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# Synthesis and evaluation of original amidoximes as antileishmanial agents

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ABSTRACT

An original series of amidoxime derivatives was synthesized using manganese(III) acetate, Buchwald–Hartwig and Heck reactions. Two amidoximes (**39** and **52**) showed interesting in vitro activities toward *Leishmania donovani* promastigotes, exhibiting 8.3 and 8.8 μM $IC_{50}$ values. Moreover, the cytotoxicity of these compounds was evaluated on human THP1 cells, giving access to the corresponding selectivity index. Among the 25 tested compounds, amidoximes **38** and **39** and diamidoximes **50** and **52** exhibited a better selectivity index than pentamidine used as a drug compound reference.



## 1. Introduction

Leishmaniasis is one of the most important parasitic diseases worldwide. It is transmitted by the bite of a sand-fly contaminated by a flagellate protozoan belonging to the genus *Leishmania*. Three different forms of the disease are encountered: visceral (VL), cutaneous (CL) and muco-cutaneous leishmaniasis (MCL). The disease is endemic in 88 countries, leading to 500,000 new cases and 50,000 death due to its visceral form caused by *Leishmania donovani*, each year.[1]

There are very few antileishmanial therapeutics, among which pentavalent antimonials are used as first-line drugs. However, they are not well tolerated and antimonial-resistant parasites have emerged in several endemic areas.[2] 1,5-Bis(4-amidinophenoxy)pentane (pentamidine, Fig. 1) is a well known antiprotozoan aromatic diamidine.[3] It is commonly used as antileishmanial drug, in case of antimonial failure.[4,5] Used in other various infections such trypanosomiasis[4,6] and HIV related *Pneumocystis jirovecii* opportunistic pneumonia,[7] pentamidine is not a well tolerated drug.[3,8]

Furthermore, at physiological pH, amidine groups are salified, decreasing membrane permeability and thus imposing a parenteral administration.[9]

Arylamidines similar to pentamidine are known to bind to the minor groove of AT DNA sequences.[10] Among the series of synthetic arylamidines, furamidine (DB75, Fig. 1) has shown interesting therapeutic activities against *Leishmania*, *Trypanosoma*, *Plasmodium* and *Pneumocystis jirovecii*, and its prodrug, pafuramidine (DB289, Fig. 1), possesses a good oral bioavailability.[11]

In view of our general interest in the preparation of antiparasitic compounds,[12] we report herein the synthesis of mono- and diarylamidoxime derivatives, presenting a 2,3-dihydrofuran heterocyclic scaffold in place of the furan scaffold of pafuramidine. Using three different strategies, manganese(III) acetate radicalar oxidative cyclization, Buchwald–Hartwig and Heck coupling reactions, we decided to vary the angles and distances between the amidoximes groups.

## 2. Results and discussion

### 2.1. Chemistry

Several β-ketosulfones (**1–5**) were synthesized using a previously reported microwave irradiated method.[13]

Thus, an aqueous solution of sodium sulfite, sodium bicarbonate and sulfonyl chlorides was irradiated at 500 W for 20 min in a microwave oven, giving the corresponding sodium sulfinates.

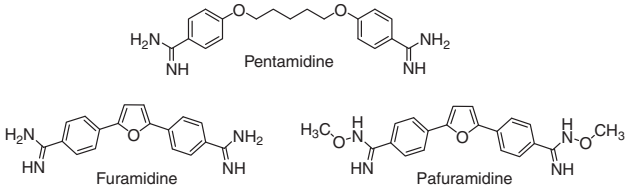


**Figure 1.**

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An ethanolic solution of the corresponding acetophenone was then added and the reaction mixture was irradiated for 10 min to give sulfones (**1–5**) (Scheme 1).

The β-ketosulfone derivatives thus obtained are presented in Table 1. All these products (**1–5**) bear an active methylene group next to the carbonyl one, and constitute promising candidates to effect a manganese(III) acetate oxidative cyclization.[14]

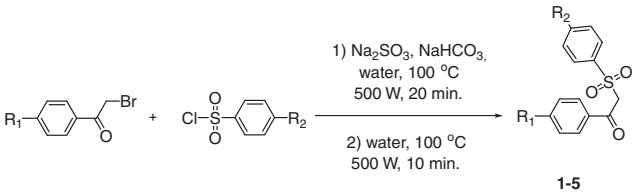
Following a previously described procedure,[15] manganese(III) acetate was dissolved in glacial acetic acid at 80 °C under nitrogen atmosphere. To this solution, β-ketosulfones **1–5** and corresponding alkene were added and the mixture was irradiated (200 W) for 60 min.

The desired 2,3-dihydrofuran derivatives (**6–15**), were obtained (Scheme 2, Table 2) in moderate to good yields.

Next, in order to develop a pharmacomodulation study, we investigated palladium-catalyzed coupling reactions of molecules **9, 10, 14, 15**, bearing a bromine atom. Thus, we examined the Buchwald–Hartwig cross-coupling reaction.

The method employed to carry out palladium-catalyzed C–N bond forming reaction (Scheme 3), used 4 mol % of palladium acetate, 4 mol % of BINAP, 1.2 equiv of arylamine and 1.4 equiv of $Cs_2CO_3$.[16]

Using *o*-, *m*- and *p*-aminobenzonitrile, a series of 12 substituted 2,3-dihydrofuran derivatives (**16–27**) was obtained (Table 3). Yields observed were better for Buchwald–Hartwig amination made on the sulfone moiety (51–87%). This difference could be attributed to the electron-attracting effect of sulfonyl group. Indeed, in the oxidative addition step, Pd(0) acts as a nucleophile and will preferentially attack the most electron-deficient position.[17]




**Scheme 1.**

**Table 1**
Microwave-assisted synthesis of β-ketosulfones

| Compound | $R_1$ | $R_2$ | Yield[a] (%) |
|---|---|---|---|
| **1** | –CN | –H | 61 |
| **2** | –H | –CN | 68 |
| **3** | –CN | –CN | 64 |
| **4** | –CN | –Br | 68 |
| **5** | –Br | –CN | 72 |

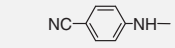
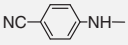
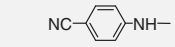
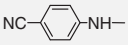
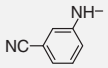
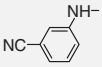
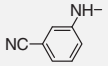
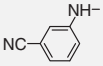
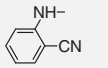
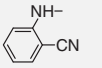
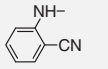
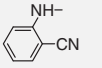
[a] Yield of isolated product based on the corresponding acetophenone.

**Table 2**
$Mn(OAc)_3$ assisted oxidative cyclizations

| Compound | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Yield[a] (%) |
|---|---|---|---|---|---|
| **6** | –CN | –H | –Ph | –Ph | 65 |
| **7** | –H | –CN | –Ph | –Ph | 56 |
| **8** | –CN | –CN | –Ph | –Ph | 57 |
| **9** | –CN | –Br | –Ph | –Ph | 54 |
| **10** | –Br | –CN | –Ph | –Ph | 30 |
| **11** | –CN | –H | –Bn | $-CH_3$ | 53 |
| **12** | –H | –CN | –Bn | $-CH_3$ | 60 |
| **13** | –CN | –CN | –Bn | $-CH_3$ | 52 |
| **14** | –CN | –Br | –Bn | $-CH_3$ | 47 |
| **15** | –Br | –CN | –Bn | $-CH_3$ | 10 |

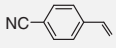
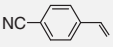
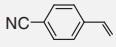
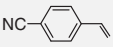
[a] Yield of isolated product based on the corresponding β-ketosulfone.

**Table 3**
Buchwald–Hartwig pallado-catalyzed coupling reactions

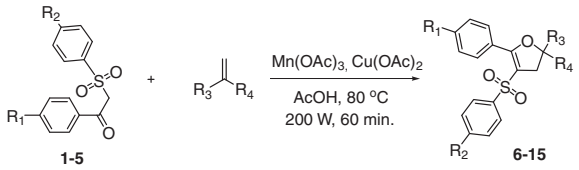
| Compound | $R_1$ | $R_2$ | $R_3/R_4$ | Yield[a] (%) |
|---|---|---|---|---|
| **16** | –CN |  | –Ph/–Ph | 51 |
| **17** |  | –CN | –Ph/–Ph | 26 |
| **18** | –CN |  | $-CH_3$/–Bn | 57 |
| **19** |  | –CN | $-CH_3$/–Bn | 26 |
| **20** | –CN |  | –Ph–Ph | 63 |
| **21** |  | –CN | –Ph/–Ph | 47 |
| **22** | –CN |  | $-CH_3$/–Bn | 78 |
| **23** |  | –CN | $-CH_3$/–Bn | 28 |
| **24** | –CN |  | –Ph/–Ph | 85 |
| **25** |  | –CN | –Ph/–Ph | 32 |
| **26** | –CN |  | $-CH_3$/–Bn | 87 |
| **27** |  | –CN | $-CH_3$/–Bn | 32 |

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

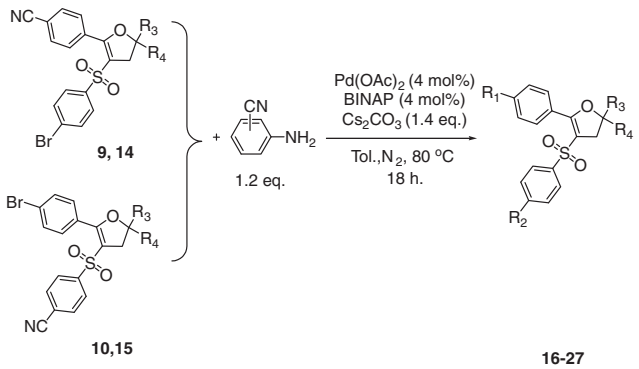
**Table 4**
Heck pallado-catalyzed coupling reactions

| Compound | $R_1$ | $R_2$ | $R_3/R_4$ | Yield[a] (%) |
|---|---|---|---|---|
| **28** | –CN |  | –Ph/–Ph | 56 |
| **29** |  | –CN | –Ph/–Ph | 30 |
| **30** | –CN |  | $-CH_3$/–Bn | 47 |
| **31** |  | –CN | $-CH_3$/–Bn | 15 |

[a] Yield of isolated product based on the corresponding dihydrofurans




**Scheme 2.**




**Scheme 3.**

Another palladium mediated coupling reaction investigated was the Heck coupling (Scheme 4). The method which was tested to carry out the Heck palladium-catalyzed C–C coupling reaction used 5 mol % of palladium acetate, 20 mol % of triphenylphosphine, 1 equiv of vinylic compound and 2 equiv of triethylamine.[18]

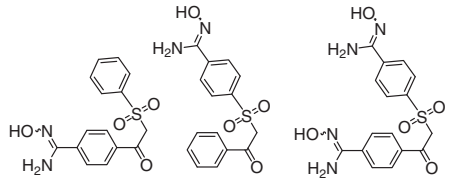
As observed for Buchwald–Hartwig amination, and most probably for same reasons, the yields observed were better for the vinylation reaction on the sulfone moiety (Table 4).

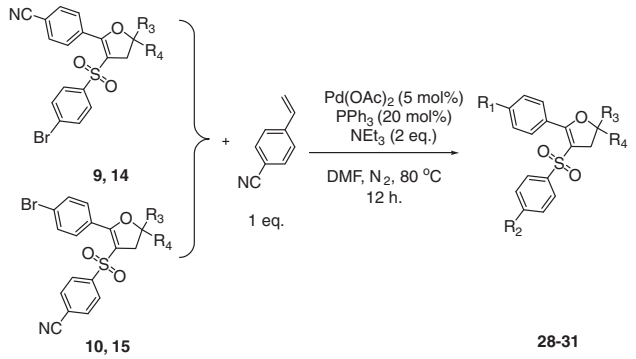
Finally, treatment of all the previously synthesized nitrile derivatives ( **1–3, 6–8, 11–13, 16–31**) with hydroxylamine hydrochloride and potassium *tert*-butoxide in DMSO[19] allowed conversion of the cyano group into amidoximes (**32–56**) in moderate to excellent yields (45–98%, mean yield = 62%) as shown in Scheme 5 and Table 5.

## 2.2. Biology

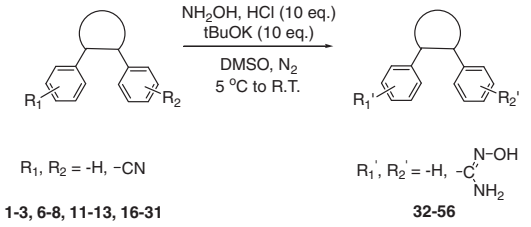
Synthesized amidoximes **32–56** were evaluated in vitro for their activity against promastigotes *Leishmania donovani* (GFP-transfected strain HOM/IN/01/2001) and for their cytotoxicity toward human monocytes THP1 (ATCC, Manassas VA, USA). THP1 cells commonly serve as in vitro model for screening antileishmanial drugs, because they can be used as host cells for the development of the intracellular stage amastigote of the parasites *Leishmania*.[20] The results of the evaluation are summarized in Table 6.

### 2.2.1. Antiparasitic activity



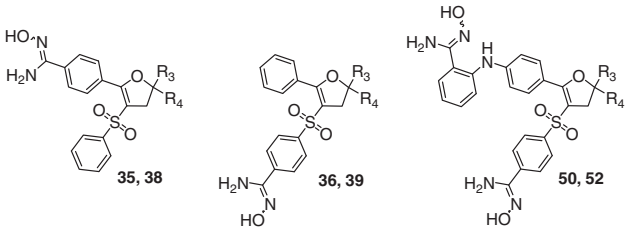




**Scheme 4.**




**Scheme 5.**

Among the tested compounds, β-ketosulfone derivatives **32–34** are amidoximes which do not present a 2,3-dihydrofuran scaffold. These compounds do not display activity toward *Leishmania*, which indicates that the amidoxime group is not sufficient for the molecules to present antileishmanial activity.




Among all other 2,3-dihydrofuran derivatives tested, 14 exhibited an antileishmanial activity which suggests that 2,3-dihydrofuran scaffold can be a valuable linker for amidoxime-containing antileishmanial compounds. Moreover, monoamidoxime compound **39**

**Table 5**
Synthesis of amidoximes from nitriles

| Nitrile substrate | Amidoxime product | Yield[a] (%) | Nitrile substrate | Amidoxime product | Yield[a] (%) |
|---|---|---|---|---|---|
| **1** | 32 | 87 | **20** | 45 | 83 |
| **2** | 33 | 83 | **21** | 46 | 52 |
| **3** | 34 | 71 | **22** | 47 | 83 |
| **6** | 35 | 94 | **23** | 48 | 89 |
| **7** | 36 | 93 | **24** | 49 | 61 |
| **8** | 37 | 98 | **25** | 50 | 52 |
| **11** | 38 | 97 | **26** | 51 | 57 |
| **12** | 39 | 95 | **27** | 52 | 45 |
| **13** | 40 | 93 | **28** | 53 | 73 |
| **16** | 41 | 72 | **29** | 54 | 70 |
| **17** | 42 | 72 | **30** | 55 | 77 |
| **18** | 43 | 80 | **31** | 56 | 51 |
| **19** | 44 | 89 | | | |

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

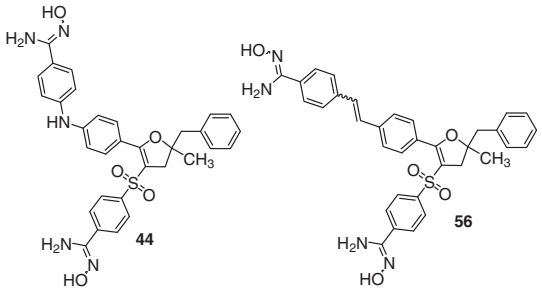
**Table 6**
In vitro activity/cytotoxicity of compounds **32–56**

| Compound | *Leishmania donovani*, promastigotes $IC_{50}$ (μM) | Cytotoxicity, THP1 monocytes $IC_{50}$ (μM) | Selectivity index (SI) |
|---|---|---|---|
| **32** | >125 | >125 | nd |
| **33** | >125 | >125 | nd |
| **34** | >125 | >125 | nd |
| **35** | 20.6 | 30.6 | 1.5 |
| **36** | 17.6 | 37.9 | 2.1 |
| **37** | 74.3 | 119.2 | 1.6 |
| **38** | 30.3 | 94.6 | 3.1 |
| **39** | 8.3 | 54.7 | 6.6 |
| **40** | 99.5 | 99.5 | 1.0 |
| **41** | 39.1 | >50 | >1.3 |
| **42** | >50 | 48.9 | <1.0 |
| **43** | >50 | 47.6 | <1.0 |
| **44** | 30.1 | 9.8 | 0.3 |
| **45** | >50 | >50 | nd |
| **46** | >50 | 48.1 | <1.0 |
| **47** | >50 | 46.6 | <1.0 |
| **48** | >50 | 44.0 | <0.9 |
| **49** | 39.1 | >50 | >1.3 |
| **50** | 13.3 | 47.8 | 3.6 |
| **51** | 48.3 | 48.4 | 1.0 |
| **52** | 8.8 | 48.1 | 5.5 |
| **53** | 50 | >10 | >0.2 |
| **54** | >50 | 41.3 | <0.9 |
| **55** | >50 | >50 | nd |
| **56** | 17.1 | 23.4 | 1.4 |
| Pentamidine | 11.2 | 31.2 | 2.8 |
| Doxorubicin | | 0.008 | |

showed better antileishmanial activity than the one of pentamidine ($IC_{50}$ = 8.3 μM, SI = 6.6). For this compound, a single amidoxime group appears to be sufficient for antileishmanial activity.

In diamidoximes series, compounds **50** and **52** exert a good activity (13.3 and 8.8 μM, respectively). These compounds bear an amidoxime group in *para*-position on the sulfone moiety, and on the other moiety a second amidoxime group in *ortho*-position. This configuration including two amidoxime groups appears to be the better combination for a good activity against *Leishmania*. Moreover, structural differences between molecules **50** and **52** are on the $R_3/R_4$ moiety. The higher activity is obtained for **52**, which bears a methyl group as $R_3$ and a benzyl group as $R_4$. Structural modulations of these substituents may improve antileishmanial activities of diamidoximes compounds.

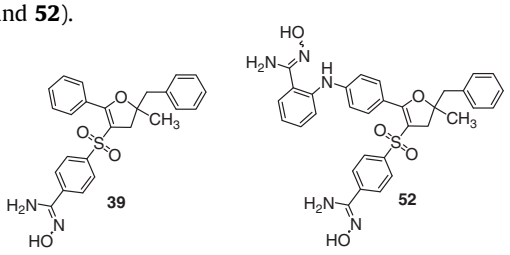
### 2.2.2. Cytotoxicity




Except from molecules **44** ($IC_{50}$ THP1 = 9.8 μM) and **56** ($IC_{50}$ THP1 = 23.4 μM), cytotoxicity of mono- and diamidoximes was ranging from low to moderate (30.6–119.2 μM).

Moreover, for the two most active compounds **39** and **52**, cytotoxicity was moderate (**39**, $IC_{50}$ THP1 = 54.7 μM, and **52**, $IC_{50}$ THP1 = 48.1 μM), which suggests that antileishmanial activity could be selective.

To sum up, comparison of antileishmanial activity and cytotoxicity has allowed to determine a selectivity index (SI). This SI is better than the one of pentamidine (2.8) in four of our molecules (**38**, **39**, **50** and **52**).




Therefore, from our study, two different models of 2,3-dihydrofurans bearing antileishmanial activity can be noted: 2,3-dihydrofurans containing two amidoximes groups, for which spatial configuration appears to present a great influence on the activity and, surprisingly, 2,3-dihydrofurans substituted with only one amidoxime group.

## 3. Conclusion

In conclusion, pallado-coupling and manganese(III) assisted reactions have allowed the synthesis of a large series of original molecules. Among 25 tested products, 12 exhibited antileishmanial activity and moderate cytotoxicity. In comparison with pentamidine, used as a reference, four molecules displayed a better selectivity index.

Molecule **39**, a monoamidoxime derivative, has the lowest $IC_{50}$ against *Leishmania donovani* promastigote (8.3 vs 11.2 μM for pentamidine), and molecule **52**, a diamidoxime derivative, also has a low $IC_{50}$ (8.8 μM). In order to identify the biological target of monoamidoxime derivatives, mechanistic studies are in progress.

## 4. Experimental

### 4.1. Chemistry

#### 4.1.1. Instruments and analyses

Microwave assisted reactions were done in a multimode microwave oven ETHOS Synth Lab Station (Ethos start, Milestone Inc.). Melting points were determined with a B-540 Büchi melting point apparatus. $^1$H NMR (200 MHz) and $^{13}$C NMR (50 MHz) spectra were recorded on a Bruker ARX 200 spectrometer in $CDCl_3$ at the Service interuniversitaire de RMN de la Faculté de Pharmacie de Marseille. $^1$H and $^{13}$C NMR chemical shifts ($\delta$) are reported in parts per million with respect to $CDCl_3$ 7.26 ppm ($^1$H) and 77 ppm ($^{13}$C). Elemental analysis was carried out at the Spectropole de la Faculté des Sciences et Techniques de Saint-Jérôme. The following adsorbent was used for flash column chromatography: Silica Gel 60 (Merck, particle size 0.063–0.200 nm, 70–230 mesh ASTM). TLC was performed on 5 × 10 cm aluminium plates coated with Silica Gel 60$F_{254}$ (Merck) in appropriate solvent. Mass spectra were run on an API-QqToF mass spectrometer.

#### 4.1.2. β-Ketosulfones synthesis

To a solution of sulfonyl chloride (6.00 mmol) in water (15 mL), sodium sulfite (1.26 g, 10 mmol) and sodium bicarbonate (0.84 g, 10 mmol) were added. The reaction mixture was heated under reflux in a microwave oven under irradiation (500 W, 100 °C) during 20 min. Then, an ethanolic solution of the corresponding acetophenone (2.05 mmol) was added. Heating of the reaction mixture was continued for 10 min under the same conditions. After cooling, the reaction mixture was neutralized with diluted hydrochloric acid. The resulting solution was filtered and the precipitate thus formed was crystallized from the appropriate solvent.

**4.1.2.1. 4-[2-(Phenylsulfonyl)acetyl]benzonitrile (1).** White solid, mp 150–151 °C (isopropyl alcohol) $^1$H NMR ($CDCl_3$), $\delta$: 4.74 (s, 2H, $CH_2$), 7.53–7.72 (m, 3H, 3CH), 7.79 (d, $J$ = 8.3, 2H, 2CH), 7.85–7.89 (m, 2H, 2CH), 8.07 (d, $J$ = 8.3, 2H, 2CH). $^{13}$C NMR ($CDCl_3$), $\delta$: 63.7 ($CH_2$), 117.5 (2C), 128.5 (2CH), 129.4 (2CH), 129.7 (2CH), 132.6 (2CH), 134.6 (CH), 138.4 (C), 138.5 (C), 197.0 (C). Anal. Calcd for $C_{15}H_{11}NO_3S$ (285.32): C, 63.14; H, 3.89; N, 4.91. Found: C, 63.32; H, 3.86; N, 4.80.

**4.1.2.2. 4-(2-Oxo-2-phenylethylsulfonyl)benzonitrile (2).** White solid, mp 148–149 °C (isopropyl alcohol) $^1$H NMR ($CDCl_3$), $\delta$: 4.79 (s, 2H, $CH_2$), 7.47–7.55 (m, 2H, 2CH), 7.63–7.70 (m, 1H, CH), 7.83–7.94 (m, 4H, 4CH), 8.04 (d, $J$ = 8.3, 2H, 2CH). $^{13}$C NMR ($CDCl_3$), $\delta$: 63.0 ($CH_2$), 117.1 (C), 118.0 (C), 129.1 (2CH), 129.2 (2CH), 129.6 (2CH), 132.9 (2CH), 134.8 (CH), 135.4 (C), 142.6 (C), 187.7 (C). Anal. Calcd for $C_{15}H_{11}NO_3S$ (285.32): C, 63.14; H, 3.89; N, 4.91. Found: C, 63.09; H, 3.88; N, 4.83.

**4.1.2.3. 4-[2-(4-Cyanophenyl)-2-oxoethylsulfonyl]benzonitrile (3).** White solid, mp 174–176 °C (isopropyl alcohol) $^1$H NMR ($CDCl_3$), $\delta$: 4.78 (s, 2H, $CH_2$), 7.84 (d, $J$ = 8.6, 2H, 2CH), 7.89 (d, $J$ = 8.6, 2H, 2CH), 8.04 (d, $J$ = 8.6, 2H, 2CH), 8.08 (d, $J$ = 8.6, 2H, 2CH). $^{13}$C NMR ($CDCl_3$), $\delta$: 63.2 ($CH_2$), 116.9 (C), 117.4 (C), 118.0 (C), 118.4 (C), 129.5 (2CH), 129.7 (2CH), 132.8 (2CH), 133.1 (2CH), 138.2 (C), 142.2 (C), 186.7 (C). Anal. Calcd for $C_{16}H_{10}N_2O_3S$ (310.33): C, 61.93; H, 3.25; N, 9.03. Found: C, 61.70; H, 3.21; N, 8.83.

**4.1.2.4. 4-[2-(4-Bromophenylsulfonyl)acetyl]benzonitrile (4).** White solid, mp 163–164 °C (isopropyl alcohol) $^1$H NMR

($CDCl_3$), $\delta$: 4.75 (s, 2H, $CH_2$), 7.68–7.75 (m, 4H, 4CH), 7.80 (d, $J$ = 8.5, 2H, 2CH), 8.06 (d, $J$ = 8.5, 2H, 2CH). $^{13}C$ NMR ($CDCl_3$), $\delta$: 63.4 ($CH_2$), 117.5 (C), 117.6 (C), 129.6 (2CH), 130.0 (2CH), 130.1 (C), 132.7 (4CH), 137.2 (C), 138.3 (C), 186.9 (C). Anal. Calcd for $C_{15}H_{10}BrNO_3S$ (364.21): C, 49.47; H, 2.77; N, 3.85. Found: C, 49.54; H, 2.74; N, 3.84.

**4.1.2.5. 4-[2-(4-Bromophenyl)-2-oxoethylsulfonyl]benzonitrile (5).** White solid, mp 229 °C (dichloromethane) $^1H$ NMR (DMSO-$d_6$), $\delta$: 5.56 (s, 2H, $CH_2$), 7.78 (d, $J$ = 7.9, 2H, 2CH), 7.87 (d, $J$ = 7.9, 2H, 2CH), 8.13 (m, 4H, 4CH). $^{13}C$ NMR (DMSO-$d_6$), $\delta$: 61.7 ($CH_2$), 116.3 (C), 117.5 (C), 128.8 (C), 128.9 (2CH), 130.9 (2CH), 131.9 (2CH), 133.3 (2CH), 134.5 (C), 143.4 (C), 188.4 (C). Anal. Calcd for $C_{15}H_{10}BrNO_3S$ (364.21): C, 49.47; H, 2.77; N, 3.85. Found: C, 49.11; H, 2.75; N, 3.78.

### 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) and copper(II) acetate (3.27 mmol, 0.59 g) in 30 mL of glacial acetic acid was heated under microwave irradiation (200 W, 80 °C) for 15 min, until dissolution. Then, the reaction mixture was cooled down to 50 °C, and a solution of **1–5** (3.27 mmol) and 1,1-diphenylethene (9.81 mmol) in 5 mL acetic acid was added. The mixture was heated under microwave irradiation (200 W, 80 °C) for 45 min. The reaction mixture was poured into 200 mL of cold water, and extracted with chloroform (3 × 40 mL). The organic extracts were collected and washed with saturated aqueous $NaHCO_3$ (3 × 40 mL) and dried ($MgSO_4$). Solvent evaporation was followed by column chromatography (gradient, from chloroform/petroleum ether (1:1) to chloroform/petroleum ether/diethyl ether (5:3:2)), and the product obtained was recrystallized from the appropriate solvent.

**4.1.3.1. 4-[5,5-Diphenyl-3-(phenylsulfonyl)-4,5-dihydrofuran-2-yl]benzonitrile (6).** White solid, mp 208–209 °C (isopropyl alcohol) $^1H$ NMR ($CDCl_3$), $\delta$: 3.80 (s, 2H, $CH_2$), 7.24–7.35 (m, 10H, 10CH), 7.40–7.61 (m, 3H, 3CH), 7.67–7.74 (m, 4H, 4CH), 7.88 (d, $J$ = 8.6, 2H, 2CH). $^{13}C$ NMR ($CDCl_3$), $\delta$: 45.4 ($CH_2$), 92.5 (C), 112.7 (C), 114.6 (C), 118.2 (C), 125.5 (4CH), 127.0 (2CH), 128.2 (2CH), 128.6 (4CH), 129.2 (2CH), 130.5 (2CH), 131.6 (2CH), 132.6 (C), 133.3 (CH), 141.1 (C), 143.3 (2C), 159.7 (C). Anal. Calcd for $C_{29}H_{21}NO_3S$ (463.55): C, 75.14; H, 4.57; N, 3.02. Found: C, 75.04; H, 4.63; N, 3.00.

**4.1.3.2. 4-(2,5,5-Triphenyl-4,5-dihydrofuran-3-ylsulfonyl)benzonitrile (7).** White solid, mp 153 °C (isopropyl alcohol) $^1H$ NMR ($CDCl_3$), $\delta$: 3.83 (s, 2H, $CH_2$), 7.26–7.35 (m, 10H, 10CH), 7.40–7.54 (m, 3H, 3CH), 7.59 (d, $J$ = 8.6, 2H, 2CH), 7.67 (d, $J$ = 8.6, 2H, 2CH), 7.73–7.78 (m, 2H, 2CH). $^{13}C$ NMR ($CDCl_3$), $\delta$: 45.3 ($CH_2$), 92.3 (C), 109.2 (C), 116.3 (C), 117.3 (C), 125.4 (4CH), 127.3 (2CH), 127.8 (C), 128.1 (4CH), 128.6 (4CH), 129.7 (2CH), 131.7 (CH), 132.6 (2CH), 143.4 (2C), 145.8 (C), 164.4 (C). Anal. Calcd for $C_{29}H_{21}NO_3S$ (463.55): C, 75.14; H, 4.57; N, 3.02. Found: C, 74.67; H, 4.62; N, 2.96.

**4.1.3.3. 4-[2-(4-Cyanophenyl)-5,5-diphenyl-4,5-dihydrofuran-3-ylsulfonyl]benzonitrile (8).** White solid, mp 197–198 °C (isopropyl alcohol) $^1H$ NMR ($CDCl_3$), $\delta$: 3.78 (s, 2H, $CH_2$), 7.26–7.39 (m, 10H, 10CH), 7.70–7.78 (m, 6H, 6CH), 7.90 (d, $J$ = 8.4, 2H, 2CH). $^{13}C$ NMR ($CDCl_3$), $\delta$: 45.1 ($CH_2$), 93.1 (C), 111.2 (C), 115.1 (C), 116.8 (C), 117.0 (C), 117.9 (C), 125.3 (4CH), 127.4 (2CH), 128.3 (2CH), 128.7 (4CH), 130.5 (2CH), 131.7 (2CH), 132.0 (C), 132.9 (2CH), 142.8 (2C), 145.1 (C), 161.6 (C). Anal. Calcd for $C_{30}H_{20}N_2O_3S$ (488.56): C, 73.75; H, 4.13; N, 5.73. Found: C, 73.45; H, 4.21; N, 5.52.

**4.1.3.4. 4-[3-(4-Bromophenylsulfonyl)-5,5-diphenyl-4,5-dihydrofuran-2-yl]benzonitrile (9).** White solid, mp 183–184 °C (isopropyl alcohol) $^1H$ NMR ($CDCl_3$), $\delta$: 3.77 (s, 2H, $CH_2$), 7.23–7.34 (m, 10H, 10CH), 7.50 (d, $J$ = 9.0, 2H, 2CH), 7.56 (d, $J$ = 9.0, 2H, 2CH), 7.74 (d, $J$ = 8.5, 2H, 2CH), 7.89 (d, $J$ = 8.5, 2H, 2CH). $^{13}C$ NMR ($CDCl_3$), $\delta$: 45.2 ($CH_2$), 92.7 (C), 112.2 (C), 114.8 (C), 118.1 (C), 125.4 (4CH), 128.2 (2CH), 128.4 (2CH), 128.5 (C), 128.6 (4CH), 130.5 (2CH), 131.7 (2CH), 132.3 (C), 132.4 (2CH), 140.1 (C), 143.1 (2C), 160.2 (C). Anal. Calcd for $C_{29}H_{20}BrNO_3S$ (542.44): C, 64.21; H, 3.72; N, 2.58. Found: C, 64.25; H, 3.80; N, 2.50.

**4.1.3.5. 4-[2-(4-Bromophenyl)-5,5-diphenyl-4,5-dihydrofuran-3-ylsulfonyl]benzonitrile (10).** White solid, mp 200 °C (isopropyl alcohol) $^1H$ NMR ($CDCl_3$), $\delta$: 3.78 (s, 2H, $CH_2$), 7.26–7.34 (m, 10H, 10CH), 7.57–7.73 (m, 8H, 8CH). $^{13}C$ NMR ($CDCl_3$), $\delta$: 45.5 ($CH_2$), 92.6 (C), 109.6 (C), 116.7 (C), 117.2 (C), 125.5 (4CH), 126.5 (C), 126.6 (C), 127.5 (2CH), 128.2 (2CH), 128.8 (4CH), 131.5 (2CH), 131.6 (2CH), 132.9 (2CH), 143.3 (2C), 145.7 (C), 163.0 (C). Anal. Calcd for $C_{29}H_{20}BrNO_3S$ (542.44): C, 64.21; H, 3.72; N, 2.58. Found: C, 64.15; H, 3.77; N, 2.54.

**4.1.3.6. 4-[5-Benzyl-5-methyl-3-(phenylsulfonyl)-4,5-dihydrofuran-2-yl]benzonitrile (11).** White solid, mp 143–144 °C (isopropyl alcohol) $^1H$ NMR ($CDCl_3$), $\delta$: 1.49 (s, 3H, $CH_3$), 2.82–3.10 (m, 4H, $2CH_2$), 7.03–7.08 (m, 2H, 2CH), 7.17–7.23 (m, 3H, 3CH), 7.38–7.55 (m, 5H, 5CH), 7.63–7.68 (m, 4H, 4CH). $^{13}C$ NMR ($CDCl_3$), $\delta$: 27.1 ($CH_3$), 41.8 ($CH_2$), 46.4 ($CH_2$), 88.9 (C), 111.7 (C), 114.2 (C), 118.2 (C), 126.7 (2CH), 127.0 (CH), 128.3 (2CH), 129.0 (2CH), 130.1 (2CH), 130.2 (2CH), 131.4 (2CH), 132.9 (CH), 133.1 (C), 135.3 (C), 141.1 (C), 160.1 (C). Anal. Calcd for $C_{25}H_{21}NO_3S$ (415.50): C, 72.27; H, 5.09; N, 3.37. Found: C, 72.07; H, 5.27; N, 3.34.

**4.1.3.7. 4-(5-Benzyl-5-methyl-2-phenyl-4,5-dihydrofuran-3-ylsulfonyl)benzonitrile (12).** Yellow oil, $^1H$ NMR ($CDCl_3$), $\delta$: 1.53 (s, 3H, $CH_3$), 2.80–3.11 (m, 4H, $2CH_2$), 7.13–7.27 (m, 5H, 5CH), 7.33–7.59 (m, 9H, 9CH). $^{13}C$ NMR ($CDCl_3$), $\delta$: 27.6 ($CH_3$), 41.2 ($CH_2$), 46.3 ($CH_2$), 88.5 (C), 108.3 (C), 115.8 (C), 117.3 (C), 126.9 (CH), 127.0 (2CH), 127.8 (2CH), 128.1 (2CH), 128.2 (C), 129.1 (2CH), 130.3 (2CH), 131.0 (CH), 132.4 (2CH), 135.4 (C), 145.9 (C), 164.7 (C). HMRS (EI): $m/z$ calcd for $C_{25}H_{21}NO_3S$ M+H$^+$: 416.1315. Found: 416.1314.

**4.1.3.8. 4-[5-Benzyl-2-(4-cyanophenyl)-5-methyl-4,5-dihydrofuran-3-ylsulfonyl]benzonitrile (13).** Yellow solid, mp 139–141 °C (isopropyl alcohol) $^1H$ NMR ($CDCl_3$), $\delta$: 1.54 (s, 3H, $CH_3$), 2.78–3.10 (m, 4H, $2CH_2$), 7.06–7.09 (m, 2H, 2CH), 7.16–7.23 (m, 3H, 3CH), 7.51 (d, $J$ = 8.4, 2H, 2CH), 7.65–7.73 (m, 6H, 6CH). $^{13}C$ NMR ($CDCl_3$), $\delta$: 27.7 ($CH_3$), 41.2 ($CH_2$), 46.4 ($CH_2$), 89.5 (C), 110.2 (C), 114.7 (C), 116.5 (C), 117.1 (C), 117.9 (C), 127.1 (3CH), 128.3 (2CH), 130.0 (2CH), 130.3 (2CH), 131.6 (2CH), 132.6 (C), 132.8 (2CH), 135.1 (C), 145.3 (C), 162.1 (C). Anal. Calcd for $C_{26}H_{20}N_2O_3S$ (440.51): C, 70.89; H, 4.58; N, 6.36. Found: C, 70.95; H, 4.71; N, 6.31.

**4.1.3.9. 4-[5-Benzyl-3-(4-bromophenylsulfonyl)-5-methyl-4,5-dihydrofuran-2-yl]benzonitrile (14).** White solid, mp 181–182 °C (isopropyl alcohol) $^1H$ NMR ($CDCl_3$), $\delta$: 1.52 (s, 3H, $CH_3$), 2.82 (d, $J$ = 13.9, 1H, CH), 2.85 (d, $J$ = 14.8, 1H, CH), 3.00 (d, $J$ = 14.8, 1H, CH), 3.02 (d, $J$ = 13.9, 1H, CH), 7.03–7.08 (m, 2H, 2CH), 7.15–7.23 (m, 3H, 3CH), 7.32 (d, $J$ = 8.6, 2H, 2CH), 7.54 (d, $J$ = 8.6, 2H, 2CH), 7.64–7.73 (m, 4H, 4CH). $^{13}C$ NMR ($CDCl_3$), $\delta$: 27.5 ($CH_3$), 41.4 ($CH_2$), 46.4 ($CH_2$), 89.1 (C), 111.2 (C), 114.4 (C), 118.1 (C), 127.1 (CH), 128.0 (C), 128.2 (2CH), 128.3 (2CH), 130.1 (2CH), 130.2 (2CH), 131.5 (2CH), 132.3 (2CH), 132.9 (C), 135.2 (C), 140.2 (C), 160.7 (C). Anal. Calcd for $C_{25}H_{20}BrNO_3S$ (494.40): C, 60.73; H, 4.08; N, 2.83. Found: C, 60.69; H, 4.16; N, 2.76.

**4.1.3.10. 4-[5-Benzyl-2-(4-bromophenyl)-5-methyl-4,5-dihydrofuran-3-ylsulfonyl]benzonitrile (15).** White solid, mp 98 °C (isopropyl alcohol) $^1$H NMR ($CDCl_3$), $\delta$: 1.52 (s, 3H, $CH_3$), 2.81 (d, $J$ = 14.0, 1H, CH), 2.87 (d, $J$ = 14.6, 1H, CH), 3.03 (d, $J$ = 14.6, 1H, CH), 3.05 (d, $J$ = 14.0, 1H, CH), 7.11–7.26 (m, 5H, 5CH), 7.41–7.65 (m, 8H, 8CH). $^{13}$C NMR ($CDCl_3$), $\delta$: 27.6 ($CH_3$), 41.3 ($CH_2$), 46.4 ($CH_2$), 88.8 (2C), 108.7 (C), 116.2 (C), 117.3 (C), 125.9 (C), 127.1 (3CH), 128.3 (2CH), 130.3 (2CH), 130.8 (2CH), 131.2 (2CH), 132.7 (2CH), 135.4 (C), 145.8 (C), 163.4 (C). Anal. Calcd for $C_{25}H_{20}BrNO_3S$ (494.40): C, 60.73; H, 4.08; N, 2.83. Found: C, 60.86; H, 4.12; N, 2.99.

### 4.1.4. General procedure for Buchwald coupling reactions

A solution of palladium acetate (0.024 mmol, 0.005 g, 0.04 equiv) and BINAP (0.024 mmol, 0.005 g, 0.04 equiv) in 20 mL of dry and degazed toluene was stirred under inert atmosphere. Then, dihydrofuran derivative (0.59 mmol, 1 equiv), corresponding aminobenzonitrile (0.71 mmol, 0.084 g, 1.2 equiv) and cesium carbonate (0.83 mmol, 0.16 g, 1.4 equiv) were added. The reaction mixture was stirred at 80 °C from 18 h, and monitored by TLC. Solvent evaporation gave a crude mixture, solubilized in dichloromethane and filtered in order to remove inorganic salts. The mixture was purified by column chromatography ($CH_2Cl_2$), and the product obtained was recrystallized from the appropriate solvent.

**4.1.4.1. 4-{4-[2-(4-Cyanophenyl)-5,5-diphenyl-4,5-dihydrofuran-3-ylsulfonyl]phenylamino}benzonitrile (16).** Yellow solid, mp 222–223 °C (isopropyl alcohol) $^1$H NMR ($CDCl_3$), $\delta$: 3.82 (s, 2H, $CH_2$), 6.61 (br s, 1H), 7.08 (d, $J$ = 8.7, 2H, 2CH), 7.13 (d, $J$ = 8.7, 2H, 2CH), 7.29–7.35 (m, 10H, 10CH), 7.57 (d, $J$ = 8.7, 2H, 2CH), 7.59 (d, $J$ = 8.7, 2H, 2CH), 7.71 (d, $J$ = 8.6, 2H, 2CH), 7.89 (d, $J$ = 8.6, 2H, 2CH). $^{13}$C NMR ($CDCl_3$), $\delta$: 45.4 ($CH_2$), 92.3 (C), 104.6 (C), 113.1 (C), 114.4 (C), 117.3 (2CH), 117.7 (2CH), 118.1 (C), 119.1 (C), 125.5 (4CH), 128.1 (2CH), 128.6 (4CH), 129.0 (2CH), 130.4 (2CH), 131.6 (2CH), 132.7 (C), 133.3 (C), 133.8 (2CH), 143.4 (2C), 145.0 (C), 145.6 (C), 159.0 (C). HMRS (EI): $m/z$ calcd for $C_{36}H_{25}N_3O_3S$ M+H$^+$: 580.1689. Found: 580.1689.

**4.1.4.2. 4-{2-[4-(4-Cyanophenylamino)phenyl]-5,5-diphenyl-4,5-dihydrofuran-3-ylsulfonyl}benzonitrile (17).** Yellow solid, mp 127 °C (isopropyl alcohol) $^1$H NMR ($CDCl_3$), $\delta$: 3.77 (s, 2H, $CH_2$), 7.15 (d, $J$ = 8.7, 2H, 2CH), 7.18 (d, $J$ = 8.7, 2H, 2CH), 7.28–7.33 (m, 10H, 10CH), 7.55 (d, $J$ = 8.7, 2H, 2CH), 7.61 (d, $J$ = 8.2, 2H, 2CH), 7.71 (d, $J$ = 8.2, 2H, 2CH), 7.86 (d, $J$ = 8.7, 2H, 2CH). 1′ (NH) not observed in these conditions. $^{13}$C NMR ($CDCl_3$), $\delta$: 45.5 ($CH_2$), 91.9 (C), 103.9 (C), 107.2 (C), 116.3 (C), 117.0 (2CH), 117.5 (2CH), 121.5 (CH), 124.9 (C), 125.5 (4CH), 127.3 (2CH), 128.1 (2CH), 128.6 (4CH), 131.8 (2CH), 132.6 (2CH), 133.9 (2CH), 143.3 (2C), 143.9 (C), 145.2 (C), 145.7 (C), 145.9 (C), 163.6 (C). HMRS (EI): $m/z$ calcd for $C_{36}H_{25}N_3O_3S$ M+H$^+$: 580.1689. Found: 580.1676.

**4.1.4.3. 4-{4-[5-Benzyl-2-(4-cyanophenyl)-5-methyl-4,5-dihydrofuran-3-ylsulfonyl]phenylamino}benzonitrile (18).** Yellow oil, $^1$H NMR ($CDCl_3$), $\delta$: 1.49 (s, 3H, $CH_3$), 2.84 (d, $J$ = 14.8, 1H, CH), 2.88 (d, $J$ = 13.9, 1H, CH), 3.00 (d, $J$ = 13.9, 1H, CH), 3.06 (d, $J$ = 14.8, 1H, CH), 6.90 (br s, 1H), 7.06–7.14 (m, 5H, 5CH), 7.18–7.23 (m, 4H, 4CH), 7.41 (d, $J$ = 8.7, 2H, 2CH), 7.55 (d, $J$ = 8.7, 2H, 2CH), 7.65 (d, $J$ = 8.7, 2H, 2CH), 7.71 (d, $J$ = 8.7, 2H, 2CH). $^{13}$C NMR ($CDCl_3$), $\delta$: 27.0 ($CH_3$), 41.9 ($CH_2$), 46.4 ($CH_2$), 88.8 (C), 104.1 (C), 112.2 (C), 114.0 (C), 117.2 (2CH), 117.5 (2CH), 118.2 (C), 119.2 (C), 126.9 (CH), 128.2 (2CH), 128.7 (2CH), 130.1 (2CH), 130.3 (2CH), 131.4 (2CH), 132.2 (C), 133.7 (2CH+1C), 135.4 (C), 145.3 (C), 145.5 (C), 159.5 (C). HMRS (EI): $m/z$ calcd for $C_{32}H_{25}N_3O_3S$ M+H$^+$: 532.1689. Found: 532.1693.

**4.1.4.4. 2-{4-[5-Benzyl-3-(4-cyanophenylsulfonyl)-5-methyl-4,5-dihydrofuran-2-yl]phenylamino}benzonitrile (19).** solid, mp 120 °C (isopropyl alcohol) $^1$H NMR ($CDCl_3$), $\delta$: 1.52 (s, 3H, $CH_3$), 2.84 (d, $J$ = 14.0, 1H, CH), 2.88 (d, $J$ = 14.5, 1H, CH), 3.04 (d, $J$ = 14.5, 1H, CH), 3.06 (d, $J$ = 14.0, 1H, CH), 7.10–7.25 (m, 10H, 10CH), 7.50–7.65 (m, 7H, 7CH). 1′ (NH) not observed in these conditions.$^{13}$C NMR ($CDCl_3$), $\delta$: 27.6 ($CH_3$), 41.6 ($CH_2$), 46.2 ($CH_2$), 88.3 (C), 105.3 (C), 111.0 (C), 115.6 (C), 116.8 (2CH), 117.7 (2CH), 118.3 (C), 119.2 (C), 124.0 (C), 127.1 (2CH), 128.3 (2CH), 129.7 (CH), 130.4 (2CH), 131.1 (2CH), 132.7 (2CH), 133.9 (2CH), 135.6 (C), 143.3 (C), 143.5 (C), 147.7 (C), 161.0 (C). HMRS (EI): $m/z$ calcd for $C_{32}H_{25}N_3O_3S$ M+H$^+$: 532.1689. Found: 532.1697.

**4.1.4.5. 3-{4-[2-(4-Cyanophenyl)-5,5-diphenyl-4,5-dihydrofuran-3-ylsulfonyl]phenylamino}benzonitrile (20).** Yellow solid, mp 209–210 °C (isopropyl alcohol) $^1$H NMR ($CDCl_3$), $\delta$: 3.81 (s, 2H, $CH_2$), 6.98 (d, $J$ = 8.8, 2H, 2CH), 7.37–7.44 (m, 14H, 14CH), 7.57 (d, $J$ = 8.8, 2H, 2CH), 7.72 (d, $J$ = 8.5, 2H, 2CH), 7.91 (d, $J$ = 8.5, 2H, 2CH). 1′ (NH) not observed in these conditions. $^{13}$C NMR ($CDCl_3$), $\delta$: 45.4 ($CH_2$), 92.3 (C), 113.3 (C), 113.7 (C), 114.4 (C), 115.9 (2CH), 118.2 (C), 118.3 (C), 122.4 (CH), 124.0 (CH), 125.5 (4CH), 126.6 (CH), 128.1 (2CH), 128.6 (4CH), 129.2 (2CH), 130.4 (2CH), 130.6 (CH), 131.6 (2CH), 132.4 (C), 133.0 (C), 141.4 (C), 143.5 (2C), 146.7 (C), 158.8 (C). HMRS (EI): $m/z$ calcd for $C_{36}H_{25}N_3O_3S$ M+NH$_4^+$: 597.1955. Found: 597.1953.

**4.1.4.6. 3-{4-[3-(4-Cyanophenylsulfonyl)-5,5-diphenyl-4,5-dihydrofuran-2-yl]phenylamino}benzonitrile (21).** Yellow solid, mp 112 °C (isopropyl alcohol) $^1$H NMR ($CDCl_3$), $\delta$: 3.77 (s, 2H, $CH_2$), 6.24 (br s, 1H), 7.08 (d, $J$ = 8.8, 2H, 2CH), 7.27–7.33 (m, 10H, 10CH), 7.37–7.41 (m, 4H, 4CH), 7.60 (d, $J$ = 8.5, 2H, 2CH), 7.71 (d, $J$ = 8.5, 2H, 2CH), 7.85 (d, $J$ = 8.8, 2H, 2CH). $^{13}$C NMR ($CDCl_3$), $\delta$: 45.4 ($CH_2$), 91.8 (C), 106.6 (C), 113.5 (C), 115.9 (2CH), 116.2 (C), 117.3 (C), 118.6 (C), 120.4 (C), 121.5 (CH), 123.0 (CH), 125.4 (4CH), 125.6 (CH), 127.2 (2CH), 128.1 (2CH), 128.5 (4CH), 130.4 (CH), 131.9 (2CH), 132.6 (2CH), 142.4 (C), 143.3 (2C), 145.2 (C), 146.0 (C), 163.8 (C). HMRS (EI): $m/z$ calcd for $C_{36}H_{25}N_3O_3S$ M+H$^+$: 580.1689. Found: 580.1681.

**4.1.4.7. 3-{4-[5-Benzyl-2-(4-cyanophenyl)-5-methyl-4,5-dihydrofuran-3-ylsulfonyl]phenylamino}benzonitrile (22).** Yellow oil, $^1$H NMR ($CDCl_3$), $\delta$: 1.49 (s, 3H, $CH_3$), 2.85 (d, $J$ = 14.8, 1H, CH), 2.90 (d, $J$ = 13.8, 1H, CH), 3.01 (d, $J$ = 13.8, 1H, CH), 3.08 (d, $J$ = 14.8, 1H, CH), 6.58 (br s, 1H), 6.96 (d, $J$ = 8.8, 2H, 2CH), 7.08–7.12 (m, 2H, 2CH), 7.21–7.24 (m, 3H, 3CH), 7.33–7.43 (m, 6H, 6CH), 7.64 (d, $J$ = 8.5, 2H, 2CH), 7.72 (d, $J$ = 8.5, 2H, 2CH). $^{13}$C NMR ($CDCl_3$), $\delta$: 27.0 ($CH_3$), 41.9 ($CH_2$), 46.4 ($CH_2$), 88.8 (C), 112.2 (C), 113.4 (C), 113.9 (C), 115.7 (2CH), 118.2 (C), 118.4 (C), 122.2 (CH), 123.6 (CH), 126.1 (CH), 126.9 (CH), 128.2 (2CH), 128.8 (2CH), 130.1 (2CH), 130.3 (2CH), 130.5 (CH), 131.4 (2CH), 132.2 (C), 133.2 (C), 135.4 (C), 141.6 (C), 146.6 (C), 159.3 (C). HMRS (EI): $m/z$ calcd for $C_{32}H_{25}N_3O_3S$ M+H$^+$: 532.1689. Found: 532.1686.

**4.1.4.8. 3-{4-[5-Benzyl-3-(4-cyanophenylsulfonyl)-5-methyl-4,5-dihydrofuran-2-yl]phenylamino}benzonitrile (23).** Yellow solid, mp 102 °C $^1$H NMR ($CDCl_3$), $\delta$: 1.51 (s, 3H, $CH_3$), 2.83 (d, $J$ = 14.0, 1H, CH), 2.88 (d, $J$ = 14.4, 1H, CH), 3.04 (d, $J$ = 14.4, 1H, CH), 3.06 (d, $J$ = 14.0, 1H, CH), 5.30 (br s, 1H), 7.00–7.65 (m, 17H, 17CH). $^{13}$C NMR ($CDCl_3$), $\delta$: 27.5 ($CH_3$), 41.6 ($CH_2$), 46.4 ($CH_2$), 88.1 (C), 106.2 (C), 113.5 (C), 116.0 (C), 116.1 (2CH), 117.4 (C), 118.6 (C), 121.1 (C), 121.2 (CH), 122.8 (CH), 125.4 (CH), 127.0 (CH), 127.1 (2CH), 128.3 (2CH), 130.4 (3CH), 131.2 (2CH), 132.6 (2CH), 135.6 (C), 142.4 (C), 144.6 (C), 146.2 (C), 164.2 (C). HMRS (EI): $m/z$ calcd for $C_{32}H_{25}N_3O_3S$ M+H$^+$: 532.1689. Found: 532.1696.

**4.1.4.9. 2-{4-[2-(4-Cyanophenyl)-5,5-diphenyl-4,5-dihydrofuran-3-ylsulfonyl]phenylamino}benzonitrile (24).** White solid, mp 98–99 °C (isopropyl alcohol) $^1$H NMR ($CDCl_3$), $\delta$: 3.82 (s, 2H, $CH_2$), 6.62 (br s, 1H), 7.05–7.12 (m, 3H, 3CH), 7.26–7.35 (m, 10H, 10CH), 7.37 (d, $J$ = 8.4, 1H, CH), 7.48–7.52 (m, 1H, CH), 7.56–7.63 (m, 3H, 3CH), 7.72 (d, $J$ = 8.3, 2H, 2CH), 7.91 (d, $J$ = 8.3, 2H, 2CH). $^{13}$C NMR ($CDCl_3$), $\delta$: 45.4 ($CH_2$), 92.3 (C), 102.6 (C), 113.2 (C), 114.4 (C), 116.8 (C), 117.5 (2CH), 118.0 (CH), 118.2 (C), 122.5 (CH), 125.5 (4CH), 128.1 (2CH), 128.6 (4CH), 129.0 (2CH), 130.4 (2CH), 131.6 (2CH), 132.7 (C), 133.5 (CH), 133.6 (C), 134.0 (CH), 143.4 (2C), 144.0 (C), 145.7 (C), 159.0 (C). HMRS (EI): $m/z$ calcd for $C_{36}H_{25}N_3O_3S$ M+H$^+$: 580.1689. Found: 580.1697.

**4.1.4.10. 2-{4-[3-(4-Cyanophenylsulfonyl)-5,5-diphenyl-4,5-dihydrofuran-2-yl]phenylamino}benzonitrile (25).** Yellow solid, mp 194 °C (isopropyl alcohol) $^1$H NMR ($CDCl_3$), $\delta$: 3.79 (s, 2H, $CH_2$), 6.51 (br s, 1H), 6.98–7.06 (m, 1H, CH), 7.19 (d, $J$ = 8.6, 2H, 2CH), 7.28–7.37 (m, 10H, 10CH), 7.42–7.50 (m, 3H, 3CH), 7.61 (d, $J$ = 8.5, 2H, 2CH), 7.71 (d, $J$ = 8.5, 2H, 2CH), 7.87 (d, $J$ = 8.6, 2H, 2CH). $^{13}$C NMR ($CDCl_3$), $\delta$: 45.6 ($CH_2$), 92.0 (C), 101.5 (C), 107.5 (C), 116.4 (C), 117.0 (CH), 117.2 (C), 117.4 (C), 117.9 (2CH), 121.7 (CH), 121.8 (C), 125.6 (4CH), 127.4 (2CH), 128.2 (2CH), 128.7 (4CH), 131.9 (2CH), 132.8 (2CH), 133.6 (CH), 134.1 (CH), 143.5 (2C), 144.2 (C), 145.0 (C), 146.1 (C), 164.8 (C). HMRS (EI): $m/z$ calcd for $C_{36}H_{25}N_3O_3S$ M+H$^+$: 580.1689. Found: 580.1681.

**4.1.4.11. 2-{4-[5-Benzyl-2-(4-cyanophenyl)-5-methyl-4,5-dihydrofuran-3-ylsulfonyl]phenylamino}benzonitrile (26).** Yellow oil, $^1$H NMR ($CDCl_3$), $\delta$: 1.48 (s, 3H, $CH_3$), 2.85 (d, $J$ = 14.8, 1H, CH), 2.87 (d, $J$ = 13.8, 1H, CH), 3.00 (d, $J$ = 13.8, 1H, CH), 3.07 (d, $J$ = 14.8, 1H, CH), 6.74 (br s, 1H), 7.04–7.11 (m, 5H, 5CH), 7.21–7.26 (m, 3H, 3CH), 7.35–7.39 (m, 1H, CH), 7.42 (d, $J$ = 8.8, 2H, 2CH), 7.48–7.52 (m, 1H, CH), 7.56–7.62 (m, 1H, CH), 7.65 (d, $J$ = 8.9, 2H, 2CH), 7.71 (d, $J$ = 8.9, 2H, 2CH). $^{13}$C NMR ($CDCl_3$), $\delta$: 27.0 ($CH_3$), 41.9 ($CH_2$), 46.4 ($CH_2$), 88.7 (C), 102.6 (C), 112.3 (C), 114.0 (C), 116.8 (C), 117.3 (2CH), 118.0 (CH), 118.2 (C), 122.5 (CH), 126.9 (CH), 128.2 (2CH), 128.7 (2CH), 130.1 (2CH), 130.3 (2CH), 131.4 (2CH), 133.2 (C), 133.5 (CH), 133.7 (C), 134.0 (CH), 135.4 (C), 144.1 (C), 145.5 (C), 159.4 (C). HMRS (EI): $m/z$ calcd for $C_{32}H_{25}N_3O_3S$ M+H$^+$: 532.1689. Found: 532.1696.

**4.1.4.12. 4-{5-Benzyl-2-[4-(4-cyanophenylamino)phenyl]-5-methyl-4,5-dihydrofuran-3-ylsulfonyl}benzonitrile (27).** Yellow solid, mp 113 °C (isopropyl alcohol) $^1$H NMR ($CDCl_3$), $\delta$: 1.52 (s, 3H, $CH_3$), 2.84 (d, $J$ = 13.9, 1H, CH), 2.89 (d, $J$ = 14.5, 1H, CH), 3.00 (d, $J$ = 14.5, 1H, CH), 3.06 (d, $J$ = 13.9, 1H, CH), 6.45 (br s, 1H), 7.11–7.66 (m, 17H, 17CH. $^{13}$C NMR ($CDCl_3$), $\delta$: 27.1 ($CH_3$), 41.6 ($CH_2$), 47.1 ($CH_2$), 88.2 (C), 107.0 (C), 109.3 (C), 115.2 (C), 118.0 (2CH), 118.7 (2CH), 120.1 (C), 121.3 (C), 122.4 (C), 127.1 (2CH), 128.4 (2CH), 130.2 (2CH), 130.6 (2CH), 131.1 (CH), 132.3 (CH), 132.4 (CH), 133.2 (CH), 136.5 (C), 141.3 (C), 141.6 (C), 143.4 (C), 146.2 (C), 163.5 (C). HMRS (EI): $m/z$ calcd for $C_{32}H_{25}N_3O_3S$ M+H$^+$: 532.1689. Found: 532.1686.

### 4.1.5. General procedure for Heck coupling reactions

A solution of dihydrofuran derivative (0.46 mmol, 1 equiv) and 4-vinylbenzonitrile (0.46 mmol, 0.059 g, 1 equiv) in 10 mL of dry and degazed DMF was stirred under inert atmosphere. Then, palladium acetate (0.023 mmol, 0.005 g, 0.05 equiv), triphenylphosphine (0.092 mmol, 0.024 g, 0.2 equiv) and triethylamine (0.92 mmol, 0.11 g, 2 equiv) were added. The reaction mixture was stirred at 80 °C from 12 h, and monitored by TLC. The reaction mixture was poured into 100 mL of cold water, and extracted with chloroform (3 × 40 mL). The organic extracts were collected and washed with brine (3 × 40 mL) and dried ($MgSO_4$). Solvent evaporation was followed by column chromatography ($CH_2Cl_2$/petroleum ether (9:1)), and the product obtained was recrystallized from the appropriate solvent.

**4.1.5.1. 4-{4-[2-(4-Cyanophenyl)-5,5-diphenyl-4,5-dihydrofuran-3-ylsulfonyl]styryl}benzonitrile (28).** White solid, mp 123 °C (isopropyl alcohol) $^1$H NMR ($CDCl_3$), $\delta$: 3.82 (s, 2H, $CH_2$), 7.19 (s, 2H, 2CH), 7.26–7.32 (m, 10H, 10CH), 7.55 (d, $J$ = 8.4, 2H, 2CH), 7.61 (d, $J$ = 8.8, 2H, 2CH), 7.66–7.70 (m, 4H, 4CH), 7.73 (d, $J$ = 8.8, 2H, 2CH), 7.90 (d, $J$ = 8.4, 2H, 2CH). $^{13}$C NMR ($CDCl_3$), $\delta$: 45.3 ($CH_2$), 92.5 (C), 111.6 (C), 112.6 (C), 114.6 (C), 118.1 (C), 118.7 (C), 125.5 (4CH), 127.2 (3CH), 127.3 (2CH), 127.5 (2CH), 128.1 (2CH), 128.6 (4CH), 130.0 (CH), 130.4 (2CH), 131.6 (2CH), 132.5 (C), 132.6 (2CH), 140.3 (C), 140.6 (C), 141.2 (C), 143.2 (2C), 159.8 (C). HMRS (EI): $m/z$ calcd for $C_{38}H_{26}N_2O_3S$ M+H$^+$: 591.1737. Found: 591.1724.

**4.1.5.2. 4-{4-[3-(4-Cyanophenylsulfonyl)-5,5-diphenyl-4,5-dihydrofuran-2-yl]styryl}benzonitrile (29).** Yellow solid, mp 234 °C (isopropyl alcohol) $^1$H NMR ($CDCl_3$), $\delta$: 3.81 (s, 2H, $CH_2$), 7.22 (s, 2H, 2CH), 7.28–7.35 (m, 10H, 10CH), 7.58–7.87 (m, 8H, 8CH), 7.71 (d, $J$ = 8.4, 2H, 2CH), 7.85 (d, $J$ = 8.8, 2H, 2CH). $^{13}$C NMR ($CDCl_3$), $\delta$: 45.6 ($CH_2$), 92.3 (C), 109.2 (C), 111.3 (C), 116.4 (C), 117.3 (C), 118.9 (C), 125.5 (4CH), 126.4 (2CH), 127.2 (2CH), 127.4 (2CH), 127.6 (C), 128.2 (2CH), 128.6 (4CH), 129.1 (CH), 130.5 (2CH), 131.1 (CH), 132.6 (2CH), 132.7 (2CH), 139.7 (C), 141.2 (C), 143.3 (2C), 145.8 (C), 163.6 (C). HMRS (EI): $m/z$ calcd for $C_{38}H_{26}N_2O_3S$ M+H$^+$: 591.1737. Found: 591.1739.

**4.1.5.3. 4-{4-[5-Benzyl-2-(4-cyanophenyl)-5-methyl-4,5-dihydrofuran-3-ylsulfonyl]styryl}benzonitrile (30).** Brown oil, $^1$H NMR ($CDCl_3$), $\delta$: 1.50 (s, 3H, $CH_3$), 2.84–3.12 (m, 4H, 2$CH_2$), 7.05–7.09 (m, 2H, 2CH), 7.17–7.22 (m, 5H, 5CH), 7.50 (d, $J$ = 8.6, 2H, 2CH), 7.55 (d, $J$ = 8.6, 2H, 2CH), 7.60–7.73 (m, 8H, 8CH). $^{13}$C NMR ($CDCl_3$), $\delta$: 27.1 ($CH_3$), 41.7 ($CH_2$), 46.4 ($CH_2$), 89.0 (C), 111.6 (C), 111.7 (C), 114.2 (C), 118.1 (C), 118.7 (C), 127.0 (CH), 127.2 (4CH), 127.3 (2CH), 128.2 (2CH), 130.0 (2CH), 130.1 (CH), 130.2 (CH), 130.3 (2CH), 131.5 (2CH), 132.6 (2CH), 133.0 (C), 135.3 (C), 140.5 (C), 140.7 (C), 140.8 (C), 160.3 (C). HMRS (EI): $m/z$ calcd for $C_{34}H_{26}N_2O_3S$ M+H$^+$: 543.1737. Found: 543.1730.

**4.1.5.4. 4-{5-Benzyl-2-[4-(4-cyanostyryl)phenyl]-5-methyl-4,5-dihydrofuran-3-ylsulfonyl}benzonitrile (31).** Yellow solid, mp 88 °C (isopropyl alcohol) $^1$H NMR ($CDCl_3$), $\delta$: 1.54 (s, 3H, $CH_3$), 2.84 (d, $J$ = 14.0, 1H, CH), 2.90 (d, $J$ = 14.5, 1H, CH), 3.07 (d, $J$ = 14.5, 1H, CH), 3.09 (d, $J$ = 14.0, 1H, CH), 7.14–7.26 (m, 9H, 9CH), 7.47–7.70 (m, 10H, 10CH). $^{13}$C NMR ($CDCl_3$), $\delta$: 27.6 ($CH_3$), 41.5 ($CH_2$), 46.4 ($CH_2$), 88.6 (C), 108.5 (C), 111.2 (C), 116.1 (C), 117.3 (C), 118.8 (C), 126.3 (2CH), 127.0 (2CH), 127.1 (2CH), 128.3 (2CH), 128.4 (CH), 128.8 (CH), 129.9 (2CH), 130.4 (2CH), 131.1 (CH), 132.5 (2CH), 132.6 (2CH), 135.5 (C), 136.4 (C), 139.0 (C), 141.2 (C), 146.0 (C), 164.0 (C). HMRS (EI): $m/z$ calcd for $C_{34}H_{26}N_2O_3S$ M+H$^+$: 543.1737. Found: 543.1715.

### 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. Then, potassium tertiobutylate (1.7 mmol, 0.19 g, 10 equiv) was slowly added. The reaction mixture was stirred at room temperature from 30 min, and the corresponding nitrile (0.17 mmol, 1 equiv) was added. The reaction mixture was stirred from 12 h and poured into 100 mL of cold water. The precipitate thus formed was crystallized from the appropriate solvent.

**4.1.6.1. *N*′-Hydroxy-4-(2-oxo-2-phenylethylsulfonyl) benzimidamide (32).** White solid, mp 192–194 °C (ethyl alcohol/diethyl

ether, (3:1)) $^1$H NMR (DMSO-$d_6$), $\delta$: 5.31 (s, 2H, $CH_2$), 5.95 (br s, 2H), 7.58–7.70 (m, 3H, 3CH), 7.79 (d, $J$ = 8.4, 2H, 2CH), 7.86–7.94 (m, 4H, 4CH), 10.00 (br s, 1H). $^{13}$C NMR (DMSO-$d_6$), $\delta$: 62.4 ($CH_2$), 125.6 (2CH), 128.2 (2CH), 129.2 (2CH), 129.4 (2CH), 134.2 (CH), 135.9 (C), 138.6 (C), 139.7 (C), 150.1 (C), 188.7 (C). HMRS (EI): $m/z$ calcd for $C_{15}H_{14}N_2O_4S$ M+H$^+$: 319.0747. Found: 319.0740.

**4.1.6.2. *N′*-Hydroxy-4-[2-(phenylsulfonyl)acetyl]benzimidamide (33).** White solid, mp 148–150 °C (ethyl alcohol/diethyl ether, (3:2)) $^1$H NMR (DMSO-$d_6$), $\delta$: 5.42 (s, 2H, $CH_2$), 5.99 (br s, 2H), 7.47–7.66 (m, 3H, 3CH), 7.88–7.97 (m, 6H, 6CH), 10.00 (br s, 1H). $^{13}$C NMR (DMSO-$d_6$), $\delta$: 62.3 ($CH_2$), 126.0 (2CH), 128.1 (2CH), 128.9 (2CH), 129.2 (2CH), 134.4 (CH), 135.9 (C), 138.6 (C), 139.6 (C), 149.8 (C), 189.3 (C). HMRS (EI): $m/z$ calcd for $C_{15}H_{14}N_2O_4S$ M+H$^+$: 319.0747. Found: 319.0740.

**4.1.6.3. *N′*-Hydroxy-4-{2-[4-(*N′*-hydroxycarbamimidoyl)phenyl]-2-oxoethylsulfonyl}benzimidamide (34).** White solid, mp 211–212 °C (ethyl alcohol/diethyl ether, (3:1)) $^1$H NMR (DMSO-$d_6$), $\delta$: 5.39 (s, 2H, $CH_2$), 6.02–6.04 (br s, 4H), 7.81 (d, $J$ = 8.2, 2H, 2CH), 7.88–7.92 (m, 4H, 4CH), 7.97 (d, $J$ = 8.2, 2H, 2CH), 10.01 (br s, 1H), 10.03 (br s, 1H). $^{13}$C NMR (DMSO-$d_6$), $\delta$: 62.3 ($CH_2$), 125.6 (2CH), 126.1 (2CH), 128.1 (2CH), 129.2 (2CH), 135.9 (C), 138.6 (2C), 139.6 (C), 149.9 (C), 150.2 (C), 188.7 (C). HMRS (EI): $m/z$ calcd for $C_{16}H_{16}N_4O_5S$ M+H$^+$: 377.0914. Found: 377.0908.

**4.1.6.4. 4-[5,5-Diphenyl-3-(phenylsulfonyl)-4,5-dihydrofuran-2-yl]-*N′*-hydroxybenzimidamide (35).** White solid, mp 163–164 °C (ethyl alcohol/water, (1:1)) $^1$H NMR (DMSO-$d_6$), $\delta$: 3.82 (s, 2H, $CH_2$), 5.95 (br s, 2H), 7.28–7.49 (m, 10H, 10CH), 7.53–7.83 (m, 9H, 9CH), 9.89 (br s, 1H). $^{13}$C NMR (DMSO-$d_6$), $\delta$: 45.2 ($CH_2$), 91.7 (C), 110.6 (C), 125.2 (2CH), 125.3 (4CH), 126.6 (2CH), 128.0 (2CH), 128.2 (C), 128.8 (4CH), 129.4 (2CH), 129.6 (2CH), 133.6 (CH), 136.2 (C), 141.3 (C), 144.0 (2C), 150.3 (C), 161.1 (C). HMRS (EI): $m/z$ calcd for $C_{29}H_{24}N_2O_4S$ M+H$^+$: 496.1430. Found: 496.1545.

**4.1.6.5. *N′*-Hydroxy-4-(2,5,5-triphenyl-4,5-dihydrofuran-3-ylsulfonyl)benzimidamide (36).** White solid, mp 157–158 °C (ethyl alcohol/water, (1:1)) $^1$H NMR (DMSO-$d_6$), $\delta$: 3.83 (s, 2H, $CH_2$), 5.96 (br s, 2H), 7.28–7.47 (m, 10H, 10CH), 7.51–7.58 (m, 3H, 3CH), 7.66–7.83 (m, 6H, 6CH), 9.99 (br s, 1H). $^{13}$C NMR (DMSO-$d_6$), $\delta$: 45.0 ($CH_2$), 91.7 (C), 110.4 (C), 125.3 (4CH), 126.3 (2CH), 126.5 (2CH), 128.0 (2CH), 128.3 (2CH), 128.7 (4CH), 129.5 (2CH), 131.6 (CH), 138.0 (C), 141.2 (C), 144.0 (2C), 149.7 (C), 161.7 (C), 1′ (C) not observed in these conditions. HMRS (EI): $m/z$ calcd for $C_{29}H_{24}N_2O_4S$ M+H$^+$: 497.1530. Found: 497.1521.

**4.1.6.6. *N′*-Hydroxy-4-{2-[4-(*N′*-hydroxycarbamimidoyl)phenyl]-5,5-diphenyl-4,5-dihydrofuran-3-ylsulfonyl}benzimidamide (37).** White solid, mp 155–156 °C (ethyl alcohol/water, (1:1)) $^1$H NMR (DMSO-$d_6$), $\delta$: 3.83 (s, 2H, $CH_2$), 6.34 (br s, 2H), 7.06 (br s, 2H), 7.29–7.46 (m, 10H, 10CH), 7.74 (d, $J$ = 8.5, 2H, 2CH), 7.80–7.91 (m, 6H, 6CH), 10.19 (br s, 1H), 10.52 (br s, 1H). $^{13}$C NMR (DMSO-$d_6$), $\delta$: 45.0 ($CH_2$), 92.1 (C), 111.1 (C), 125.2 (4CH), 126.4 (2CH), 126.6 (2CH), 126.8 (2CH), 128.1 (2CH), 128.8 (4CH), 129.7 (2CH), 129.8 (C), 130.4 (C), 130.5 (C), 137.2 (C), 141.4 (C), 143.9 (2C), 150.7 (C), 160.9 (C). HMRS (EI): $m/z$ calcd for $C_{30}H_{26}N_4O_5S$ M+H$^+$: 555.1697. Found: 555.1695.

**4.1.6.7. 4-[5-Benzyl-5-methyl-3-(phenylsulfonyl)-4,5-dihydrofuran-2-yl]-*N′*-hydroxybenzimidamide (38).** White solid, mp 58–61 °C (ethyl alcohol/water, (1:1)) $^1$H NMR (DMSO-$d_6$), $\delta$: 1.42 (s, 3H, $CH_3$), 2.75–3.03 (m, 4H, $2CH_2$), 5.90 (br s, 2H), 7.11–7.23 (m, 5H, 5CH), 7.47–7.65 (m, 7H, 7CH), 7.71 (d, $J$ = 8.4, 2H, 2CH), 9.83 (br s, 1H). $^{13}$C NMR (DMSO-$d_6$), $\delta$: 26.8 ($CH_3$), 41.6 ($CH_2$), 45.4 ($CH_2$), 88.5 (C), 109.4 (C), 124.9 (2CH), 126.3 (2CH), 126.9 (CH), 127.4 (C), 128.2 (2CH), 129.0 (2CH), 129.5 (2CH), 130.5 (2CH), 133.2 (CH), 135.4 (C), 136.0 (C), 141.5 (C), 150.5 (C), 161.8 (C). HMRS (EI): $m/z$ calcd for $C_{25}H_{24}N_2O_4S$ M+H$^+$: 449.1530. Found: 449.1528.

**4.1.6.8. 4-(5-Benzyl-5-methyl-2-phenyl-4,5-dihydrofuran-3-ylsulfonyl)-*N′*-hydroxybenzimidamide (39).** White solid, mp 76–80 °C (ethyl alcohol/water, (1:1)) $^1$H NMR (DMSO-$d_6$), $\delta$: 1.43 (s, 3H, $CH_3$), 2.77–3.04 (m, 4H, $2CH_2$), 5.98 (br s, 2H), 7.14–7.19 (m, 5H, 5CH), 7.38–7.52 (m, 7H, 7CH), 7.79 (d, $J$ = 8.4, 2H, 2CH), 9.99 (br s, 1H). $^{13}$C NMR (DMSO-$d_6$), $\delta$: 26.9 ($CH_3$), 41.4 ($CH_2$), 45.5 ($CH_2$), 88.5 (C), 109.2 (C), 126.2 (2CH), 126.3 (2CH), 126.8 (CH), 128.0 (2CH), 128.2 (2CH), 128.7 (C), 129.2 (2CH), 130.5 (2CH), 131.0 (C), 136.0 (C), 137.7 (C), 141.5 (C), 149.8 (C), 162.4 (C). HMRS (EI): $m/z$ calcd for $C_{25}H_{24}N_2O_4S$ M+H$^+$: 449.1530. Found: 449.1530.

**4.1.6.9. 4-{5-Benzyl-2-[4-(*N′*-hydroxycarbamimidoyl)phenyl]-5-methyl-4,5-dihydrofuran-3-ylsulfonyl}-*N′*-hydroxybenzimidamide (40).** White solid, mp 114–117 °C (ethyl alcohol/water, (1:1)) $^1$H NMR (DMSO-$d_6$), $\delta$: 1.43 (s, 3H, $CH_3$), 2.73–3.03 (m, 4H, $2CH_2$), 6.23 (br s, 2H), 7.10 (br s, 2H), 7.13–7.20 (m, 5H, 5CH), 7.49–7.56 (m, 4H, 4CH), 7.72–7.84 (m, 4H, 4CH), 10.10 (br s, 1H), 10.28 (br s, 1H). $^{13}$C NMR (DMSO-$d_6$), $\delta$: 26.8 ($CH_3$), 41.4 ($CH_2$), 45.5 ($CH_2$), 88.8 (C), 109.7 (C), 125.7 (2CH), 126.3 (2CH), 126.5 (2CH), 126.8 (CH), 128.2 (2CH), 129.2 (2CH), 130.1 (C), 130.4 (2CH), 133.4 (C), 135.9 (C), 137.2 (C), 141.6 (C), 150.4 (C), 152.7 (C), 161.6 (C). HMRS (EI): $m/z$ calcd for $C_{26}H_{26}N_4O_5S$ M+H$^+$: 507.1697. Found: 507.1718.

**4.1.6.10. *N′*-Hydroxy-4-[4-{2-[4-(*N′*-hydroxycarbamimidoyl)-phenyl]-5,5-diphenyl-4,5-dihydrofuran-3-ylsulfonyl}phenylamino]benzimidamide (41).** White solid, mp 146–147 °C (ethyl alcohol/water, (1:1)) $^1$H NMR (DMSO-$d_6$), $\delta$: 3.79 (s, 2H, $CH_2$), 5.74 (br s, 2H), 5.94 (br s, 2H), 7.04–7.95 (m, 22H, 22CH), 9.00 (br s, 1H), 9.52 (br s, 1H), 9.88 (br s, 1H). $^{13}$C NMR (DMSO-$d_6$), $\delta$: 45.3 ($CH_2$), 91.3 (C), 112.1 (C), 114.8 (2CH), 118.8 (2CH), 125.2 (2CH), 125.3 (4CH), 126.7 (2CH), 127.4 (2CH), 128.0 (2CH), 128.8 (4CH), 129.5 (2CH), 136.0 (C), 136.6 (C), 141.8 (C), 144.2 (C), 144.3 (2C), 148.2 (C), 150.5 (C), 150.8 (C), 159.4 (C), 167.5 (C). HMRS (EI): $m/z$ calcd for $C_{36}H_{31}N_5O_5S$ M+H$^+$: 646.2119. Found: 646.2099.

**4.1.6.11. *N′*-Hydroxy-4-[2-{4-[4-(*N′*-hydroxycarbamimidoyl)-phenylamino]phenyl}-5,5-diphenyl-4,5-dihydrofuran-3-ylsulfonyl]benzimidamide (42).** Yellow solid, mp 132 °C (ethyl alcohol/water, (1:1)) $^1$H NMR (DMSO-$d_6$), $\delta$: 3.83 (s, 2H, $CH_2$), 5.95 (br s, 4H), 7.23–7.85 (m, 22H, 22CH), 8.89 (br s, 1H), 9.34 (br s, 1H), 9.97 (br s, 1H). $^{13}$C NMR (DMSO-$d_6$), $\delta$: 45.3 ($CH_2$), 91.0 (C), 101.2 (C), 108.3 (C), 116.6 (2CH), 117.2 (2CH), 119.9 (C), 120.2 (C), 125.3 (4CH), 126.3 (2CH), 126.4 (2CH), 128.0 (2CH), 128.7 (4CH), 131.3 (2CH), 134.0 (2CH), 138.0 (C), 141.6 (C), 144.1 (2C), 144.4 (C), 146.8 (C), 149.8 (C), 161.3 (C). HMRS (EI): $m/z$ calcd for $C_{36}H_{31}N_5O_5S$ M+H$^+$: 646.2119. Found: 646.2098.

**4.1.6.12. 4-[4-{5-Benzyl-2-[4-(*N′*-hydroxycarbamimidoyl)phenyl]-5-methyl-4,5-dihydrofuran-3-ylsulfonyl}phenylamino]-*N′*-hydroxybenzimidamide (43).** White solid, mp 75–76 °C (ethyl alcohol/water, (1:1)) $^1$H NMR (DMSO-$d_6$), $\delta$: 1.41 (s, 3H, $CH_3$), 2.79–3.04 (m, 4H, $2CH_2$), 5.74 (br s, 2H), 5.90 (br s, 2H), 7.05–7.24 (m, 10H, 10CH), 7.36 (d, $J$ = 8.4, 2H, 2CH), 7.48–7.66 (m, 3H, 3CH), 7.72 (d, $J$ = 8.4, 2H, 2CH), 8.98 (br s, 1H), 9.51 (br s, 1H), 9.82 (br s, 1H). $^{13}$C NMR (DMSO-$d_6$), $\delta$: 26.7 ($CH_3$), 41.8 ($CH_2$), 45.5 ($CH_2$), 88.0 (C), 110.8 (C), 114.8 (2CH), 117.2 (2CH), 118.6 (2CH), 124.8 (2CH), 126.7 (2CH), 126.8 (CH), 128.3 (2CH), 129.1 (2CH), 129.3 (C), 130.3 (C), 130.5 (2CH), 132.7 (C), 135.4 (C),

136.2 (C), 141.9 (C), 146.3 (C), 147.9 (C), 150.4 (C), 160.1 (C). HMRS (EI): *m*/*z* calcd for $C_{32}H_{31}N_5O_5S$ M+H$^+$: 598.2119. Found: 598.2125.

**4.1.6.13. 4-[5-Benzyl-2-{4-[4-(*N*′-hydroxycarbamimidoyl)phenylamino]phenyl}-5-methyl-4,5-dihydrofuran-3-ylsulfonyl]-*N*′-hydroxybenzimidamide (44).** Yellow solid, mp 126 °C (ethyl alcohol/water, (1:1)) $^1$H NMR (DMSO-$d_6$), $\delta$: 1.40 (s, 3H, $CH_3$), 2.71–3.09 (m, 4H, $2CH_2$), 5.71 (br s, 2H), 5.97 (br s, 2H), 7.20–7.88 (m, 17H, 17CH), 8.76 (br s, 1H), 9.23 (br s, 1H), 9.97 (br s, 1H). $^{13}$C NMR (DMSO-$d_6$), $\delta$: 26.7 ($CH_3$), 41.8 ($CH_2$), 45.4 ($CH_2$), 87.7 (C), 100.9 (C), 107.5 (C), 116.3 (2CH), 117.2 (2CH), 119.9 (C), 121.2 (C), 126.1 (2CH), 126.2 (CH), 126.8 (2CH), 128.2 (2CH), 130.5 (2CH), 130.8 (2CH), 133.9 (2CH), 136.1 (C), 137.5 (C), 141.8 (C), 143.7 (C), 147.0 (C), 149.8 (C), 161.9 (C). HMRS (EI): *m*/*z* calcd for $C_{32}H_{31}N_5O_5S$ M+H$^+$: 598.2119. Found: 598.2122.

**4.1.6.14. *N*′-Hydroxy-3-[4-{2-[4-(*N*′-hydroxycarbamimidoyl)phenyl]-5,5-diphenyl-4,5-dihydrofuran-3-ylsulfonyl}phenylamino]benzimidamide (45).** White solid, mp 211–212 °C (ethyl alcohol/water, (1:1)) $^1$H NMR (DMSO-$d_6$), $\delta$: 3.78 (s, 2H, $CH_2$), 5.80 (br s, 2H), 5.94 (br s, 2H), 7.04 (d, $J$ = 8.4, 2H, 2CH), 7.28–7.55 (m, 16H, 16CH), 7.73–7.86 (m, 4H, 4CH), 8.94 (br s, 1H), 9.64 (br s, 1H), 9.88 (br s, 1H). $^{13}$C NMR (DMSO-$d_6$), $\delta$: 45.4 ($CH_2$), 91.2 (C), 112.0 (C), 114.4 (2CH), 117.0 (CH), 119.9 (CH), 120.5 (CH), 125.1 (2CH), 125.3 (4CH), 128.0 (2CH), 128.5 (C), 128.8 (4CH), 128.9 (2CH), 129.4 (2CH), 129.5 (C), 134.8 (C), 135.9 (C), 140.9 (C), 144.2 (2C), 148.7 (C), 150.4(C), 151.0 (C), 159.2 (C), 1 (CH) not observed in these conditions. HMRS (EI): *m*/*z* calcd for $C_{36}H_{31}N_5O_5S$ M+H$^+$: 646.2119. Found: 646.2104.

**4.1.6.15. *N*′-Hydroxy-3-[4-{3-[4-(*N*′-hydroxycarbamimidoyl)phenylsulfonyl]-5,5-diphenyl-4,5-dihydrofuran-2-yl}phenylamino]benzimidamide (46).** Yellow solid, mp 135 °C (ethyl alcohol/water, (1:1)) $^1$H NMR (DMSO-$d_6$), $\delta$: 3.81 (s, 2H, $CH_2$), 5.79 (br s, 2H), 5.93 (br s, 2H), 7.09–7.80 (m, 22H, 22CH), 8.81 (br s, 1H), 9.63 (br s, 1H), 9.96 (br s, 1H). $^{13}$C NMR (DMSO-$d_6$), $\delta$: 45.3 ($CH_2$), 90.6 (C), 106.8 (C), 114.3 (2CH), 115.5 (C), 115.8 (CH), 117.5 (CH), 119.0 (2CH), 119.7 (CH), 125.3 (4CH), 126.3 (2CH), 127.9 (2CH), 128.7 (4CH), 129.3 (CH), 131.4 (2CH), 134.7 (C), 137.7 (C), 141.5 (C), 141.8 (C), 144.2 (2C), 147.1 (C), 149.8 (C), 151.1 (C), 161.6 (C). HMRS (EI): *m*/*z* calcd for $C_{36}H_{31}N_5O_5S$ M+H$^+$: 646.2119. Found: 646.2104.

**4.1.6.16. 3-[4-{5-Benzyl-2-[4-(*N*′-hydroxycarbamimidoyl)phenyl]-5-methyl-4,5-dihydrofuran-3-ylsulfonyl}phenylamino]-*N*′-hydroxybenzimidamide (47).** White solid, mp 100–101 °C (ethyl alcohol/water, (1:1)) $^1$H NMR (DMSO-$d_6$), $\delta$: 1.41 (s, 3H, $CH_3$), 2.72–3.01 (m, 4H, $2CH_2$), 5.81 (br s, 2H), 5.91 (br s, 2H), 7.03–7.38 (m, 12H, 12CH), 7.52–7.56 (m, 3H, 3CH), 7.73 (d, $J$ = 8.4, 2H, 2CH), 8.93 (br s, 1H), 9.65 (br s, 1H), 9.83 (br s, 1H). $^{13}$C NMR (DMSO-$d_6$), $\delta$: 26.7 ($CH_3$), 41.8 ($CH_2$), 45.5 ($CH_2$), 87.9 (C), 110.8 (C), 114.4 (2CH), 116.7 (CH), 119.7 (CH), 120.3 (CH), 124.8 (2CH), 126.8 (CH), 128.2 (2CH), 128.6 (2CH), 129.1 (2CH), 129.3 (C), 129.4 (CH), 130.1 (C), 130.5 (2CH), 134.9 (C), 135.4 (C), 136.1 (C), 141.0 (C), 148.3 (C), 150.4 (C), 151.1 (C), 160.0 (C). HMRS (EI): *m*/*z* calcd for $C_{32}H_{31}N_5O_5S$ M+H$^+$: 598.2119. Found: 598.2119.

**4.1.6.17. 3-[4-{5-Benzyl-3-[4-(N′-hydroxycarbamimidoyl)phenylsulfonyl]-5-methyl-4,5-dihydrofuran-2-yl}phenylamino]-*N*′-hydroxybenzimidamide (48).** Yellow solid, mp 114 °C (ethyl alcohol/water, (1:1)) $^1$H NMR (DMSO-$d_6$), $\delta$: 1.38 (s, 3H, $CH_3$), 2.73–3.02 (m, 4H, $2CH_2$), 5.82 (br s, 2H), 5.97 (br s, 2H), 6.95–7.80 (m, 17H, 17CH), 8.70 (br s, 1H), 9.64 (br s, 1H), 9.97 (br s, 1H). $^{13}$C NMR (DMSO-$d_6$), $\delta$: 26.6 ($CH_3$), 45.4 ($CH_2$), 41.9 ($CH_2$), 87.3 (C), 106.0 (C), 114.2 (2CH), 115.6 (CH), 118.4 (CH), 118.8 (C), 119.5 (CH), 126.2 (4CH), 126.8 (CH), 128.2 (2CH), 129.2 (CH), 130.5 (2CH), 130.9 (2CH), 134.7 (C), 136.2 (C), 137.5 (C), 141.7 (C), 142.1 (C), 146.4 (C), 149.9 (C), 151.2 (C), 162.3 (C). HMRS (EI): *m*/*z* calcd for $C_{32}H_{31}N_5O_5S$ M+H$^+$: 646.2119. Found: 646.2126.

**4.1.6.18. *N*′-Hydroxy-2-[4-{2-[4-(*N*′-hydroxycarbamimidoyl)phenyl]-5,5-diphenyl-4,5-dihydrofuran-3-ylsulfonyl}phenylamino]benzimidamide (49).** White solid, mp 129–131 °C (ethyl alcohol/water, (1:1)) $^1$H NMR (DMSO-$d_6$), $\delta$: 3.79 (s, 2H, $CH_2$), 5.94 (br s, 2H), 6.01 (br s, 2H), 7.03 (d, $J$ = 8.5, 2H, 2CH), 7.28–7.95 (m, 20H, 20CH), 9.16 (br s, 1H), 9.87 (br s, 2H). $^{13}$C NMR (DMSO-$d_6$), $\delta$: 45.3 ($CH_2$), 91.4 (C), 105.2 (C), 111.9 (C), 115.8 (2CH), 115.9 (2CH), 117.5 (C), 122.2 (C), 124.1 (CH), 126.2 (2CH), 125.3 (4CH), 127.4 (CH), 128.0 (2CH), 128.5 (CH), 128.8 (4CH), 129.5 (2CH), 131.3 (C), 134.4 (CH), 134.7 (C), 136.0 (C), 144.2 (2C), 148.1 (C), 150.5 (C), 159.7 (C). HMRS (EI): *m*/*z* calcd for $C_{36}H_{31}N_5O_5S$ M+H$^+$: 646.2119. Found: 646.2119.

**4.1.6.19. *N*′-Hydroxy-2-[4-{3-[4-(*N*′-hydroxycarbamimidoyl)phenylsulfonyl]-5,5-diphenyl-4,5-dihydrofuran-2-yl}phenylamino]benzimidamide (50).** Yellow solid, mp 210 °C (ethyl alcohol/water, (1:1)) $^1$H NMR (DMSO-$d_6$), $\delta$: 3.83 (s, 2H, $CH_2$), 5.95–6.04 (br s, 4H), 7.13–7.78 (m, 22H, 22CH), 9.90–9.97 (br s, 3H). $^{13}$C NMR (DMSO-$d_6$), $\delta$: 45.3 ($CH_2$), 90.8 (C), 107.5 (C), 116.0 (2CH), 118.0 (CH), 118.8 (C), 120.8 (2CH), 125.3 (4CH), 126.2 (2CH), 126.3 (2CH), 127.9 (2CH), 128.7 (4CH), 129.4 (CH), 131.4 (2CH), 137.8 (C), 139.8 (C), 141.7 (C), 144.1 (2C), 145.9 (C), 149.8 (C), 152.2 (C), 161.5 (C). 1′ (C) not observed in these conditions. HMRS (EI): *m*/*z* calcd for $C_{36}H_{31}N_5O_5S$ M+H$^+$: 646.2119. Found: 646.2105.

**4.1.6.20. 2-[4-{5-Benzyl-2-[4-(*N*′-hydroxycarbamimidoyl)phenyl]-5-methyl-4,5-dihydrofuran-3-ylsulfonyl}phenylamino]-*N*′-hydroxybenzimidamide (51).** White solid, mp 117–118 °C (ethyl alcohol/water, (1:1))$^1$H NMR (DMSO-$d_6$), $\delta$: 1.41 (s, 3H, $CH_3$), 2.72–2.94 (m, 4H, $2CH_2$), 5.90 (br s, 2H), 6.02 (br s, 2H), 7.01–7.28 (m, 9H, 9CH), 7.36 (d, $J$ = 8.7, 2H, 2CH), 7.51 (d, $J$ = 8.3, 2H, 2CH), 7.59–7.63 (m, 1H, CH), 7.72 (d, $J$ = 8.3, 2H, 2CH), 7.78–7.82 (m, 1H, CH), 9.83 (br s, 2H), 9.92 (br s, 1H). $^{13}$C NMR (DMSO-$d_6$), $\delta$: 26.8 ($CH_3$), 41.8 ($CH_2$), 45.5 ($CH_2$), 88.1 (C), 110.8 (C), 116.0 (2CH), 118.8 (CH), 121.7 (CH), 124.9 (CH), 126.9 (CH), 128.2 (2CH), 128.6 (2CH), 128.9 (CH), 129.1 (2CH), 129.5 (CH), 130.5 (2CH), 131.3 (C), 134.4 (C), 134.7 (C), 135.4 (C), 136.1 (C), 139.3 (C), 147.3 (C), 150.5 (C), 152.1 (C), 160.3 (C). HMRS (EI): *m*/*z* calcd for $C_{32}H_{31}N_5O_5S$ M+H$^+$: 598.2119. Found: 598.2126.

**4.1.6.21. 2-[4-{5-Benzyl-3-[4-(*N*′-hydroxycarbamimidoyl)phenylsulfonyl]-5-methyl-4,5-dihydrofuran-2-yl}phenylamino]-*N*′-hydroxybenzimidamide (52).** Yellow solid, mp 105 °C (ethyl alcohol/water, (1:1)) $^1$H NMR (DMSO-$d_6$), $\delta$: 1.40 (s, 3H, $CH_3$), 2.71–3.09 (m, 4H, $2CH_2$), 5.97 (br s, 4H), 7.04–7.78 (m, 17H, 17CH), 8.89 (br s, 1H), 9.86 (br s, 1H), 9.97 (br s, 1H). $^{13}$C NMR (DMSO-$d_6$), $\delta$: 26.4 ($CH_3$), 41.6 ($CH_2$), 45.2 ($CH_2$), 87.3 (C), 103.3 (C), 106.9 (C), 115.8 (2CH), 117.4 (C), 120.0 (C), 120.3 (CH), 122.4 (CH), 125.9 (2CH), 126.5 (CH), 127.9 (2CH), 130.2 (2CH), 130.5 (2CH), 130.7 (CH), 134.0 (CH), 134.3 (2CH), 135.9 (C), 137.3 (C), 141.7 (C), 145.0 (C), 145.3 (C), 149.6 (C), 161.8 (C). HMRS (EI): *m*/*z* calcd for $C_{32}H_{31}N_5O_5S$ M+H$^+$: 646.2119. Found: 646.2127.

**4.1.6.22. *N*′-Hydroxy-4-[4-{2-[4-(*N*′-hydroxycarbamimidoyl)phenyl]-5,5-diphenyl-4,5-dihydrofuran-3-ylsulfonyl}styryl]-benzimidamide (53).** White solid, mp 129 °C (ethyl alcohol/water, (1:1)) $^1$H NMR (DMSO-$d_6$), $\delta$: 3.83 (s, 2H, $CH_2$), 5.85 (br s, 2H), 5.95 (br s, 2H), 7.31–7.42 (m, 12H, 12CH), 7.70–7.80 (m, 12H, 12CH), 9.71 (br s, 1H), 9.89 (br s, 1H). $^{13}$C NMR (DMSO-

$d_6$), $\delta$: 45.2 ($CH_2$), 91.7 (C), 110.8 (C), 125.2 (2CH), 125.3 (4CH), 125.9 (2CH), 126.9 (2CH), 127.1 (2CH), 127.3 (2CH), 128.0 (CH), 128.2 (2CH), 128.3 (CH), 128.7 (4CH), 129.4 (2CH), 131.7 (C), 133.3 (C), 136.2 (C), 137.0 (C), 139.5 (C), 142.1 (C), 144.0 (2C), 150.3 (C), 150.6 (C), 160.9 (C). HMRS (EI): *m*/*z* calcd for $C_{38}H_{32}N_4O_5S$ M+H$^+$: 657.2166. Found: 657.2184.

**4.1.6.23. *N*′-Hydroxy-4-[4-{3-[4-(*N*′-hydroxycarbamimidoyl)-phenylsulfonyl]-5,5-diphenyl-4,5-dihydrofuran-2-yl}styryl]benzimidamide (54).** Yellow solid, mp 133 °C (ethyl alcohol/water, (1:1)) $^1$H NMR (DMSO-$d_6$), $\delta$: 3.85 (s, 2H, $CH_2$), 5.85 (br s, 2H), 5.96 (br s, 2H), 7.29–7.54 (m, 12H, 12CH), 7.63–7.95 (m, 12H, 12CH), 9.71 (br s, 1H), 9.99 (br s, 1H). $^{13}$C NMR (DMSO-$d_6$), $\delta$: 45.2 ($CH_2$), 91.6 (C), 110.2 (C), 125.3 (4CH), 125.8 (2CH), 126.3 (2CH), 126.4 (2CH), 126.5 (2CH), 126.7 (2CH), 128.0 (2CH), 128.7 (4CH), 130.0 (2CH), 130.4 (CH), 130.7 (CH), 132.9 (C), 133.0 (C), 137.3 (C), 137.8 (C), 140.2 (C), 141.3 (C), 144.0 (2C), 149.8 (C), 150.6 (C), 161.3 (C). HMRS (EI): *m*/*z* calcd for $C_{38}H_{32}N_4O_5S$ M+H$^+$: 657.2166. Found: 657.2178.

**4.1.6.24. 4-[4-{5-Benzyl-2-(4-[*N*′-hydroxycarbamimidoyl)-phenyl]-5-methyl-4,5-dihydrofuran-3-ylsulfonyl}styryl]-*N*′-hydroxybenzimidamide (55).** White solid, mp 145–147 °C (ethyl alcohol/water, (1:1)) $^1$H NMR (DMSO-$d_6$), $\delta$: 1.41 (s, 3H, $CH_3$), 2.75–3.02 (s, 4H, $2CH_2$), 5.83 (br s, 2H), 5.89 (br s, 2H), 7.10–7.21 (m, 5H, 5CH), 7.40–7.52 (m, 6H, 6CH), 7.66–7.74 (m, 8H, 8CH), 9.69 (br s, 1H), 9.81 (br s, 1H). $^{13}$C NMR (DMSO-$d_6$), $\delta$: 26.8 ($CH_3$), 42.8 ($CH_2$), 45.4 ($CH_2$), 88.4 (C), 109.6 (C), 124.8 (2CH), 125.8 (2CH), 126.8 (3CH), 126.9 (2CH), 127.2 (CH), 127.3 (2CH), 128.2 (2CH), 129.0 (C), 129.1 (2CH), 130.4 (2CH), 131.5 (CH), 133.2 (C), 135.6 (C), 136.0 (C), 137.1 (C), 139.9 (C), 141.8 (C), 150.3 (C), 150.6 (C), 161.6 (C). HMRS (EI): *m*/*z* calcd for $C_{34}H_{32}N_4O_5S$ M+H$^+$: 609.2166. Found: 609.2173.

**4.1.6.25. 4-[5-Benzyl-2-{4-[4-(*N*′-hydroxycarbamimidoyl)styryl]-phenyl}-5-methyl-4,5-dihydrofuran-3-ylsulfonyl]-*N*′-hydroxybenzimidamide (56).** Yellow solid, mp 110 °C (ethyl alcohol/water, (1:1)) $^1$H NMR (DMSO-$d_6$), $\delta$: 1.44 (s, 3H, $CH_3$), 2.73–3.05 (m, 4H, $2CH_2$), 5.84 (br s, 2H), 5.99 (br s, 2H), 7.14–7.84 (m, 19H, 19CH), 9.70 (br s, 1H), 9.99 (br s, 1H). $^{13}$C NMR (DMSO-$d_6$), $\delta$: 26.8 ($CH_3$), 41.6 ($CH_2$), 45.5 ($CH_2$), 88.3 (C), 109.0 (C), 109.3 (C), 125.8 (2CH), 126.0 (2CH), 126.5 (CH), 126.6 (2CH), 126.7 (2CH), 126.8 (CH), 127.6 (2CH), 128.2 (2CH), 129.7 (2CH), 130.5 (CH), 132.9 (2CH), 136.0 (C), 137.7 (C), 139.0 (C), 141.5 (C), 141.6 (C), 141.7 (C), 149.8 (C), 150.7 (C), 161.9 (C). HMRS (EI): *m*/*z* calcd for $C_{34}H_{32}N_4O_5S$ M+H$^+$: 609.2166. Found: 609.2177.

### 4.2. Biology

#### 4.2.1. General

Cell culture media (RPMI 1640 and M199), foetal calf serum (FCS), L-glutamine, non essential amino acids and others medium additives were from Eurobio (Paris, France). All other chemicals were of highest chemical purity and were purchased from Sigma except contrary mention. Stock solutions of amidoxime derivatives were prepared in DMSO. Stock solutions of reference drugs (doxorubicin and pentamidine) were prepared in DMSO. Flow cytometry was performed at the Faculté de Pharmacie de Marseille, using a FACSort flow cytometer apparatus (Becton Dickinson, Paris, France), equipped with an argon laser (power of 15 mW, and wavelength of 488 nm).

#### 4.2.2. Cytotoxic assays on human monocytes THP1

Cytotoxicity was assessed on human monocytes THP1 (ATCC, Manassas VA, USA) by flow cytometry as described previously.[21] Late log-phase THP1 cells were incubated in RPMI 1640 (without phenol red) supplemented with 10% FSC, 2% L-glutamine and 1% penicillin–streptomycin mix (complete RPMI medium) and a range of compound concentrations incorporated in duplicate (final DMSO concentration less than 0.5% v/v). Appropriate controls treated with or without solvent (DMSO), and various concentrations of doxorubicin (positive control) and pentamidine were added to each set of experiments. After 72 h incubation at 37 °C and 6% $CO_2$, cell growth was measured by flow cytometry after staining monocytes with 5 μL of propidium iodide. Antiproliferative activity was evaluated by counting the number of live cells in a 100 μL sample. Inhibitory concentration 50% ($IC_{50}$ THP1) was defined as the concentration of drug required to induce a 50% in the THP1 cell proliferation compared to the control. $IC_{50}$ was calculated by non-linear regression analysis processed on dose–response curves, using GraphPad Prism (version 4.03) software. $IC_{50}$ values represent the mean value calculated from three independent experiments.

#### 4.2.3. Antileishmanial activity

The effects of the tested compounds on the growth of *Leishmania donovani* promastigotes (GFP-transfected strain HOM/IN/01/2001, kindly provided by Dr. N. Singh, Lucknow, India) were assessed by flow cytometry as described previously by Singh and Dube.[22] Briefly, promastigotes in late log-phase in M199 medium supplemented with 10% FCS and 500 μg/mL of G418 were incubated at an average density of $10^5$ parasites/mL in 24-well plates with various concentrations of compounds dissolved in DMSO (final concentration less than 0.5% v/v) incorporated in duplicate. Appropriate controls treated by DMSO or pentamidine (reference drug) were added to each set of experiments. After a 72-h incubation period at 27 °C, parasite growth was determined using a FACSort flow cytometer. Settings were: Forward Scatter (FSC-H), size: Voltage E-1, gain 1, mode Lin; Side Scatter (SSC-H), granulosity: Voltage 489, gain 1, mode Lin; Fluorescence 1 (FL1), green fluorescence: Voltage 505, gain 1, mode Log. Pentamidine and amphotericin B were used as the reference drug. Inhibitory concentration 50% ($IC_{50}$ *Ld*) was defined as the concentration of drug required to induce a 50% in the *Leishmania* proliferation compared to the control. $IC_{50}$ was calculated by non-linear regression analysis processed on dose–response curves, using GraphPad Prism (version 4.03) software. $IC_{50}$ values represent the mean value 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:10.1016/j.bmc.2010.06.099.

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