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Research Article

Synthesis of deuterium-labelled 6-[5-(4-amidinophenyl)furan-2-yl]nicotinamidine and *N*-alkoxy-6-{5-[4-(*N*-alkoxyamidino)phenyl]-furan-2-yl}-nicotinamidines

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Summary

6-[5-(4-Amidinophenyl)furan-2-yl]nicotinamidine-d_4 (**5**) was synthesized from 6-[5-(4-cyanophenyl)furan-2-yl]nicotinonitrile-d_4 (**3**), through the *bis*-*O*-acetoxy-amidoxime followed by hydrogenation. Compound **3** was prepared from 6-(furan-2-yl)-nicotinonitrile by a Heck coupling reaction with 4-bromobenzonitrile-d_4, a product of selective cyanation reaction of 1,4-dibromobenzene-d_4 with Cu(1)CN. Deuterium-labelled *N*-methoxy-6-{5-[4-(*N*-methoxy-amidinophenyl]-furan-2-yl}-nicotinamidines were prepared *via* methylation of their respective amidoximes with dimethyl sulfate-d_6 in aqueous sodium hydroxide in good yields. Copyright © 2004 John Wiley & Sons, Ltd.

Key Words: deuterium-labelled; prodrug; cyanation; Heck reaction; Suzuki coupling

Introduction

2,5-*Bis*[4-methoxy-amidinophenyl]furan (**I**), a prodrug, is an orally effective antitrypanosomal compound which is currently entered into Phase II clinical trials.[1,2] The prodrug undergoes a multistep bioconversion *in vivo* to yield the active drug furamidine (**II**).[3–6] The establishment of the bioconversion pathway of **I** into **II** was significantly aided by the synthesis of deuterium labelled **I** and **II** (Figure 1).[7]

As part of an effort to develop antitrypanosomal compounds that are more effective than **I/II** we have found that aza-analogs of these compounds show excellent activity against *Trypanosoma brucei rhodesiense* (*T. b. r.*) both *in vitro* and *in vivo* in a mouse model.[8] Specifically, **III** which is a prodrug of **IV**, has

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shown very promising oral activity giving cures in the virulent STIB900 mouse model *T. b. r.* at the low dosage of 5 mg/kg which is superior to the activity of **I** in the same model. In view of the efficacy of **III** against *T. b. r.*, preclinical toxicity and metabolism studies have been initiated in anticipation of clinical trials. It is expected that labelling of the phenyl group of **III** and **IV** with deuterium (d_4-analog) will serve as reasonable mass spectroscopy internal standards for metabolism studies. For comparative metabolism studies, we also require the d-4 substituted *O*-ethyl analog of **III**. It is hypothesized that metabolism of **III** will likely be similar to that of **I**. However, because **III** is a disymmetric molecule it will be necessary to determine if one of the two different methoximes is preferentially metabolized. Studies focusing on the *in vivo* fate of the two different methoxime methyl groups should be greatly aided by having samples of the di-*O*-methyl-d_3 analog and the two isomeric mono-*O*-methyl-d_3 analogs of **III**. Consequently, in this report we describe the syntheses of the novel isotopically labelled compounds **5-d_4**, **6a-d_4**, **6b-d_4**, **11**, **12**, **16-d_3** and **18-d_6** for use in preclinical studies.

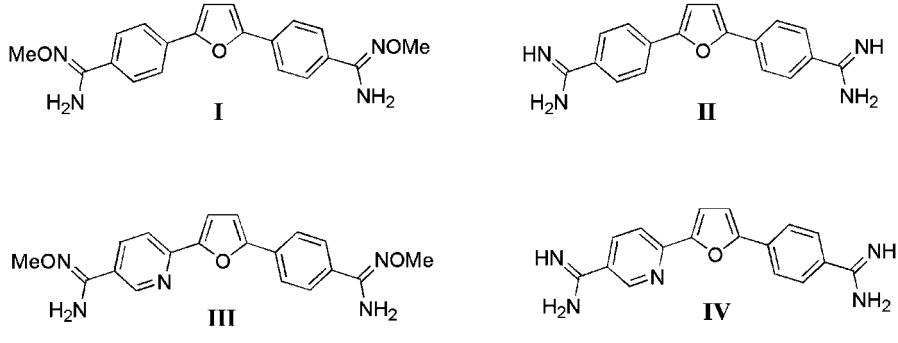
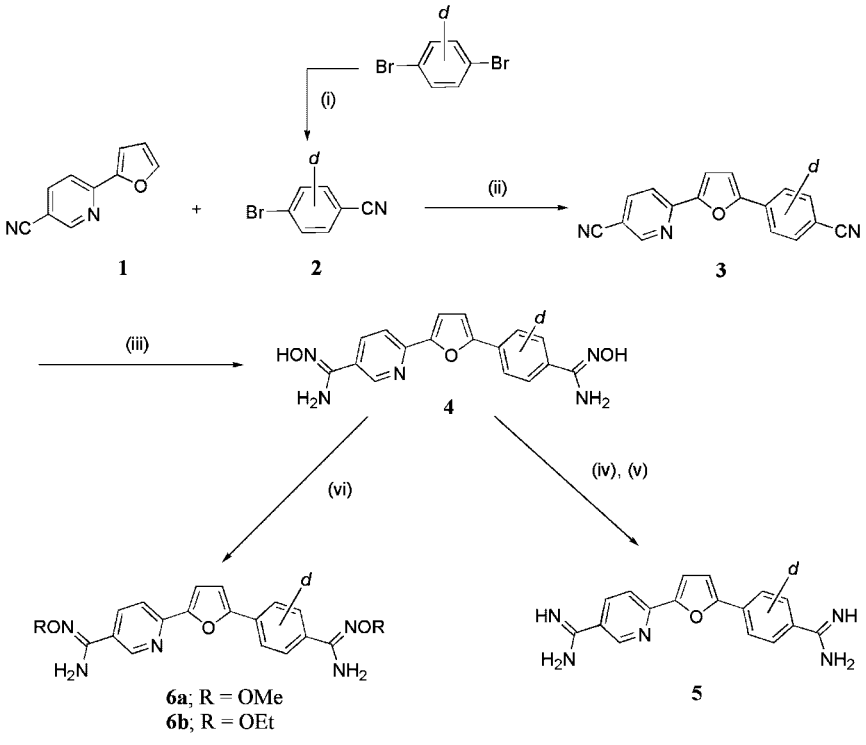


Figure 1.

Results and discussion

As outlined in Scheme 1, 6-[5-(4-amidinophenyl)furan-2-yl]nicotinamidine-d_4 **(5)** was synthesized from 6-[5-(4-cyanophenyl)furan-2-yl]nicotinonitrile-d_4 **(3)**, through the *bis*-*O*-acetoxyamidoxime followed by hydrogenation. Compound **3** was obtained from 6-(furan-2-yl)nicotinonitrile **(1)** via Heck reaction with 4-bromobenzonitrile-d_4, a product of selective temperature-dependent cyanation of the commercially available 1,4-dibromobenzene-d_4 with an equimolar amount of Cu(1)CN at 110–120°C. The prodrugs, *N*-methoxy- and *N*-ethoxy-6-{5-[4-(*N*-alkoxyamidino)phenyl]-furan-2-yl}-nicotinamidine-d_4 (**6a**, **6b**) were prepared via alkylation of the di-amidoxime **4** with the appropriate dialkyl sulfate in aqueous sodium hydroxide solution at 0°C in good yields.

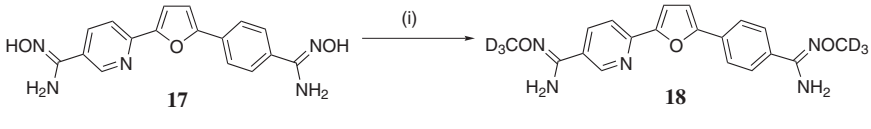
As shown in Scheme 2, *N*-methoxy-6-{5-[4-(*N*-methoxyamidino-phenyl]-furan-2-yl}-nicotinamidine-d_3 (**12**) bearing a deuterium-labelled methoxy group on the pyridine sector was obtained in five steps starting with



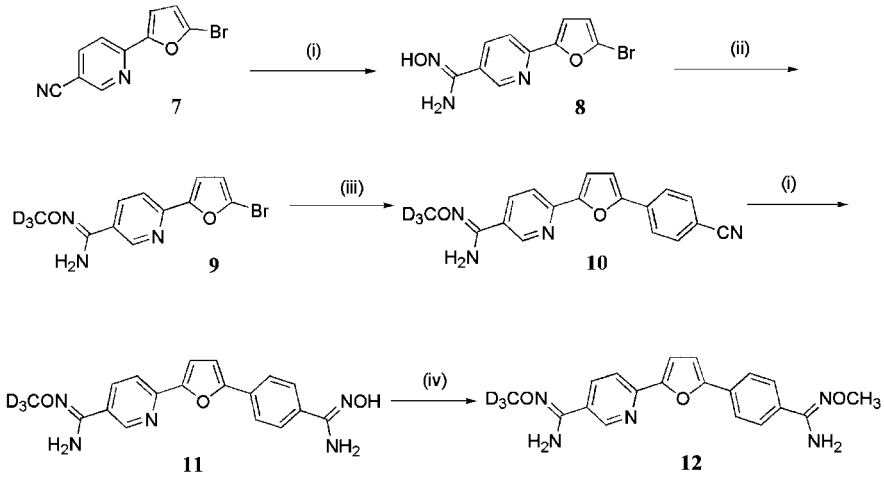
Scheme 1. Reagents and conditions: (i) Cu(1)CN, DMF, 110-120°C; (ii) $Pd(PPh_3)_4$, DMF; (iii) NH_2 OH.HCl/KO-t-Bu, DMSO' (iv) AcOH/Ac_2O; (v) H_2/Pd-C, AcOH. (vi) $(R)_2$ SO_4/NaOH, dioxane, 0°C

amidoxime formation from readily available 6-(5-bromo-furan-2-yl)-nicotinonitrile (**7**).[8] Methylation of the amidoxime **8** with dimethyl sulfate-d_6 furnished 6-(5-bromo-furan-2-yl)-*N*-methoxy-nicotinamidine-d_3 (**9**). Suzuki coupling of **9** with 4-cyanophenyl boronic acid gave **10** in good yield. Again, treatment of **10** with hydroxylamine hydrochloride and potassium *tert*-butoxide in DMSO at ambient temperature gave 6-{5-[4-(*N*-hydroxy-amidinophenyl]-furan-2-yl}-*N*-methoxy-nicotinamidine-d_3 (**11**) in 92% yield. Subsequent methylation of **11** with dimethyl sulfate afforded **12**.

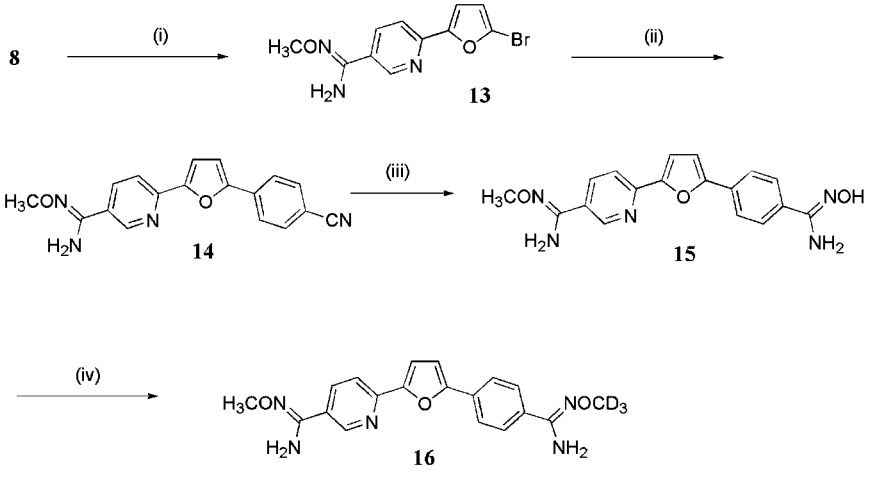
A multi-step synthesis similar to that described for **12**, outlined in Scheme 3, shows the preparation of *N*-methoxy-6-{5-[4-(*N*-methoxyamidino-phenyl]-furan-2-yl}-nicotinamidine-d_3 (**16**), which bears a deuterium-labelled methoxy group on the phenyl sector. The only difference was that methylation with



Reagents and conditions: (i) $(CD_3)_2SO_4$/NaOH, dioxane, 0 °C



Scheme 2. Reagents and conditions: (i) $NH_2OH.HCl$/KO-t-Bu, DMSO; (ii) $(CD_3)_2SO_4$/NaOH, dioxane, 0°C (iii) $Pd(PPh_3)_4$, 4-cyanophenylboronic acid (iv) $(CH_3)_2SO_4$/NaOH, dioxane, 0°C



Scheme 3. Reagents and conditions: (i) $(CH_3)_2SO_4$/NaOH, dioxane, 0°C, (ii) $Pd(PPh_3)_4$, 4-cyanophenylboronic acid; (iii) $NH_2OH.HCl$/KO-t-Bu, DMSO; (iv) $(CD_3)_2SO_4$/NaOH, dioxane, 0°C

dimethyl sulfate-d_6 was conducted in the last step. *N*-Methoxy-6-{5-[4-(*N*-methoxyamidino-phenyl]-furan-2-yl}-nicotinamidine-d_6 **(18)** was prepared by direct methylation of the *N*-hydroxy-6-{5-[4-(*N*-hydroxyamidino-phenyl]-furan-2-yl}-nicotinamidine **(17)**[8] with dimethyl sulfate-d_6 (Equation (1)). The hydrochloride salts of all the oximes, **4-d_4**, **6a-d_4**, **6b-d_4**, **11**, **12**, **16-d_3** and **18-d_6** were made by passing hydrogen chloride gas into an ethanolic solution of their free bases.

Conclusion

An efficient five-step synthesis of **5** and four-step syntheses of **6a** and **6b** starting from 1,4-dibromobenzene-d_4 have been developed. Selective labelling of the two different methoxyamidine groups of **IV** has been achieved using dimethyl sulfate-d_6 as the source of deuterium. A five-step approach for the synthesis of **12** starting from **7** has been described. Similarly a five-step process also starting from **7** yields the other isomeric *O*-methyl-d_3 compound **16**. Direct methylation of **17** with dimethyl sulfate-d_6 provided **18**-d_6. No detectable loss of deuterium was observed during the synthesis of any of the target compounds. The use of these deuterium labelled compounds in metabolism and pharmacokinetic studies will be described in due course.

Experimental section

Melting points were recorded using a Mel-Temp 3.0 capillary melting point apparatus and are uncorrected. TLC analysis was carried out on silica gel 60 F_{254} precoated aluminum sheets and detected under UV light. ^1H and ^{13}C NMR spectra were recorded employing a Varian GX400 or Varian Unity Plus 300 spectrometer, and chemical shifts (δ) are in ppm relative to TMS as internal standard. Mass spectra were obtained from the Georgia Institute of Technology, Atlanta, GA. Elemental analyses were obtained from Atlantic Microlab Inc. (Norcross, GA) and are within $\pm$ 0.31 of the theoretical values. The compounds reported as salts frequently analyzed correctly for fractional moles of waters of hydration. All chemicals and solvents were purchased from Aldrich Chemical Co., Fisher Scientific or Icons isotopes. 1,4-Dibromobenzene-d_4 (98 atom% D) and dimethyl sulfate-d_6 (99 atom% D) were obtained from Aldrich. All solvents were reagent grade.

4-Bromobenzonitrile-d_4 (2): A mixture of 1,4-dibromobenzene-d_4 (8.4 g, 35 mmol) and Cu(1)CN (3.14 g, 35 mmol) in DMF (150 ml) was heated at 110–120°C for 24 h. The reaction mixture was poured onto water and the solid which formed was extracted by using ethylacetate (300 ml, 3 times) from aq. NH_4OH. The solvent was evaporated and the precipitate purified by chromatography (SiO_2, hexanes/ether 90:10). Yield 54%, mp 110–111°C. IR (cm^{-1}); 2224, 1560, 1550, 1375, 1309, 1141, 1021, 703. EIMS (m/z, rel.int.): 185 (M^+, 100), 132 (10), 106 (80), 92 (5), 78 (25). High resolution EIMS calcd. for C_7D_4NBr: 184.9778. Observed 184.97978.

6-[5-(4-Cyano-phenyl)-furan-2-yl]-nicotinonitrile-d_4 (3): A mixture of 6-(furan-2-yl)nicotinonitrile (1) (3.4 g, 20 mmol), 4-bromobenzonitrile-d_4 **(2)** (3.7 g, 20 mmol), tetrakis(triphenylphosphine)-palladium(0) (600 mg) and potassium acetate (5 g, 50 mmol) in dry DMF (60 ml) was heated under nitrogen at 120°C for overnight. The reaction mixture was then poured onto cold water. The precipitate which formed was collected, dissolved in methylene chloride, and the solution was passed through celite to remove Pd. The

solution was evaporated, the solid was filtered and purified to afford **3** (SiO_2, hexanes/EtOAc, 30:70), in 61% yield; mp 297–299°C. ^{1}H NMR (DMSO-d_6); δ 7.41 (d, J = 3.6 Hz, 1 H), 7.47 (d, J = 3.6 Hz, 1 H), 8.09 (d, J = 8.1 Hz 1 H), 8.34 (d, J = 8.1 Hz, 1 H), 8.99 (s, 1 H). EIMS (m/z, rel.int.): 275 (M^+, 100), 247 (5), 144 (20), 103 (20). High resolution EIMS calcd. for $C_{17}H_5D_4N_3O$: 275.09967. Observed 275.09948. *Anal*. Calcd. for $C_{17}H_5D_4N_3O$: C, 74.16; H + D as H, 3.27. Found: C, 73.88; H + D as H, 3.33.

N-Hydroxy-6-{5-[4-N-hydroxyamidino-phenyl]-furan-2-yl}-nicotinamidine-d_4 (4): A mixture of hydroxylamine hydrochloride (10.4 g, 150 mmol, 10 eq.) in anhydrous DMSO (80 ml) was cooled to 5°C under nitrogen and potassium *t*-butoxide (16.8 g, 150 mmol, 10 eq.) was added in portions. The mixture was stirred for 30 min. To this mixture was added the *bis*-cyano derivative **3** (4.12 g; 15 mmol, 1 eq.). The reaction mixture was stirred for 24 h at room temperature. The reaction mixture was then poured slowly onto ice-water (200 ml water and 200 ml ice). The precipitate was filtered and washed with water and then ethanol to afford **4** (as free base) in 94% yield; mp 245–247°C. ^{1}H NMR (DMSO-d_6); δ 5.79 (s, 2 H), 5.93 (s, 2 H), 7.18 (d, J = 3.6 Hz, 1 H), 7.26 (d, J = 3.6 Hz, 1 H), 7.91 (d, J = 8.1 Hz, 1 H), 8.11 (d, J = 8.1 Hz, 1 H). 8.89 (s, 1 H), 9.64 (s, 1 H), 9.81 (s, 1 H). ^{13}C NMR; δ 153.6, 152.5, 150.3, 148.7, 148.2, 146.7, 133.6, 132.4, 129.8, 127.2, 117.7, 111.7, 109. (**4 hydrochloride salt**); mp 281–283°C dec. MS (m/z, rel.int, Fab., thioglycerol); 342 ($M^+ + 1$, 100), 326 (40), 293 (5), 267 (5). High resolution mass calcd. for $C_{17}H_{12}D_4N_5O_3$: 342.15042. Observed 342.14950. *Anal*. Calcd. for $C_{17}H_{11}D_4N_5O_3$-3.0HCl-1.0H_2O: C, 43.55; H + D as H, 4.27; N, 14.94. Found: C, 43.46; H + D as H, 4.28; N, 14.70.

6-[5-(4-Amidino-phenyl)-furan-2-yl]-nicotinamidine-d_4 acetate salt (5): To a solution of **4** (0.341 g, 1 mmol) in glacial acetic acid (10 ml) was slowly added acetic anhydride (0.35 ml). After stirring overnight, TLC indicated complete acylation of the starting material. The reaction mixture was poured onto ice-water, the precipitate was filtered, washed with water and dried. To the precipitate in glacial acetic acid (13 ml), and ethanol (20 ml) was added 10% palladium on carbon (80 mg). The mixture was placed on a Parr hydrogenation apparatus at 50 psi for 4 h at room temperature. The mixture was filtered through hyflo and the filter pad washed with water. The filtrate was evaporated under reduced pressure and the precipitate was collected and washed with ether to give **5** in 79% yield, mp 263–265°C dec. ^{1}H NMR (D_2O/DMSO-d_6); δ 1.89 (s, 2xCH_3), 7.28 (s, 1H), 7.33 (s, 1H), 7.98 (s, 1H), 8.24 (s, 1H), 8.99 (s, 1H). MS (m/z, rel.int, Fab., thioglycerol); 310 ($M^+ + 1$, 100), 273 (20), 237 (40). High resolution mass calcd. for $C_{17}H_{12}D_4N_5O$: 310.16059. Observed 310.16000. *Anal*. Calcd. for $C_{17}H_{11}D_4N_5O$-2.0AcOH-2.0H_2O: C, 54.18; H + D as H, 5.80; N, 15.04. Found: C, 54.31; H + D as H, 5.77; N, 14.82.

N-Methoxy-6-{5-[4-(N-methoxyamidino-phenyl]-furan-2-yl}-nicotinamidine-d_4 (6a): To a solution of **4** (0.511 g, 1.5 mmol) in dioxane (6 ml) and 2 N NaOH (12 ml) at 0–5°C, was slowly added dimethyl sulfate (0.568 g, 4.5 mmol) in dioxane (5 ml). The reaction mixture was further stirred for 2 h at room temperature and then extracted with ethylacetate (150 ml, 3 times). The solvent was evaporated and the residue was purified by chromatography (SiO_2, hexanes/EtOAc, 40:60) to give **6a** (free base) in 58% yield; mp 162–163°C. ^{1}H NMR (DMSO-d_6); δ 3.77 (s, 3H), 3.79 (s, 3H), 6.14 (s, 2H), 6.30 (s, 2H), 7.24 (d, J = 3.6 Hz, 1H), 7.30 (d, J = 3.6 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 8.11 (dd, J = 8.4, 2.4 Hz, 1H), 8.87 (d, J = 2.4 Hz, 1H). ^{13}C NMR; δ 153.6, 152.5, 150.5, 149.0, 148.5, 146.9, 134.1, 131.6, 130.2, 126.5, 117.7, 112.0, 109.2, 60.7, 60.6. EIMS (m/z, rel.int.); 369 (M^+, 65), 322 (30), 275 (100), 247 (5). High resolution EIMS calcd. for $C_{19}H_{15}D_4N_5O_3$: 369.17390. Observed 369.17379. (**6a hydrochloride salt**); mp 206–208°C dec. *Anal*. Calcd. for $C_{19}H_{15}D_4N_5O_3$-3.0HCl-0.75H_2O: C, 46.35; H + D as H, 4.78; N, 14.22. Found: C, 46.57; H + D as H, 4.93; N, 14.01.

N-Ethoxy-6-{5-[4-(N-ethoxyamidino-phenyl]-furan-2-yl}-nicotinamidine-d_4 (6b): The same procedure described for **6a** was used by employing diethyl sulfate instead of dimethyl sulfate. Free base of **6b**, yield 75%; mp 175–176.5°C. ^{1}H NMR (DMSO-d_6); δ 1.25 (m, 6H), 4.03 (m, 4H), 6.07 (s, 2H), 6.22 (s, 2H), 7.23 (d, J = 3.6 Hz, 1H), 7.30 (d, J = 3.6 Hz, 1H), 7.93 (d, J = 8.7 Hz, 1H), 8.11 (dd, J = 8.7, 2.4 Hz, 1H), 8.86 (d, J = 2.4 Hz, 1H). ^{13}C NMR; δ 153.6, 152.5, 150.4, 148.8, 148.5, 146.9, 134.0, 131.8, 130.1, 126.7, 117.7, 111.9, 109.2, 68.0, 67.8, 14.8. EIMS (m/z, rel.int.); 397 (M^+, 40), 336 (15), 275 (100), 247 (5), 144 (10). High resolution EIMS calcd. for $C_{21}H_{19}D_4N_5O_3$: 397.20520. Observed 397.20470. (**6b hydrochloride salt**); mp 200–201.5°C dec. *Anal*. Calcd. for $C_{21}H_{19}D_4N_5O_3$-3.0HCl-1.2H_2O: C, 47.73; H + D as H, 5.38; N, 13.25. Found: C, 47.91; H + D as H, 5.45; N, 12.94.

6-(5-Bromo-furan-2-yl)-N-hydroxy-nicotinamidine (8): The same procedure described for **4** was used, starting with 6-(5-bromo-furan-2-yl)-nicotinonitrile **(7)**.[8] Yield 97%; mp 217–218°C. ^{1}H NMR (DMSO-d_6); δ 6.02 (s, 2H), 6.80 (d, J = 3.6 Hz, 1H), 7.20 (d, J = 3.6 Hz, 1H), 7.73 (d, J = 8.4 Hz 1H), 8.09 (dd, J = 8.4, 2.1 Hz, 1H), 8.86 (d, J = 2.1 Hz, 1H), 9.92 (s, 1H). EIMS (m/z, rel.int.); 281 (M^+, 100), 265 (70), 250 (50), 186 (50), 169 (30). High resolution EIMS calcd. for $C_{10}H_8BrN_3O_2$: 280.97999. Observed 280.98038.

6-(5-Bromo-furan-2-yl)-N-methoxy-nicotinamidine-d_3 (9): The same procedure described for **6a** was used, starting with **8** and employing dimethyl sulfate-d_6 instead of dimethyl sulfate. Yield 86%; mp 171.5–172°C (analytically pure from the reaction mixture). ^{1}H NMR (DMSO-d_6); δ 6.26 (s, 2H), 6.78 (d, J = 3.6 Hz, 1H), 7.19 (d, J = 3.6 Hz, 1H), 7.71 (d, J = 8.4 Hz 1H), 8.07 (dd, J = 8.4, 2.4 Hz, 1H), 8.82 (d, J = 2.4 Hz, 1H). ^{13}C NMR; δ 154.6, 148.8, 147.7, 146.8, 134.2, 126.9, 123.3, 117.6, 114.5, 112.0. *Anal*. Calcd. for

$C_{11}H_7D_3BrN_3O_2$: C, 44.16; H + D as H, 3.34; N, 14.04. Found: C, 44.09; H + D as H, 3.33; N, 13.89.

6-[5-(4-Cyano-phenyl)-furan-2-yl]-N-methoxy-nicotinamidine-d_3 (10): To a stirred solution of **9** (2.99 g, 10 mmol), and tetrakis(triphenylphosphine) palladium (300 mg) in toluene (20 ml) under a nitrogen atmosphere was added 10 ml of a 2 M aqueous solution of Na_2CO_3 followed by 4-cyanophenyl boronic acid (2.14 g, 12 mmol) in 8 ml of methanol. The vigorously stirred mixture was warmed to 80°C for 24 h, then concentrated, and partitioned between ethylacetate (300 ml) and 2 M aqueous Na_2CO_3 (50 ml) containing 5 ml of concentrated ammonia. The organic layer was dried (Na_2SO_4), and then concentrated to dryness under reduced pressure to afford **10** in 71% yield after chromatography (SiO_2, hexanes/EtOAc, 30:70); mp 196–196.5°C. ^{1}H NMR (DMSO-d_6); δ 6.29 (s, 2H), 7.31 (d, J = 3.6 Hz, 1H), 7.42 (d, J = 3.6 Hz, 1H), 7.92 (d, J = 8.4 Hz, 2H), 7.96 (d, J = 8.4 Hz, 1H). 8.04 (d, J = 8.4 Hz, 2H), 8.12 (dd, J = 8.4, 1.5 Hz, 1H), 8.86 (d, J = 1.5 Hz, 1H). ^{13}C NMR; δ 153.6, 152.2, 148.9, 148.2, 147.0, 134.1, 133.6, 132.9, 126.9, 124.2, 118.8, 118.1, 112.1, 111.8, 109.8. EIMS (m/z, rel.int.); 321 (M^+, 100), 287 (30), 271 (30), 245 (5), 218 (15). High resolution EIMS calcd. for $C_{18}H_{11}D_3N_4O_2$: 321.13051. Observed 321.13106. *Anal.* Calcd. for $C_{18}H_{11}D_3N_4O_2$: C, 67.28; H + D as H, 4.36. Found: C, 67.37; H + D as H, 4.50.

6-{5-[4-(N-Hydroxyamidino-phenyl]-furan-2-yl}-N-methoxy-nicotinamidine-d_3 (11): The same procedure described for **4** was used, starting with **10**. Free base of 11, yield 92%, mp 201–203°C. ^{1}H NMR (DMSO-d_6); δ 5.90 (s, 2H), 6.28 (s, 2H), 7.21 (d, J = 3.6 Hz, 1H), 7.28 (d, J = 3.6 Hz, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H), 7.93 (d, J = 8.4 Hz, 1H), 8.10 (dd, J = 8.4, 1.5 Hz, 1H), 8.85 (d, J = 1.5 Hz, 1H), 9.74 (s, 1H). ^{13}C NMR; δ 153.7, 152.4, 150.4, 149.0, 148.5, 146.9, 134.1, 132.6, 130.0, 126.5, 125.8, 123.5, 117.7, 111.9, 109.0. EIMS (m/z, rel.int.); 354 (M^+, 40), 338 (80), 321 (1 0 0), 304 (10), 272 (35). High resolution EIMS calcd. for $C_{18}H_{14}D_3N_5O_3$: 354.15197. Observed 354.15339. (**11 hydrochloride salt**); mp 233–235°C. *Anal.* Calcd. for $C_{18}H_{14}D_3N_5O_3$-3.0HCl-0.5H_2O: C, 45.72; H + D as H, 4.44; N, 14.81. Found: C, 45.69; H + D as H, 4.42; N, 14.78.

N-Methoxy-6-{5-[4-(N-methoxyamidino-phenyl]-furan-2-yl}-nicotinamidine-d_3 (12): The same procedure described for **6a** was used, starting with **11**. Free base of **12**, yield 65%, mp 169–169.5°C. ^{1}H NMR (DMSO-d_6); δ 3.76 (s, 3H), 6.13 (s, 2H), 6.28 (s, 2H), 7.21 (d, J = 3.6 Hz, 1H), 7.28 (d, J = 3.6 Hz, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.86 (d, J = 8.4 Hz, 2H), 7.93 (d, J = 8.4 Hz, 1H), 8.09 (dd, J = 8.4, 2.1 Hz, 1H), 8.85 (d, J = 2.1 Hz, 1H). ^{13}C NMR; δ 153.6, 152.5, 150.5, 148.9, 148.5, 146.9, 134.0, 131.8, 130.3, 126.4, 126.1, 123.4, 117.7, 111.9, 109.1, 60.5. EIMS (m/z, rel.int.); 368 (M^+, 100), 338 (10), 321 (15), 287 (40), 245 (10). High resolution EIMS calcd. for $C_{19}H_{16}D_3N_5O_3$: 368.16762. Observed 368.16896. (**12 hydrochloride salt**); mp 224–226°C. *Anal.* Calcd. for

$C_{19}H_{16}D_3N_5O_3$-3.0HCl-1.3H_2O: C, 45.53; H + D as H, 4.91; N, 13.97. Found: C, 45.53; H + D as H, 4.98; N, 13.83.

6-(5-Bromo-furan-2-yl)-N-methoxy-nicotinamidine (13): The same procedure described for **6a** was used, starting with **8**. Yield 90%; mp 170.5–171°C (analytically pure from the reaction mixture). ^{1}H NMR (DMSO-d_6); δ 3.78 (s, 3H), 6.29 (s, 2H), 6.80 (d, J = 3.6 Hz, 1H), 7.21 (d, J = 3.6 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 8.08 (dd, J = 8.4, 2.1 Hz, 1H), 8.83 (d, J = 2.1 Hz, 1H). ^{13}C NMR; δ 154.6, 148.8, 147.6, 146.8, 134.2, 126.8, 123.2, 117.5, 114.4, 111.9, 60.7. *Anal*. Calcd. for $C_{11}H_{10}BrN_3O_2$: C, 44.62; H, 3.40. Found: C, 44.70; H, 3.34.

6-[5-(4-Cyano-phenyl)-furan-2-yl]-N-methoxy-nicotinamidine (14): The same procedure described for **10** was used, starting with **13**. Yield 68%; mp 196–197°C after chromatography (SiO_2, hexanes/EtOAc, 30:70). ^{1}H NMR (DMSO-d_6); δ 3.79 (s, 3H), 6.31 (s, 2H), 7.35 (d, J = 3.6 Hz, 1H), 7.45 (d, J = 3.6 Hz, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 8.4 Hz, 1H). 8.07 (d, J = 8.4 Hz, 2H), 8.13 (dd, J = 8.4, 2.1 Hz, 1H), 8.88 (d, J = 2.1 Hz, 1H). ^{13}C NMR; δ 153.6, 152.2, 148.9, 148.2, 147.0, 134.1, 133.6, 132.9, 126.9, 124.2, 118.8, 118.1, 112.1, 111.8, 109.8, 60.8. *Anal*. Calcd. for $C_{18}H_{14}N_4O_2$: C, 67.91; H, 4.43. Found: C, 67.84; H, 4.47.

6-{5-[4-(N-Hydroxyamidino-phenyl]-furan-2-yl}-N-methoxy-nicotinamidine (15): The same procedure described for **4** was used, starting with **14**. Free base of **15**, yield 92%, mp 212–213.5°C. ^{1}H NMR (DMSO-d_6); δ 3.79 (s, 3H), 5.90 (s, 2H), 6.30 (s, 2H), 7.22 (d, J = 3.6 Hz, 1H), 7.30 (d, J = 3.6 Hz, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.89 (d, J = 8.4 Hz, 2H), 7.94 (d, J = 8.1 Hz, 1H), 8.10 (dd, J = 8.1, 2.1 Hz, 1H), 8.85 (d, J = 2.1 Hz, 1H), 9.75 (s, 1H). ^{13}C NMR; δ 153.8, 152.4, 150.3, 149.0, 148.6, 146.9, 134.1, 132.7, 130.0, 126.5, 125.8, 123.5, 117.7, 112.0, 109.0, 60.8. EIMS (m/z, rel.int.); 351 (M^+, 45), 335 (46), 318 (100), 271 (50). High resolution EIMS calcd. for $C_{18}H_{17}N_5O_3$: 351.13314. Observed 351.13815. (**15 hydrochloride salt**); mp 239–241°C dec. *Anal*. Calcd. for $C_{18}H_{17}N_5O_3$-3.0HCl-0.7H_2O: C, 45.67; H, 4.55; N, 14.79. Found: C, 45.64; H, 4.46; N, 14.65.

N-Methoxy-6-{5-[4-(N-methoxyamidino-phenyl]-furan-2-yl}-nicotinamidine-d_3 (16): The same procedure described for **6a** was used, starting with **15** and employing dimethyl sulfate-d_6 instead of dimethyl sulfate. Free base of **16**, yield 60%, mp 168.5–169.5°C. ^{1}H NMR (DMSO-d_6); δ 3.79 (s, 3H), 6.14 (s, 2H), 6.30 (s, 2H), 7.24 (d, J = 3.6 Hz, 1H), 7.30 (d, J = 3.6 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.88 (d, J = 8.4 Hz, 2H), 7.94 (d, J = 8.4 Hz, 1H), 8.10 (dd, J = 8.4, 2.1 Hz, 1H), 8.86 (d, J = 2.1 Hz, 1H). ^{13}C NMR; δ 153.7, 152.5, 150.5, 149.0, 148.5, 146.9, 134.1, 131.8, 130.3, 126.5, 126.2, 123.5, 117.8, 112.0, 109.2, 60.7. EIMS (m/z, rel.int.); 368 (M^+, 100), 338 (10), 321 (15), 287 (35), 245 (10). High resolution EIMS calcd. for $C_{19}H_{16}D_3N_5O_3$: 368.16762. Observed 368.16933. (**16 hydrochloride salt**); mp 208–210°C. *Anal*. Calcd. for

$C_{19}H_{16}D_3N_5O_3$-3.0HCl-1.9H_2O: C, 44.57; H + D as H, 5.04; N, 13.67. Found: C, 44.51; H + D as H, 5.04; N, 13.42.

N-Methoxy-6-{5-[4-(N-methoxyamidino-phenyl]-furan-2-yl}-nicotinamidine-d_6 (18): The same procedure described for **6a** was used, starting with **17** and employing dimethyl sulfate-d_6 instead of dimethyl sulfate. Free base of **18**, yield 57%, mp 168.5–169°C. ^{1}H NMR (DMSO-d_6); δ 6.12 (s, 2H), 6.28 (s, 2H), 7.23 (d, J = 3.6 Hz, 1H), 7.29 (d, J = 3.6 Hz, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H), 7.92 (d, J = 8.4 Hz, 1H), 8.10 (dd, J = 8.4, 2.1 Hz, 1H), 8.84 (d, J = 2.1 Hz, 1H). ^{13}C NMR; δ 153.6, 152.5, 150.5, 149.0, 148.5, 146.9, 134.1, 131.8, 130.3, 126.5, 126.2, 123.5, 117.7, 112.0, 109.2. EIMS (m/z, rel.int.); 371 (M^+, 100), 338 (20), 321 (25), 287 (35), 245 (5). High resolution EIMS calcd. for $C_{19}H_{13}D_6N_5O_3$: 371.18645. Observed 371.18789. (**18 hydrochloride salt**); mp 225–226.5°C. *Anal.* Calcd. for $C_{19}H_{13}D_6N_5O_3$-3.0HCl-2.0H_2O: C, 44.15; H + D as H, 5.03; N, 13.55. Found: C, 44.24; H + D as H, 5.16; N, 13.49.

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