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SYNTHESIS OF METABOLITES OF THE PRODRUG 2, 5-BIS(4-*O*-METHOXYAMIDINOPHENYL)FURAN

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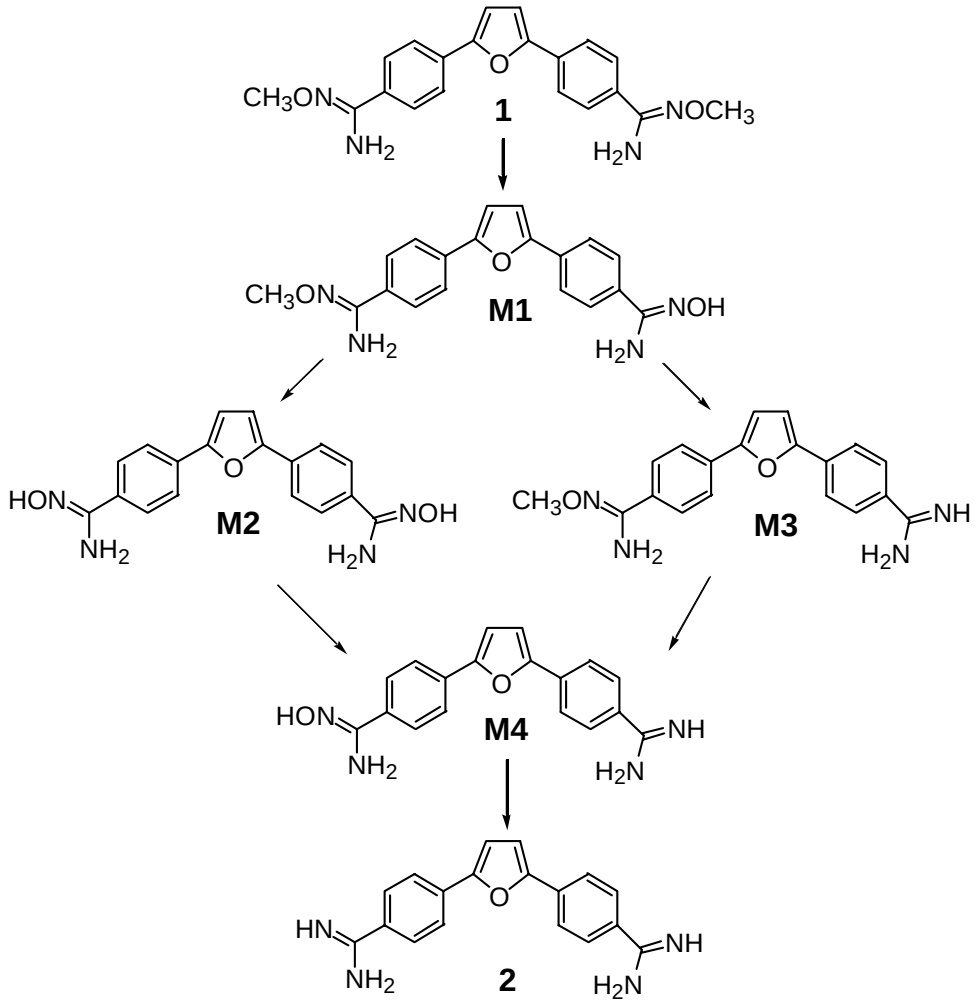
Abstract- The synthesis of three metabolites of the prodrug 2,5-bis-(4-*O*-methoxyamidinophenyl)furan (**1**), 2-(4-hydroxyamidinophenyl)-5-(4-methoxyamidinophenyl)furan (**M1)**, 2-(4-amidinophenyl)-5-(4-ethoxyamidinophenyl)furan (**M3)** and 2-(4-amidinophenyl)-5-(4-hydroxyamidinophenyl)furan (**M4),** is reported. The key step in each of the syntheses involves the Heck reaction.

INTRODUCTION

2,5-Bis(4-*O*-methoxyamidinophenyl)furan (**1**), a prodrug of the antimicrobial agent, 2,5-bis(4-amidinophenyl)furan (**2**), is effective when administered orally in an immunosupressed rat model for *Pneumocystis carinii* pneumonia (PCP) and it also shows excellent activity in mouse models for human African trypanosomiasis (See Figure 1).[1,2] The bis-*O*-methylamidoxime prodrug is currently undergoing phase II clinical trial against both of these diseases.[2] MS spectral evidence suggests that **1** is converted to **2** *via* a series of stepwise *O*-demethylations and dehydroxylations. Four major metabolites 2-(4-hydroxyamidinophenyl)-5-(4-methoxyamidinophenyl)furan (**M1)**, 2,5-bis(4-hydroxyamidinophenyl)furan (**M2)**, 2-(4-amidinophenyl)-5-(4-methoxyamidinophenyl)furan (**M3)** and 2-(4-amidinophenyl)-5-(4-hydroxyamidinophenyl)furan (**M4)** in the bioconversion of **1** were detected using ion trap MS with electrospray ionization (Figure 1).[3] To unequivocally identify these metabolites, it is important to unambiguously synthesize them. We have previously reported the synthesis of **M2**. [1] In this article, we report the synthesis of the postulated metabolites (**M1**, **M3** and **M4**).

Figure 1**: METABOLIC PATHWAY OF** 1 **TO** 2

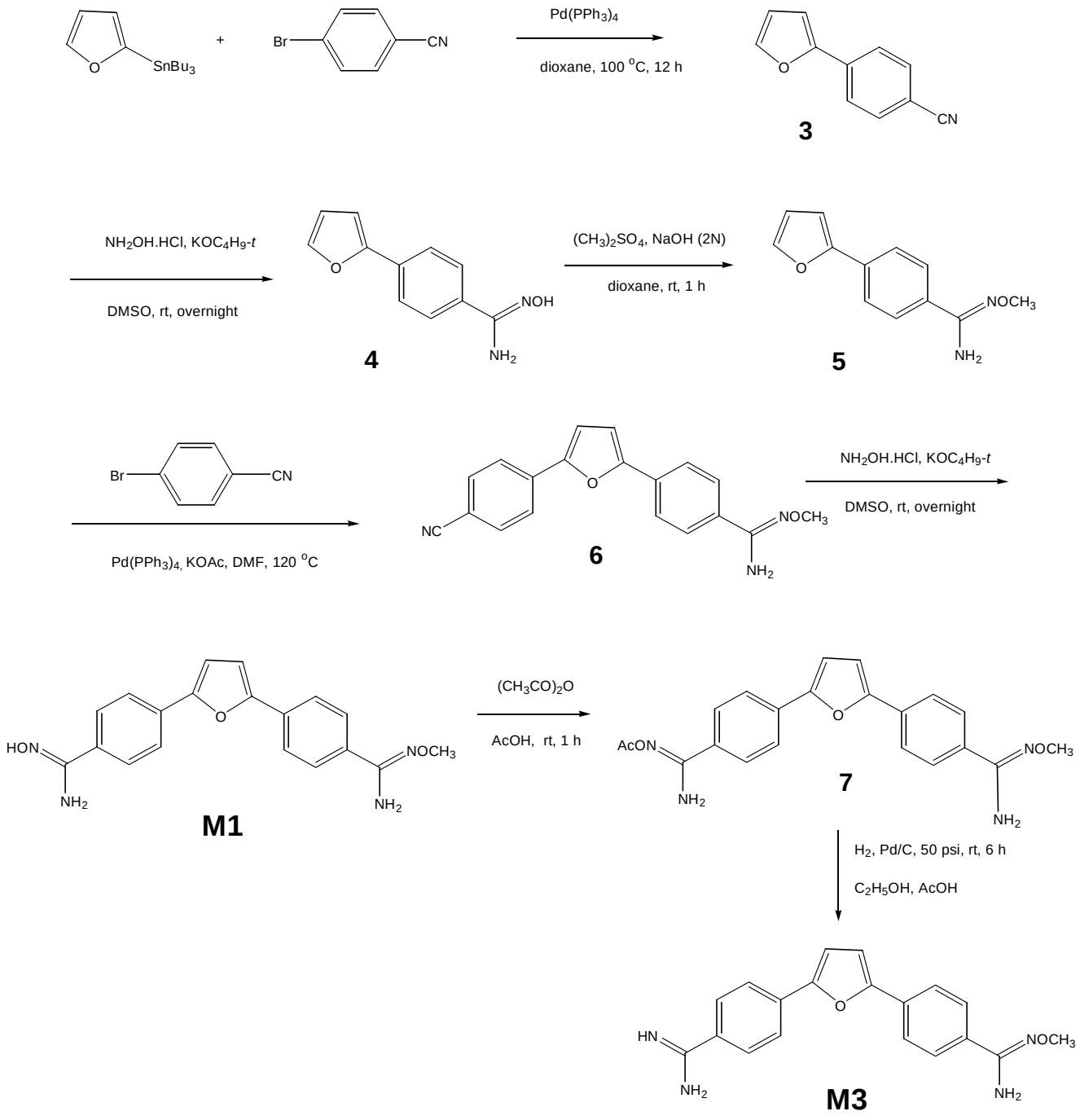


RESULTS AND DISCUSSION

Our approach to the synthesis of **M1** is outlined in *Scheme 1*. 2-(4-Cyanophenyl)furan (**3**) was prepared according to a literature method.[4] When **3** was treated with hydroxylamine hydrochloride and potassium *tert*-butoxide in DMSO at an ambient temperature, **4** was obtained in 90 % yield. Compound (**5**) was obtained in 80 % yield by treating the amidoxime (**4**) with dimethyl sulfate in the presence of sodium hydroxide (2N) in dioxane at 0 °C.[5] Heck coupling of the methoxyamidoxime (**5**) with *p*-bromobenzonitrile in presence of potassium acetate and Pd(0) catalyst gave 2-(4-cyanophenyl)-5-(4-methoxyamidino-phenyl)furan (**6)** in 40 % yield. The relatively low yield of **6** obtained here is typical of Heck coupling reactions with furans[6] and other related Pd catalysed couplings with furan.[7] 2-(4-Hydroxyamidinophenyl)-5-(4-methoxyamidinophenyl)furan (**M1)** was obtained when **6** was reacted

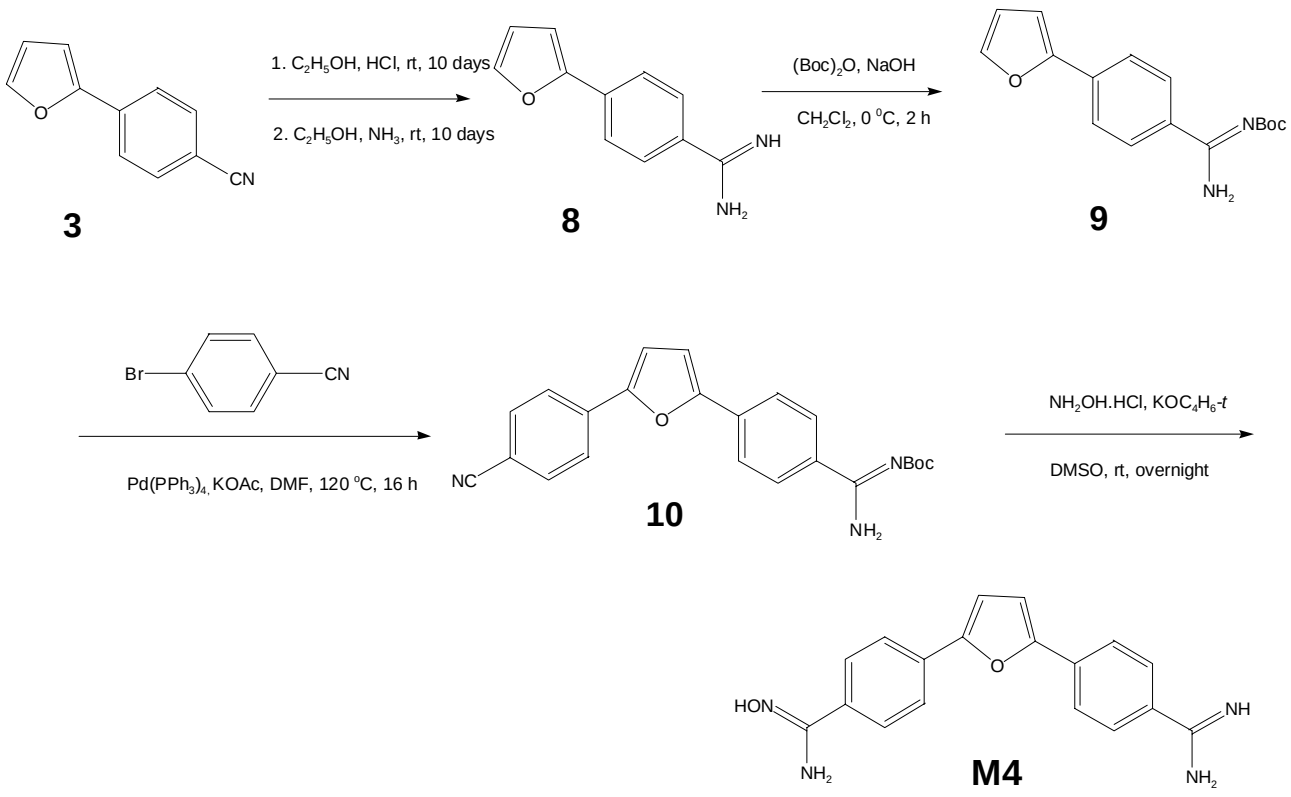
at room temperature for 12 h with hydroxylamine hydrochloride and potassium *tert*-butoxide in DMSO solution to give an 85 % yield. The hydrochloride salt of **M1** was made by passing hydrogen chloride gas into an ethanol solution of the free base. Acetylation of **M1** with acetic anhydride in acetic acid yielded 2-(4-acetoxyamidinophenyl)-5-(4-methoxyamidinophenyl)furan (**7**) in 90 % yield. Pd/C catalysed hydrogenation[8] of **7** in acetic acid-ethanol mixture gave the metabolite 2-(4-amidinophenyl)-5-(4-methoxyamidinophenyl)furan (**M3)** in 65 % yield. Thus the synthesis of the metabolites (**M1**) and (**M3**) was achieved in reasonably good yields using straightforward approaches.

Scheme 1



The synthesis of **M4** turned out to be much more difficult. *Scheme 2* outlines the first of three approaches we explored for the synthesis of **M4.** The reaction of **3** under Pinner conditions yielded the amidine (**8**) in 50 % yield. Attempted Heck reaction of the amidine (**8**) with *p*-bromobenzonitrile failed; ammonia was eliminated to reform **3**. To avoid this problem the butoxycarbonyl (Boc) protected amidine (**9**) was prepared in high yield by treating the amidine with di-*tert*-butyl dicarbonate in DCM at 0 °C.[9] The Heck reaction of **9** with *p*-bromobenzonitrile in DMF under Pd(0) catalysis gave **10** but in rather low yield (23 %). When **10** was treated with hydroxylamine hydrochloride and potassium *tert*-butoxide as previously described, the metabolite (**M4**) was obtained in quite low yield (3 %). Interestingly, the Boc protecting group was also removed during this process.

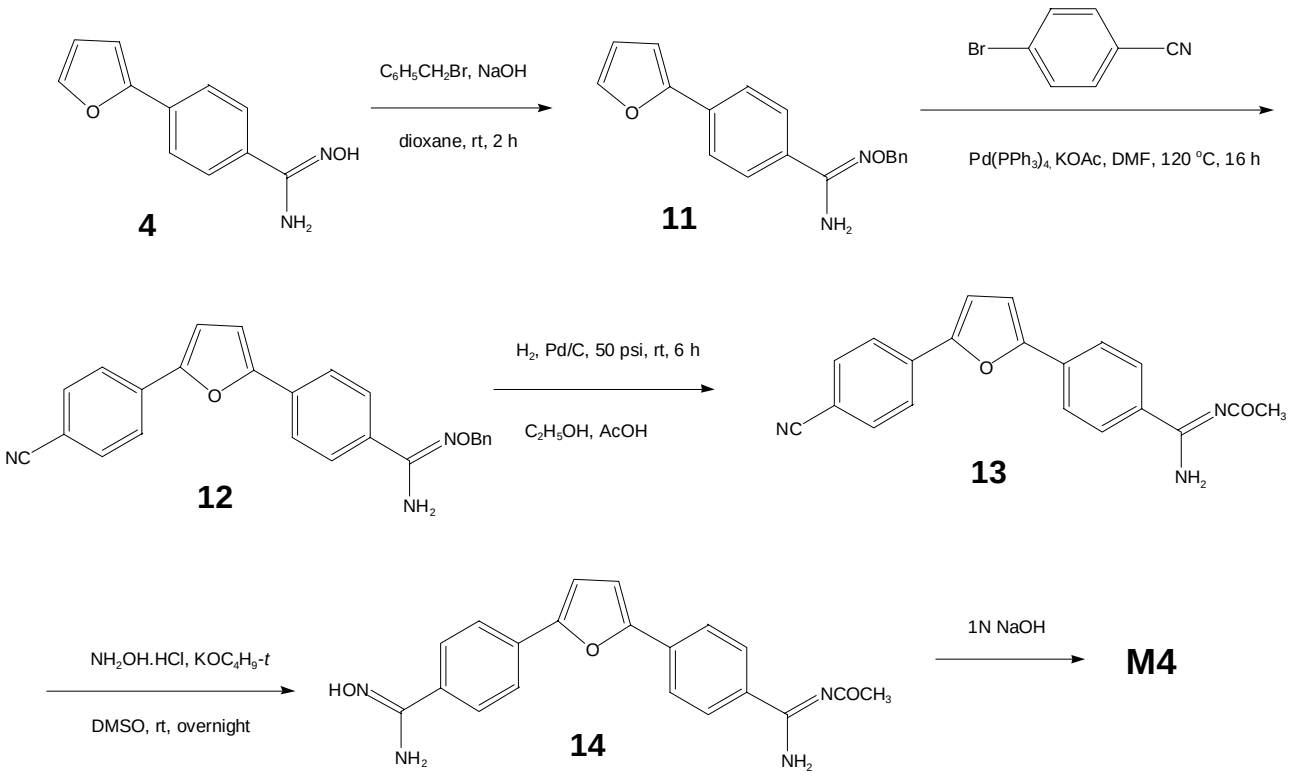
Scheme 2



In an attempt to obtain **M4** in higher yield, we decided to use a different strategy as outlined in *Scheme 3*. Benzyloxyamidoxime (**11**) was prepared in 80 % yield using the same procedure employed for **5**, but benzyl bromide was used instead of dimethyl sulfate.[5,10] The Heck reaction of **11** with *p*-bromobenzonitrile gave compound (**12**) in 30 % yield. In this approach, we decided to make the amidine unit prior to converting the cyano group to the amidoxime. Palladium catalyzed hydrogenation of **12** gave the

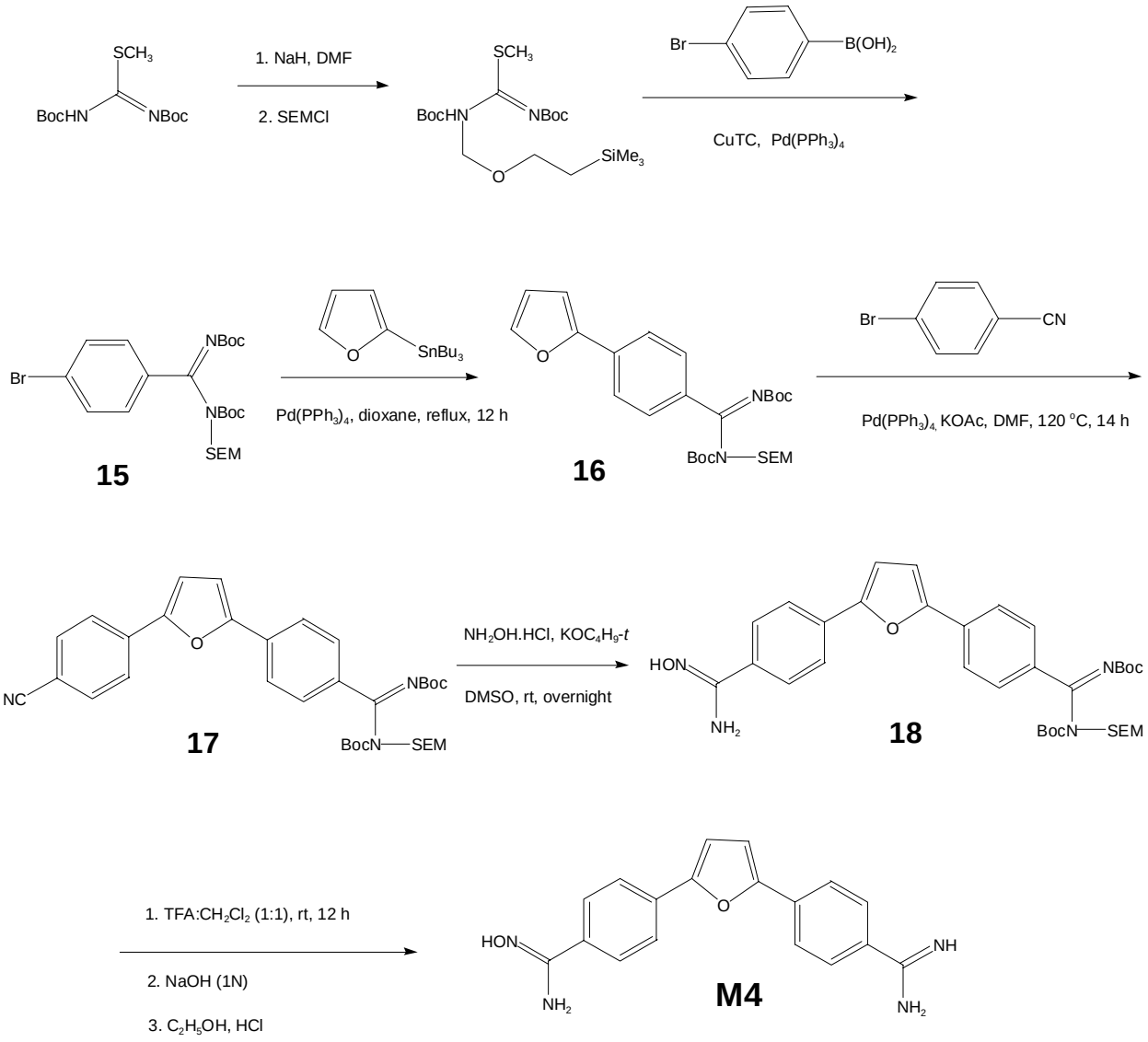
N-acetylamidine (**13**) in 25 % yield. Then **13** was reacted with hydroxylamine hydrochloride and potassium *tert*-butoxide to yield an oily compound, which was purified to obtain 2-(4-*N*-acetylamidinophenyl)-5-(4-hydroxyamidinophenyl)furan (**14**) in 50 % yield. When **14** was deacetylated by treatment with 1N NaOH at room temperature it gave **M4** in the unsatisfactory yield of 5 %.

Scheme 3



The final approach which we used is outlined in *Scheme 4* and employs a fully protected amidine group as recently described by Liebeskind.[11] Compound (**15**) was prepared according to the literature procedure.[11] Stille coupling of **15** with 2-(tributylstannyl)furan gave **16** in 80 % yield. Compound (**16**) was subjected to Heck reaction conditions with *p*-bromobenzonitrile which gave compound (**17**) in 32 % yield. Again the yield obtained from the Heck coupling process is consistent with that reported for similar reactions with furans. Conversion of the cyano group to amidoxime as previously described gave **18** in 70 % yield. Deprotection of the blocked amidine group was achieved by treatment with trifluoroacetic acid in dichloromethane. The hydrochloride salt of **M4** was obtained in 33 % yield after isolation of the free base using NaOH solution and subsequent treatment with ethanolic HCl .

Scheme 4



In conclusion, three major metabolites of the prodrug (**1**, **M1**, **M3** and **M4**) were synthesized in reasonable yields and provide samples which confirm their presence in the bioconversion process of **1** to **2** as previously outlined.[3]

EXPERIMENTAL

Melting points were determined with a Mel-Temp 3.0 capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity+300 or a Varian VRX 400 instrument, with peak assignment relative to residual DMSO (2.49 ppm) or $CHCl_3$ (7.24 ppm). MS spectra were recorded on a VG instruments 70-SE spectrometer at the Georgia Institute of Technology, Atlanta, GA. Elemental analysis were performed by Atlantic Microlab, Norcross, GA. Unless otherwise stated all

the reagent chemicals and solvents (including anhydrous solvents) were purchased from Aldrich Chemical Co., Fisher Scienticfic, or Lancaster synthesis and used as received. 2-(4-Cyanophenyl)furan[4] and 4-bromo-1-{1,3-bis(*tert*-butoxycarbonyl)-3-[2(trimethylsilyl)ethoxymethyl]}amidinobenzene[10] were prepared according to literature methods.

2-(4-*N*-Hydroxyamidinophenyl)furan (4):

Hydroxylamine hydrochloride (6.9 g, 100 mmol) was suspended in anhydrous DMSO (40 mL) and the suspension was cooled in an ice bath. KOC_4H_9-*t* (11.2 g, 100 mmol) was added portion wise under nitrogen atmosphere and the solution was stirred at rt for 1 h. Then 2-(4-cyanophenyl)furan (1.69 g, 10 mmol) was added at once and the reaction mixture was stirred overnight at rt. It was poured into ice-water and the product was filtered and the 2-(4-hydroxyamidinophenyl)furan was recrytallised from ethanol. Yield: 1.85 g (90%). Colorless crystals, mp 129-130 ^oC. ^1H NMR δ 5.83 (br, 2H, NH_2, exchangeable with D_2O), 6.61 (q, 1H, J = 3.3 Hz), 7.00 (d, 1H, J = 3.3 Hz), 7.76 (m, 5H, Ar), 9.65 (s, 1H, OH, exchangeable with D_2O); ^{13}C NMR δ 106.3, 112.1, 123.04, 125.84, 130.6, 132.1, 143.1, 150.4, 152.6. Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.85. Found: C, 65.57; H, 4.80; N, 13.58.

2-(4-*N*-Methoxyamidinophenyl)furan (5):

2-(4-*N*-Hydroxyamidinophenyl)furan (1.61 g, 8 mmol) was dissolved in dioxane (10 mL) and cooled to 0 ºC. 2N NaOH (80 mL) solution was added slowly followed by dimethyl sulfate (1.3 g, 10 mmol) in dioxane (5 mL) dropwise. After addition was complete the ice-bath was removed and the mixture was stirred at room temperature for 1 h. After TLC showed the disappearance of the amidoxime, the mixture was extracted with EtOAc (3 x 50 mL), combined organic layers were washed with water, brine and dried over Na_2SO_4. The organic layer was filtered and the solvent was removed under reduced pressure. The crude product was purified by passing thru a short silica gel column using 30% ethyl acetate in hexanes as an eluent. The compound crystallized from the eluent as a pale yellow solid, mp 89.5-90 ^oC. Yield: 1.38 g (80%). ^1H NMR δ 3.75 (s, 3H, OCH_3), 6.16 (br, 2H, NH_2, exchangeable with D_2O), 6.59 (q, 1H, J = 3.3 Hz), 7.01 (d, 1H, J = 3.3 Hz), 7.75 (m, 5H, Ar); ^{13}C NMR δ 60.6, 106.6, 112.2, 123.0, 126.2, 131.0, 132.0, 143.2, 150.8, 152.5. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.35; H, 5.68; N, 12.67.

2-(4-Cyanophenyl)-5-(4-*N*-methoxyamidinophenyl)furan (6):

2-(4-*N*-Methoxyamidinophenyl)furan (1.08 g, 5 mmol) was treated with 4-bromobenzonitrile (910 mg, 5 mmol) in the presence of tetrakis(triphenylphosphine)palladium(0) (288 mg, 0.25 mmol) and potassium

acetate (735 mg, 7.5 mmol) in DMF (10 mL). The mixture was heated at 120 ^{o}C for 16 h. The reaction mixture was cooled to rt and extracted with dichloromethane (3 x100 mL), the solution was filtered through Celite. The filtrate was washed with water repeatedly and the DCM solution was dried (Na_2SO_4), filitered and concentrated under reduced pressure. Flash chromatography of the crude product on silica gel with DCM-hexanes (1:1) afforded 635 mg (40 %) of pure yellow solid, mp 163-164 ^{o}C. ^{1}H NMR δ 3.95 (s, 3H, OCH_3), 4.83 (br, 2H, NH_2, exchangeable with D_2O), 6.83 (q, 1H, *J* = 3.3 Hz), 6.91 (d, 1H, *J* = 3.3 Hz), 7.74 (m, 8H, Ar); ^{13}C NMR δ 61.5, 108.5, 110.2, 110.5, 118.9, 123.8, 124.0, 126.2, 131.2, 131.7, 132.6, 134.2, 151.2, 151.6, 154.2. EI-MS m/z: 317 (M^+), 286, 271, 216, 140. Anal. Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.76; H, 4.82; N, 13.03.

2-(4-Hydroxyamidinophenyl)-5-(4-methoxyamidinophenyl)furan (M1):

The same procedure described for compound (**4**) was used with the following reagents. Hydroxylamine hydrochloride (1.38 g, 20 mmol), potassium *tert*-butoxide (2.24g, 20 mmol), anhydrous DMSO (10 mL) and compound (**6**) (634 mg, 2 mmol). Yield of **M1**: 595 mg (85 %). The hydrochloric acid salt was made by passing HCl gas through an ethanol solution of **M1.** The precipitate was washed with ether and after drying gave pure yellow solid, mp 162-163 ^{o}C. ^{1}H NMR δ 3.75 (s, 3H, OCH_3), 5.86 (br, 2H, NH_2, exchangeable with D_2O), 6.11 (br, 2H, NH_2, exchangeable with D_2O), 7.14 (s, 2H, Furan), 7.77 (m, 8H, Ar), 9.72 (s, 1H, OH, exchangeable with D_2O); ^{13}C NMR δ 60.6, 108.9, 109.1, 123.1, 125.8, 126.2, 130.2, 130.6, 131.3, 132.2, 150.3, 150.6, 152.3, 152.6. EI-MS m/z: 350 (M^+), 334, 317, 286, 244, 216, 189, 136. Anal. Calcd for $C_{19}H_{18}N_4O_3$: C, 65.13; H, 5.17; N, 15.99. Found: C, 64.98; H, 5.19; N, 15.82.

2-(4-Acetoxyamidinophenyl)-5-(4-methoxyamidinophenyl)furan (7):

2-(4-*N*-Hydroxyamidinophenyl)-5-(4-*N*-methoxyamidinophenyl)furan (350 mg, 1 mmol) was dissolved in glacial acetic acid (5 mL) and acetic anhydride (0.5 mL) was added and the mixture was stirred overnight at rt. TLC indicated complete acylation of the starting material. The residue was poured over ice-water mixture, the precipitate was filtered and washed well with water and dried to get pure yellow powder, mp 191-192 ^{o}C. Yield: 355 mg (90%). ^{1}H NMR δ 2.19 (s, 3H, $COCH_3$), 3.85 (s, 3H, OCH_3), 6.16 (br, 2H, NH_2, exchangeable with D_2O), 6.85 (br, 2H, NH_2, exchangeable with D_2O), 7.19 (d, 1H, *J* = 3.3 Hz, furan), 7.23 (d, 1H, *J* = 3.3 Hz, furan), 7.87 (m, 8H, Ar); ^{13}C NMR δ 19.8, 60.6, 109.1, 109.6, 123.26, 126.2, 127.2, 130.3, 130.5, 131.4, 131.6, 150.6, 152.2, 152.7, 155.9, 168.4. EI-MS m/z: 393 (MH^+), 345, 335, 307, 288, 271, 225, 187. Anal. Calcd for $C_{21}H_{20}N_4O_4$: C, 64.27; H, 5.13; N, 14.27. Found: C, 64.30; H, 5.15; N, 14.37.

2-(4-Amidinophenyl)-5-(4-methoxyamidinophenyl)furan (M3):

5 (392 mg, 0.75 mmol) was dissolved in glacial acetic acid (20 mL) and ethanol (20 mL) was added. To the mixture was added 200 mg of palladium on carbon (10 %) and the mixture was hydrogenated at 60 psi on a Parr apparatus for 4 h. The mixture was filtered over Celite and the solution was concentrated to give the amidine (**M3**) as its acetic acid salt. The hydrochloride salt of **M3** was obtained by isolation of the free base using NaOH solution and subsequent treatment with ethanolic HCl. Yellow solid, 65 %, mp 264-265 °C. ^{1}H NMR δ 3.85 (s, 3H, OCH_3), 7.38 (d, 1H, *J* = 3.6 Hz, furan), 7.43 (d, 1H, *J* = 3.6 Hz), 7.86-8.09 (m, 8H, Ar), 9.29 (br, 2H, NH_2, exchangeable with D_2O), 9.51 (br, 2H, NH_2, exchangeable with D_2O); ^{13}C NMR δ 62.1, 110.9, 112.0, 123.8, 124.3, 126.2, 127.8, 128.1, 129.1, 133.0, 134.5, 152.1, 153.0, 155.8, 165.3. FAB-MS Calcd for $C_{19}H_{18}N_4O_2$: 334.371. Found: 334.378. Anal. Calcd for $C_{19}H_{18}N_4O_2$-2HCl-2H_2O: C, 51.47; H, 5.45; N, 12.63. Found: C, 51.38; H, 5.29; N, 12.30.

2-(4-Amidinophenyl)furan (8):

2-(4-Cyanophenyl)furan (**3**) was subjected to the Pinner sequence according to a published procedure[12] and gave 2-(4-amidinophenyl)furan (**8**) in 50 % yield. The dark brown solid obtained directly from the ammonia/ ethanol solution was washed with NaOH solution, water and ethanol and after drying gave pure solid, mp 197-198 °C. ^{1}H NMR δ 6.61 (q, 1H, *J* = 3.3 Hz, furan), 7.07 (d, 1H, *J* = 3.8 Hz, furan), 7.70-7.95 (m, 5H, Ar and furan); ^{13}C NMR δ 107.3, 112.3, 123.0, 127.5, 132.2, 132.7, 143.6, 152.2, 162.6. Anal. Calcd for $C_{11}H_{10}N_2O$-0.5H_2O: C, 67.67; H, 5.67; N, 14.34. Found: C, 67.47; H, 5.76; N, 14.39.

2-(4-*N*-Butoxycarbonylamidinophenyl)furan (9):

A solution of sodium hydroxide (1.0 g, 25 mmol) in water (20 mL) was added dropwise at 0 °C to a stirred suspension of 2-(4-amidinophenyl)furan (**8**) (1.86 g, 10 mmol) in THF (20 mL), and di-*tert*-butyl dicarbonate (2.2 g, 10 mmol) was added immediately thereafter. After 1 h at 0 °C, ethyl acetate was added and the organic phase was separated, washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated under reduced pressure. Crystallisation of the solid residue from hexane-dichloromathane gave pure **9** (2.68 g, 93%). Pale yellow crystals, 143-144 °C. ^{1}H NMR δ 1.44 (s, 9H, $3CH_3$), 6.51 (q, 1H, *J* = 3.8 Hz), 6.79 (d, 1H, *J* = 3.8 Hz), 7.52 (d, 1H, *J* = 3.8 Hz), 7.65 (d, 2H, *J* = 8.0 Hz, Ar), 7.85 ((d, 2H, *J* = 8.0 Hz, Ar); ^{13}C NMR δ 28.1, 79.7, 106.9, 111.9, 123.6, 127.6, 133.2, 134.0, 142.9, 152.8, 155.8, 161.7. EI-MS m/z: 286 (M^+), 230, 212, 186, 170, 140, 115. Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.11; H, 6.33; N, 9.78. Found: C, 67.15; H, 6.39; N, 9.71.

2-(4-*N*-Butoxycarbonylamidinophenyl)-5-(4-cyanophenyl)furan (10):

The same procedure described for **6** was used with the following reagents: 2-(4-butoxycarbonyl-

phenyl)furan (**9**) (1.43 g, 5 mmol), *p*-bromobenzonitrile (910 mg, 5 mmol), KOAc (735 mg, 7.5 mmol) and $Pd(PPh_3)_4$ (288 mg, 0.25 mmol) in DMF (10 mL). Flash chromatography of the crude product on silica gel with DCM-hexanes (1:1) afforded a yellow solid which precipitated from the eluent, mp 177-178 °C. Yield of **10**: 445 mg (23%). ^{1}H NMR δ 1.50 (s, 9H, $3CH_3$), 6.81 (d, 1H, *J* = 3.6 Hz), 6.86 (d, 1H, *J* = 3.6 Hz), 7.60-7.97 (m, 8H, Ar); ^{13}C NMR δ 28.1, 80.4, 109.6, 110.4, 110.5, 118.8, 123.6, 123.8, 128.0, 132.5, 132.9, 133.3, 133.9, 152.0, 153.5, 162.8, 166.4. EI-MS m/z: 388 (MH^+), 331, 314, 288, 270, 154, 116. Anal. Calcd for $C_{23}H_{21}N_3O_3$: C, 71.30; H, 5.46; N, 10.84. Found: C, 71.43; H, 5.59; N, 10.90.

2-(4-Amidinophenyl)-5-(4-hydroxyamidinophenyl)furan (M4):

The same procedure described for **4** was used with the following reagents: Hydroxylamine hydrochloride (534 mg, 7.7 mmol), potassium *tert*-butoxide (862 mg, 7.7 mmol), anhydrous DMSO (4 mL) and compound (**10**) (300 mg, 0.77 mmol). During the course of the reaction deprotection of the Boc group also occurred. The yield of **M4** was very low (7 mg, 3 %), yellow solid, mp 272-273 °C. ^{1}H NMR δ 6.85 (br, 2H, $2NH_2$, exchangeable with D_2O), 7.10 (d, 1H, *J* = 3.6 Hz), 7.18 (d, 1H, *J* = 3.6 Hz), 7.80-8.15 (m, 8H, Ar), 9.05 (br, 2H, NH_2, exchangeable with D_2O), 9.88 (br, 1H, OH, exchangeable with D_2O); ^{13}C NMR δ 109.5, 111.0, 123.8, 124.3, 126.4, 127.1, 130.3, 130.5, 132.4, 133.2, 151.1, 152.0, 153.5, 158.5. EI-MS m/z: 321 (MH^+), 303, 279, 256, 238. The hydrochloride salt of **M4** was made for analysis by passing hydrogen chloride gas into an ethanol solution of the free base. Anal. Calcd for $C_{18}H_{16}N_4O_3$-2HCl-2.4H_2O: C, 49.62; H, 5.27. Found: C, 49.87; H, 5.55.

2-(4-Benzyloxyamidinophenyl)furan (11):

The same procedure described for **5** was used with the following reagents: amidoxime (**4**) (4.04 g, 20 mmol), benzyl bromide (4.26 g, 25 mmol), 2N NaOH (60 mL) and dioxane (50 mL). The crude product was purified by passing thru a short silica gel column using 30% ethyl acetate in hexanes as an eluent. The compound crystallized from the eluent as a pale yellow solid, mp 110-111 °C. The yield of 2-(4-benzyloxy-amidinophenyl)furan (**11**) was 2.34 g (80%). ^{1}H NMR δ 4.82 (br, 2H, NH_2, exchangeable with D_2O), 5.15 (s, 2H, $PhCH_2$), 6.48 (q, 1H, *J* = 3.9 Hz), 6.71 (d, 1H, *J* = 3.6 Hz), 7.31-7.50 (m, 5H, Ar), 7.76-7.71 (m, 4H, Ar); ^{13}C NMR δ 74.3, 106.5, 112.1, 123.0, 126.2, 127.2, 127.6, 128.1, 131.0, 131.2, 138.8, 143.2, 150.9, 152.5. EI-MS m/z: 292(M+), 201, 186, 70, 140, 115, 91, 77. Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.51; N, 9.58. Found: C, 73.72; H, 5.61; N, 9.42.

2-(4-Benzyloxyamidinophenyl)-5-(4-cyanophenyl)furan (12):

The Heck reaction procedure described for **6** was used with the following reagents: 2-(4-benzyloxy-

amidinophenyl)furan (**9**) (1.46 g, 5 mmol), *p*-bromobenzonitrile (910 mg, 5 mmol), KOAc (735 mg, 7.5 mmol) and $Pd(PPh_3)_4$ (288 mg, 0.25 mmol) in DMF (10 mL). Flash chromatography of the crude product on silica gel with DCM-hexanes (1:1) afforded 490 mg (30 %) of pure yellow solid (**12**), mp 154-155 °C. ^{1}H NMR δ 4.83 (br, 2H, NH_2, exchangeable with D_2O), 5.18 (s, 2H, $PhCH_2$), 6.82 (d, 1H, *J* = 3.8 Hz), 6.90 (d, 1H, *J* = 3.8 Hz), 7.32-7.49 (m, 5H, Ar), 7.65-7.82 (m, 4H, Ar); ^{13}C NMR δ 74.4, 108.9, 109.1, 123.1, 125.8, 126.3, 127.3, 128.1, 130.2, 130.7, 131.3, 132.3, 138.8, 150.4, 151.0, 152.4, 152.6. EI-MS m/z: 393 (M+), 302, 287, 272, 214, 140, 91, 77. Anal. Calcd for $C_{25}H_{19}N_3O_2$: C, 76.31; H, 4.86; N, 10.68. Found: C, 76.39; H, 4.84; N, 10.45.

2-(4-*N*-Acetylamidinophenyl)-5-(4-cyanophenyl)furan (13):

Compound (**12**) (393 mg, 0.61 mmol) was hydrogenated in acetic acid (25 mL) and ethanol (25 mL) using Pd/C (200 mg) at 60 psi. The pure amidine (**13**) crystallized from ethanol as yellow powder (yield: 83 mg, 25%), mp 258-259 °C. ^{1}H NMR δ 1.78 (s, 3H, $COCH_3$), 1.86 (s, 3H, CH_3COO), 5.20 (br, 2H, NH_2, exchangeable with D_2O), 7.11 (d, 1H, *J* = 3.3 Hz), 7.32 (d, 1H, *J* = 3.3 Hz), 7.80-8.01 (m, 8H, Ar); ^{13}C NMR δ 23.1, 106.3, 108.9, 112.1, 114.1, 121.5, 122.8, 123.0, 125.8, 125.9, 129.4, 132.5, 150.2, 150.3, 152.6, 154.8, 168.6. FAB-MS Calcd for $C_{20}H_{15}N_3O_2$: 329.116. Found: 329.112. Anal. Calcd for $C_{20}H_{15}N_3O_2$-1.2H_2O: C, 68.42; H, 4.99; N, 11.97. Found: C, 68.29; H, 5.31; N, 11.68.

2-(4-*N*-Acetylamidinophenyl)-5-(4-hydroxyamidinophenyl)furan (14):

The same procedure described for **4** was used with the following reagents: 2-(4-amidinophenyl)-5-(4-cyanophenyl)furan (**13**) (75 mg, 0.22 mmol), hydroxylamine hydrochloride (157 mg, 2.2 mmol), potassium *tert*-butoxide (254 mg, 2.2 mmol), anhydrous DMSO (2 mL). The yellow solid obtained was washed with water and on drying gave **14**, mp >300 °C. Yield: 47 mg (50 %). ^{1}H NMR δ 1.88 (s, 3H, $COCH_3$), 5.85 (br, 4H, $2NH_2$, exchangeable with D_2O), 7.05 (d, 1H, *J* = 2.7 Hz), 7.11 (d, 1H, *J* = 2.7 Hz), 7.73-7.83 (m, 8H, Ar), 9.71 (s, 1H, OH, exchangeable with D_2O); ^{13}C NMR δ 22.9, 108.5, 109.4, 113.1, 123.7, 124.1, 126.5, 128.5, 129.1, 131.1, 132.2, 139.3, 151.4, 152.5, 153.4, 170.8. EI-MS m/z: 363 (MH^+), 333, 317, 306, 271, 248, 168, 115, 77. Anal. Calcd for $C_{20}H_{18}N_4O_3$- 1.3H_2O: C, 62.11; H, 5.39; N, 14.48. Found: C, 62.29; H, 5.51; N, 14.19. This *N*-acetyl derivative on treatment with 1N NaOH at room temperature for 5 h gave **M4** in 5 % yield.

2-(4-{1,3-Bis(*tert*-butoxycarbonyl)-3-[2-(trimethylsilyl)ethoxymethyl]}amidinophenyl)furan (**16**):

Stille coupling reaction of **15** with 2-tributylstannylfuran in dioxane at reflux temperature for 15 h gave the compound (**16**) in 80 % yield as an oil. ^{1}H NMR δ 0.02 (s, 9H), 0.99 (t, 2H, *J* = 8.1 Hz,), 1.05(s, 9H),

1.25(s, 9H), 3.75 (t, 2H, *J* = 8.1 Hz), 5.25 (s, 2H), 6.48 (q, 1H, *J* = 3.8 Hz,), 6.71 (d, 1H, *J* = 3.8 Hz), 7.48-7.67 (m, 5H); HRMS (FAB): Calcd for $C_{27}H_{40}N_2O_6Si$: 516.265; Found: 516.256. EI-MS m/z: 517 (MH^+), 461, 441, 405, 376, 332, 289, 276, 249. Anal. Calcd for $C_{27}H_{40}N_2O_6Si$: C, 62.76; H, 7.80. Found: C, 62.40; H, 7.40.

2-(4-{1,3-Bis(*tert*-butoxycarbonyl)-3-[2-(trimethylsilyl)ethoxymethyl]}-5-(4-amidinophenyl)-5-(4-cyanophenyl)furan (**17**):

The same procedure described for compound (**6**) was used with the following reagents: **16** (2.58 g, 5 mmol), *p*-bromobenzonitrile (910 mg, 5 mmol), KOAc (735 mg, 7.5 mmol) and $Pd(PPh_3)_4$ (288 mg, 0.25 mmol) in DMF (10 mL). Yield: 986 mg (32 %). Semi-solid; ^{1}H NMR δ -0.02 (s, 9H), 0.77 (t, 2H *J* = 8.0 Hz), 1.06(s, 9H), 1.37(s, 9H), 3.72 (t, 2H, *J* = 8.3 Hz), 5.30 (s, 2H), 6.79 (q, 1H, *J* = 3.0 Hz), 7.05 (d, 1H, *J* = 3.8 Hz), 7.48-7.67 (m, 8H); HRMS (FAB): Calcd for $C_{34}H_{43}N_3O_6Si$: 617.292; Found: 617.289. EI-MS m/z: 618 (MH+), 544, 517, 506, 461, 415, 388, 376, 286, 259. Anal. Calcd for $C_{34}H_{43}N_3O_6Si$: C, 66.09; H, 7.01; N, 6.80. Found: C, 66.24; H, 7.35; N, 6.57.

2-(4-{1,3-Bis(*tert*-butoxycarbonyl)-3-[2(trimethylsilyl)ethoxymethyl]}-5-(4-amidinophenyl)-5-(4-hydroxyamidinophenyl)furan (**18**):

The same procedure described for compound (**4**) was used with the following reagents: **17** (617 mg, 1 mmol), hydroxylamine hydrochloride (690 mg, 10 mmol), potassium *tert*-butoxide (1.2 g, 10 mmol), anhydrous DMSO (10 mL). Compound (**18**) was obtained in a yield of 455 mg (70 %). Yellow solid, recrytallised from ethanol, mp: 268-269 ^{o}C. ^{1}H NMR δ -0.01 (s, 9H), 0.97 (t, 2H, *J* = 8.0 Hz,), 1.12(s, 9H), 1.29(s, 9H), 4.35 (t, 2H, *J* = 8.0 Hz,), 5.88 (s, 2H), 6.82 (q, 1H, *J* = 3.2 Hz,), 7.11 (d, 1H, *J* = 3.4 Hz), 7.74-7.97 (m, 8H, Ar), 9.73 (s, 1H, OH, exchangeable with D_2O); HRMS (FAB): Calcd for $C_{34}H_{46}N_4O_7Si$: 650.313; Found: 651.327 (MH+). EI-MS m/z: 651 (MH+), 565, 523, 467, 421, 377, 286, 251. Anal. Calcd for $C_{34}H_{46}N_4O_7Si$: C, 62.74; H, 7.12. Found: C, 62.89; H, 7.26.

2-(4-Amidinophenyl)-5-(4-hydroxyamidinophenyl)furan (M4):

Compound (**18)** (400 mg, 0.61 mmol) was treated with a solution of TFA (5 mL) and CH_2Cl_2 (5 mL) and the mixture was allowed to stir at rt for 12 h. Ether was added to the reaction mixture and the solid was filtered. Then it was basified with 1N NaOH and the solid was filtered. Finally the free base was dissolved in ethanol and HCl gas was passed to obtain the HCl salt of **M4**. The yellow solid which precipitated was washed with ether and dried to yield 65 mg (33 %). The spectral and analytical data obtained were identical with the sample of **M4** obtained according to *Scheme 2*.

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