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Graphical abstract

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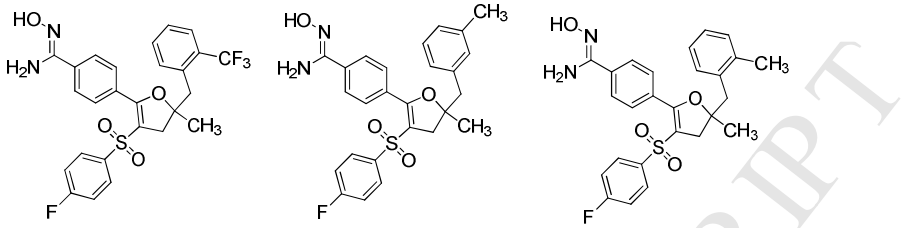

52
IC_{50} *Ldp* = **4.8** µM
IC_{50} *Lda* = **10.2** µM

59
IC_{50} *Ldp* = **5.6** µM
IC_{50} *Lda* = **6.7** µM

60
IC_{50} *Ldp* = **2.1** µM
IC_{50} *Lda* = **7.2** µM

Ldp = Leishmania amazonensis promastigotes
Lda = Leishmania amazonensis amastigotes

Original antileishmanial hits: variations around amidoximes.

Clémence Tabélé,[a] Viviane dos S. Faiões,[b] Fabien Grimaud,[a] Eduardo Caio Torres-Santos,[b] Omar Khoumeri,[a] Christophe Curti,[a,*] Patrice Vanelle.[a,*]

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A B S T R A C T

In continuation to our previous findings on amidoximes' antiparasitic activities, a new series of 23 original derivatives was designed and obtained by convergent synthesis. First, new terminal alkenes were synthesized by cross-coupling reaction. Then, cyclization was performed between terminal alkenes and β-ketosulfones using manganese(III) acetate reactivity. Twenty-three amidoximes were tested for their *in vitro* activity against *Leishmania amazonensis* promastigotes and their toxicity on murine macrophages. Seven of the tested compounds exhibited an antileishmanial activity at lower than 10 µM with moderate to low toxicity. Six of these molecules showed activity at lower than 10 µM against promastigotes and toxicity at higher than 50 µM were selected and evaluated for their activity against intracellular *Leishmania amazonensis* amastigotes. Modulating chemical substituents in position 2 of dihydrofuran highly influenced their antileishmanial activities. The introduction of a methyl or trifluoromethyl group on the benzene ring of the benzyl group had a positive influence on activity without significantly increasing toxicity (**52, 59, 60**).

Highlights:

- Synthesis of amidoxime derivatives with valuable antileishmanial activities
- Radical synthesis of monoamidoxime derivatives mediated by manganese(III) acetate
- Cytotoxicity evaluated on murine macrophages
- Activity tested on *Leishmania amazonensis* promastigotes (strain MHOM/BR/77/LTB0016)
- Activity tested on *Leishmania amazonensis* amastigotes

Keywords:
Amidoximes
Dihydrofuran
Manganese(III) acetate
Pharmacomodulation
Cytotoxicity *in vitro*
Antiprotozoan activity *in vitro*

1. Introduction

Despite the existence of several active therapeutics,[1-2] leishmaniasis remains a neglected disease and a major public health problem[3] worldwide, with 98 countries reporting endemic leishmaniasis transmission.[4] Discovery of effective antileishmanial treatments is therefore a challenge in the fight against this neglected parasitosis.

As part of our focus on the synthesis of molecules with potential antiinfectious properties,[5-8] our laboratory extensively studied the radical synthesis of amidoxime derivatives mediated by manganese(III) acetate. $Mn(OAc)_3$ is able to realize a radical oxidative cyclization on various substrates, such as β-diketones,[9] β-ketoesters,[10] β-ketoamides[11] or β-ketophosphonates.[12]

The reaction between β-ketosulfones and terminal alkenes allowed us to synthesize more than 50 mono- and diamidoximes, some of them showed valuable antiparasitic activities.[13-15]

2,3-Dihydrofuran derivatives substituted both with a phenylamidoxime in position 5 and a 4-fluorophenylsulfonyl in position 4 displayed the best activities coupled with moderate to low toxicity. Moreover, the substitution by a methylene in position 2 was shown to have an influence on the antileishmanial activity.[15] Accordingly, we decided to explore the influence of substituents in position 2 on antileishmanial activity. The retrosynthetic approach yielding such derivatives is depicted in Figure 1.

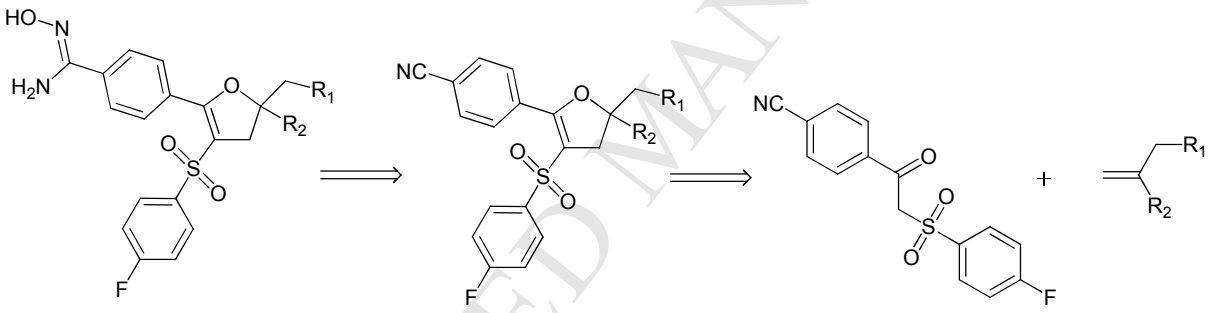


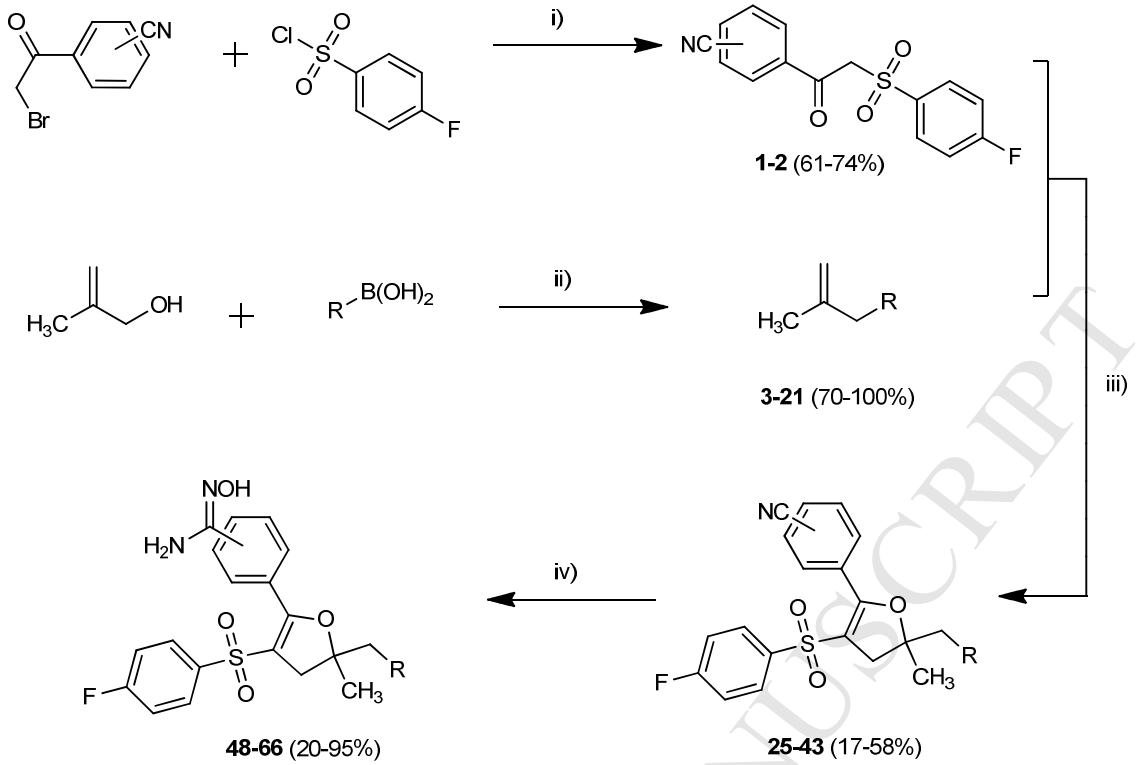
Figure 1: Retrosynthetic pathway to antileishmanial amidoximes

The antileishmanial activities of the monoamidoxime derivatives (**45-67**) were thereby evaluated against *Leishmania amazonensis* promastigotes, as well as their cytotoxicity against peritoneal murine macrophages. The most promising compounds were selected and evaluated for their activities against *Leishmania amazonensis* amastigotes.

2. Results and discussion

2.1 Chemistry

Monoamidoxime derivatives (**48-66**) were obtained by a convergent synthesis as illustrated in Figure 2.

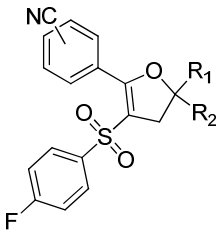


Reagents and conditions: (i) $NaHCO_3$, Na_2SO_3, H_2O, MW, 100 °C, 200 W, 1 h. (ii) Cs_2CO_3 (2 equiv.), $Pd(OAc)_2$ (0.5 mol%), Xantphos (2 mol%), MW, 120-140 °C, 200 W, 1.5-2 h, air (iii) $Mn(OAc)_3$ (2.1 equiv.), $Cu(OAc)_2$ (1 equiv.), AcOH, MW, 80 °C, 200 W, 80 min. (iv) *t*BuOK (10 equiv.), $NH_2OH.HCl$ (10 equiv.), 0 °C RT, DMSO, 18 h, Ar.

Figure 2: Synthetic pathway of monoamidoximes 48-66.

Previously reported methods were used to synthesize the starting material. Thus, β-ketosulfones **(1-2)** were obtained through a nucleophilic substitution of the bromine atom of the corresponding bromoacetophenone by a 4-fluorophenylsulfonyl group of an extemporaneously synthesized sodium 4-fluorophenylsulfonate under microwave irradiation.[16] Terminal alkenes **(3-21)**, as they were not commercially available, were obtained by a pallado-catalyzed reaction between a boronic acid and methylallyl alcohol.[17-18]

β-Ketosulfones and terminal alkenes thus obtained were reacted under microwave irradiation through an oxidative free-radical cyclization mediated by manganese(III) acetate, yielding the dihydrofuran moiety. This reaction has been extensively studied by our team,[19-20] and largely depends on the degree of substitution of the alkene used. In the present study, all alkenes are disubstituted and as expected, the desired 2,3-dihydrofuran derivatives (**22-44**) were obtained in moderate to good yields (Figure 3, Table 1). 2,3-Dihydrofuran derivatives (**22-24, 44**) were directly obtained from commercial alkenes.



22–44

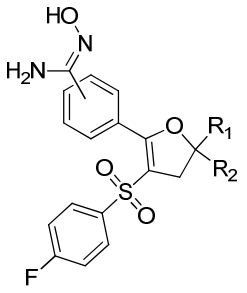
Figure 3: Nitrile derivatives.

Table 1: $Mn(OAc)_3$ assisted oxidative cyclizations

Compound	Nitrile	R_1	R_2	Yield (%)[a]
22	*para*	-Bz	$-CH_3$	61
23	*para*	$-C_2H_5$	$-C_2H_5$	64
24	*para*	$-C_5H_{10}-$		69
25	*para*	-*p*-CN-Bz	$-CH_3$	52
26	*para*	-*m*-CN-Bz	$-CH_3$	17
27	*para*	-*p*-CF_3-Bz	$-CH_3$	65
28	*para*	-*m*-CF_3-Bz	$-CH_3$	50
29	*para*	-*o*-CF_3-Bz	$-CH_3$	62
30	*para*	-3,5-CF_3-Bz	$-CH_3$	32
31	*para*	-*p*-NO_2-Bz	$-CH_3$	46
32	*para*	-*m*-NO_2-Bz	$-CH_3$	36
33	*para*	-*p*-OCH_3-Bz	$-CH_3$	26
34	*para*	-*3,4,5*-OCH_3-Bz	$-CH_3$	34
35	*para*	-*p*-CH_3-Bz	$-CH_3$	58
36	*para*	-*m*-CH_3-Bz	$-CH_3$	17
37	*para*	-*o*-CH_3-Bz	$-CH_3$	55
38	*para*	-*p*-CH_2OH-Bz	$-CH_3$	45
39	*para*	-*m*-CH_2OH-Bz	$-CH_3$	48
40	*para*	(1,1'-biphenyl-4-yl)methyl	$-CH_3$	52
41	*para*	(2-fluoro-1,1'-biphenyl-4-yl)methyl	$-CH_3$	37
42	*para*	3-(4-(trifluoromethyl)phenyl)allyl	$-CH_3$	26
43	*para*	-*o*-Br-Bz	$-CH_3$	29
44	*meta*	-Bz	$-CH_3$	29

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

Cyano derivatives synthesized by manganese(III) acetate-mediated reactions (**22-44**) reacted with hydroxylamine hydrochloride and potassium *tert*-butoxide in DMSO,[21] providing amidoximes **45-67** (Figure 4) in moderate to excellent yields (20-95%) as shown in Table 2.



45-67

Figure 4: Monoamidoxime derivatives.

Table 2: Synthesis and structure of amidoxime derivatives

Compound	amidoxime	R_1	R_2	Yield (%)[a]
45	*para*	-Bz	$-CH_3$	85
46	*para*	$-C_2H_5$	$-C_2H_5$	63
47	*para*	$-C_5H_{10}-$		48
48	*para*	-*p*-$CNOHNH_2$-Bz	$-CH_3$	64
49	*para*	-*m*-$CNOHNH_2$-Bz	$-CH_3$	87
50	*para*	-*p*-CF_3-Bz	$-CH_3$	56
51	*para*	-*m*-CF_3-Bz	$-CH_3$	48
52	*para*	-*o*-CF_3-Bz	$-CH_3$	40
53	*para*	-3,5-CF_3-Bz	$-CH_3$	78
54	*para*	-*p*-NO_2-Bz	$-CH_3$	72
55	*para*	-*m*-NO_2-Bz	$-CH_3$	61
56	*para*	-*p*-OCH_3-Bz	$-CH_3$	41
57	*para*	-*3,4,5*-OCH_3-Bz	$-CH_3$	50
58	*para*	-*p*-CH_3-Bz	$-CH_3$	76
59	*para*	-*m*-CH_3-Bz	$-CH_3$	69
60	*para*	-*o*-CH_3-Bz	$-CH_3$	50
61	*para*	-*p*-CH_2OH-Bz	$-CH_3$	53
62	*para*	-*m*-CH_2OH-Bz	$-CH_3$	57
63	*para*	(1,1'-biphenyl-4-yl)methyl	$-CH_3$	74
64	*para*	(2-fluoro-1,1'-biphenyl-4-yl)methyl	$-CH_3$	95
65	*para*	3-(4-(trifluoromethyl)phenyl)allyl	$-CH_3$	85
66	*para*	-*o*-Br-Bz	$-CH_3$	20
67	*meta*	-Bz	$-CH_3$	83

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

2.2 Biology

All amidoxime synthesized (**45-67**) were evaluated for both their antileishmanial activity against *Leishmania amazonensis* promastigotes and their cytotoxicity against murine macrophages. Amidoxime **45** was previously tested and showed good activity against *Leishmania donovani* promastigotes.[14] This molecule, which bears no substituent on its benzyl moiety, was used as a reference to evaluate the effect of substitution, on the phenyl ring of the benzyl group by a variety of substituents, on the antileishmanial activity. Inhibitory concentrations 50% (IC_{50}) and cytotoxic concentrations 50 (CC_{50}) were determined, as well as their selectivity indexes (SI). For each assay, three independent experiments in triplicate were performed. Results are summarized in Table 3.

Table 3: Biological evaluation of amidoxime 45-67 against Leishmania amazonensis promastigotes

Compound	Amido--xime	R_1	R_2	Activity *L. amazonensis* promastigotes IC_{50} (µM)[a]	Cytotoxicity murine macrophages CC_{50} (µM)[a]	Selectivity Index[b]
45	*para*	-Bz	$-CH_3$	5.4 ± 1.0	102 ± 2.8	18.9
46	*para*	$-C_2H_5$	$-C_2H_5$	30.2 ± 2.3	91.4 ± 0.8	3.0
47	*para*	$-C_5H_{10}-$		49.5 ± 1.2	92.9 ± 3.4	1.9
48	*para*	-*p*-$CNOHNH_2$-Bz	$-CH_3$	> 100[c]	42.2 ± 1.4	ND[e]
49	*para*	-*m*-$CNOHNH_2$-Bz	$-CH_3$	> 100 [c]	50.2 ± 1.7	ND[e]
50	*para*	-*p*-CF_3-Bz	$-CH_3$	8.2 ± 0.6	103.2 ± 13.6	12.6
51	*para*	-*m*-CF_3-Bz	$-CH_3$	6.7 ± 0.2	49.8 ± 0.7	7.4
52	*para*	-*o*-CF_3-Bz	$-CH_3$	4.8 ± 0.2	104.9 ± 3.9	21.9
53	*para*	-3,5-CF_3-Bz	$-CH_3$	5.4 ± 0.9	43.1 ± 0.8	8.0
54	*para*	-*p*-NO_2-Bz	$-CH_3$	16.7 ± 1.2	97.4 ± 1.2	5.8
55	*para*	-*m*-NO_2-Bz	$-CH_3$	11.6 ± 1.3	86.6 ± 2.3	7.5
56	*para*	-*p*-OCH_3-Bz	$-CH_3$	24.0 ± 0.3	> 100[c]	> 4.2
57	*para*	-*3,4,5*-OCH_3-Bz	$-CH_3$	45.6 ± 2.2	92.3 ± 2.4	2.0
58	*para*	-*p*-CH_3-Bz	$-CH_3$	23.2 ± 1.1	54.4 ± 2.4	2.3
59	*para*	-*m*-CH_3-Bz	$-CH_3$	5.6 ± 0.9	111.5 ± 7.3	19.9
60	*para*	-*o*-CH_3-Bz	$-CH_3$	2.1 ± 0.4	77.6 ± 6.2	37.0
61	*para*	-*p*-CH_2OH-Bz	$-CH_3$	> 100[c]	> 100[c]	ND[e]
62	*para*	-*m*-CH_2OH-Bz	$-CH_3$	> 100[c]	> 100[c]	ND[e]
63	*para*	(1,1'-biphenyl-4-yl)methyl	$-CH_3$	14.8 ± 0.3	33.9 ± 0.9	2.3
64	*para*	(2-fluoro-1,1'-biphenyl-4-yl)methyl	$-CH_3$	12.2 ± 1.1	24.5 ± 0.6	2.0
65	*para*	3-(4-(trifluoromethyl)phenyl)allyl	$-CH_3$	17.2 ± 0.5	43.9 ± 0.6	2.6
66	*para*	-*o*-Br-Bz	$-CH_3$	9.1 ± 1.4	109.1 ± 1.6	12.0
67	*meta*	-Bz	$-CH_3$	74.7 ± 3.6	> 200[c]	> 2.7
Pentamidine[d]				5.7 ± 0.12	8.5 ± 1.25	1.5

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

[b] Selectivity Index was calculated according to the formula : SI = (Murine macrophages CC_{50}) / (*L. amazonensis* IC_{50}).

[c] Determination of the IC_{50} or CC_{50} value was limited by lack of solubility in the culture medium.

[d] Pentamidine was used as antileishmanial drug compound of reference.

[e] ND = not determinable.

Antileishmanial evaluation against promastigotes revealed that five amidoximes (**45, 52, 53, 59, 60**) showed higher activity than that of the reference drug pentamidine. The good activity of amidoxime **45** against *Leishmania amazonensis* was also found against *Leishmania donovani*, suggests that monoamidoximes' antileishmanial activities are not limited to one *Leishmania* species alone. Cytotoxicity of all tested derivatives against murine macrophages remained low in comparison with that of pentamidine itself. The selectivity indexes of 21 of the tested amidoximes are higher than pentamidine selectivity indexes. Moderate to low cytotoxicities were also previously described[13-15] with other monoamidoxime derivatives against HepG2, J774A.1 and THP1 cells, making these molecules strong candidates for further biological evaluations.

On the other hand, the influence of the substitution of the benzyl group was clearly demonstrated. A dramatic decrease in the antileishmanial activity was observed upon replacement of the benzyl group

by an aliphatic (**46**) or alicyclic (**47**) residue. It was noticed also that the introduction of a nitro (**54**, **55**), a bromo (**66**) or one or more methoxyl groups (**56**, **57**) in the benzene ring of the benzyl group results in lowering the activity against *Leishmania amazonensis* promastigotes. Moreover, the presence of a second amidoxime (**48, 49**) or of a hydroxymethyl substituent in the molecule (**61**, **62**) led to a decrease of its antileishmanial activity. Increasing the length of the substituent in position 2 with a biphenyl (**63**, **64**) or an allyl (**65**) decreased antileishmanial activities and increased cytotoxicities.

Derivatives in which the benzyl group bears a methyl (**58-60**) or a trifluoromethyl (**50-53**) substituent showed the best antileishmanial activities. *Ortho*-substituted derivatives (**52**, **60**) showed better activities than pentamidine and reference monoamidoxime **45**, clearly indicating the importance of this position. Antileishmanial activities decreased with *meta*-substituted derivatives (**51, 59**) and even further with *para*-substituted derivatives (**50**, **58**).

The 6 molecules displaying an activity against *Leishmania amazonensis* promastigotes at lower than 10 µM and toxicity on murine macrophage at higher than 50 µM were selected as good candidates for evaluation against intracellular *Leishmania amazonensis* amastigotes. These molecules are depicted in Figure 5 and results are summarized in Table 4.

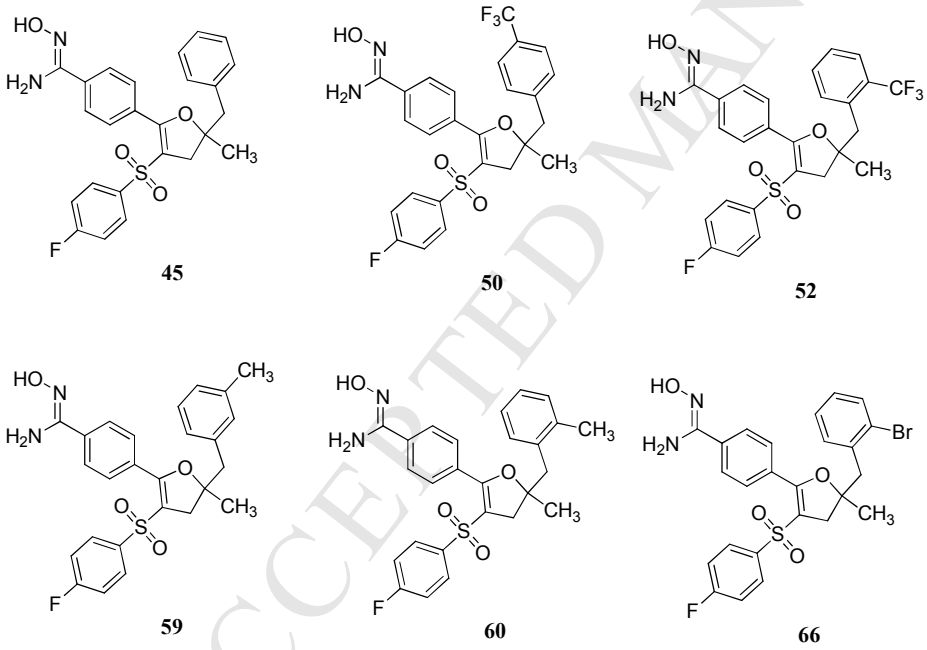


Figure 5: Hit amidoximes

Table 4: Biological evaluation of selected amidoxime derivatives against *Leishmania amazonensis* amastigotes

Compound	Activity *L. amazonensis* promastigotes IC_{50} (µM)[a]	Activity *L. amazonensis* amastigotes IC_{50} (µM)[a]	Cytotoxicity murine macrophages CC_{50} (µM)[a]	Selectivity Index[b]
45	5.4 ± 1.0	7.9 ± 1.1	102 ± 2.8	12.9
50	8.2 ± 0.6	> 20	103.2 ± 13.6	ND[d]
52	4.8 ± 0.2	10.2 ± 1.1	104.9 ± 3.9	10.3
59	5.6 ± 0.9	6.7 ± 1.2	111.5 ± 7.3	16.6
60	2.1 ± 0.4	7.2 ± 1.2	77.6 ± 6.2	10.8
66	9.1 ± 1.4	9.3 ± 1.2	109.1 ± 1.6	11.7
Pentamidine[c]	5.7 ± 0.12	1.9 ± 0.12	8.5 ± 1.25	4.5

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

[b] Selectivity Index was calculated according to the formula : SI = (Murine macrophages CC_{50}) / (*L. amazonensis amastigotes* IC_{50}).

[c] Pentamidine was used as antileishmanial drug compound of reference.

[d] ND = not determinable.

Antileishmanial activities for five of the six tested molecules were confirmed against *Leishmania amazonensis* amastigotes. All Selectivity Indexes were higher than 10. Amidoxime **59** exhibited the best activity (6.7 µM) and the lowest toxicity (111.5 µM). Moreover, it had a selectivity index as high as 16.6, almost fourfold better than that of pentamidine itself. Therefore, we selected this molecule as an excellent drug candidate for further biological evaluation.

3. Conclusion

Twenty-three amidoximes were synthesized and evaluated for their antileishmanial activities. Our findings confirm the antiprotozoan potential of these derivatives, as previously described against *Leishmania donovani*, *Plasmodium falciparum*, and as described here against *Leishmania amazonensis*. Valuable activities were often coupled with moderate to low toxicities, and 5 hits were identified for their activities against *Leishmania amazonensis* amastigotes. Several structural constraints were found, rationalizing subsequent syntheses. While dihydrofurane monoamidoximes can be considered as new original structures with antiprotozoan properties, the pharmacological mechanism remains unknown. Accordingly, *in vivo* evaluation and a mechanistic study are currently in progress on the five hit amidoximes described in the present study.

4. Experimental

4.1 Chemistry

4.1.1 General

TLC were performed on 5 cm × 10 cm aluminium plates coated with silica gel (layer 0.2 mm) $60F_{254}$ (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. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ or DMSO, with tetramethylsilane (Me_4Si) as an internal reference using a Bruker ARX 200 spectrometer operating at 250 MHz for ^{1}H-NMR and 63 MHz for ^{13}C-NMR; spectra were carried out at the NMR InterUniversity Unit of Pharmacy College, Aix-Marseille University. The ^{1}H chemical shifts are quoted in parts per million as δ downfield from tetramethylsilane (δ 0.00) as an internal standard and the ^{13}C chemical shifts were referenced to the solvent peaks: $CDCl_3$ (76.9 ppm) or DMSO-*d6* (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). Elemental analysis and mass spectra, run on an API-QqToF mass spectrometer, were carried out at the Spectropole Unit of Saint Jerome Sciences College, Aix-Marseille University. All commercial reagents were used without purification.

4.1.2 General procedure for preparation of β-Ketosulfones (1-2)

Sodium sulfite (1.26 g, 10 mmol) and sodium bicarbonate (0.84 g, 10 mmol) were added to a solution of *p*-fluorobenzenesulfonyl chloride (1.17 g, 6.00 mmol) in water (15 mL). The reaction mixture was heated under reflux in a microwave oven under irradiation (500 W, 100 °C) for 15 min. Then, an ethanolic solution of 4-(2-bromoacetyl)benzonitrile or 3-(2-bromoacetyl)benzonitrile (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-(4-fluorophenylsulfonyl)acetyl)benzonitrile (1)[14] White powder, yield 82 %, m.p. 162 °C isopropyl alcohol). δ ^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.74 (s, 2H, CH_2), 7.21-7.30 (m, 2H, 2CH), 7.82 (d, *J* = 8.4 Hz, 2H, 2CH), 7.88-7.94 (m, 2H, 2CH), 8.08 (d, *J* = 8.4 Hz, 2H, 2CH). ^{13}C NMR ($CDCl_3$), d: 63.7 (CH_2), 116.8 (d, *J* = 22.7 Hz, 2CH), 117.5 (C), 117.7 (C), 129.7 (2CH), 131.6 (d, *J* = 9.9 Hz, 2CH), 132.7 (2CH), 134.2 (d, *J* = 3.3 Hz, C), 138.3 (C), 166.3 (d, *J* = 258.3 Hz, C), 187.0 (C).

4.1.2.2. 3-(2-((4-Fluorophenyl)sulfonyl)acetyl)benzonitrile (2) Yellow solid, yield 74%, m.p. 136 °C (isopropyl alcohol). δ ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.9 Hz, 2H), 7.96 – 7.82 (m, 3H), 7.65 (t, *J* = 7.7 Hz, H), 7.24 (dd, *J* = 9.4, 7.6 Hz, 2H), 4.74 (s, 2H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 186.5 (C), 166.4 (d, *J* = 258.7 Hz, C), 137.2 (CH), 136.4 (C), 134.4 (d, *J* = 3.2 Hz, C), 133.1 (d, *J* = 23.3 Hz, 2CH), 131.8 (CH), 131.6 (CH), 130.1 (CH), 117.5 (C), 116.9 (d, *J* = 22.8 Hz, 2CH), 113.8 (C), 63.6 (CH_2). HRMS (ESI +) m/z calcd for $C_{15}H_{10}FNO_3S$ $[M+NH_4]^+$: 321.0704 Found: 321.0705.

4.1.3 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.) and copper(II) acetate (3.27 mmol, 0.59 g, 1 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 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 × 40 mL). The organic extracts were collected and washed with saturated aqueous $NaHCO_3$ (3 × 40 mL) and dried ($MgSO_4$). Solvent was evaporated under reduced pressure and crude product was purified by column chromatography with an appropriate solvent; the product obtained was recrystallized from the appropriate solvent.

4.1.3.1. 4-(5,5-Diethyl-3-((4-fluorophenyl)sulfonyl)-4,5-dihydrofuran-2-yl)benzonitrile (23) Yellow oil, yield 64%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.82 – 7.64 (m, 6H), 7.15 (d, *J* = 8.6 Hz, 2H), 2.82 (s, 2H), 1.68 (q, *J* = 7.4 Hz, 2H), 1.66 (q, *J* = 7.4 Hz, 2H), 0.84 (t, *J* = 7.4 Hz, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.3 (d, *J* = 255.8 Hz, C), 161.1 (C), 137.5 (d, *J* = 3.2 Hz, C), 133.2 (C), 131.6 (2CH), 130.3 (2CH), 129.7 (d, *J* = 9.4 Hz, 2CH), 118.2 (C), 116.4 (d, *J* = 22.6 Hz, 2CH), 114.4 (C), 111.4 (C), 92.3 (C), 39.7 (CH_2), 31.7 ($2CH_2$), 7.5 ($2CH_3$). Anal. calcd for $C_{21}H_{20}FNO_3S$ (385.1148): C, 65.44; H, 5.23; N, 3.63; S, 8.32. Found: C, 65.32; H, 5.11; N, 3.26; S, 7.98.

4.1.3.2. 4-(3-((4-Fluorophenyl)sulfonyl)-1-oxaspiro[4.5]dec-2-en-2-yl)benzonitrile (24) Colorless oil, yield 69%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.74 (m, 6H), 7.15 (d, *J* = 8.3 Hz, 2H), 2.82 (s, 2H), 2.03 – 1.07 (m, 10H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.3 (d, *J* = 255.8 Hz, C), 160.5 (C), 137.5 (d, *J* = 3.1 Hz, C), 133.3 (C), 131.5 (2CH), 130.3 (2CH), 129.6 (d, *J* = 9.4 Hz, 2CH), 118.2 (C), 116.5 (d, *J* = 22.6 Hz, 2CH), 114.3 (C), 111.3 (C), 89.3 (C), 42.9 (CH_2), 36.7 ($2CH_2$), 24.6 (CH_2), 22.5 ($2CH_2$). Anal. calcd for $C_{22}H_{20}FNO_3S$ (397.1148): C, 66.48; H, 5.07; N, 3.52; S, 8.07. Found: C, 66.26; H, 4.78; N, 3.24; S, 7.86.

4.1.3.3. 4-(5-(4-Cyanobenzyl)-3-((4-fluorophenyl)sulfonyl)-5-methyl-4,5-dihydrofuran-2-yl)benzonitrile (25) Colorless oil, yield 52%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.6 Hz, 2H), 7.67 (d, *J* = 8.6 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 7.14 (d, *J* = 8.5 Hz, 2H), 3.04 (d, *J* = 13.9 Hz, H), 2.98 (d, *J* = 14.9 Hz, H), 2.96 (d, *J* = 13.9 Hz, H), 2.87 (d, *J* = 14.9 Hz, H), 1.46 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.4 (d, *J* = 256.6 Hz, C), 160.0 (C), 140.8 (C), 137.1 (d, *J* = 3.1 Hz, C), 132.5 (C), 131.9 (2CH), 131.6 (2CH), 131.0 (2CH), 130.0 (2CH), 129.6 (d, *J* = 9.5 Hz, 2CH), 118.4 (C), 118.0 (C), 116.4 (d, *J* = 22.6 Hz, 2CH), 114.6 (C), 111.9 (C), 111.2 (C), 88.2 (C), 46.4 (CH_2), 42.2 (CH_2), 27.0 (CH_3). Anal. calcd for $C_{26}H_{19}FN_2O_3S$ (458.1100): C, 68.11; H, 4.18; N, 6.11; S, 6.99. Found: C, 68.10; H, 4.03; N, 6.22; S, 7.18.

4.1.3.4. 3-((5-(4-Cyanophenyl)-4-((4-fluorophenyl)sulfonyl)-2-methyl-2,3-dihydrofuran-2-yl)methyl)benzonitrile (26) Colorless oil, yield 17%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.5 Hz, 2H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.55 – 7.47 (m, H), 7.38 (s, H), 7.37 – 7.32 (m, 2H), 7.13 (d, *J* = 8.5 Hz, 2H), 3.02 (d, *J* = 14.1 Hz, H), 2.95 (d, *J* = 14.9 Hz, H), 2.93 (d, *J* = 14.1 Hz, H), 2.87 (d, *J* = 14.9 Hz, H), 1.47 (s, 3H).^{13}C NMR (63 MHz, $CDCl_3$) δ 165.3 (d, *J* = 256.4 Hz, C), 160.1 (C), 137.1 (d, *J* = 3.2 Hz, C), 136.9 (C), 134.6 (CH), 133.6 (CH), 132.5 (C), 131.7 (2CH), 130.8 (CH), 130.0 (2CH), 129.6 (d, *J* = 9.5 Hz, 2CH), 129.1 (CH), 118.3 (C), 118.0 (C), 116.5 (d, *J* = 22.6 Hz, 2CH), 114.6 (C), 112.5 (C), 111.9 (C), 88.2 (C), 45.9 (CH_2), 42.0 (CH_2), 27.2 (CH_3). Anal. calcd for $C_{26}H_{19}FN_2O_3S$ (458.1100): C, 68.11; H, 4.18; N, 6.11; S, 6.99. Found: C, 68.10; H, 4.03; N, 6.22; S, 7.18.

4.1.3.5. 4-(3-((4-Fluorophenyl)sulfonyl)-5-methyl-5-(4-(trifluoromethyl)benzyl)-4,5-dihydrofuran-2-yl)benzonitrile (27) Colorless oil, yield 40%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.97 – 7.83 (m, 4H), 7.80 – 7.71 (m, 2H), 7.67 (d, *J* = 7.8 Hz, 2H), 7.42 (d, *J* = 7.6 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H), 3.39 – 3.00 (m, 4H), 1.72 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.3 (d, *J* = 256.4 Hz, C), 160.2 (C), 139.5 (C), 137.0 (d, *J* = 3.2 Hz, C), 132.7 (C), 131.6 (2CH), 130.6 (2CH), 130.0 (2CH), 129.6 (d, *J* = 9.5 Hz, 2CH), 129.4 (q, *J* = 36.1 Hz, C), 125.1 (q, *J* = 3.7 Hz, 2CH), 123.9 (q, *J* = 229.8 Hz, C), 118.1 (C), 116.5 (d, *J* = 22.7 Hz, 2CH), 114.5 (C), 111.7 (C), 88.4 (C), 46.2 (CH_2), 41.9 (CH_2), 27.2 (CH_3). HRMS (ESI +) m/z calcd for $C_{26}H_{19}F_4NO_3S$ [M+H]+: 502.1095. Found: 502.1096.

4.1.3.6. 4-(3-((4-Fluorophenyl)sulfonyl)-5-methyl-5-(3-(trifluoromethyl)benzyl)-4,5-dihydrofuran-2-yl)benzonitrile (28) Yellow oil, yield 50%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.68 (bs, 4H), 7.47 – 7.51 (m, 3H), 7.37 (s, H), 7.34 – 7.24 (m, 2H), 7.05 (d, *J* = 8.5 Hz, 2H), 3.08 (d, *J* = 14.1

Hz, H), 2.94 (d, *J* = 14.9 Hz, H), 2.91 (d, *J* = 14.1 Hz, H), 2.89 (d, *J* = 14.9 Hz, H), 1.51 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.2 (d, *J* = 256.0 Hz, C), 160.2 (C), 137.1 (d, *J* = 3.2 Hz, C), 136.3 (C), 133.5 (CH), 132.6 (C), 131.5 (2CH), 130.5 (q, *J* = 32.2 Hz, C), 130.0 (2CH), 129.4 (d, *J* = 9.5 Hz, 2CH), 128.8 (CH), 127.0 (q, *J* = 3.7 Hz, CH), 123.9 (q, *J* = 3.7 Hz, CH), 123.9 (q, *J* = 272.4 Hz, C), 118.1 (C), 116.3 (d, *J* = 22.7 Hz, 2CH), 114.5 (C), 111.8 (C), 88.3 (C), 46.0 (CH_2), 41.7 (CH_2), 27.4 (CH_3). Anal. calcd for $C_{26}H_{19}F_4NO_3S$ (501.1022): C, 62.27; H, 3.82; N, 2.79; S, 6.39. Found: C, 62.36; H, 3.61; N, 2.66; S, 6.17.

4.1.3.7. 4-(3-((4-Fluorophenyl)sulfonyl)-5-methyl-5-(2-(trifluoromethyl)benzyl)-4,5-dihydrofuran-2-yl)benzonitrile (29) Yellow oil, yield 62%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.7 Hz, 2H), 7.72 (d, *J* = 8.7, 2H), 7.60 – 7.54 (m, 3H), 7.40 - 7.38 (m, 2H), 7.13 – 7.06 (m, 3H), 3.28 – 3.15 (m, 2H), 2.90 (d, *J* = 15.0 Hz, H), 2.81 (d, *J* = 15.0 Hz, H),1.45 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.2 (d, *J* = 256.0 Hz, C), 159.7 (C), 137.0 (d, *J* = 3.2 Hz, C), 134.4 (d, *J* = 1.8 Hz, C), 132.8 (C), 132.2 (CH), 131.6 (2CH), 131.5 (CH), 130.1 (2CH), 129.6 (C), 129.5 (d, *J* = 9.2 Hz, 2CH), 127.2 (CH), 126.1 (q, *J* = 5.5 Hz, CH), 124.2 (q, *J* = 274.4 Hz, C), 118.1 (C), 116.3 (d, *J* = 23.0 Hz, 2CH), 114.5 (C), 112.0 (C), 89.0 (C), 42.3 (CH_2), 41.5 (CH_2), 27.2 (CH_3). HRMS (ESI +) m/z calcd for $C_{26}H_{19}F_4NO_3S$ [M+H]+: 502.1095. Found: 502.1092.

4.1.3.8. 4-(5-(3,5-Bis(trifluoromethyl)benzyl)-3-((4-fluorophenyl)sulfonyl)-5-methyl-4,5-dihydrofuran-2-yl)benzonitrile (30) Colorless oil, yield 32%.^{1}H NMR (250 MHz, $CDCl_3$) δ 7.74 (s, H), 7.71 (bs, 4H), 7.58 (s, 2H), 7.53 (d, *J* = 8.9 Hz, H), 7.52 (d, *J* = 8.8 Hz, H), 7.06 (d, *J* = 8.5 Hz, 2H), 3.15 (d, *J* = 14.2 Hz, H), 3.02 (d, *J* = 14.2 Hz, H), 2.94 (d, *J* = 15.0 Hz, H), 2.86 (d, *J* = 15.0 Hz, H), 1.52 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.3 (d, *J* = 256.6 Hz, C), 159.9 (C), 138.0 (C), 136.9 (d, *J* = 3.2 Hz, C), 132.3 (C), 131.6 (2CH), 131.6 (q, *J* = 33.3 Hz, 2C), 130.3 (q, *J* = 2.6 Hz, 2CH), 130.0 (2CH), 129.4 (d, *J* = 9.5 Hz, 2CH), 123.0 (q, *J* = 272.8 Hz, 2C), 121.1 (q, *J* = 3.7 Hz, CH), 118.0 (C), 116.4 (d, *J* = 22.7 Hz, 2CH), 114.7 (C), 112.1 (C), 87.7 (C), 45.7 (CH_2), 42.0 (CH_2), 27.2 (CH_3).

4.1.3.9. 4-(3-((4-Fluorophenyl)sulfonyl)-5-methyl-5-(4-nitrobenzyl)-4,5-dihydrofuran-2-yl)benzonitrile (31) Orange oil, yield 46%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.7 Hz, 2H), 7.71 (d, *J* = 8.6 Hz, 2H), 7.68 (d, *J* = 8.7 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, H), 7.57 (d, *J* = 8.8 Hz, H), 7.26 (d, *J* = 8.6 Hz, 2H), 7.10 (d, *J* = 8.5 Hz, 2H), 3.09 (d, *J* = 13.9 Hz, H), 3.02 (d, *J* = 13.9 Hz, H), 3.00 (d, *J* = 14.9 Hz, H), 2.90 (d, *J* = 14.9 Hz, H), 1.48 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.4 (d, *J* = 256.7 Hz, C), 160.0 (C), 147.1 (C), 143.0 (C), 137.0 (d, *J* = 3.2 Hz, C), 132.5 (C), 131.7 (2CH), 131.1 (2CH), 130.0 (2CH), 129.7 (d, *J* = 9.5 Hz, 2CH), 123.4 (2CH), 118.0 (C), 116.5 (d, *J* = 22.6 Hz, 2CH), 114.7 (C), 112.0 (C), 88.2 (C), 46.2 (CH_2), 42.2 (CH_2), 27.1 (CH_3). Anal. calcd for $C_{25}H_{19}FN_2O_5S$ (478.0999): C, 62.75; H, 4.00; N, 5.85; S, 6.70. Found: C, 62.49; H, 3.78; N, 5.79; S, 6.52.

4.1.3.10. 4-(3-((4-Fluorophenyl)sulfonyl)-5-methyl-5-(3-nitrobenzyl)-4,5-dihydrofuran-2-yl)benzonitrile (32) Orange oil, yield 36%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.0 Hz, H), 7.98 (s, H), 7.69 (bs, 4H), 7.53 (d, *J* = 8.9 Hz, H), 7.51 (d, *J* = 8.9 Hz, H), 7.43 (d, *J* = 7.6 Hz, H), 7.37 (d, *J* = 7.7 Hz, H), 7.06 (d, *J* = 8.5 Hz, 2H), 3.11 (d, *J* = 14.1 Hz, H), 2.99 (d, *J* = 14.1 Hz, H), 2.92 (s, 2H), 1.51 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.3 (d, *J* = 256.3 Hz, C), 160.1 (C), 148.2 (C), 137.4 (C), 137.0 (d, *J* = 3.1 Hz, C), 136.4 (CH), 132.5 (C), 131.6 (2CH), 130.1 (2CH), 129.55 (d, *J* = 9.5 Hz, 2CH), 129.3 (CH), 124.9 (CH), 122.1 (CH), 118.0 (C), 116.4 (d, *J* = 22.6 Hz, 2CH), 114.5 (C), 111.5 (C), 88.2 (C), 45.8 (CH_2), 41.9 (CH_2), 27.2 (CH_3). Anal. calcd for $C_{25}H_{19}FN_2O_5S$ (478.0999): C, 62.75; H, 4.00; N, 5.85; S, 6.70. Found: C, 62.86; H, 3.78; N, 5.63; S, 6.26.

4.1.3.11. 4-(3-((4-Fluorophenyl)sulfonyl)-5-(4-methoxybenzyl)-5-methyl-4,5-dihydrofuran-2-yl)benzonitrile (33) Green oil, yield 26%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.69 (m, 4H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.06 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.5 Hz, 2H), 6.73 (d, *J* = 8.6 Hz, 2H), 3.79 (s, 3H), 2.92 (d, *J* = 14.8 Hz, H), 2.97 (d, *J* = 14.1 Hz, H), 2.85 (d, *J* = 14.8 Hz, H), 2.76 (d, *J* = 14.1 Hz, H), 1.50 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.1 (d, *J* = 255.4 Hz, C), 160.4 (C), 158.7 (C), 137.3 (d, *J* = 3.1 Hz, C), 133.0 (C), 131.5 (2CH), 131.2 (2CH), 130.8 (2CH), 129.4 (d, *J* = 9.5 Hz, 2CH), 127.3 (C), 118.1 (C), 116.2 (d, *J* = 22.7 Hz, 2CH), 114.4 (C), 113.6 (2CH), 111.5 (C), 89.2 (C), 55.1 (CH_3), 45.5 (CH_2), 41.4 (CH_2), 27.4 (CH_3). Anal. calcd for $C_{26}H_{22}FNO_4S$ (463.1254): C, 67.37; H, 4.78; N, 3.02. Found: C, 67.49; H, 4.57; N, 2.73.

4.1.3.12. 4-(3-((4-Fluorophenyl)sulfonyl)-5-methyl-5-(3,4,5-trimethoxybenzyl)-4,5-dihydrofuran-2-yl)benzonitrile (34) Orange oil, yield 34%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.72 – 7.64 (m, 4H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 6.29 (s, 2H), 3.83 (s, 3H), 3.65 (s, 6H), 3.03 (d, *J* = 14.8 Hz, H), 2.98 (d, *J* = 14.1 Hz, H), 2.84 (d, *J* = 14.8 Hz, H), 2.75 (d, *J* = 14.1 Hz, H), 1.52 (s, 3H).^{13}C NMR (63 MHz, $CDCl_3$) δ 165.2 (d, *J* = 256.0 Hz, C), 160.1 (C), 152.9 (2C), 137.2 (C), 137.1 (d, *J* = 3.2 Hz, C), 132.9 (C), 131.5 (2CH), 130.5 (C), 130.0 (2CH), 129.3 (d, *J* = 9.5 Hz, 2CH), 118.0 (C), 116.4 (d, *J* = 22.7 Hz, 2CH), 114.4 (C), 111.6 (C), 107.3 (2CH), 88.9 (C), 60.8 (CH_3), 55.9 ($2CH_3$), 46.8 (CH_2), 41.7 (CH_2), 27.5 (CH_3). Anal. calcd for $C_{28}H_{26}FNO_6S$ (523.1465): C, 64.23; H, 5.01; N, 2.68; S, 6.12. Found: C, 63.91; H, 4.70; N, 2.60; S, 5.87.

4.1.3.13. 4-(3-((4-Fluorophenyl)sulfonyl)-5-methyl-5-(4-methylbenzyl)-4,5-dihydrofuran-2-yl)benzonitrile (35) Colorless oil, yield 58%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.6 Hz, 2H), 7.90 (d, *J* = 9.0 Hz, 2H), 7.80 (d, *J* = 7.6 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.11 – 7.01 (m, 4H), 3.01 (d, *J* = 14.8 Hz, H), 2.98 (d, *J* = 14.0 Hz, H), 2.83 (d, *J* = 14.8 Hz, H), 2.79 (d, *J* = 14.0 Hz, H), 2.32 (s, 3H), 1.50 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.2 (d, *J* = 255.4 Hz, C), 160.4 (C), 137.3 (d, *J* = 3.2 Hz, C), 136.6 (C), 133.0 (C), 132.2 (C), 131.5 (2CH), 130.1 (2CH), 130.1 (2CH), 129.5 (d, *J* = 9.4 Hz, 2CH), 128.9 (2CH), 118.1 (C), 116.2 (d, *J* = 22.6 Hz, 2CH), 114.3 (C), 111.5 (C), 89.1 (C), 46.0 (CH_2), 41.5 (CH_2), 27.4 (CH_3), 21.0 (CH_3). Anal. calcd for $C_{26}H_{22}FNO_3S$ (447.1304): C, 69.78; H, 4.96; N, 3.13; S, 7.17. Found: C, 69.99; H, 4.98; N, 3.02; S, 7.12.

4.1.3.14. 4-(3-((4-Fluorophenyl)sulfonyl)-5-methyl-5-(3-methylbenzyl)-4,5-dihydrofuran-2-yl)benzonitrile (36) Yellow oil, yield 17%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.90 – 7.75 (m, 4H), 7.69 (d, *J* = 9.0 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.25 – 7.01 (m, 3H), 6.88 (s, H), 3.01 (d, *J* = 14.8 Hz, H), 2.98 (d, *J* = 14.0 Hz, H), 2.83 (d, *J* = 14.8 Hz, H), 2.79 (d, *J* = 14.0 Hz, H), 2.25 (s, 3H), 1.51 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.2 (d, *J* = 255.4 Hz, C), 160.4 (C), 137.3 (d, *J* = 3.2 Hz, C), 136.8 (C), 133.7 (C), 132.2 (C), 131.5 (2CH), 130.1 (2CH), 129.7 (CH), 129.5 (d, *J* = 9.4 Hz, 2CH), 128.2 (CH), 126.8 (CH), 126.0 (CH), 118.1 (C), 116.2 (d, *J* = 22.6 Hz, 2CH), 114.3 (C), 111.8 (C), 89.1 (C), 46.0 (CH_2), 41.5 (CH_2), 22.1 (CH_3), 21.4 (CH_3). Anal. calcd for $C_{26}H_{22}FNO_3S$ (447.1304): C, 69.78; H, 4.96; N, 3.13; S, 7.17. Found: C, 69.99; H, 4.98; N, 3.02; S, 7.12.

4.1.3.15. 4-(3-((4-Fluorophenyl)sulfonyl)-5-methyl-5-(2-methylbenzyl)-4,5-dihydrofuran-2-yl)benzonitrile (37) Yellow oil, yield 55%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.72 – 7.59 (m, 4H), 7.55 – 7.37 (m, 2H), 7.12 – 6.97 (m, 6H), 3.25 – 2.58 (m, 4H), 2.19 (s, 3H), 1.50 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.2 (d, *J* = 255.4 Hz, C), 160.4 (C), 137.3 (d, *J* = 3.2 Hz, C), 137.0 (C), 133.9 (C), 133.1 (C), 131.5 (2CH), 131.0 (CH), 130.8 (CH), 130.1 (2CH), 129.5 (d, *J* = 9.4 Hz, 2CH), 127.2 (CH), 125.8 (CH), 118.1 (C), 116.2 (d, *J* = 22.6 Hz, 2CH), 114.3 (C), 111.5 (C), 89.1 (C), 46.0 (CH_2), 41.8 (CH_2), 22.7 (CH_3), 19.4 (CH_3). Anal. calcd for $C_{26}H_{22}FNO_3S$ (447.1304): C, 69.78; H, 4.96; N, 3.13; S, 7.17. Found: C, 69.99; H, 4.98; N, 3.02; S, 7.12.

4.1.3.16. 4-(3-((4-Fluorophenyl)sulfonyl)-5-(4-(hydroxymethyl)benzyl)-5-methyl-4,5-dihydrofuran-2-yl)benzonitrile (38) Yellow oil, yield 45%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.3 Hz, 2H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.8 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 7.06 (d, *J* = 7.9 Hz, 2H), 5.19 (bs, H), 4.47 (s, 2H), 2.97 (d, *J* = 13.8 Hz, H), 2.96 (d, *J* = 14.9 Hz, H), 2.89 (d, *J* = 13.8 Hz, H), 2.81 (d, *J* = 14.9 Hz, H), 1.45 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.5 (d, *J* = 252.2 Hz, C), 160.1 (C), 140.8 (C), 137.0 (d, *J* = 2.9 Hz, C), 133.9 (C), 132.9 (C), 131.8 (2CH), 129.9 (2CH), 129.8 (2CH), 129.5 (d, *J* = 9.8 Hz, 2CH), 126.1 (2CH), 118.1 (C), 116.5 (d, *J* = 22.8 Hz, 2CH), 113.1 (C), 111.0 (C), 89.3 (C), 62.6 (CH_2), 44.9 (CH_2), 40.8 (CH_2), 26.7 (CH_3). Anal. calcd for $C_{26}H_{22}FNO_4S$ (463.1254): C, 67.37; H, 4.78; N, 3.02; S, 6.92. Found: C, 67.27; H, 4.68; N, 2.92; S, 6.90.

4.1.3.17. 4-(3-((4-Fluorophenyl)sulfonyl)-5-(3-(hydroxymethyl)benzyl)-5-methyl-4,5-dihydrofuran-2-yl)benzonitrile (39) Yellow oil, yield 48%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.56 – 7.47 (m, 2H), 7.34 (d, *J* = 8.8 Hz, 2H), 7.17 (d, *J* = 7.6 Hz, H), 7.15 – 7.10 (m, 2H), 6.98 (d, *J* = 7.1 Hz, H), 5.18 (bs, H), 4.42 (s, 2H), 2.99 (d, *J* = 13.8 Hz, H), 2.95 (d, *J* = 14.9 Hz, H), 2.90 (d, *J* = 13.8 Hz, H), 2.81 (d, *J* = 14.9 Hz, H), 1.47 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.5 (d, *J* = 252.3 Hz, C), 160.2 (C), 142.1 (C), 137.1 (d, *J* = 2.9 Hz, C), 135.3 (C), 132.9 (C), 131.7 (2CH), 129.9 (2CH), 129.4 (d, *J* = 9.8 Hz, 2CH), 128.4 (CH), 128.3 (CH), 127.7 (CH), 124.8 (CH), 118.1 (C), 116.5 (d, *J* = 22.8 Hz, 2CH), 113.1 (C), 111.1 (C), 89.3 (C), 62.7 (CH_2), 45.2 (CH_2), 40.8 (CH_2), 26.8 (CH_3). Anal. calcd for $C_{26}H_{22}FNO_4S$ (463.1254): C, 67.37; H, 4.78; N, 3.02; S, 6.92. Found: C, 67.52; H, 4.67; N, 2.83; S, 6.92.

4.1.3.18. 4-(5-([1,1'-Biphenyl]-4-ylmethyl)-3-((4-fluorophenyl)sulfonyl)-5-methyl-4,5-dihydrofuran-2-yl)benzonitrile (40) Yellow oil, yield 52%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.69 (m, 4H), 7.56 (d, *J* = 7.5 Hz, 2H), 7.53 – 7.31 (m, 7H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 8.5 Hz, 2H), 3.06 (d, *J* = 14.8 Hz, H), 3.05 (d, *J* = 13.9 Hz, H), 2.89 (d, *J* = 14.8 Hz, H), 2.88 (d, *J* = 13.9 Hz, H), 1.53 (s, 3H).^{13}C NMR (63 MHz, $CDCl_3$) δ 165.1 (d, *J* = 255.7 Hz, C), 160.3 (C), 140.2 (C), 139.8 (C), 137.2 (d, *J* = 3.2 Hz, C), 134.4 (C), 133.0 (C), 131.5 (2CH), 130.7 (2CH), 130.1 (2CH), 129.5 (d, *J* = 9.5 Hz, 2CH), 128.9 (2CH), 127.5 (CH), 126.8 (2CH), 126.8 (2CH), 118.1 (C), 116.2 (d, *J* = 22.6 Hz, 2CH), 114.3 (C), 111.7 (C), 89.0 (C), 46.1 (CH_2), 41.7 (CH_2), 30.9 (CH_3). Anal. calcd for $C_{31}H_{24}FNO_3S$ (509.1461): C, 73.06; H, 4.75; N, 2.75. Found: C, 72.99; H, 4.46; N, 2.55.

4.1.3.19. 4-(5-((2-Fluoro-[1,1'-biphenyl]-4-yl)methyl)-3-((4-fluorophenyl)sulfonyl)-5-methyl-4,5-dihydrofuran-2-yl)benzonitrile (41) Yellow oil, yield 37%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.71 (s, 4H), 7.65 – 7.22 (m, 8H), 7.13 – 6.75 (m, 4H), 3.05 (d, *J* = 14.9 Hz, H), 3.04 (d, *J* = 14.0 Hz, H), 2.90 (d, *J* = 14.9 Hz, H), 2.89 (d, *J* = 14.0 Hz, H), 1.53 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.3 (d, *J* = 255.9 Hz, C), 161.8 (C), 160.3 (C), 137.22 (d, *J* = 3.3 Hz, C), 136.8 (C), 136.6 (C), 135.1 (C), 132.8 (C), 131.6 (C), 131.6 (2CH), 130.4 (d, *J* = 4.0 Hz, CH), 130.1 (2CH), 129.5 (d, *J* = 9.5 Hz, 2CH), 128.8 (2CH), 128.6 (2CH), 127.9 (CH), 126.3 (d, *J* = 3.4 Hz, CH), 117.9 (d, *J* = 22.9 Hz, CH), 116.4 (d, *J* = 22.6 Hz, 2CH), 114.5 (C), 111.9 (C), 88.7 (C), 45.8 (CH_2), 41.9 (CH_2), 27.2 (CH_3). Anal. calcd for $C_{31}H_{23}F_2NO_3S$ (527.1367): C, 70.57; H, 4.39; N, 2.65; S, 6.08. Found: C, 70.42; H, 4.65; N, 2.44; S, 6.12.

4.1.3.20. (E)-4-(3-((4-Fluorophenyl)sulfonyl)-5-methyl-5-(3-(4-(trifluoromethyl)phenyl)allyl)-4,5-dihydrofuran-2-yl)benzonitrile (42) Yellow oil, yield 26%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.73 – 7.63 (m, 2H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.00 (d, *J* = 8.5 Hz, 2H), 6.42 (d, *J* = 15.8 Hz, H), 6.19 – 6.05 (m, H), 3.01 (d, *J* = 14.8 Hz, H), 2.90 (d, *J* = 14.8 Hz, H), 2.62 (dd, *J* = 14.3, 7.3 Hz, H), 2.53 (dd, *J* = 14.3, 7.3 Hz, H), 1.50 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.2 (d, *J* = 256.1 Hz, C), 160.4 (C), 140.0 (C), 137.31 (d, *J* = 3.2

Hz, C), 133.4 (CH), 132.8 (C), 131.6 (2CH), 130.1 (2CH), 129.6 (d, *J* = 9.4 Hz, 2CH), 129.5 (q, *J* = 32.5 Hz, C), 126.2 (2CH), 125.6 (q, *J* = 3.8 Hz, 2CH), 125.5 (CH), 124.1 (q, *J* = 271.9 Hz, C), 118.0 (C), 116.3 (d, *J* = 22.6 Hz, 2CH), 114.5 (C), 111.7 (C), 88.6 (C), 44.4 (CH_2), 42.2 (CH_2), 26.8 (CH_3). Anal. calcd for $C_{28}H_{21}F_4NO_3S$ (527.1178): C, 63.75; H, 4.01; N, 2.66; S, 6.08. Found: C, 63.97; H, 3.95; N, 2.44; S, 5.95.

4.1.3.21. 4-(5-(2-Bromobenzyl)-3-((4-fluorophenyl)sulfonyl)-5-methyl-4,5-dihydrofuran-2-yl)benzonitrile (43) Yellow oil, yield 29%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.3 Hz, H), 7.74 (d, *J* = 8.3 Hz, H), 7.51 – 7.32 (m, 2H), 7.24 – 6.90 (m, 8H), 3.43 (d, *J* = 10.2 Hz, H), 3.34 (d, *J* = 10.2 Hz, H), 3.13 (d, *J* = 14.6 Hz, H), 2.82 (d, *J* = 14.6 Hz, H), 1.47 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.3 (d, *J* = 255.5 Hz, C), 160.1 (C), 137.2 (d, *J* = 3.2 Hz, C), 135.3 (C), 133.2 (CH), 133.0 (C), 132.8 (C), 132.4 (CH), 131.6 (2CH), 130.2 (2CH), 129.8 (C), 129.6 (d, *J* = 9.5 Hz, 2CH), 128.8 (CH), 127.3 (CH), 116.4 (d, *J* = 22.6 Hz, 2CH), 114.4 (C), 111.9 (C), 89.2 (C), 44.9 (CH_2), 41.9 (CH_2), 27.6 (CH_3). Anal. calcd for $C_{25}H_{19}BrFNO_3S$ (511.0253): C, 58.60; H, 3.74; N, 2.73; S, 6.26. Found: C, 58.62; H, 3.84; N, 2.78; S, 6.12.

4.1.3.22. 3-(5-Benzyl-3-((4-fluorophenyl)sulfonyl)-5-methyl-4,5-dihydrofuran-2-yl)benzonitrile (44) White oil, yield 29%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.88 – 7.72 (m, 3H), 7.56 – 7.48 (m, 3H), 7.25 – 7.16 (m, 3H), 7.13 – 7.06 (m, 4H), 3.06 (d, *J* = 14.8 Hz, H), 3.04 (d, *J* = 13.8 Hz, H), 2.86 (d, *J* = 14.8 Hz, H), 2.88 (d, *J* = 13.8, H), 1.53 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 160.00 (C), 137.2 (d, *J* = 3.7 Hz, C), 135.3 (C), 133.9 (d, *J* = 4.1 Hz, 2CH), 132.6 (CH), 130.3 (2CH), 130.0 (C), 129.6 (CH), 129.4 (CH), 128.7 (CH), 128.3 (2CH), 127.1 (CH), 118.0 (C), 116.3 (d, *J* = 22.5 Hz, 2CH), 112.3 (C), 111.2 (C), 88.9 (C), 45.5 (CH_2), 41.5 (CH_2), 27.4 (CH_3). 1 C did not appear under these conditions. HRMS (ESI +) m/z calcd for $C_{25}H_{20}FNO_3S$ [M+H]+: 434.1221 Found: 434.1222.

4.1.4 General procedure for amidoxime 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 to 5 °C. Potassium terbutoxide (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 h. The mixture obtained was poured into cold water and the precipitate thus formed was filtrated and crystallized from the appropriate solvent.

4.1.4.1. 4-(5,5-Diethyl-3-((4-fluorophenyl)sulfonyl)-4,5-dihydrofuran-2-yl)-N'-hydroxybenzimidamide (46) Brown solid, yield 63%, m.p. 123 °C (ethanol/water, 1:1). ^{1}H NMR (250 MHz, DMSO) δ 9.85 (s, H), 7.76 – 7.73 (m, 4H), 7.57 – 7.54 (m, 2H), 7.46 – 7.40 (m, 2H), 5.93 (bs, 2H), 2.81 (s, 2H), 1.65-1.62 (m, 4H), 0.79 (bs, 6H). ^{13}C NMR (63 MHz, DMSO) δ 162.5 (C), 150.2 (C), 137.9 (d, *J* = 2.9 Hz, C), 135.5 (C), 129.6 (d, *J* = 9.7 Hz, 2CH), 128.9 (2CH), 128.8 (C), 124.8 (2CH), 116.7 (d, *J* = 22.8 Hz, 2CH), 109.2 (C), 91.3 (C), 38.5 (CH_2), 31.2 ($2CH_2$), 7.2 ($2CH_3$). 1 C did not appear under these conditions. HRMS (ESI +) m/z calcd for $C_{21}H_{23}FN_2O_4S$ $[M+H]^+$: 419.1363. Found: 419.1433.

4.1.4.2. 4-(3-((4-Fluorophenyl)sulfonyl)-1-oxaspiro[4.5]dec-2-en-2-yl)-N'-hydroxybenzimidamide (47) Beige solid, yield 48%, m.p. 94 °C (ethanol/water, 1:1). ^{1}H NMR (250 MHz, DMSO) δ 9.85 (s, H), 7.83 – 7.72 (m, 4H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.45 – 7.38 (m, 2H), 5.93 (bs, 2H), 2.81 (s, 2H), 1.73 – 1.39 (m, 10H). ^{13}C NMR (63 MHz, DMSO) δ 161.9 (C), 150.1 (C), 137.9 (d, *J* = 2.9 Hz, C), 135.5 (C), 129.5 (d, *J* = 9.8 Hz, 2CH), 129.1 (2CH), 128.8 (C), 124.7 (2CH), 116.6 (d, *J* = 22.8 Hz, 2CH), 109.1 (C), 88.5 (C), 42.2 (CH_2), 35.9 ($2CH_2$), 30.1 (CH_2), 22.1 ($2CH_2$). 1 C did not appear

under these conditions. HRMS (ESI +) m/z calcd for $C_{22}H_{23}FN_2O_4S$ $[M+H]^+$: 431.1363. Found: 431.1436.

4.1.4.3. 4-((4-((4-Fluorophenyl)sulfonyl)-5-(4-(N'-hydroxycarbamimidoyl)phenyl)-2-methyl-2,3-dihydrofuran-2-yl)methyl)-N'-hydroxybenzimidamide (48) White solid, yield 64%, m.p. 124 °C (ethanol/water, 1:1). ^{1}H NMR (250 MHz, DMSO) δ 9.88 (s, H), 9.68 (s, H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.56 – 7.43 (m, 6H), 7.32-7.25 (m, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 5.91 (bs, 2H), 5.82 (bs, 2H), 3.04 – 2.79 (m, 4H), 1.44 (s, 3H). ^{13}C NMR (63 MHz, DMSO) δ 164.6 (d, *J* = 252.3 Hz, C), 162.0 (C), 150.9 (C), 150.4 (C), 137.7 (d, *J* = 3.2 Hz, C), 136.9 (C), 135.6 (C), 131.9 (C), 130.4 (2CH), 129.5 (d, *J* = 10.1 Hz, 2CH), 129.0 (2CH), 128.8 (C), 125.2 (2CH), 125.0 (2CH), 116.6 (d, *J* = 22.5 Hz, 2CH), 109.4 (C), 88.6 (C), 45.2 (CH_2), 41.3 (CH_2), 27.1 (CH_3). HRMS (ESI +) m/z calcd for $C_{26}H_{25}FN_4O_5S$ $[M+H]^+$: 525.1602. Found: 525.1602.

4.1.4.4. 3-((4-((4-Fluorophenyl)sulfonyl)-5-(4-(N'-hydroxycarbamimidoyl)phenyl)-2-methyl-2,3-dihydrofuran-2-yl)methyl)-N'-hydroxybenzimidamide (49) White solid, yield 87%, m.p. 97 °C (ethanol/water, 1:1). ^{1}H NMR (250 MHz, DMSO) δ 9.86 (s, H), 9.67 (s, H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.60 – 7.46 (m, 6H), 7.33 – 7.12 (m, 4H), 5.91 (bs, 2H), 5.82 (bs, 2H), 3.05 – 2.80 (m, 4H), 1.45 (s, 3H). ^{13}C NMR (63 MHz, DMSO) δ 164.5 (d, *J* = 252.3 Hz, C), 162.1 (C), 150.7 (C), 150.3 (C), 137.7 (d, *J* = 2.8 Hz, C), 135.7 (C), 135.5 (C), 133.1 (C), 130.9 (CH), 129.3 (d, *J* = 9.6 Hz, 2CH), 129.0 (2CH), 128.7 (C), 127.9 (CH), 127.6 (CH), 124.8 (2CH), 123.9 (CH), 116.5 (d, *J* = 23.0 Hz, 2CH), 109.3 (C), 88.4 (C), 45.4 (CH_2), 41.3 (CH_2), 27.0 (CH_3). HRMS (ESI +) m/z calcd for $C_{26}H_{25}FN_4O_5S$ $[M+H]^+$: 525.1602. Found: 525.1602.

4.1.4.5. 4-(3-((4-Fluorophenyl)sulfonyl)-5-methyl-5-(4-(trifluoromethyl)benzyl)-4,5-dihydrofuran-2-yl)-N'-hydroxybenzimidamide (50) White solid, yield 56%, m.p. 86 °C (ethanol/water, 1:1). ^{1}H NMR (250 MHz, DMSO) δ 9.84 (s, H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.61 – 7.29 (m, 10H), 5.92 (bs, 2H), 3.06 – 2.84 (m, 4H), 1.46 (s, 3H). ^{13}C NMR (63 MHz, DMSO) δ 164.4 (d, *J* = 252.3 Hz, C), 161.8 (C), 150.1 (C), 140.8 (C), 137.7 (d, *J* = 2.7 Hz, C), 135.5 (C), 131.1 (2CH), 129.3 (d, *J* = 9.6 Hz, 2CH), 129.2 (q, *J* = 30.0 Hz, C), 128.8 (2CH),128.6 (C), 124.8 (4CH), 116.5 (d, *J* = 22.8 Hz, 2CH), 109.5 (C), 88.0 (C), 45.0 (CH_2), 41.3 (CH_2), 26.9 (CH_3). 1 C did not appear under these conditions. HRMS (ESI +) m/z calcd for $C_{26}H_{22}F_4N_2O_4S$ $[M+H]^+$: 535.1309. Found: 535.1312.

4.1.4.6. 4-(3-((4-Fluorophenyl)sulfonyl)-5-methyl-5-(3-(trifluoromethyl)benzyl)-4,5-dihydrofuran-2-yl)-N'-hydroxybenzimidamide (51) White solid, yield 48%, m.p. 88 °C (ethanol/water, 1:1). ^{1}H NMR (250 MHz, DMSO) δ 9.87 (s, H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.58 – 7.27 (m, 10H), 5.94 (bs, 2H), 3.12 (d, *J* = 14.1 Hz, H), 3.05 (d, *J* = 14.1 Hz, H), 2.93 (d, *J* = 15.2 Hz, H), 2.86 (d, *J* = 15.2 Hz, H), 1.46 (s, 3H). ^{13}C NMR (63 MHz, DMSO) δ 164.4 (d, *J* = 252.3 Hz, C), 161.6 (C), 150.1 (C), 137.5 (d, *J* = 2.7 Hz, C), 137.2 (C), 135.4 (C), 134.3 (CH), 129.3 (d, *J* = 9.6 Hz, 2CH), 128.9 (CH), 128.9 (q, *J* = 30.7 Hz, C), 128.7 (2CH),128.4 (C), 126.8 (q, *J* = 3.8 Hz, CH), 125.2 (q, *J* = 248.7 Hz, C), 124.6 (2CH), 123.4 (q, *J* = 3.7 Hz, CH), 116.4 (d, *J* = 22.8 Hz, 2CH), 109.3 (C), 87.9 (C), 44.6 (CH_2), 41.1 (CH_2), 27.0 (CH_3). HRMS (ESI +) m/z calcd for $C_{26}H_{22}F_4N_2O_4S$ $[M+H]^+$: 535.1309. Found: 535.1306.

4.1.4.7. 4-(3-((4-Fluorophenyl)sulfonyl)-5-methyl-5-(2-(trifluoromethyl)benzyl)-4,5-dihydrofuran-2-yl)-N'-hydroxybenzimidamide (52) White solid, yield 40%, m.p. 89-90 °C (ethanol/water, 1:1). ^{1}H NMR (250 MHz, DMSO) δ 9.90 (s, H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.65 – 7.31 (m, 10H), 5.96 (bs, 2H), 3.27 – 3.14 (m, 2H), 2.85 (bs, 2H), 1.41 (s, 3H). ^{13}C NMR (63 MHz, DMSO) δ 164.5 (d, *J* = 252.3 Hz, C), 161.5 (C), 150.2 (C), 137.5 (d, *J* = 2.8 Hz, C), 135.6 (C), 134.6 (d, *J* = 1.4 Hz, C), 132.6 (CH), 132.2 (CH), 129.5 (d, *J* = 9.5 Hz, 2CH), 128.9 (2CH), 128.5 (C), 128.1 (q, *J* =

28.5 Hz, C), 127.5 (CH), 125.9 (q, *J* = 5.5 Hz, CH), 124.9 (2CH), 124.4 (q, *J* = 273.9 Hz, C), 116.6 (d, *J* = 23.0 Hz, 2CH), 109.6 (C), 88.1 (C), 41.8 (CH_2), 40.5 (CH_2), 27.1 (CH_3). HRMS (ESI +) m/z calcd for $C_{26}H_{22}F_4N_2O_4S$ $[M+H]^+$: 535.1309. Found: 535.1310.

4.1.4.8. 4-(5-(3,5-Bis(trifluoromethyl)benzyl)-3-((4-fluorophenyl)sulfonyl)-5-methyl-4,5-dihydrofuran-2-yl)-N'-hydroxybenzimidamide (53) White solid, yield 78%, m.p. 85 °C (ethanol/water, 1:1). ^{1}H NMR (250 MHz, DMSO) δ 9.86 (s, H), 7.95 – 7.91 (m, 3H), 7.76 – 7.71 (m, 2H), 7.54 – 7.49 (m, 4H), 7.32 - 7.25 (m, 2H), 5.94 (bs, 2H), 3.23 (bs, 2H), 2.88 (bs, 2H), 1.49 (s, 3H). ^{13}C NMR (63 MHz, DMSO) δ 164.4 (d, *J* = 252.9 Hz, C), 161.4 (C), 150.0 (C), 139.5 (C), 137.5 (d, *J* = 2.6 Hz, C), 135.6 (C), 131.1 (bs, 2CH), 129.8 (q, *J* = 32.6 Hz, 2C), 129.2 (d, *J* = 9.6 Hz, 2CH), 128.7 (2CH), 128.2 (C), 124.6 (2CH), 123.3 (q, *J* = 273.0 Hz, 2C), 120.6 (bs, CH), 116.4 (d, *J* = 22.8 Hz, 2CH), 109.4 (C), 87.6 (C), 44.1 (CH_2), 41.2 (CH_2), 27.1 (CH_3). HRMS (ESI +) m/z calcd for $C_{27}H_{21}F_7N_2O_4S$ $[M+H]^+$: 603.1110. Found: 603.1062.

4.1.4.9. 4-(3-((4-Fluorophenyl)sulfonyl)-5-methyl-5-(4-nitrobenzyl)-4,5-dihydrofuran-2-yl)-N'-hydroxybenzimidamide (54) Beige solid, yield 72%, m.p. 116 °C (ethanol/water, 1:1). ^{1}H NMR (250 MHz, DMSO) δ 9.84 (s, H), 8.02 (d, *J* = 8.2 Hz, 2H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.59 – 7.26 (m, 8H), 5.92 (bs, 2H), 3.15 (d, *J* = 13.5 Hz, H), 3.09 (d, *J* = 13.5 Hz, H), 2.98 (d, *J* = 15.0 Hz, H), 2.90 (d, *J* = 15.0 Hz, H), 1.49 (s, 3H). ^{13}C NMR (63 MHz, DMSO) δ 164.4 (d, *J* = 252.5 Hz, C), 161.7 (C), 150.1 (C), 146.3 (C), 144.1 (C), 137.6 (d, *J* = 3.1 Hz, C), 135.5 (C), 131.5 (2CH), 129.5 (d, *J* = 9.7 Hz, 2CH), 128.8 (2CH), 128.5 (C), 124.8 (2CH), 122.9 (2CH), 116.4 (d, *J* = 22.8 Hz, 2CH), 109.5 (C), 87.9 (C), 44.9 (CH_2), 41.2 (CH_2), 27.1 (CH_3). HRMS (ESI +) m/z calcd for $C_{25}H_{22}FN_3O_6S$ $[M+H]^+$: 512.1286. Found: 512.1290.

4.1.4.10. 4-(3-((4-Fluorophenyl)sulfonyl)-5-methyl-5-(3-nitrobenzyl)-4,5-dihydrofuran-2-yl)-N'-hydroxybenzimidamide (55) Beige solid, yield 61%, m.p. 87 °C (ethanol/water, 1:1). ^{1}H NMR (250 MHz, DMSO) δ 9.85 (s, H), 8.08 - 7.26 (m, 12H), 5.93 (bs, 2H), 3.20 – 2.84 (m, 4H), 1.49 (s, 3H). ^{13}C NMR (63 MHz, DMSO) δ 164.4 (d, *J* = 252.7 Hz, C), 161.7 (C), 150.1 (C), 147.3 (C), 138.2 (C), 137.4 (d, *J* = 2.8 Hz, C), 137.1 (CH), 135.5 (C), 129.4 (CH), 129.3 (d, *J* = 9.7 Hz, 2CH), 128.8 (2CH), 128.4 (C), 124.8 (CH), 124.7 (2CH), 121.8 (CH), 116.5 (d, *J* = 22.8 Hz, 2CH), 109.4 (C), 87.9 (C), 44.4 (CH_2), 41.1 (CH_2), 27.1 (CH_3). HRMS (ESI +) m/z calcd for $C_{25}H_{22}FN_3O_6S$ $[M+H]^+$: 512.1286. Found: 512.1289.

4.1.4.11. 4-(3-((4-Fluorophenyl)sulfonyl)-5-(4-methoxybenzyl)-5-methyl-4,5-dihydrofuran-2-yl)-N'-hydroxybenzimidamide (56) White solid, yield 41%, m.p. 81 °C (ethanol/water, 1:1). ^{1}H NMR (250 MHz, DMSO) 9.84 (s, H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.56 – 7.47 (m, 4H), 7.35 – 7.28 (m, 2H), 7.04 (d, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 8.5 Hz, 2H), 5.92 (bs, 2H), 3.72 (s, 3H), 2.98 – 2.78 (m, 4H), 1.43 (s, 3H). ^{13}C NMR (63 MHz, DMSO) δ 164.4 (d, *J* = 252.0 Hz, C),161.9 (C), 158.0 (C), 150.2 (C), 137.7 (d, *J* = 3.0 Hz, C), 135.5 (C), 131.3 (2CH), 129.4 (d, *J* = 9.6 Hz, 2CH), 128.8 (2CH), 128.7 (C), 127.7 (C), 124.7 (2CH), 116.4 (d, *J* = 22.8 Hz, 2CH), 113.3 (2CH), 109.2 (C), 88.6 (C), 54.9 (CH_3), 44.4 (CH_2), 41.0 (CH_2), 26.8 (CH_3). HRMS (ESI +) m/z calcd for $C_{26}H_{25}FN_2O_5S$ $[M+H]^+$: 497.1468. Found: 497.1463.

4.1.4.12. 4-(3-((4-Fluorophenyl)sulfonyl)-5-methyl-5-(3,4,5-trimethoxybenzyl)-4,5-dihydrofuran-2-yl)-N'-hydroxybenzimidamide (57) Pink solid, yield 50%, m.p. 98 °C (ethanol/water, 1:1). ^{1}H NMR (250 MHz, DMSO) δ 9.89 (s, H), 7.74 (d, *J* = 7.8 Hz, 2H), 7.56 – 7.51 (m, 4H), 7.34 – 7.27 (m, 2H), 6.44 (s, 2H), 5.94 (bs, 2H), 3.63 – 3.57 (m, 9H), 3.04 (d, *J* = 14.5 Hz, H), 2.94 (d, *J* = 13.6 Hz, H), 2.84 (d, *J* = 14.5 Hz, H), 2.82 (d, *J* = 13.6 Hz, H), 1.50 (s, 3H). ^{13}C NMR (63 MHz, DMSO) δ 164.5 (d, *J* = 251.6 Hz, C), 161.7 (C), 152.4 (2C), 150.1 (C), 137.8 (d, *J* = 2.7 Hz, C), 136.3 (C), 135.6

(C), 131.5 (C), 129.1 (d, *J* = 9.5 Hz, 2CH), 128.9 (2CH), 128.7 (C), 124.7 (2CH), 116.5 (d, *J* = 22.9 Hz, 2CH), 109.1 (C), 107.5 (2CH), 88.4 (C), 60.1 (CH_3), 55.5 ($2CH_3$), 45.8 (CH_2), 41.1 (CH_2), 27.4 (CH_3). HRMS (ESI +) m/z calcd for $C_{28}H_{29}FN_2O_7S$ $[M+H]^+$: 557.1680. Found: 557.1678.

4.1.4.13. 4-(3-((4-Fluorophenyl)sulfonyl)-5-methyl-5-(4-methylbenzyl)-4,5-dihydrofuran-2-yl)-N'-hydroxybenzimidamide (58) Beige solid, yield 76%, m.p. 101 °C (ethanol/water, 1:1). ^{1}H NMR (250 MHz, DMSO) δ 9.84 (s, H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.58 – 7.31 (m, 6H), 7.00 – 6.95 (m, 4H), 5.92 (bs, 2H), 2.98 – 2.76 (m, 4H), 2.25 (s, 3H), 1.43 (s, 3H). ^{13}C NMR (63 MHz, DMSO) δ 164.3 (d, *J* = 235.3 Hz, C), 161.8 (C), 150.2 (C), 137.7 (d, *J* = 2.9 Hz, C), 135.6 (C), 135.4 (C), 132.7 (C), 130.1 (2CH), 129.3 (d, *J* = 9.8 Hz, 2CH), 128.9 (2CH), 128.7 (C), 128.6 (2CH), 124.7 (2CH), 116.5 (d, *J* = 22.7 Hz, 2CH), 109.2 (C), 88.5 (C), 44.9 (CH_2), 41.0 (CH_2), 26.8 (CH_3), 20.7 (CH_3). HRMS (ESI +) m/z calcd for $C_{26}H_{25}FN_2O_4S$ $[M+H]^+$: 481.1592. Found: 481.1591.

4.1.4.14. 4-(3-((4-Fluorophenyl)sulfonyl)-5-methyl-5-(3-methylbenzyl)-4,5-dihydrofuran-2-yl)-N'-hydroxybenzimidamide (59) Yellow solid, yield 69%, m.p. 95 °C (ethanol/water, 1:1). ^{1}H NMR (250 MHz, DMSO) δ 9.86 (s, H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.54 – 7.09 (m, 6H), 7.12 – 6.91 (m, 4H), 5.93 (bs, 2H), 2.97 – 2.77 (m, 4H), 2.19 (s, 3H), 1.45 (s, 3H). ^{13}C NMR (63 MHz, DMSO) δ 164.4 (d, *J* = 251.9 Hz, C), 161.9 (C), 150.1 (C), 137.7 (d, *J* = 2.9 Hz, C), 136.9 (CH), 135.7 (CH), 135.5 (C), 131.1 (C), 129.3 (d, *J* = 9.8 Hz, 2CH), 128.9 (2CH), 128.7 (C), 127.9 (CH), 127.3 (CH+C), 124.7 (2CH), 116.5 (d, *J* = 23.0 Hz, 2CH), 109.2 (C), 88.4 (C), 45.3 (CH_2), 41.0 (CH_2), 27.0 (CH_3), 21.0 (CH_3). HRMS (ESI +) m/z calcd for $C_{26}H_{25}FN_2O_4S$ $[M+H]^+$: 481.1592. Found: 481.1590.

4.1.4.15. 4-(3-((4-Fluorophenyl)sulfonyl)-5-methyl-5-(2-methylbenzyl)-4,5-dihydrofuran-2-yl)-N'-hydroxybenzimidamide (60) White solid, yield 50%, m.p. 138 °C (ethanol/water, 1:1). ^{1}H NMR (250 MHz, DMSO) δ 9.84 (s, H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.65 – 7.24 (m, 6H), 7.09 – 6.91 (m, 4H), 5.91 (bs, 2H), 3.01 – 2.17 (m, 4H), 2.18 (s, 3H), 1.44 (s, 3H). ^{13}C NMR (63 MHz, DMSO) δ 164.4 (d, *J* = 251.9 Hz, C), 161.8 (C), 150.2 (C), 137.7 (d, *J* = 2.9 Hz, C), 136.9 (C), 135.4 (C), 134.4 (C), 131.0 (CH), 130.2 (CH), 129.4 (d, *J* = 9.8 Hz, 2CH), 128.9 (C), 128.8 (2CH), 126.7 (CH), 125.5 (CH), 124.8 (2CH), 116.6 (d, *J* = 22.5 Hz, 2CH), 109.3 (C), 89.1 (C), 41.7 (CH_2), 41.6 (CH_2), 26.9 (CH_3), 19.9 (CH_3). HRMS (ESI +) m/z calcd for $C_{26}H_{25}FN_2O_4S$ $[M+H]^+$: 481.1592. Found: 481.1591.

4.1.4.16. 4-(3-((4-Fluorophenyl)sulfonyl)-5-(4-(hydroxymethyl)benzyl)-5-methyl-4,5-dihydrofuran-2-yl)-N'-hydroxybenzimidamide (61) White solid, yield 53%, m.p. 116 °C (ethanol/water, 1:1). ^{1}H NMR (250 MHz, DMSO) δ 9.86 (s, H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.55 – 7.48 (m, 4H), 7.35 (t, *J* = 8.8 Hz, 2H), 7.13 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 8.1 Hz, 2H), 5.92 (bs, 2H), 5.21 (t, *J* = 5.5 Hz, H), 4.47 (d, *J* = 5.5 Hz, 2H), 3.00 – 2.77 (m, 4H), 1.43 (s, 3H). ^{13}C NMR (63 MHz, DMSO) δ 164.4 (d, *J* = 252.1 Hz, C), 161.8 (C), 150.2 (C), 140.8 (C), 137.7 (d, *J* = 2.7 Hz, C), 135.5 (C), 134.1 (C), 130.1 (2CH), 129.3 (d, *J* = 9.7 Hz, 2CH), 128.9 (2CH), 128.7 (C), 126.2 (2CH), 124.8 (2CH), 116.5 (d, *J* = 22.8 Hz, 2CH), 109.2 (C), 88.5 (C), 62.7 (CH_2), 45.0 (CH_2), 41.1 (CH_2), 26.8 (CH_3). HRMS (ESI +) m/z calcd for $C_{26}H_{25}FN_2O_5S$ $[M+H]^+$: 497.1541. Found: 497.1540.

4.1.4.17. 4-(3-((4-Fluorophenyl)sulfonyl)-5-(3-(hydroxymethyl)benzyl)-5-methyl-4,5-dihydrofuran-2-yl)-N'-hydroxybenzimidamide (62) White solid, yield 57%, m.p. 103 °C (ethanol/water, 1:1). ^{1}H NMR (250 MHz, DMSO) δ 9.87 (s, H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.55– 7.49 (m, 4H), 7.32 (t, *J* = 8.8 Hz, 2H), 7.18 – 6.98 (m, 4H), 5.94 (bs, 2H), 5.22 (t, *J* = 5.5 Hz, H), 4.44 (d, *J* = 5.5 Hz, 2H), 2.99 (d, *J* = 13.8 Hz, H), 2.97 (d, *J* = 14.5 Hz, H), 2.91 (d, *J* = 13.8 Hz, H), 2.82 (d, *J* = 14.5 Hz, H), 1.44 (s, 3H). ^{13}C NMR (63 MHz, DMSO) δ 164.4 (d, *J* = 251.7 Hz, C), 162.0 (C), 150.2 (C), 142.2 (C), 137.8 (d, *J* = 2.0 Hz, C), 135.6 (C), 135.5 (C), 129.3 (d, *J* = 9.6 Hz, 2CH), 129.0 (2CH), 128.7 (C), 128.6 (CH), 128.5 (CH), 127.8 (CH), 124.8 (CH), 124.7 (2CH), 116.5 (d, *J* = 22.7

Hz, 2CH), 109.2 (C), 88.5 (C), 62.8 (CH_2), 45.3 (CH_2), 41.1 (CH_2), 26.9 (CH_3). HRMS (ESI +) m/z calcd for $C_{26}H_{25}FN_2O_5S$ $[M+H]^+$: 497.1541. Found: 497.1541.

4.1.4.18. 4-(5-([1,1'-Biphenyl]-4-ylmethyl)-3-((4-fluorophenyl)sulfonyl)-5-methyl-4,5-dihydrofuran-2-yl)-N'-hydroxybenzimidamide (63) White solid, yield 74%, m.p. 96 °C (ethanol/water, 1:1). ^{1}H NMR (250 MHz, DMSO) δ 9.85 (s, H), 7.75 – 7.19 (m, 17H), 5.93 (bs, 2H), 3.06 – 2.82 (m, 4H),1.47 (s, 3H). ^{13}C NMR (63 MHz, DMSO) δ 164.4 (d, *J* = 252.1 Hz, C), 161.9 (C), 150.2 (C), 139.7 (C), 138.4 (C), 137.7 (d, *J* = 2.9 Hz, C), 135.5 (C), 135.2 (C), 130.9 (2CH), 129.3 (d, *J* = 9.7 Hz, 2CH), 129.0 (2CH), 128.9 (2CH), 128.7 (C), 127.4 (CH), 126.5 (2CH), 126.1 (2CH), 124.8 (2CH), 116.5 (d, *J* = 22.8 Hz, 2CH), 109.4 (C), 88.5 (C), 44.9 (CH_2), 41.3 (CH_2), 26.8 (CH_3). HRMS (ESI +) m/z calcd for $C_{31}H_{27}FN_2O_4S$ $[M+H]^+$: 543.1676. Found: 543.1666.

4.1.4.19. 4-(5-((2-Fluoro-[1,1'-biphenyl]-4-yl)methyl)-3-((4-fluorophenyl)sulfonyl)-5-methyl-4,5-dihydrofuran-2-yl)-N'-hydroxybenzimidamide (64) White solid, yield 95%, m.p. 117 °C (ethanol/water, 1:1). ^{1}H NMR (250 MHz, DMSO) δ 9.84 (s, H), 7.76 – 7.04 (m, 16H), 5.92 (bs, 2H), 3.06 – 2.84 (m, 4H), 1.48 (s, 3H). ^{13}C NMR (63 MHz, DMSO) δ 164.4 (d, *J* = 251.9 Hz, C), 161.8 (C), 150.2 (C), 138.2 (d, *J* = 2.3 Hz, C), 138.0 (C), 137.8 (d, *J* = 7.8 Hz, CH), 137.7 (d, *J* = 2.8 Hz, CH), 135.5 (C), 134.9 (C), 129.4 (d, *J* = 9.6 Hz, 2CH), 128.8 (2CH), 128.7 (C), 128.6 (4CH), 127.8 (CH), 126.9 (C), 124.8 (2CH), 117.8 (d, *J* = 23.0 Hz, CH), 116.5 (d, *J* = 23.0 Hz, 2CH), 109.5 (C), 88.3 (C), 44.6 (CH_2), 41.3 (CH_2), 26.8 (CH_3). 1 C did not appear under these conditions. HRMS (ESI +) m/z calcd for $C_{31}H_{26}F_2N_2O_4S$ $[M+H]^+$: 561.1581. Found: 561.1655.

4.1.4.20. 4-(3-((4-Fluorophenyl)sulfonyl)-5-methyl-5-((E)-3-(4-(trifluoromethyl)phenyl)allyl)-4,5-dihydrofuran-2-yl)-N'-hydroxybenzimidamide (65) White solid, yield 85%, m.p. 91 °C (ethanol/water, 1:1). ^{1}H NMR (250 MHz, DMSO) δ 9.86 (s, H), 7.75 – 7.18 (m, 12H), 6.57 – 6.51 (m, H), 6.36 – 6.27 (m, H), 5.92 (bs, 2H), 3.02 (d, *J* = 14.7 Hz, H), 2.89 (d, *J* = 14.7 Hz, H), 2.50 – 2.60 (m, 2H), 1.48 (s, 3H). ^{13}C NMR (63 MHz, DMSO) δ 164.4 (d, *J* = 252.1 Hz, C), 162.0 (C), 150.2 (C), 140.7 (C), 137.8 (d, *J* = 3.0 Hz, C), 135.6 (C), 132.4 (C), 129.4 (d, *J* = 9.8 Hz, 2CH), 129.5 (q, *J* = 32.5 Hz, C), 129.0 (2CH), 128.7 (CH), 127.1 (CH), 126.6 (2CH), 125.4 (q, *J* = 3.7 Hz, 2CH), 124.8 (2CH), 124.1 (q, *J* = 271.9 Hz, C), 116.4 (d, *J* = 23.0 Hz, 2CH), 109.4 (C), 88.2 (C), 43.8 (CH_2), 41.4 (CH_2), 26.7 (CH_3). HRMS (ESI +) m/z calcd for $C_{28}H_{24}F_4N_2O_4S$ $[M+H]^+$: 561.1393. Found: 561.1390.

4.1.4.21. 4-(5-(2-Bromobenzyl)-3-((4-fluorophenyl)sulfonyl)-5-methyl-4,5-dihydrofuran-2-yl)-N'-hydroxybenzimidamide (66) Yellow solid, yield 20%, m.p. 92 °C (ethanol/water, 1:1). ^{1}H NMR (250 MHz, DMSO) δ 9.85 (s, H), 7.74 – 7.01 (m, 12H), 5.92 (bs, 2H), 3.21 (d, *J* = 14.7 Hz, H), 3.16 (d, *J* = 14.7 Hz, H), 3.04 (d, *J* = 13.5 Hz, H), 2.87 (d, *J* = 13.5 Hz, H), 1.48 (s, 3H). ^{13}C NMR (63 MHz, DMSO) δ 164.5 (d, *J* = 251.9 Hz, C), 161.6 (C), 150.2 (C), 137.6 (d, *J* = 3.2 Hz, C), 135.5 (C), 135.3 (C), 132.7 (CH), 132.6 (C), 129.4 (d, *J* = 9.5 Hz, 2CH), 129.0 (CH), 128.9 (2CH), 128.5 (CH), 127.5 (CH), 125.1 (C), 124.7 (2CH), 116.4 (d, *J* = 23.0 Hz, 2CH), 109.4 (C), 88.3 (C), 44.1 (CH_2), 41.5 (CH_2), 27.1 (CH_3). HRMS (ESI +) m/z calcd for $C_{25}H_{22}BrFN_2O_4S$ $[M+H]^+$: 545.0540. Found: 545.0546.

4.1.4.22. 3-(5-Benzyl-3-((4-fluorophenyl)sulfonyl)-5-methyl-4,5-dihydrofuran-2-yl)-N'-hydroxybenzimidamide (67) White solid, yield 83%, m.p. 67-69 °C (ethanol/water, 1:1).^{1}H NMR (250 MHz, DMSO) δ 9.80 (s, H), 7.86 (s, H), 7.79 – 7.74 (m, H), 7.63 – 7.59 (m, 2H), 7.47 – 7.35 (m, 4H), 7.25 – 7.17 (m, 5H), 5.92 (bs, 2H), 3.05 – 2.80 (m, 4H), 1.46 (s, 3H). ^{13}C NMR (63 MHz, DMSO) δ 164.4 (d, *J* = 251.9 Hz, C), 161.9 (C), 150.2 (C), 137.6 (d, *J* = 3.2 Hz, C), 135.8 (C), 133.0 (C), 130.3 (2CH), 129.6 (CH), 129.4 (d, *J* = 9.2 Hz, 2CH), 128.3 (C), 128.0 (2CH), 127.7 (CH), 127.5 (CH), 126.7 (CH), 126.1 (CH), 116.5 (d, *J* = 23.0 Hz, 2CH), 109.4 (C), 88.5 (C), 45.3 (CH_2), 41.1 (CH_2), 26.7 (CH_3). HRMS (ESI +) m/z calcd for $C_{25}H_{23}FN_2O_4S$ $[M+H]^+$: 467.1435. Found: 467.1432.

4.2 Biology

4.2.1. Parasites

Leishmania amazonensis (MHOM/BR/77/LTB0016) was maintained as promastigotes at 26 °C in Schneider's insect medium (Sigma-Aldrich, St Louis, MO, USA) with 10% and heat-inactivated fetal calf serum (HIFCS), 100 μg/mL streptomycin and 100 U/mL penicillin. Parasites were maintained until the 10th passage; subsequently, new cultures were obtained from infected animals.

4.2.2. Antipromastigote activity

L. amazonensis promastigotes were cultivated in Schneider's insect medium supplemented with 10% HIFCS as above, in either absence or presence of different concentrations of prototypes. The culture was initiated with 1.0×10^6 cells/mL and maintained at 26 °C for 72 h. The cell viability was estimated by resazurin assay. The 50% inhibitory concentration (IC_{50}) was determined by logarithmic regression analysis using GraphPrism 5 software.

4.2.3. Antiamastigote activity

To evaluate the effect of the substances on intracellular amastigotes, resident peritoneal macrophages of BALB/c mice were plated in RPMI (Sigma-Aldrich, St. Louis, USA) at $1x10^6$/mL in Lab-Tek 8-chamber slides (Nunc, Roskilde, Denmark) and incubated at 37 °C in 5% CO_2 for 1 h. The resulting monolayers were washed with pre-warmed phosphate-buffered saline to remove non-adherent cells. Stationary-phase of *L. amazonensis* promastigotes were added at 3:1 parasite/macrophage ratio, and the cultures were incubated for additional 4 hours. After incubation, the chambers were washed again to remove free parasites, the substances were added and the chambers were incubated for 72h. Next, the slides were stained using an Instant Prov hematological dye system (Newprov, Curitiba, Brazil) and then examined under light microscopy. The number of infected cells and intracellular amastigotes was determined by counting at least 100 macrophages per sample. Concentration effect curves were fitted using nonlinear regression using Graph Pad Prism 5.0 and IC_{50} values determined.

4.2.4. Cytotoxicity assay

Peritoneal macrophages were harvested by peritoneal washing with 5 ml of RPMI 1640 medium supplemented with 10% HIFCS, 2 mM L-glutamine, 1 mM pyruvate, 100 μg/mL streptomycin and 100 U/mL penicillin. The peritoneal cell suspension was adjusted to 1.0×10^6 cells/mL and then plated in triplicate in 96-well plates (Falcon Co, Franklin Lakes, USA). Cultures were incubated for 1 h at 37°C in a 5% CO_2 atmosphere. Afterwards, the cells were washed to remove nonadherent cells and incubated in either absence or presence of different concentrations of prototypes for 72 h. The cell viability was estimated by resazurin assay. The 50% inhibitory concentration (IC_{50}) was determined by logarithmic regression analysis using GraphPrism 5 software.

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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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