrile (22). Yellow oil, yield 28%. Compound purified by silica gel column chromatography eluting with petroleum ether, dichloromethane and ethyl acetate (6:3.5:0.5). ¹H NMR (CDCl₃, 200 MHz, δ ppm): 1.69 (s, 3 H, CH₃), 3.5 (d, 1 H, CH₂, J = 14.6 Hz), 3.25 (d, 1 H, CH₂, J = 14.6 Hz), 7.06-7.20 (m, 4 H, CH), 7.42-7.48 (m, 2 H, CH), 7.65-7.74 (m, 4 H, CH), 7.83-7.88 (m, 2 H, CH). ¹³C NMR (CDCl₃, 50 MHz, δ ppm): 28.9 (CH₃), 45.6 (CH₂), 89.0 (C), 112.1 (C), 114.6 (C), 116.4 (d, 2 CH, J = 22.6 Hz), 118.0 (C), 121.8 (C), 125.8 (2 CH), 129.5 (d, 2 CH, J = 9.6 Hz), 130.2 (2 CH), 131.6 (2 CH), 131.7 (2 CH), 132.5 (C), 137.0 (d, C, J = 3.1 Hz), 143.3 (C), 159.9 (C), 165.3 (d, C, J = 256.7 Hz). Anal. calcd for C₂₄H₁₇BrFNO₃S (497.00): C, 57.84; H, 3.44; N, 2.81. Found: C, 57.97; H, 3.38; N, 2.67. IR (cm⁻¹) 2231 (-CN nitrile), 1320 (O=S=O), 1146 (O=S=O).

4.1.4.12 4-[5-(4-chlorophenyl)-3-(4-fluorophenylsulfonyl)-5-methyl-4,5-dihydrofuran-2-yl]benzonitrile (23). White powder, yield 15%, m.p. 131-134 °C (diethyl ether). Compound purified by silica gel column chromatography eluting with petroleum ether, dichloromethane and diethyl ether (5.5:4:0.5). ¹H NMR (CDCl₃, 200 MHz, δ ppm): 1.71 (s, 3 H, CH₃), 3.18 (d, 1 H, CH₂, J = 14.7 Hz), 3.27 (d, 1 H, CH₂, J = 14.7 Hz), 7.09 (d, 2 H, CH, J = 8.3 Hz), 7.18-7.35 (m, 4 H, CH), 7.67-7.76 (m, 4 H, CH), 7.85 (d, 2 H, CH, J = 8.3 Hz). ¹³C NMR (CDCl₃, 50 MHz, δ ppm): 29.1 (CH₃), 45.8 (CH₂), 89.1 (C), 112.2 (C), 114.8 (C), 116.6 (d, 2 CH, J = 22.6 Hz), 118.1 (C), 125.6 (2 CH), 128.9 (2 CH), 129.8 (d, 2 CH, J = 9.5 Hz), 130.4 (2 CH), 131.7 (2 CH), 133.9 (C), 137.2 (d, C, J = 3.2 Hz), 142.8 (2 C), 160.0 (C), 1 (C) was not observed under these experimental conditions. Anal. calcd for C₂₄H₁₇ClFNO₃S (453.06): C, 63.50; H, 3.77; N, 3.09. Found: C, 63.83; H, 3.71; N, 2.90.

4.1.5 General procedure for Suzuki-Miyaura cross-coupling

A solution of 4-[5-(4-bromophenyl)-3-(4-fluorophenylsulfonyl)-5-methyl-4,5-dihydrofuran-2-yl]benzonitrile (**22**) (200 mg, 1.01 mmol, 1 equiv.), boronic acid (1.5 equiv.), tetrakis(triphenylphosphine)palladium(0) (35.24 mg, 0.03 mmol, 0.03 equiv.) and potassium carbonate (350.7 mg, 2.54 mmol, 2.5 equiv.) in dry and degassed toluene/ethanol (9:1) was stirred 1.5 h at 110 °C

under microwave irradiation. Then the reaction mixture was evaporated and filtrated on Celite 545 using dichloromethane as solvent. The filtrate was poured into 100 mL of water and extracted with dichloromethane (3 × 40 mL). The organics extracts were collected and washed with saturated aqueous NaHCO₃ (3 × 40 mL) and dried (MgSO₄). Solvent was evaporated under reduced pressure and crude product was purified by column chromatography with an appropriate solvent.

4.1.5.1 4-[3-(4-fluorophenylsulfonyl)-5-methyl-5-(4'-methylbiphenyl-4-yl)-4,5-dihydrofuran-2-yl]benzonitrile (24). Yellow powder, yield 29%, m.p. 135 °C (diethyl ether). Compound purified by silica gel column chromatography eluting with petroleum ether, dichloromethane and ethyl acetate (6:3.5:0.5). ¹H NMR (CDCl₃, 200 MHz, δ ppm): 1.79 (s, 3 H, CH₃), 2.41 (s, 3 H, CH₃), 3.35 (d, 1 H, CH₂, *J* = 14.6 Hz), 3.35 (d, 1 H, CH₂, *J* = 14.6 Hz), 7.10-7.94 (m, 16 H, CH). ¹³C NMR (CDCl₃, 50 MHz, δ ppm): 21.0 (CH₃), 28.9 (CH₃), 45.7 (CH₂), 89.5 (C), 112.0 (C), 114.5 (C), 116.4 (d, 2 CH, *J* = 21.9 Hz), 118.0 (C), 124.4 (2 CH), 126.7 (2 CH), 127.1 (2 CH), 129.5 (2 CH), 129.6 (d, 2 CH, *J* = 10.2 Hz), 130.3 (2 CH), 131.5 (2 CH), 132.7 (2 C), 137.3 (d, C, *J* = 8.0 Hz), 140.8 (2 C), 142.8 (C), 160.1 (C), 165.2 (d, C, *J* = 256.4 Hz). Anal. calcd for C₃₁H₂₄FNO₃S (509.14): C, 73.06; H, 4.75; N, 2.75. Found: C, 72.78; H, 4.77; N, 2.57.

4.1.5.2 4'-[5-(4-cyanophenyl)-4-(4-fluorophenylsulfonyl)-2-methyl-2,3-dihydrofuran-2-yl]biphenyl-4-carbonitrile (25). White powder, yield 87%, m.p. 185 °C (diethyl ether). Compound purified by silica gel column chromatography eluting with dichloromethane. ¹H NMR (CDCl₃, 200 MHz, δ ppm): 1.70 (s, 3 H, CH₃), 3.23 (d, 1 H, CH₂, *J* = 14.7 Hz), 3.35 (d, 1 H, CH₂, *J* = 14.7 Hz), 7.09-7.18 (m, 2 H, CH), 7.40 (d, 2 H, CH, *J* = 8.3 Hz), 7.56-7.77 (m, 10 H, CH), 7.88 (d, 2 H, CH, *J* = 8.3 Hz). ¹³C NMR (CDCl₃, 50 MHz, δ ppm): 29.1 (CH₃), 45.8 (CH₂), 89.3 (C), 111.3 (C), 112.2 (C), 114.8 (C), 116.6 (d, 2 CH, *J* = 22.7 Hz), 124.9 (2 CH), 127.6 (4 CH), 129.8 (d, 2 CH, *J* = 9.5 Hz), 130.4 (2 CH), 131.7 (2 CH), 132.6 (2 C), 132.7 (2 CH), 137.2 (d, C, *J* = 3.3 Hz), 138.9 (2 C), 144.7 (C), 144.8 (C), 160.1 (C), 1 (C) was not observed under these experimental conditions. Anal. calcd for C₃₁H₂₁FN₂O₃S (520.12): C, 71.52; H, 4.07; N, 5.38. Found: C, 71.39; H, 3.97; N, 5.28.

4.1.5.3 4-[3-(4-fluorophenylsulfonyl)-5-(4-(furan-2-yl)phenyl)-5-methyl-4,5-dihydrofuran-2-yl]benzonitrile (26). Orange powder, yield 83%, m.p. 94-95 °C (diethyl ether). Compound purified by silica gel column chromatography eluting with petroleum ether, dichloromethane and diethyl ether (5:4.5:0.5). ¹H NMR (CDCl₃, 200 MHz, δ ppm): 1.74 (s, 3 H, CH₃), 3.21 (d, 1 H, CH₂, *J* = 14.7 Hz), 3.31 (d, 1 H, CH₂, *J* = 14.7 Hz), 6.47 (dd, 1 H, CH, *J* = 3.3 Hz), 6.66 (d, 1 H, CH, *J* = 3.3 Hz), 7.08-7.17 (m, 2 H, CH), 7.26-7.32 (m, 3 H, CH), 7.76 (d, 1 H, CH, *J* = 3.3 Hz), 7.62-7.76 (m, 5 H, CH), 7.87-7.91 (m, 2 H, CH). ¹³C NMR (CDCl₃, 50 MHz, δ ppm): 29.0 (CH₃), 45.7 (CH₂), 89.5 (C), 105.6 (CH), 111.8 (CH), 112.0 (C), 114.7 (C), 116.5 (d, 2 CH, *J* = 22.7 Hz), 124.0 (2 CH), 124.5 (2 CH), 129.7 (d, 2 CH, *J* = 9.5 Hz), 130.1 (C), 130.4 (2 CH), 131.7 (2 CH), 132.7 (C), 137.2 (C), 142.5 (CH), 143.1 (2 C), 153.2 (C), 160.1 (C), 1 (C) was not observed under these experimental conditions. Anal. calcd for C₂₈H₂₀FNO₄S (485.10): C, 69.26; H, 4.15; N, 2.88. Found: C, 67.53; H, 4.41; N, 2.65.

4.1.5.1 4-[3-(4-fluorophenylsulfonyl)-5-methyl-5-(3'-nitrobiphenyl-4-yl)-4,5-dihydrofuran-2-yl]benzonitrile (27). Yellow powder, yield 33%, m.p. 162 °C (isopropanol). Compound purified by silica gel column chromatography eluting with petroleum ether, dichloromethane and diethyl ether (5:4.5:0.5). ¹H NMR (CDCl₃, 200 MHz, δ ppm): 1.77 (s, 3 H, CH₃), 3.24 (d, 1 H, CH₂, *J* = 14.7 Hz), 3.34 (d, 1 H, CH₂, *J* = 14.7 Hz), 7.10-7.92 (m, 16 H, CH). ¹³C NMR (CDCl₃, 50 MHz, δ ppm): 29.2 (CH₃), 45.8 (CH₂), 77.3 (CH), 89.4 (C), 112.2 (C), 114.7 (C), 116.6 (d, 2 CH, *J* = 22.7 Hz), 118.1 (C), 124.5 (2 CH), 128.3 (2 CH), 128.5 (CH), 129.7 (C), 129.8 (d, 2 CH, *J* = 9.3 Hz), 130.4 (2 CH), 131.7 (2 CH), 131.9 (CH), 132.5 (CH), 132.7 (C), 135.5 (C), 137.2 (d, C, *J* = 2.5 Hz), 144.3 (C), 149.2 (C), 160.1 (C), 1 (C) was not observed under these experimental conditions. HRMS (ESI +) *m/z* calcd for C₃₀H₂₁FN₂O₅S [M+H]⁺: 540.1155 Found: 540.1226.

4.1.5.2 4-[3-(4-fluorophenylsulfonyl)-5-methyl-5-(4-(pyridin-4-yl)phenyl)-4,5-dihydrofuran-2-yl]benzonitrile (28). Yellow powder, yield 44%, m.p. 173 °C (diethyl ether). Compound purified by silica gel column chromatography eluting with dichloromethane. ¹H NMR (CDCl₃, 200 MHz, δ ppm): 1.76 (s, 3 H, CH₃), 3.23 (d, 1 H, CH₂, *J* = 14.7 Hz), 3.34 (d, 1 H, CH₂, *J* = 14.7 Hz), 7.08-7.16 (m, 2 H, CH), 7.40-7.77 (m, 12 H, CH), 7.87-7.91 (m, 2 H, CH). ¹³C NMR (CDCl₃, 50 MHz, δ ppm): 29.2 (CH₃), 45.8 (CH₂), 89.3 (C), 112.2 (C), 114.8 (C), 116.6 (d, 2 CH, *J* = 22.7 Hz), 118.1 (C), 125.1 (2 CH), 127.5 (4 CH), 129.8 (d, 2 CH, *J* = 9.5 Hz), 130.4 (4 CH), 131.7 (2 CH), 132.6 (2 C), 137.3 (d, C, *J* = 7.5 Hz), 145.7 (2 C), 160.0 (C), 1 (C) was not observed under these experimental conditions. Anal. calcd for C₂₉H₂₁FN₂O₃S (496.12): C, 70.15; H, 4.26; N, 5.64. Found: C, 69.44; H, 4.23; N, 5.21.

4.1.5.3 4'-[5-(4-cyanophenyl)-4-(4-fluorophenylsulfonyl)-2-methyl-2,3-dihydrofuran-2-yl]biphenyl-2-carbonitrile (29). Yellow powder, yield 50%, m.p. 166 °C (diethyl ether). Compound purified twice by silica gel column chromatography eluting with petroleum ether, dichloromethane and diethyl ether (5:4.5:0.5), and petroleum ether, dichloromethane and diethyl ether (5:2:3). ¹H NMR (CDCl₃, 200 MHz, δ ppm): 1.78 (s, 3 H, CH₃), 3.26 (d, 1 H, CH₂, *J* = 14.7 Hz), 3.35 (d, 1 H, CH₂, *J* = 14.7 Hz), 7.10-7.19 (m, 2 H, CH), 7.40-7.58 (m, 6 H, CH), 7.63-7.78 (m, 6 H, CH), 7.89-7.93 (m, 2 H, CH). ¹³C NMR (CDCl₃, 50 MHz, δ ppm): 29.2 (CH₃), 45.8 (CH₂), 89.3 (C), 111.2 (CH), 112.2 (C), 114.7 (C), 116.6 (d, 2 CH, *J* = 22.6 Hz), 124.6 (2 CH), 127.9 (CH), 129.2 (2 CH), 129.8 (d, 2 CH, *J* = 9.4 Hz), 130.0 (CH), 130.4 (2 CH), 131.7 (2 CH), 132.7 (CH), 132.9 (2 C), 133.9 (2 C), 137.2 (C), 137.8 (C), 144.5 (2 C), 144.8 (2 C). Anal. calcd for C₃₁H₂₁FN₂O₃S (520.12): C, 71.52; H, 4.07; N, 5.38. Found: C, 71.36; H, 4.17; N, 5.07.

4.1.5.4 4'-[5-(4-cyanophenyl)-4-(4-fluorophenylsulfonyl)-2-methyl-2,3-dihydrofuran-2-yl]biphenyl-3-carbonitrile (30). Yellow powder, yield 38%, m.p. 135 °C (diethyl ether). Compound purified twice by silica gel column chromatography eluting with petroleum ether, dichloromethane and diethyl ether (5:4.5:0.5), and petroleum ether, dichloromethane and diethyl ether (5:2:3). ¹H NMR (CDCl₃, 200 MHz, δ ppm): 1.77 (s, 3 H, CH₃), 3.23 (d, 1 H, CH₂, *J* = 14.7 Hz), 3.35 (d, 1 H, CH₂, *J* = 14.7 Hz), 7.09-7.18 (m, 2 H, CH), 7.39-7.44 (m, 2 H, CH), 7.53-7.83 (m, 10 H, CH), 7.88-7.92 (m, 2 H, CH). ¹³C NMR (CDCl₃, 50 MHz, δ ppm): 29.2 (CH₃), 45.8 (CH₂), 89.3 (C), 112.2 (C), 113.2 (C), 116.6 (d, 2 CH, *J* = 22.6 Hz), 124.9 (2 CH), 127.5 (2 CH), 129.8 (CH), 129.8 (d, 2 CH, *J* = 9.5 Hz), 130.4 (2 CH), 130.6 (CH), 131.0 (CH), 131.4 (CH), 131.7 (2 CH), 132.6 (2 C), 137.2 (C), 138.6 (2 C), 141.5 (2 C), 144.6 (2 C), 160.1 (C). Anal. calcd for C₃₁H₂₁FN₂O₃S (520.12): C, 71.52; H, 4.07; N, 5.38. Found: C, 70.77; H, 3.95; N, 5.15.

4.1.5.5 4-[3-(4-fluorophenylsulfonyl)-5-methyl-5-(3',4',5'-trimethoxybiphenyl-4-yl)-4,5-dihydrofuran-2-yl]benzonitrile (31). Orange oil, yield 95%. Compound purified by silica gel column chromatography eluting with petroleum ether, dichloromethane and diethyl ether (5:4.5:0.5). ¹H NMR (CDCl₃, 200 MHz, δ ppm): 1.77 (s, 3 H, CH₃), 3.23 (d, 1 H, CH₂, *J* = 14.7 Hz), 3.34 (d, 1 H, CH₂, *J* = 14.7 Hz), 3.89 (s, 3 H, CH₃), 3.92 (s, 6 H, CH₃), 6.74 (s, 2 H, CH), 7.08-7.17 (m, 2 H, CH), 7.36 (d, 2 H, CH, *J* = 8.3 Hz), 7.53 (d, 2 H, CH, *J* = 8.3 Hz), 7.68-7.75 (m, 2 H, CH), 7.74 (d, 2 H, CH, *J* = 8.2 Hz), 7.90 (d, 2 H, CH, *J* = 8.2 Hz). ¹³C NMR (CDCl₃, 50 MHz, δ ppm): 29.1 (CH₃), 45.8 (CH₂), 56.2 (2 CH₃), 61.0 (CH₃), 89.5 (C), 104.3 (2 CH₂), 112.1 (C), 114.7 (C), 116.5 (d, 2 CH, *J* = 22.7 Hz), 118.1 (C), 124.6 (2 CH), 127.4 (2 CH), 129.6 (d, 2 CH, *J* = 9.6 Hz), 130.4 (2 CH), 131.7 (2 CH), 132.8 (2 C), 137.9 (C), 141.2 (2 C), 143.3 (2 C), 153.7 (2 C), 160.1 (C). Anal. calcd for C₃₃H₂₈FO₆S (585.16): C, 67.68; H, 4.82; N, 2.39. Found: C, 67.78; H, 4.97; N, 1.98.

4.1.6 General procedure for amidoximes synthesis from nitriles

A suspension of hydroxylamine hydrochloride (1.7 mmol, 0.12 g, 10 equiv.) in 8 mL of DMSO was stirred under inert atmosphere and cooled down to 5 °C. Potassium tertbutoxide (1.7 mmol, 0.19 g, 10 equiv.) was added progressively and the reaction mixture was stirred for 30 min. Then the

corresponding nitrile was added (0.17 mmol, 1 equiv.) and the reaction mixture was stirred for 12-72 h. The mixture obtained was poured into cold water and the precipitate thus formed was filtrated and crystallized from the appropriate solvent.

4.1.6.1 4-[5-benzyl-3-(2-fluorophenylsulfonyl)-5-methyl-4,5-dihydrofuran-2-yl]-N'-

hydroxybenzimidamide (32). White powder, yield 55%, m.p. 172-173 °C (ethanol/water, 1:1). ¹H NMR (DMSO-*d*₆, 200 MHz, δ ppm): 1.44 (s, 3 H, CH₃), 2.77-3.08 (m, 4 H, CH₂), 5.89 (bs, 2 H, NH₂), 7.12-7.21 (m, 5 H, CH), 7.29-7.37 (m, 2 H, CH), 7.45 (d, 2 H, CH, *J* = 8.4 Hz), 7.59-7.75 (m, 4 H, CH), 9.82 (s, 1 H, OH). ¹³C NMR (DMSO-*d*₆, 50 MHz, δ ppm): 26.5 (CH₃), 41.3 (CH₂), 45.3 (CH₂), 88.8 (C), 109.1 (C), 117.6 (d, CH, *J* = 20.9 Hz), 124.8 (2 CH), 125.0 (d, CH, *J* = 2.6 Hz), 126.9 (CH), 128.2 (2 CH), 128.8 (C), 128.9 (d, C, *J* = 13.5 Hz), 129.0 (2 CH), 129.4 (CH), 130.4 (2 CH), 135.7 (C), 136.0 (C), 136.2 (d, CH, *J* = 8.8 Hz), 150.3 (C), 162.9 (C), 1 (C) was not observed under these experimental conditions. HRMS (ESI +) *m/z* calcd for C₂₅H₂₃FN₂O₄S [M+H]⁺: 467.1435 Found: 467.1435.

4.1.6.2 4-[5-benzyl-3-(3-fluorophenylsulfonyl)-5-methyl-4,5-dihydrofuran-2-yl]-N'-

hydroxybenzimidamide (33). White powder, yield 69%, m.p. 82 °C (ethanol/water, 1:1). ¹H NMR (DMSO-*d*₆, 200 MHz, δ ppm): 1.0 (s, 3 H, CH₃), 2.86 (d, 1 H, CH, *J* = 13.9 Hz), 2.87 (d, 1 H, CH, *J* = 14.6 Hz), 3.02 (d, 1 H, CH, *J* = 13.9 Hz), 3.06 (d, 1 H, CH, *J* = 14.6 Hz), 4.92 (bs, 2 H, NH₂), 7.07-7.11 (m, 2 H, CH), 7.17-7.29 (m, 6 H, CH), 7.34-7.42 (m, 1 H, CH), 7.60 (d, 2 H, CH, *J* = 8.6 Hz), 7.66 (d, 2 H, CH, *J* = 8.6 Hz). 1 (H) was not observed under these experimental conditions (OH). ¹³C NMR (DMSO-*d*₆, 50 MHz, δ ppm): 27.3 (CH₃), 41.6 (CH₂), 46.5 (CH₂), 88.6 (C), 109.5 (C), 114.0 (d, CH, *J* = 24.1 Hz), 119.9 (d, CH, *J* = 21.6 Hz), 122.5 (d, CH, *J* = 3.3 Hz), 125.2 (2 CH), 127.0 (CH), 128.2 (2 CH), 129.7 (2 CH), 130.0 (C), 130.3 (2 CH), 130.7 (d, CH, *J* = 7.7 Hz), 134.8 (C), 135.4 (C), 143.8 (d, CH, *J* = 6.2 Hz), 151.9 (C), 162.2 (d, C, *J* = 251.8 Hz), 162.7 (C), HRMS (ESI +) *m/z* calcd for C₂₅H₂₃FN₂O₄S [M+H]⁺: 467.1435 Found: 467.1439.

4.1.6.3 4-[5-benzyl-5-methyl-3-[2-(trifluoromethyl)phenylsulfonyl]-4,5-dihydrofuran-2-yl]-N'-

hydroxybenzimidamide (34). Orange powder, yield 48%, m.p. 148 °C (ethanol/water, 1:1). ¹H NMR (DMSO-*d*₆, 200 MHz, δ ppm): 1.45 (s, 3 H, CH₃), 2.71-2.98 (m, 4 H, CH₂), 5.88 (bs, 2 H, NH₂), 7.11-7.13 (m, 2 H, CH), 7.22-7.24 (m, 3 H, CH), 7.47 (d, 2 H, CH, *J* = 8.4 Hz), 7.67-7.97 (m, 6 H, CH), 9.82 (s, 1 H, OH). ¹³C NMR (DMSO-*d*₆, 50 MHz, δ ppm): 26.8 (CH₃), 41.6 (CH₂), 45.3 (CH₂), 88.7 (C), 108.7 (C), 123.2 (q, C, *J* = 295.0 Hz), 124.8 (2 CH), 126.6 (C), 126.9 (CH), 128.2 (2 CH), 128.8 (CH), 128.9 (C), 129.1 (2 CH), 130.5 (2 CH), 131.1 (CH), 133.5 (CH), 133.9 (CH), 133.7 (C), 135.9 (C), 139.4 (C), 150.2 (C), 162.6 (C). HRMS (ESI +) *m/z* calcd for C₂₆H₂₃F₃N₂O₄S [M+H]⁺: 517.1403 Found: 517.1404.

4.1.6.4 4-[5-benzyl-5-methyl-3-[3-(trifluoromethyl)phenylsulfonyl]-4,5-dihydrofuran-2-yl]-N'-

hydroxybenzimidamide (35). White powder, yield 63%, m.p. 71 °C (ethanol/water, 1:1). ¹H NMR (CDCl₃, 200 MHz, δ ppm): 1.51 (s, 3 H, CH₃), 2.84 (d, 1 H, CH, *J* = 13.9 Hz), 2.90 (d, 1 H, CH, *J* = 14.5 Hz), 3.02 (d, 1 H, CH, *J* = 13.9 Hz), 3.07 (d, 1 H, CH, *J* = 14.5 Hz), 4.96 (bs, 2 H, NH₂), 7.05-7.10 (m, 2 H, CH), 7.16-7.19 (m, 3 H, CH), 7.46-7.56 (m, 2 H, CH), 7.56 (d, 2 H, CH, *J* = 8.4 Hz), 7.67 (d, 2 H, CH, *J* = 8.4 Hz), 7.73-7.83 (m, 2 H, CH). 1 (H) was not observed under these experimental conditions (OH). ¹³C NMR (CDCl₃, 50 MHz, δ ppm): 27.3 (CH₃), 41.4 (CH₂), 46.4 (CH₂), 88.7 (C), 109.6 (C), 123.1 (q, C, *J* = 273.0 Hz), 123.8 (q, CH, *J* = 3.7 Hz), 125.3 (2 CH), 127.0 (CH), 128.2 (2 CH), 129.2 (q, CH, *J* = 3.7 Hz), 129.6 (2 CH), 129.8 (CH), 129.9 (CH), 130.2 (2 CH), 131.3 (q, C, *J* = 33.3 Hz), 134.8 (C), 135.3 (C), 142.8 (C), 151.8 (C), 163.2 (C). 1 (C) was not observed under these experimental conditions. HRMS (ESI +) *m/z* calcd for C₂₆H₂₃F₃N₂O₄S [M+H]⁺: 517.1403 Found: 517.1405.

4.1.6.5 4-[5-benzyl-3-(2,6-difluorophenylsulfonyl)-5-methyl-4,5-dihydrofuran-2-yl]-N'-

hydroxybenzimidamide (36). White powder, yield 50%, m.p. 98 °C (ethanol/water, 1:1). ¹H NMR

(DMSO-*d*₆, 200 MHz, δ ppm): 1.42 (s, 3 H, CH₃), 2.82-3.12 (m, 4 H, CH₂), 5.87 (bs, 2 H, NH₂), 7.00-7.32 (m, 7 H, CH), 7.44-7.48 (m, 2 H, CH), 7.64-7.70 (m, 3 H, CH), 9.81 (s, 1 H, OH). ¹³C NMR (DMSO-*d*₆, 50 MHz, δ ppm): 26.6 (CH₃), 41.1 (CH₂), 45.4 (CH₂), 89.0 (C), 110.8 (C), 113.7 (dd, 2 CH, $J_1 = 3.7$ Hz, $J_2 = 22.7$ Hz), 124.8 (2 CH), 126.9 (CH), 128.2 (2 CH), 128.7 (C), 128.9 (2 CH), 130.4 (2 CH), 135.6 (C), 135.9 (C), 136.4 (dd, CH, $J_1 = 11.0$ Hz, $J_2 = 12.1$ Hz), 150.3 (C), 159.1 (dd, 2 C, $J_1 = 4.0$ Hz, $J_2 = 257.6$ Hz), 162.8 (C). 1 (C) was not observed under these experimental conditions. HRMS (ESI +) m/z calcd for C₂₅H₂₂F₂N₂O₄S [M+H]⁺: 485.1341 Found: 485.1339.

4.1.6.6 4-[5-benzyl-3-(2,4-difluorophenylsulfonyl)-5-methyl-4,5-dihydrofuran-2-yl]-N'-

hydroxybenzimidamide (37). White powder, yield 30%, m.p. 117 °C (ethanol/water, 1:1). ¹H NMR (DMSO-*d*₆, 200 MHz, δ ppm): 1.46 (s, 3 H, CH₃), 2.71-3.06 (m, 4 H, CH₂), 5.88 (bs, 2 H, NH₂), 7.17-7.22 (m, 6 H, CH), 7.43-7.53 (m, 3 H, CH), 7.68-7.72 (m, 3 H, CH), 9.82 (s, 1 H, OH). ¹³C NMR (DMSO-*d*₆, 50 MHz, δ ppm): 26.7 (CH₃), 40.1 (CH₂), 45.4 (CH₂), 88.9 (C), 106.4 (C), 109.0 (C), 124.9 (2 CH), 126.9 (CH), 128.0 (dd, C, $J_1 = 2.9$ Hz, $J_2 = 16.0$ Hz), 128.2 (2 CH), 128.8 (C), 129.0 (2 CH), 130.4 (3 CH), 133.8 (dd, CH, $J_1 = 1.1$ Hz, $J_2 = 11.3$ Hz), 135.9 (C), 150.4 (C), 163.1 (C), 165.3 (dd, C, $J_1 = 12.1$ Hz, $J_2 = 254.0$ Hz), 1 (C) and 1 (CH) were not observed under these experimental conditions. HRMS (ESI +) m/z calcd for C₂₅H₂₂F₂N₂O₄S [M+H]⁺: 485.1341 Found: 485.1336.

4.1.6.7 4-[3-(4-fluorophenylsulfonyl)-5,5-diphenyl-4,5-dihydrofuran-2-yl]-N'-

hydroxybenzimidamide (38). White solid, yield 84%, m.p. 170 °C (ethanol/water, 1:1). ¹H NMR (DMSO-*d*₆, 200 MHz, δ ppm): 3.81 (s, 2 H, CH₂), 7.24-7.43 (m, 12 H, CH), 7.72-7.81 (m, 6 H, CH), 10.55 (s, 1 H, OH), 2 hydrogens (NH₂) were not observed under these experimental conditions. ¹³C NMR (DMSO-*d*₆, 50 MHz, δ ppm): 44.9 (CH₂), 92.1 (C), 111.3 (C), 116.6 (d, 2 CH, $J = 23$ Hz), 125.2 (4 CH), 126.5 (2 CH), 128.0 (2 CH), 128.8 (4 CH), 129.7 (2 CH), 129.9 (d, 2 CH, $J = 10$ Hz), 132.8 (C), 137.4 (d, C, $J = 2.8$ Hz), 143.8 (2 C), 153.9 (C), 160.8 (C), 164.8 (d, C, $J = 250.5$ Hz), 1 (C) was not observed under these experimental conditions. HRMS (ESI +) m/z calcd for C₂₉H₂₃FN₂O₄S [M+H]⁺: 515.1436 Found: 515.1430.

4.1.6.8 4-[3-(4-fluorophenylsulfonyl)-5-methyl-5-phenyl-4,5-dihydrofuran-2-yl]-N'-

hydroxybenzimidamide (39). White solid, yield 47%, m.p. 174 °C (ethanol/water, 1:1). ¹H NMR (DMSO-*d*₆, 200 MHz, δ ppm): 1.68 (s, 3 H, CH₃), 3.17 (d, 1 H, CH, $J = 14.8$ Hz), 3.23 (d, 1 H, CH, $J = 14.8$ Hz), 5.95 (s, 2 H, NH₂), 6.85-7.98 (m, 13 H, CH), 9.87 (s, 1 H, OH). ¹³C NMR (DMSO-*d*₆, 50 MHz, δ ppm): 28.9 (CH₃), 46.1 (CH₂), 88.9 (C), 111.2 (C), 116.3 (d, 2 CH, $J = 22.8$ Hz), 124.6 (2 CH), 125.3 (2 CH), 128.1 (CH), 129.0 (2 CH), 129.4 (CH), 129.6 (CH), 130.1 (d, 2 CH, $J = 9.8$ Hz), 131.5 (d, C, $J = 8.9$ Hz), 136.0 (C), 145.4 (d, C, $J = 4.5$ Hz), 150.7 (C), 160.3 (C), 162.2 (C). 1 (C) was not observed under these experimental conditions. HRMS (ESI +) m/z calcd for C₂₄H₂₁FN₂O₄S [M+H]⁺: 452.1206 Found: 452.1213.

4.1.6.9 4-[3-(4-fluorophenylsulfonyl)-5-(4-methoxyphenyl)-5-phenyl-4,5-dihydrofuran-2-yl]-N'-

hydroxybenzimidamide (40). Yellow oil, yield 28%. ¹H NMR (DMSO-*d*₆, 200 MHz, δ ppm): 3.71-3.86 (m, 2 H, CH₂), 3.72 (s, 3 H, CH₃), 6.02 (s, 2 H, NH₂), 6.87-6.91 (m, 3 H, CH), 7.30-7.40 (m, 9 H, CH), 7.71-7.78 (m, 5 H, CH), 9.92 (s, 1 H, OH). ¹³C NMR (DMSO-*d*₆, 50 MHz, δ ppm): 41.2 (CH₂), 55.6 (CH₃), 92.1 (C), 110.8 (C), 114.3 (2 CH), 117.1 (d, 2 CH, $J = 23.0$ Hz), 125.5 (4 CH), 127.1 (2 CH), 128.2 (CH), 128.5 (C), 129.0 (2 CH), 129.7 (2 CH), 130.2 (d, 2 CH, $J = 9.7$ Hz), 136.0 (C), 136.4 (C), 137.9 (C), 144.5 (C), 150.7 (C), 159.2 (C), 161.6 (C). 1 (C) was not observed under these experimental conditions. HRMS (ESI +) m/z calcd for C₃₀H₂₅FN₂O₅S [M+H]⁺: 544.1468 Found: 544.1541.

4.1.6.10 4-[5-(4-bromophenyl)-3-(4-fluorophenylsulfonyl)-5-methyl-4,5-dihydrofuran-2-

yl]-N'-hydroxybenzimidamide (41). White solid, yield 60%, m.p. 88-90 °C (ethanol/water, 1:1). ¹H NMR (DMSO-*d*₆, 200 MHz, δ ppm): 1.64 (s, 3 H, CH₃), 3.08 (d, 1 H, CH₂, $J = 14.7$ Hz), 3.25 (d, 1 H, CH₂, $J = 14.7$ Hz), 5.91 (s, 2 H, NH₂), 7.30-7.77 (m, 12 H, CH), 9.84 (s, 1 H, OH). ¹³C NMR (DMSO-*d*₆, 50 MHz, δ ppm): 28.7 (CH₃), 45.7 (CH₂), 88.9 (C), 110.2 (C), 117.1 (d, 2 CH, $J = 23$ Hz), 121.3

(C), 125.3 (2 CH), 126.9 (2 CH), 128.6 (C), 129.6 (2 CH), 130.1 (d, 2 CH, $J = 9.8$ Hz), 131.9 (2 CH), 136.3 (C), 137.9 (d, C, $J = 2.9$ Hz), 144.6 (C), 150.5 (C), 161.8 (C), 1 (C) was not observed under these experimental conditions. HRMS (ESI +) m/z calcd for $C_{24}H_{20}BrFN_2O_4S$ $[M+H]^+$: 530.0311 Found: 530.0383. IR (cm^{-1}) 3469-3225 (-OH, NH₂), 1640 (-C=N-), 1314 (O=S=O), 1147 (O=S=O).

4.1.6.11 4-[3-(4-fluorophenylsulfonyl)-5-(2-methoxyphenyl)-5-methyl-4,5-dihydrofuran-2-yl]-*N'*-hydroxybenzimidamide (42). White solid, yield 100%, m.p. 88-90 °C (ethanol/water, 1:1). ¹H NMR (DMSO-*d*₆, 200 MHz, δ ppm): 0.62-0.69 (m, 3 H, CH₃), 1.91-2.04 (m, 2 H, CH₂), 3.08 (d, 1 H, CH₂, $J = 15.4$ Hz), 3.21 (d, 1 H, CH₂, $J = 15.4$ Hz), 3.75 (s, 3 H, CH₃), 5.92 (s, 2 H, NH₂), 6.87-7.05 (m, 2 H, CH), 7.24-7.40 (m, 4 H, CH), 7.63-7.77 (m, 6 H, CH), 9.84 (s, 1 H, OH). ¹³C NMR (DMSO-*d*₆, 50 MHz, δ ppm): 8.3 (CH₃), 32.4 (CH₂), 43.7 (CH₂), 56.1 (CH₃), 90.8 (C), 110.8 (C), 112.5 (CH), 117.1 (d, 2 CH, $J = 22.9$ Hz), 120.7 (CH), 125.5 (2 CH), 125.8 (CH), 128.9 (C), 129.5 (3 CH), 130.0 (d, 2 CH, $J = 9.8$ Hz), 131.5 (C), 136.2 (C), 138.2 (d, C, $J = 2.9$ Hz), 150.7 (C), 155.3 (C), 161.8 (C), 1 (C) was not observed under these experimental conditions. HRMS (ESI +) m/z calcd for $C_{26}H_{25}FN_2O_5S$ $[M+H]^+$: 496.1468 Found: 496.1539.

4.1.6.12 4-[3-(4-fluorophenylsulfonyl)-5-methyl-5-(4'-methylbiphenyl-4-yl)-4,5-dihydrofuran-2-yl]-*N'*-hydroxybenzimidamide (43). Yellow solid, yield 100%, m.p. 150 °C (ethanol/water, 1:1). ¹H NMR (DMSO-*d*₆, 200 MHz, δ ppm): 1.70 (s, 3 H, CH₃), 2.30 (s, 3 H, CH₃), 3.14 (d, 1 H, CH₂, $J = 14.7$ Hz), 3.28 (d, 1 H, CH₂, $J = 14.7$ Hz), 5.91 (s, 2 H, NH₂), 7.21-7.78 (m, 16 H, CH), 9.84 (s, 1 H, OH). ¹³C NMR (DMSO-*d*₆, 50 MHz, δ ppm): 21.1 (CH₃), 45.8 (CH₂), 88.9 (C), 109.7 (C), 116.7 (d, 2 CH, $J = 22.9$ Hz), 124.8 (2 CH), 124.9 (2 CH), 125.5 (2 CH), 126.6 (2 CH), 128.4 (C), 129.2 (2 CH), 129.6 (2 CH), 129.8 (d, 2 CH, $J = 9.8$ Hz), 135.8 (C), 136.7 (C), 136.9 (C), 137.7 (d, C, $J = 2.9$ Hz), 139.5 (C), 143.5 (C), 150.2 (C), 161.6 (C), 1 (C) was not observed under these experimental conditions. HRMS (ESI +) m/z calcd for $C_{31}H_{27}FN_2O_4S$ $[M+H]^+$: 542.1676 Found: 542.1748.

4.1.6.13 4-[5-(4-chlorophenyl)-3-(4-fluorophenylsulfonyl)-5-methyl-4,5-dihydrofuran-2-yl]-*N'*-hydroxybenzimidamide (44). Yellow solid, yield 50%, m.p. 83-85 °C (ethanol/water, 1:1). ¹H NMR (DMSO-*d*₆, 200 MHz, δ ppm): 1.69 (s, 3 H, CH₃), 3.20 (d, 1 H, CH₂, $J = 14.7$ Hz), 3.29 (d, 1 H, CH₂, $J = 14.7$ Hz), 5.94 (s, 2 H, NH₂), 7.30-7.96 (m, 12 H, CH), 9.90 (s, 1 H, OH). ¹³C NMR (DMSO-*d*₆, 50 MHz, δ ppm): 28.7 (CH₃), 45.7 (CH₂), 89.0 (C), 110.3 (C), 117.1 (d, 2 CH, $J = 22.8$ Hz), 125.3 (2 CH), 126.7 (2 CH), 128.7 (C), 129.0 (2 CH), 129.6 (2 CH), 130.1 (d, 2 CH, $J = 9.8$ Hz), 132.8 (C), 136.4 (C), 138.0 (d, C, $J = 2.9$ Hz), 144.2 (C), 150.6 (C), 161.9 (C), 1 (C) was not observed under these experimental conditions. HRMS (ESI +) m/z calcd for $C_{24}H_{20}ClFN_2O_4S$ $[M+H]^+$: 486.0816 Found: 486.0889.

4.1.6.14 4'-{4-[4-fluorophenylsulfonyl]-5-[4-(*N'*-hydroxycarbamimidoyl)phenyl]-2-methyl-2,3-dihydrofuran-2-yl]-*N'*-hydroxybiphenyl-4-carboximidamide (45). White solid, yield 100%, m.p. 154 °C (ethanol/water, 1:1). ¹H NMR (DMSO-*d*₆, 200 MHz, δ ppm): 1.74 (s, 3 H, CH₃), 3.19 (d, 1 H, CH₂, $J = 14.7$ Hz), 3.34 (d, 1 H, CH₂, $J = 14.7$ Hz), 5.87 (s, 2 H, NH₂), 5.95 (s, 2 H, NH₂), 7.35-7.78 (m, 16 H, CH), 9.70 (s, 1 H, OH), 9.88 (s, 1 H, OH). ¹³C NMR (DMSO-*d*₆, 50 MHz, δ ppm): 28.8 (CH₃), 45.8 (CH₂), 88.9 (C), 109.7 (C), 116.7 (d, 2 CH, $J = 22.8$ Hz), 124.8 (2 CH), 124.8 (2 CH), 125.9 (2 CH), 126.3 (2 CH), 126.8 (2 CH), 128.3 (C), 129.2 (2 CH), 129.7 (d, 2 CH, $J = 9.7$ Hz), 132.5 (C), 135.9 (C), 137.6 (d, C, $J = 2.9$ Hz), 138.9 (C), 139.8 (C), 144.1 (C), 150.1 (C), 150.5 (C), 161.6 (C), 1 (C) was not observed under these experimental conditions. HRMS (ESI +) m/z calcd for $C_{31}H_{27}FN_4O_5S$ $[M+H]^+$: 586.1686 Found: 586.1769.

4.1.6.15 4-[3-[4-fluorophenylsulfonyl]-5-[4-(furan-2-yl)phenyl]-5-methyl-4,5-dihydrofuran-2-yl]-*N'*-hydroxybenzimidamide (46). Yellow powder, yield 76%, m.p. 120 °C (ethanol/water, 1:1). ¹H NMR (CDCl₃, 200 MHz, δ ppm): 1.66 (s, 3 H, CH₃), 3.08 (d, 1 H, CH₂, $J = 14.7$ Hz), 3.19 (d, 1 H, CH₂, $J = 14.7$ Hz), 5.90 (bs, 2 H, NH₂), 6.54-6.57 (m, 1 H, CH), 6.81-6.93 (m, 2 H, CH), 7.35-7.94 (m, 12 H, CH), 9.82 (s, 1 H, OH). ¹³C NMR (CDCl₃, 50 MHz, δ ppm): 28.7

(CH₃), 56.0 (CH₂), 88.7 (C), 106.6 (CH), 112.6 (CH), 116.6 (d, 2 CH, $J = 24.1$ Hz), 123.9 (2 CH), 124.0 (2 CH), 125.3 (2 CH), 126.6 (2 CH), 129.5 (d, 2 CH, $J = 6.7$ Hz), 130.1 (C), 131.9 (2 C), 140.8 (C), 143.3 (C), 143.7 (CH), 144.4 (C), 153.3 (2 C), 160.3 (C), 162.2 (C). HRMS (ESI +) m/z calcd for C₂₈H₂₃FN₂O₅S [M+H]⁺: 518.1312 Found: 518.1312.

4.1.6.16 4-[3-(4-fluorophenylsulfonyl)-5-methyl-5-(3'-nitrophenyl-4-yl)-4,5-

dihydrofuran-2-yl]-N'-hydroxybenzimidamide (47). Brown powder, yield 55%, m.p. 76-78 °C (ethanol/water, 1:1). ¹H NMR (CDCl₃, 200 MHz, δ ppm): 1.70 (s, 3 H, CH₃), 3.14 (d, 1 H, CH₂, $J = 14.7$ Hz), 3.30 (d, 1 H, CH₂, $J = 14.7$ Hz), 5.91 (bs, 2 H, NH₂), 7.34-7.97 (m, 16 H, CH), 9.84 (s, 1 H, OH). ¹³C NMR (CDCl₃, 50 MHz, δ ppm): 28.8 (CH₃), 40.1 (CH₂), 89.3 (C), 110.3 (C), 117.1 (d, 2 CH, $J = 23.0$ Hz), 121.6 (C), 122.8 (C), 125.4 (2 CH), 125.6 (2 CH), 127.8 (2 CH), 128.8 (C), 129.7 (2 CH), 130.1 (d, 2 CH, $J = 9.8$ Hz), 131.0 (CH), 133.8 (CH), 136.4 (C), 137.6 (C), 138.1 (d, C, $J = 3.1$ Hz), 141.6 (CH), 145.6 (C), 148.9 (CH), 150.6 (C), 162.0 (C), 1 (C) was not observed under these experimental conditions. HRMS (ESI +) m/z calcd for C₃₀H₂₄FN₃O₆S [M+H]⁺: 573.1370 Found: 573.1443.

4.1.6.17 4-{3-[4-fluorophenylsulfonyl]-5-methyl-5-[4-(pyridin-4-yl)phenyl]-4,5-

dihydrofuran-2-yl]-N'-hydroxybenzimidamide (48). White solid, yield 100%, m.p. 116 °C (ethanol/water, 1:1). ¹H NMR (DMSO-*d*₆, 200 MHz, δ ppm): 1.71 (s, 3 H, CH₃), 3.15 (d, 1 H, CH₂, $J = 14.9$ Hz), 3.29 (d, 1 H, CH₂, $J = 14.9$ Hz), 5.91 (s, 2 H, NH₂), 7.30-7.39 (m, 2 H, CH), 7.50-7.58 (m, 3 H, CH), 7.66-7.79 (m, 9 H, CH), 8.59-8.61 (m, 2 H, CH), 9.84 (s, 1 H, OH). ¹³C NMR (DMSO-*d*₆, 50 MHz, δ ppm): 28.8 (CH₃), 45.8 (CH₂), 88.8 (C), 109.8 (C), 116.7 (d, 2 CH, $J = 22.8$ Hz), 124.9 (2 CH), 125.1 (2 CH), 127.1 (4 CH), 128.3 (C), 129.2 (2 CH), 129.6 (CH), 129.8 (CH), 135.9 (C), 136.5 (C), 137.6 (d, C, $J = 2.9$ Hz), 145.8 (C), 146.4 (C), 150.1 (C), 150.3 (2 CH), 161.5 (C), 1 (C) was not observed under these experimental conditions. HRMS (ESI +) m/z calcd for C₂₉H₂₄FN₃O₄S [M+H]⁺: 529.1472 Found: 529.1544.

4.1.6.18 4-[5-(2'-cyanobiphenyl-4-yl)-3-(4-fluorophenylsulfonyl)-5-methyl-4,5-

dihydrofuran-2-yl]-N'-hydroxybenzimidamide (49). White powder, yield 60%, m.p. 101 °C (ethanol/water, 1:1). ¹H NMR (CDCl₃, 200 MHz, δ ppm): 1.73 (s, 3 H, CH₃), 3.17 (d, 1 H, CH₂, $J = 15.1$ Hz), 3.30 (d, 1 H, CH₂, $J = 15.1$ Hz), 5.91 (bs, 2 H, NH₂), 7.16-7.94 (m, 16 H, CH), 9.84 (s, 1 H, OH). ¹³C NMR (CDCl₃, 50 MHz, δ ppm): 29.1 (CH₃), 45.9 (CH₂), 89.3 (C), 110.2 (C), 110.8 (C), 116.4 (d, 2 CH, $J = 22.5$ Hz), 119.0 (C), 124.7 (2 CH), 125.5 (2 CH), 128.7 (CH), 128.8 (C), 129.5 (2 CH), 129.7 (2 CH), 130.1 (d, 2 CH, $J = 9.8$ Hz), 130.6 (CH), 134.1 (CH), 134.4 (CH), 136.4 (C), 137.6 (C), 138.1 (C), 144.4 (C), 145.7 (C), 150.6 (C), 162.0 (C), 1 (C) was not observed under these experimental conditions. HRMS (ESI +) m/z calcd for C₃₁H₂₄FN₃O₄S [M+H]⁺: 553.1472 Found: 553.1575.

4.1.6.19 4'-{4-[4-fluorophenylsulfonyl]-5-[4-(N'-hydroxycarbamimidoyl)phenyl]-2-

methyl-2,3-dihydrofuran-2-yl]-N'-hydroxybiphenyl-3-carboximidamide (50). White solid, yield 91%, m.p. 122 °C (ethanol/water, 1:1). ¹H NMR (DMSO-*d*₆, 200 MHz, δ ppm): 1.74 (s, 3 H, CH₃), 3.20 (d, 1 H, CH₂, $J = 14.8$ Hz), 3.34 (d, 1 H, CH₂, $J = 14.8$ Hz), 5.95 (s, 4 H, NH₂), 7.36-7.94 (m, 16 H, CH), 9.68 (s, 1 H, OH), 9.88 (s, 1 H, OH). ¹³C NMR (DMSO-*d*₆, 50 MHz, δ ppm): 28.9 (CH₃), 45.8 (CH₂), 88.9 (C), 109.7 (C), 116.7 (d, 2 CH, $J = 23$ Hz), 123.8 (CH), 124.8 (2 CH), 124.9 (2 CH), 126.9 (2 CH), 127.2 (CH), 128.4 (C), 128.8 (CH), 129.8 (2 CH), 129.7 (d, 2 CH, $J = 9.9$ Hz), 135.9 (C), 136.7 (C), 137.6 (d, C, $J = 2.9$ Hz), 139.3 (C), 139.4 (C), 144.0 (C), 150.1 (C), 150.7 (C), 161.6 (C), 1 (C) and 1 (CH) were not observed under these experimental conditions. HRMS (ESI +) m/z calcd for C₃₁H₂₇FN₄O₅S [M+H]⁺: 586.1686 Found: 586.1758.

4.1.6.20 4-[3-(4-fluorophenylsulfonyl)-5-methyl-5-(3',4',5'-trimethoxybiphenyl-4-yl)-4,5-

dihydrofuran-2-yl]-N'-hydroxybenzimidamide (51). White solid, yield 91%, m.p. 80 °C (ethanol/water, 1:1). ¹H NMR (DMSO-*d*₆, 200 MHz, δ ppm): 1.70 (s, 3 H, CH₃), 3.14 (d, 1 H, CH₂, $J = 14.5$ Hz), 3.31 (d, 1 H, CH₂, $J = 14.5$ Hz), 3.65 (s, 3 H, CH₃), 3.81 (s, 6 H, CH₃), 5.92 (s, 2 H, NH₂),

6.85 (s, 2 H, CH₂), 7.31-7.45 (m, 4 H, CH), 7.61-7.79 (m, 8 H, CH), 9.84 (s, 1 H, OH). ¹³C NMR (DMSO-*d*₆, 50 MHz, δ ppm): 28.8 (CH₃), 45.8 (CH₂), 55.9 (2 CH₃), 60.0 (CH₃), 88.9 (C), 104.2 (2 CH), 109.7 (C), 116.7 (d, 2 CH, J = 22.8 Hz), 124.5 (2 CH), 125.9 (2 CH), 127.0 (2 CH), 128.3 (C), 129.1 (2 CH), 129.7 (d, 2 CH, J = 9.8 Hz), 135.5 (C), 135.9 (C), 137.2 (C), 137.6 (d, C, J = 2.9 Hz), 143.7 (C), 150.1 (C), 153.2 (3 C), 161.6 (C), 1 (C) was not observed under these experimental conditions. HRMS (ESI +) m/z calcd for C₃₃H₃₁FN₂O₇S [M+H]⁺: 618.1836 Found: 618.1909.

4.2 Biology

4.2.1. General

Reagents for cell culture media and compound screening included Schneider's medium (Invitrogen), RPMI 1640 (PAA), foetal calf serum (FCS) (PAA), L-glutamine-penicillin-streptomycin solution (Sigma), thiazolyl blue tetrazolium bromide (MTT) and dimethyl sulfoxide (DMSO) (Sigma). Stock solutions of amidoxime derivatives and reference drugs (doxorubicin, amphotericin B, pentamidine, chloroquine and doxycycline all from Sigma) were prepared in DMSO.

4.2.2. *In vitro* cytotoxicity evaluation

The evaluation of the tested molecules cytotoxicity on the HepG2 (hepatocarcinoma cell line purchased from ATCC, ref HB-8065) and J774A.1 (mouse macrophage cell line ECACC, Salisbury UK) cell lines was performed according to the method of Mosman^[31] with slight modifications. Briefly, cells 5×10^3 in 100 μ L of complete medium [RPMI supplemented with 10% foetal bovine serum, 1% L-glutamine (200 mM) and penicillin (100 U/mL) / streptomycin (100 μ g/mL)] were inoculated into each well of 96-well plates and incubated at 37 °C in a humidified 6% CO₂, 14% O₂, 80% N₂ atmosphere. After 24 h incubation, 100 μ L of medium with various product concentrations (final DMSO concentration less than 0.5% v/v) was added and the plates were incubated for 72 h. Appropriate controls treated with or without solvent (DMSO), and various concentrations of doxorubicin (positive control) were added to each set of experiments. Duplicate assays were performed for each sample. At the end of the treatment and incubation, the medium was aspirated from the wells and 100 μ L MTT solution (0.5mg/ml in RPMI 1640) was added to each well. Cells were incubated for 6 h at 37 °C to allow MTT oxidation by mitochondrial dehydrogenase in the viable cells. After this time, the MTT solution was aspirated and DMSO (100 μ L) was added to each well to dissolve the resulting blue formazan crystals. Plates were shaken vigorously (300 rpm) for a few minutes. The absorbance was measured at 570 nm with 630 nm as reference wavelength, using a microplate spectrophotometer. DMSO was used as blank and doxorubicin as positive control. Cell viability was calculated as percentage of control (cells incubated without compound). The 50% cytotoxic concentrations (J774A.1 CC₅₀ and HepG2 CC₅₀) were determined by non-linear regression analysis processed on dose-response curves, using Table Curve software 2D v.5.0. CC₅₀ values represent the mean value calculated from three independent experiments.

4.2.3. *In vitro* antileishmanial activity

The effects of the tested compounds on the growth of *Leishmania donovani* promastigotes were assessed by MTT assay.^[31] Briefly, promastigotes in log-phase in Schneider's medium supplemented with 20% fetal calf serum (FCS), 2 mM L-glutamine and antibiotics (100 U/mL penicillin and 100 μ g/mL streptomycin), were incubated at an average density of 10^6 parasites/mL in sterile 96-well plates with various concentrations of compounds dissolved in DMSO (final concentration less than 0.5% v/v), in duplicate. Appropriate controls treated by DMSO, pentamidine or amphotericin B

(reference drugs) were added to each set of experiments. After a 72 h incubation period at 27 °C, parasite metabolic activity was determined. Each plate-well was then microscope-examined to detect possible precipitate formation. 10 µL of MTT solution (10 mg/mL) was added to each well followed by incubation for another 4 hours. The enzyme reaction was then stopped by adding of 100 µL of 50% isopropanol – 10% sodium dodecyl sulfate.^[38] Plates were shaken vigorously for a few minutes and the absorbance measured in a plate reader at 570 nm. Inhibitory concentration 50% (IC₅₀) was defined as the concentration of drug required to inhibit by 50% the metabolic activity of *Leishmania donovani* promastigotes compared to the control. IC₅₀ were calculated by non-linear regression analysis processed on dose–response curves, using TableCurve 2D V5 software. IC₅₀ values represent the mean value calculated from three independent experiments.

4.2.4. *In vitro* antiplasmodial activity

The evaluation of antiplasmodial activity was conducted on a K1 *in vitro* culture-adapted *Plasmodium falciparum* strain (clone of W2), resistant to chloroquine, pyrimethamine and proguanil. Cultures were maintained in fresh A+ human erythrocytes at 2.5% haematocrit in complete medium (RPMI 1640 with 25 mM HEPES, 25 mM NaHCO₃, 10% of A+ human serum) at 37 °C under reduced O₂ atmosphere (gas mixture 6% CO₂, 14% O₂, 80% N₂). Parasitaemia was maintained daily between 1% and 6%. The *Plasmodium falciparum* drug susceptibility test was carried out by comparing quantities of DNA in treated and control cultures of parasite in human erythrocytes according to a SYBR Green I fluorescence-based method using a 96-well fluorescence plate reader. Parasite culture was synchronized at ring stage with 5% sorbitol. Compounds were incubated in a total assay volume of 200 µL (RPMI, 2% haematocrit and 1% parasitaemia) for 72 h in a humidified atmosphere (6% CO₂, 14% O₂, 80% N₂) at 37 °C, in 96-well flat-bottom plates. Duplicate assays were performed for each sample. After incubation, 125 µL supernatant was discarded and cells were washed twice with 150 µL 1X PBS. 15 µL re-suspended cells were transferred to 96-well flat bottom non- sterile black plates (Greiner Bio-one). 15 µL of the SYBR Green lysis buffer (2XSYBR Green, 20 mM Tris base pH 7.5, 20 mM EDTA, 0.008% w/v saponin, 0.08% w/v Triton X-100) was added to each well. A negative control (treated by DMSO) and positive controls (doxycycline and chloroquine) were added to each set of experiments. Plates were incubated for 0.25 h at 37 °C and then read on a TECAN Infinite F-200 spectrophotometer with excitation and emission wavelengths at 497 and 520 nm respectively. The concentrations of compounds required to induce a 50% decrease in parasite growth (*Pf*K1 IC₅₀) were calculated from three independent experiments.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:

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Tables:

Table 1. Mn(OAc)₃ assisted oxidative cyclization.

Compound	R ¹	R ²	R ³	Mn(OAc) ₃ (Equiv.)	Cu(OAc) ₂ (equiv.)	Yield (%) ^a
12	<i>o</i> -fluoro-C ₆ H ₅ -	CH ₃ -	Bz-	2.1	1	58
13	<i>m</i> -fluoro-C ₆ H ₅ -	CH ₃ -	Bz-	2.1	1	48
14	<i>o</i> -(CF ₃)-C ₆ H ₅ -	CH ₃ -	Bz-	2.1	1	21
15	<i>m</i> -(CF ₃)-C ₆ H ₅ -	CH ₃ -	Bz-	2.1	1	53
16	<i>o,o</i> -difluoro-C ₆ H ₅ -	CH ₃ -	Bz-	2.1	1	82
17	<i>o,p</i> -difluoro-C ₆ H ₅ -	CH ₃ -	Bz-	2.1	1	29
18	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ -	Ph-	2.1	1	50
19	<i>p</i> -fluoro-C ₆ H ₅ -	Ph-	Ph-	2.1	1	43
20	<i>p</i> -fluoro-C ₆ H ₅ -	Ph-	<i>p</i> -(OMe)-C ₆ H ₅ -	2.1	1	0
20	<i>p</i> -fluoro-C ₆ H ₅ -	Ph-	<i>p</i> -(OMe)-C ₆ H ₅ -	4	2	27
21	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ CH ₂ -	<i>o</i> -(OMe)-C ₆ H ₅ -	4	2	22
22	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ -	<i>p</i> -bromo-C ₆ H ₅ -	4	2	28
23	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ -	<i>p</i> -chloro-C ₆ H ₅ -	2.1	1	15

^a Yield of isolated product based on the corresponding β-ketosulfone.**Table 2.** Assessment of reaction parameters for Suzuki-Miyaura cross-coupling reaction.

Assay N ^o	Base	Solvent	Temperature (°C)	Reaction time (h)	Yield (%) ^a
1	K ₂ CO ₃	Toluene	100	24	27
2	K ₂ CO ₃	DME	80	72	21
3	K ₂ CO ₃	Toluene:Ethanol (9:1)	110	48	45
4	K ₂ CO ₃	DMF	140 ^b	1	90
5	<i>t</i> BuOK	DMF	140	48	22
6	K ₂ CO ₃	Toluene:Ethanol (9:1)	140 ^b	1.5	100

^a Yield of isolated product based on the corresponding boronic acid.^b Reaction carried out under microwave irradiation

Table 3. Suzuki-Miyaura cross-coupling reactions.

Compound	R^4	Yield (%) ^a
24		100
25		87
26		83
27		33
28		44
29		50
30		38
31		95

^a Yield of isolated product based on the corresponding boronic acid.**Table 4.** Synthesis and structure of amidoxime derivatives 32-51. **32-51**

Compound	R^1	R^2	R^3	Yield (%) ^a
32	<i>o</i> -fluoro- C_6H_5 -	CH_3 -	Bz-	55
33	<i>m</i> -fluoro- C_6H_5 -	CH_3 -	Bz-	69
34	<i>o</i> -(CF_3)- C_6H_5 -	CH_3 -	Bz-	48

35	<i>m</i> -(CF ₃)-C ₆ H ₅ -	CH ₃ -	Bz-	63
36	<i>o,o</i> -difluoro-C ₆ H ₅ -	CH ₃ -	Bz-	50
37	<i>o,p</i> -difluoro-C ₆ H ₅ -	CH ₃ -	Bz-	30
38	<i>p</i> -fluoro-C ₆ H ₅ -	C ₆ H ₅ -	C ₆ H ₅ -	84
39	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ -	C ₆ H ₅ -	47
40	<i>p</i> -fluoro-C ₆ H ₅ -	C ₆ H ₅ -	<i>p</i> -(OMe)-C ₆ H ₅ -	28
41	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ -	<i>p</i> -bromo-C ₆ H ₅ -	60
42	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ CH ₂ -	<i>o</i> -(OMe)-C ₆ H ₅ -	100
43	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ -	4'-methylbiphenyl-4-yl	100
44	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ -	<i>p</i> -chloro-C ₆ H ₅ -	50
45	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ -	<i>N'</i> -hydroxybiphenyl-4-carboximidamide	100
46	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ -	4-(furan-2-yl)phenyl	76
47	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ -	3'-nitrobiphenyl-4-yl	55
48	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ -	4-(pyridin-4-yl)phenyl	100
49	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ -	2'-cyanobiphenyl-4-yl	60
50	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ -	<i>N'</i> -hydroxybiphenyl-3-carboximidamide	91
51	<i>p</i> -fluoro-C ₆ H ₅ -	CH ₃ -	3',4',5'-trimethoxybiphenyl-4-yl	91

^a Yield of isolated product based on the corresponding nitrile derivative.

Table 5. Biological evaluation of amidoxime derivatives.

Compound	Activity <i>L. donovani</i> <i>Ld</i> promastigotes IC ₅₀ (μM) ^a	Cytotoxicity J774A.1 CC ₅₀ (μM) ^a	Antileishmanial Selectivity Index ^b	Activity <i>P.</i> <i>falciparum</i> PfK1 IC ₅₀ (μM) ^a	Cytotoxicity Hep G2 CC ₅₀ (μM) ^a	Antiplasmodial Selectivity Index ^c
32	9.16 (± 0.4)	29.09 (± 5.2)	3.2	> 10 ^d	61.73 (± 1.2)	< 6.2
33	13.10 (± 0.5)	28.34 (± 6.4)	2.2	7.16 (± 0.9)	59.63 (± 2.3)	8.3
34	15.45 (± 3.2)	23.48 (± 4.8)	1.5	> 10 ^d	57.47 (± 1.2)	< 5.7
35	11.89 (± 1.6)	14.52 (± 3.2)	1.2	6.54 (± 0.5)	33.43 (± 1.4)	5.1
36	22.10 (± 1.3)	26.98 (± 7.6)	1.2	2.76 (± 0.4)	91.41 (± 4.3)	33.2
37	32.50 (± 0.5)	41.52 (± 9.3)	1.3	8.21 (± 1.2)	90.62 (± 5.3)	11.0
38	15.65 (± 2.3)	10.21 (± 1.8)	0.7	3.90 (± 1.0)	19.18 (± 0.5)	4.9
39	> 50 ^d	29.69 (± 5.7)	< 0.6	> 10 ^d	68.29 (± 3.4)	< 6.8
40	> 50 ^d	11.29 (± 3.1)	< 0.2	4.17 (± 0.8)	29.42 (± 1.8)	7.0
41	10.75 (± 0.1)	10.47 (± 0.8)	1.0	> 10 ^d	19.19 (± 0.4)	< 1.9
42	12.43 (± 1.5)	9.88 (± 1.0)	0.8	7.88 (± 0.8)	27.00 (± 1.4)	3.4
43	11.83 (± 0.6)	7.91 (± 1.5)	0.7	> 10 ^d	13.70 (± 0.7)	< 1.4
44	48.39 (± 0.2)	31.53 (± 4.6)	0.7	> 10 ^d	61.38 (± 1.9)	< 6.1
45	> 50 ^d	3.94 (± 0.7)	< 0.08	4.93 (± 0.3)	15.30 (± 2.6)	3.1
46	> 25 ^d	4.56 (± 1.4)	< 0.2	> 10 ^d	7.01 (± 1.6)	< 0.7
47	14.13 (± 2.8)	11.14 (± 1.0)	0.8	5.82 (± 0.8)	> 50 ^d	> 8.6
48	27.99 (± 5.2)	6.75 (± 1.4)	0.2	3.20 (± 0.1)	30.30 (± 1.0)	9.5
49	20.98 (± 2.7)	9.29 (± 0.6)	0.4	> 10 ^d	58.29 (± 2.9)	< 5.8
50	> 50 ^d	11.00 (± 1.0)	< 0.2	4.34 (± 0.7)	19.03 (± 3.0)	4.4
51	> 25 ^d	5.22 (± 0.7)	< 0.2	5.03 (± 0.3)	> 50 ^d	> 9.9

Doxorubicin^e	-	0.01	-	-	0.02	-
Amphotericine B^f	0.15	6.91	47.1			
Pentamidine^f	5.52	0.56	0.1			
Chloroquine^g				0.50	30	60
Doxycycline^g				5.00	20	4

^a The values are means $\pm$ SD of three independent experiments.

^b Selectivity Index was calculated according to the formula : $SI = (J774A.1 \text{ CC}_{50}) / (L. \text{ donovani } IC_{50})$.

^c Selectivity Index was calculated according to the formula : $SI = (\text{HepG2 } CC_{50}) / (K1 \text{ } IC_{50})$.

^d Determination of the IC_{50} or CC_{50} value was limited by lack of solubility in the culture medium.

^e Doxorubicin was used as a cytotoxic drug compound of reference.

^f Amphotericin B and pentamidine were used as antileishmanial drug compounds of reference.

^g Chloroquine and doxycycline were used as antiplasmodial drug compounds of reference.

Figure caption:

Figure 1. 4-(5-benzyl-3-(4-fluorophenylsulfonyl)-5-methyl-4,5-dihydrofuran-2-yl)-*N'*-hydroxy benzimidamide.

Figure 2. Pharmacomodulations carried out on the dihydrofuran scaffold.

Figures:

Figure 1.

Figure 2.

Schemes:

Scheme 1. monoamidoxime derivatives synthetic pathway.

Reagents and conditions: (i) NaHCO_3 , Na_2SO_3 , H_2O -ethanol (9:1), MW, 100 °C, 200 W, 1 h. (ii) $t\text{BuOK}$, ether, 45 °C, atm Ar, 13 h. (iii) $\text{Mn}(\text{OAc})_3$, $\text{Cu}(\text{OAc})_2$, AcOH, 80 °C, 200 W, 80 min. (iv) MW, 140 °C, Ar, 1.5 h, $\text{Pd}(\text{PPh}_3)_4$, K_2CO_3 , toluene-ethanol (9:1). (v) $t\text{BuOK}$, $\text{NH}_2\text{OH}\cdot\text{HCl}$, 0 °C RT, DMSO, 18 h, Ar.

Highlights:

- Synthesis of amidoxime derivatives with valuable antiparasitic activities
- Radical synthesis of monoamidoxime derivatives mediated by manganese(III) acetate
- Pharmacomodulations carried out through Suzuki-Miyaura cross-coupling reactions
- Cytotoxicity evaluated on mouse J774A.1 macrophages and human HepG2
- Activity tested on *Leishmania donovani* promastigotes (strain MHOM/IN/00/DEVI)

Microwave-assisted synthesis of β -ketosulfones

Compound	R ¹	Yield (%) ^a
1	<i>o</i> -fluoro-C ₆ H ₅ -	48
2	<i>m</i> -fluoro-C ₆ H ₅ -	70
3	<i>o</i> -(CF ₃)-C ₆ H ₅ -	71
4	<i>m</i> -(CF ₃)-C ₆ H ₅ -	85
5	<i>o,o</i> -difluoro-C ₆ H ₅ -	74
6	<i>o,p</i> -difluoro-C ₆ H ₅ -	72
7	<i>p</i> -fluoro-C ₆ H ₅ -	82

^a Yield of isolated product based on the corresponding acetophenone.

Synthesis of alkenes

Compound	R ²	R ³	Yield (%) ^a
8	Ph-	Ph-	81
9	Ph-	<i>p</i> -(OMe)-C ₆ H ₅ -	60
10	CH ₃ CH ₂ -	<i>o</i> -(OMe)-C ₆ H ₅ -	92
11	CH ₃ -	<i>p</i> -bromo-C ₆ H ₅ -	100

^a Yield of isolated product based on the corresponding ketone.

COMPOUND 7 ^1H NMR CDCl_3

COMPOUND 7 ^{13}C NMR CDCl_3

COMPOUND 22 ^1H NMR CDCl_3

COMPOUND 22 ¹³C NMR CDCl₃

COMPOUND 41 ¹³C NMR DMSO