Supporting information

Novel potent BRAF inhibitors: towards 1 nM compounds through optimization of the central phenyl ring

Delphine Ménard,[†] Ion Niculescu-Duvaz,[†] Harmen P. Dijkstra,[†] Dan Niculescu-Duvaz,[†] Bart M. J. M. Suijkerbuijk,[†] Alfonso Zambon,[†] Arnaud Nourry,[†] Esteban Roman,[†] Lawrence Davies,[†] Helen A. Manne,[†] Frank Friedlos,[†] Ruth Kirk,[‡] Steven Whittaker,[‡] Adrian Gill,[§] Richard Taylor,[§] Richard Marais,[‡] Caroline J. Springer[†,]*

*To whom correspondence should be addressed. Phone: +44 20 8722 4214. Fax: +44 20 8722 4046

E-mail: caroline.springer@icr.ac.uk

[†]The Institute of Cancer Research UK Centre for Cancer Therapeutics, 15 Cotswold Road, Sutton, Surrey SM2 5NG, United Kingdom

Contents of Support Information

I. Chemistry-Synthesis and chemical data of final compounds:

1. Compounds **21 f-m** following Procedure A

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(2-methoxy-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-7-yloxy)phenyl)urea (21f). 1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(4-(2,3-diaminopyridin-4-yloxy)-2-methoxyphenyl)urea **11f** (155 mg, 0.33 mmol) afforded the title compound (38 mg, 23%) after purification by chromatography on silica gel (EtOAc:DCM 1:1, then EtOAc:MeOH 95:5) as a pink powder (R_f 0.33, EtOAc:MeOH 95:5) following procedure A. ^{1}H-NMR δ: 3.87 (s, 3H, CH_3), 5.95 (d, 1H, J=5.9, H_{Py}), 6.71 (dd, 1H, J=8.8 and J=2.5, H_{arom}), 6.95 (d, 1H, J=2.5, H_{arom}), 7.60 (m, 2H, H_{arom}), 7.76 (d, 1H, J=5.9, H_{Py}), 8.10 (m, 2H, H_{arom}), 8.30 (s, 1H, NH_{urea}), 9.73 (s, 1H, NH_{urea}), 11.14 (s, 1H, NH_{Py}), 11.32 (s, 1H, NH_{Py}). ^{13}C-NMR δ: 56.2, 104.1, 105.3, 111.5, 116.1, 116.3, 119.5, 122.1, 122.6, 123.7, 125.2, 126.8, 132.0, 139.2, 141.2, 145.8, 146.8, 149.0, 149.1, 152.1, 154.1. LC-MS: *m/z* 494 ($[M+H]^+$, 100). HRMS: *m/z* calcd for $C_{21}H_{15}ClF_3N_5O_4$ ($[M+H]^+$): 494.0837; found: 494.0833.

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(2-(dimethylamino)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-7-yloxy)phenyl)urea (21g). 1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(4-(2,3-diaminopyridin-4-yloxy)-2-(dimethylamino)phenyl)urea **11g** (142 mg, 0.3 mmol) afforded the title compound (139 mg, 93%) as a pale brown powder following procedure A. ^{1}H-NMR δ: 2.67 (s, 6H, CH_3), 6.41 (d, 1H, J=6.0, H_{Py}), 6.88 (dd, 1H, J= 8.8 and J=2.4, H_{arom}), 7.09 (d, 1H, J=1.5, H_{arom}), 7.61 (d, 1H, J=8.7, H_{arom}), 7.66 (dd, 1H, J= 8.7 and J=2.2, H_{arom}), 7.78 (d, 1H, J=6.0, H_{Py}), 8.06 (d, 1H, J=8.8, H_{arom}), 8.12 (d, 1H, J=2.2, H_{arom}), 8.47 (s, 1H, NH_{urea}), 10.10 (s, 1H, NH_{urea}), 11.24 (s, 1H, NH_{Py}), 11.48 (bs, 1H, NH_{Py}). ^{13}C-NMR δ: 43.9 (2), 105.3, 112.0, 113.0, 115.3, 116.1, 116.2, 121.9, 122.4, 123.7, 126.6, 130.1, 131.9, 139.4, 140.4, 144.1, 145.9, 146.3, 148.9, 152.3, 154.0. LC-MS: *m/z* 507 ($[M+H]^+$, 100). HRMS: *m/z* calcd for $C_{22}H_{18}ClF_3N_6O_3$ ($[M+H]^+$): 507.1153; found: 507.1151.

1-(4-(2,3-Dihydro-2-oxo-1*H*-benzo[*d*]imidazol-4-yloxy)-2,3-dimethylphenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (21h). 1-(4-(2,3-Diaminopyridin-4-yloxy)-2,3-dimethylphenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea **11h** (174 mg, 0.37 mmol) afforded the title compound (178 mg, 97%) as a pale pink powder following procedure A. ^{1}H-NMR δ: 2.09 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 6.12 (d, 1H, J=5.8, H_{Py}), 6.95 (d, 1H, J=8.4, H_{arom}), 7.48 (d, 1H, J=8.6, H_{arom}), 7.58 (d, 1H, J=8.5, H_{arom}), 7.65-7.72 (m, 2H, H_{arom} +H_{Py}), 8.14 (s, 1H, H_{arom}), 8.46 (s, 1H, NH_{urea}), 9.64 (s, 1H, NH_{urea}), 11.21 (s, 1H, NH_{Py}), 11.32 (s, 1H, NH_{Py}). ^{13}C-NMR δ: 12.5, 14.3, 104.1, 112.4, 116.0, 117.9, 121.6, 122.0, 122.3, 123.7, 126.6, 128.7, 131.0, 131.8, 134.0, 139.5, 139.7, 145.6, 146.5, 147.4, 152.8, 153.8. LC-MS: *m/z*

492 ([M+H]$^+$, 100). HRMS: *m/z* calcd for $C_{22}H_{17}ClF_3N_5O_3$ ([M+H]$^+$): 492.1049; found: 492.1050.

1-(4-(2,3- Dihydro-2-oxo-1*H*-imidazo[4,5-*b*]pyridin-7-yloxy) -2-(trifluoromethyl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (21i). 1-(4-(2,3-Diaminopyridin-4-yloxy)-2-(trifluoromethyl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea **11i** (114 mg, 0.22 mmol) afforded the title compound (76 mg, 63%) as a brown powder following procedure A. ^{1}H-NMR δ: 6.53 (d, 1H, J=5.9, H_{Py}), 7.44 (m, 1H, J=8.9, H_{arom}), 7.49 (s, 1H, H_{arom}), 7.63 (broad s, 2H, H_{arom}), 7.83 (d, 1H, J=5.8, H_{Py}), 7.88 (d, 1H, J=8.9, H_{arom}), 8.11 (s, 1H, NH_{urea}), 8.29 (s, 1H, H_{arom}), 9.81 (s, 1H, NH_{urea}), 11.26 (s, 1H, NH_{Py}), 11,48 (s, 1H, NH_{Py}). ^{13}C-NMR δ: 106.6, 113.8, 116.5, 116.7, 121.5, 121.9, 122.4, 122.7, 123.3, 123.7, 126.5, 126.8, 129.0, 131.9, 139.0, 141.1, 144.0, 147.1, 150.8, 152.6, 154.1. LC-MS: *m/z* 532 ([M+H]$^+$, 100). HRMS: *m/z* calcd for $C_{21}H_{12}ClF_6N_5O_3$ ([M+H]$^+$): 532.0614; found: 532.0611.

1-(4-(2,3-Dihydro-2-oxo-1*H*-imidazo[4,5-*b*]pyridin-7-yloxy)-2-(phenyl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (21j). 1-(4-(2,3-Diaminopyridin-4-yloxy)-2-(phenyl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea **11j** (152 mg, 0.30 mmol) afforded the title compound (24 mg, 15%) as a grey powder following procedure A. ^{1}H-NMR δ: 6.50 (bs, 1H, H_{Py}), 7.04 (s, 1H, H_{arom}), 7.12 (s, 1H, J=7.6, H_{arom}), 7.37-7.60 (m, 5H, H_{arom}), 7.49 (d, 1H, J=5.4, H_{Py}), 7.56 (m, 1H, H_{arom}), 7.75-7.95 (m, 3H, H_{arom}), 8.03 (s, 1H, NH_{urea}), 9.42 (s, 1H, NH_{urea}), 11.19 (s, 1H, NH_{Py}), 11,35 (s, 1H, NH_{Py}). ^{13}C-NMR δ: 105.9, 113.3, 116.4, 118.8, 121.0, 121.6, 122.0, 122.6, 123.7, 125.4, 126.4, 126.7, 127.7, 128.7, 128.9, 131.8, 131.9, 135.4, 137.4, 139.3, 141.2, 145.1, 146.9, 150.3, 152.7, 154.1. LC-MS: *m/z* 540 ([M+H]$^+$, 100). HRMS: *m/z* calcd for $C_{26}H_{17}ClF_3N_5O_3$ ([M+H]$^+$): 540.1055; found: 540.1050

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(3-fluoro-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-7-yl-oxy)phenyl)urea (21k). 1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(4-(2,3-diaminopyridin-4-yl-oxy)-3-fluorophenyl)urea **11k** (0.14 g, 0.316 mmol) afforded the title compound (4 mg, 3%) following procedure A. ^{1}H-NMR δ: 6.31 (d, 1H, J=5.9, H_{Py}), 7.23 (d, 1H, J=9.0, H_{arom}), 7.29 (d, 1H, J=9.0, H_{arom}), 7.61-7.70 (m, 3H, H_{arom}), 7.75 (d, 1H, J=5.9, H_{Py}), 8.09 (s, 1H, H_{arom}), 9.30 (s, 1H, NH_{urea}), 9.42 (s, 1 H, NH_{urea}), 11.23 (s, 1H, NH_{Py}), 11.37 (s, 1H, NH_{Py}). LC-MS: *m/z* 482 ([M+H]$^+$, 100). HRMS: *m/z* calcd for $C_{20}H_{12}ClF_4N_5O_3$ ([M+H]$^+$): 482.06376; found: 482.06318.

1-(4-(2,3-Dihydro-2-oxo-1*H*-imidazo[4,5-*b*]pyridin-7-yloxy)-2-chlorophenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (21l). 1-(4-(2,3-Diaminopyridin-4-yloxy)-2-chlorophenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea **11l** (68 mg, 0.14 mmol) afforded the title compound (72 mg, 96%) as a brown powder following procedure A. ^{1}H-NMR δ: 6.49 (d, 1H, J=5.8, H_{Py}), 7.16 (dd, 1H, J=9.0 and

J=2.6, H_{arom}), 7.38 (m, 1H, H_{arom}), 7.64 (m, 2H, H_{arom}),7.79 (d, 1H, J=5.8, H_{Py}), 8.01-8.12 (m, 2H, H_{arom}), 8.58 (broad s, 1H, NH_{urea}), 8.91 (m, 1H, NH_{Py}), 10.16 (s, 1H, NH_{urea}) , 11.25 (s, 1H, NH_{Py}). ^{13}C-NMR δ: 106.1, 113.5, 116.4, 118.8, 120.5, 122.3, 122.7, 123.4, 123.8, 127.0, 132.0, 132.5, 139.1, 140.5, 142.1, 145.0, 145.9, 149.5, 152.2, 154.1. LC-MS: *m/z* 498 ($[M+H]^+$, 100). HRMS: *m/z* calcd for $C_{20}H_{12}Cl_2F_3N_5O_3$ ($[M+H]^+$): 498.0351; found: 498.0348.

1-(4-(2,3-Dihydro-2-oxo-1*H*-imidazo[4,5-*b*]pyridin-7-yloxy)-2-methylphenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (21m). 1-(4-(2,3-Diaminopyridin-4-yloxy)-2-methylphenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea **11m** (94 mg, 0.21 mmol) afforded the title compound (79 mg, 79%) as a brown powder following procedure A. ^{1}H-NMR δ: 1.35 (s, 3H, CH_3), 6.35 (d, 1H, J=6.0, H_{Py}), 6.95-7.13 (m, 2H, H_{arom}), 7.62 (broad s, 2H, H_{arom}), 7.75-7.79 (m, 2H, $J_{Py,6}$=6.0, $H_{Py,6}$+ H_{arom}), 8.12 (m, 2H, H_{arom}+ NH_{urea}), 9.48 (s, 1H, NH_{urea}), 11.18 (s, 1H, NH_{Py}), 11.35 (s, 1H, NH_{Py}). ^{13}C-NMR δ: 17.7, 105.4, 113.3, 116.1, 117.4, 121.4, 121.9, 122.5, 123.5, 126.8, 131.1, 131.9, 133.8, 139.4, 140.5, 142.7, 145.8, 146.4, 149.5, 152.6, 153.9. LC-MS: *m/z* 478 ($[M+H]^+$, 100). HRMS: *m/z* calcd for $C_{21}H_{15}ClF_3N_5O_3$ ($[M+H]^+$): 478.0892; found: 478.0894.

2. Compounds **21c-e/n-y; 22a-f; 23a-c** following Procedure B

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(3-methyl-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-7-yloxy)phenyl)urea (21c). 7-(4-Amino-2-methylphenoxy)-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one **2c** (20 mg, 0.08 mmol) afforded the title compound (27 mg, 72%) following procedure B. ^{1}H-NMR δ: 2.13 (s, 3H, CH_3), 6.17 (d, 1H, J=5.7, H_{Py}), 7.05 (d, 1H, J=8.6, H_{arom}), 7.35 (d, 1H, J=8.8, H_{arom}), 7.48 (s, 1H), 7.60-7.65 (m, 2H), 7.72 (d, 1H, J=5.7, H_{Py}), 8.12 (s, 1H), 8.86 (s, 1H, NH_{urea}), 9.17 (s, 1 H, NH_{urea}), 11.17 (s, 1H, NH_{Py}), 11.31 (s, 1H, NH_{Py}). ^{13}C-NMR δ: 15.8, 104.1, 112.2, 116.7, 117.9, 121.3, 121.6, 122.3, 123.0, 123.9, 126.7, 130.1, 132.0, 136.6, 139.4, 141.4, 146.1, 146.6, 146.7, 152.4, 154.2. LC-MS: *m/z* 478 ($[M+H]^+$, 100). HRMS: *m/z* calcd for $C_{21}H_{15}ClF_3N_5O_3$ ($[M+H]^+$): 478.0894; found: 478.0894.

1-(4-(2,3-Dihydro-2-oxo-1*H*-imidazo[4,5-*b*]pyridin-7-yl-oxy)-2-fluorophenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (21d). 7-(4-Amino-3-fluorophenoxy)-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one **2d** (26 mg, 0.1 mmol) and 1-chloro-4-isocyanato-2-(trifluoromethyl)benzene (23 mg, 0.1 mmol) afforded the title compound (40 mg, 83%) following procedure B. ^{1}H-NMR δ: 6.45 (d, 1H, J=5.9, H_{Py}), 6.98 (d, 1H, H_{arom}), 7.23 (d, 1H, H_{arom}), 7.63 (broad s, 2H, H_{arom}), 7.79 (d, 1H, H_{Py}), 8.05 (s, 1H, H_{arom}),

8.12 (s, 1H, H_{arom}), 8.69 (s, 1H, NH_{urea}), 9.49 (s, 1H, NH_{urea}), 11.22 (s, 1H, NH_{Py}), 11.42 (s, 1H, NH_{Py}). LC-MS: *m/z* 481 ([M+H]$^+$, 100). HRMS: *m/z* calcd for $C_{20}H_{12}ClF_4N_5O_3$ ([M+H]$^+$): 482.0638; found: 482.0639.

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-7-yl-oxy)naphthalen-1-yl)urea (21e) 7-(4-Aminonaphthalen-1-yl-oxy)-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one **2e** (94 mg, 0.32 mmol) and 1-chloro-4-isocyanato-2-(trifluoromethyl)benzene (77 mg, 0.35 mmol) afforded the title compound as a brown solid (25 mg, 15%) following procedure B. ^{1}H-NMR δ: 6.21 (d, 1H, J = 5.9, H_{Py}), 7.20 (m, 1H, H_{arom}), 7.56 – 7.67 (m, 4H, $H_{arom+Py}$), 7.79 – 7.87 (m, 2H, H_{arom}), 7.94 – 7.97 (m, 1H, H_{arom}), 8.23 – 8.31 (m, 2H, H_{arom}), 10.52 (s, NH, NH_{Py}), 11.26 (s, NH, NH_{Py}). LC-MS: *m/z* 514 ([M + H]$^+$, 100). HRMS: *m/z* calcd for $C_{24}H_{15}ClF_3N_5O_3$ ([M+H]$^+$): 514.0894; found: 514.0894.

1-(4-(2,3-Dihydro-2-oxo-1*H*-imidazo[4,5-*b*]pyridin-7-yloxy)-2-(methylthio)phenyl)-3-(3-(trifluoromethyl)phenyl)urea (21n). 7-(4-Amino-3-(methylthio)phenoxy)-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one **2a** (66 mg, 0.23 mmol) afforded the title compound (65 mg, 60%) as a white powder following procedure B. ^{1}H-NMR δ: 2.46 (s, 3H, CH_3), 6.42 (d, 1H, J=5.9, H_{Py}), 6.99 (dd, 1H, J=8.4 and J=2.7, H_{arom}), 7.19 (d, 1H, J=2.7, H_{arom}), 7.31 (d, 1H, J=7.6, H_{arom}), 7.53 (m, 1H, H_{arom}), 7.57 (m, 1H, H_{arom}), 7.78 (d, 1H, J=5.9, H_{Py}), 7.83 (d, 1H, J=8.8, H_{arom}), 8.02 (m, 1H, H_{arom}), 8.15 (s, 1H, NH_{urea}), 9.63 (s, 1H, NH_{urea}), 11.17 (s, 1H, NH_{Py}), 11.35 (bs, 1H, NH_{Py}). ^{13}C-NMR δ: 15.7, 105.6, 113.0, 113.8, 117.3, 117.9, 119.2, 121.5, 124.0, 125.1, 129.3, 129.8, 131.3, 133.3, 140.5, 141.2, 145.3, 146.9, 150.3, 152.5, 154.1. LC-MS: *m/z* 476 ([M+H]$^+$, 100). HRMS: *m/z* calcd for $C_{21}H_{16}F_3N_5O_3S$ ([M+H]$^+$): 476.0998; found: 476.1004.

1-(2-Fluoro-5-(trifluoromethyl)phenyl)-3-(2-(methylthio)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-7-yloxy)phenyl)urea (21o). 7-(4-Amino-3-(methylthio)phenoxy)-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one **2a** (100 mg, 0.35 mmol) afforded the title compound (109 mg, 63%, purity 79%) as a brown powder following procedure B. ^{1}H-NMR δ: 2.46 (s, 3H, CH_3), 6.42 (d, 1H, J=5.9, H_{Py}), 6.98 (dd, 1H, J=8.7 Hz and J=2.6, H_{arom}), 7.19 (d, 1H, J=2.7, H_{arom}), 7.39 (m, 1H, H_{arom}), 7.51 (m, 1H, H_{arom}), 7.77 (m, 2H, J=5.9, H_{arom} + H_{Py}), 8.64 (m, 2H, NH_{urea} +H_{arom}), 9.52 (s, 1H, NH_{urea}), 11.23 (s, 1H, NH_{Py}), 11.40 (bs, 1H, NH_{Py}). ^{13}C-NMR δ: 15.5, 105.8, 113.7, 115.3, 116.0, 116.2, 117.1, 118.8, 121.7, 124.9, 128.7, 129.3, 132.4, 132.9, 133.5, 139.4, 145.6, 145.8, 150.4, 152.6, 153.9. ^{19}F NMR δ: -60.7, -123.6. LC-MS: *m/z* 494 ([M+H]$^+$, 100). HRMS: *m/z* calcd for $C_{21}H_{15}F_4N_5O_3S$ ([M+H]$^+$): 494.0904; found: 494.0902.

1-(4-(2,3-Dihydro-2-oxo-1*H*-imidazo[4,5-*b*]pyridin-7-yloxy)-3-methoxyphenyl)-3-(3-

(trifluoromethyl)phenyl)urea (21p). 7-(4-Amino-2-methoxyphenoxy)-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one **2b** (16 mg, 0.06 mmol) afforded the title compound (21 mg, 78%) as a pale yellow powder following procedure B. ^{1}H-NMR δ: 3.75 (s, 3H, CH_3), 5.94 (d, 1H, J=3.9, H_{Py}), 6.99 (d, 1H, J=8.5, H_{arom}), 7.24 (d, 1H, J=7.8, H_{arom}), 7.36 (d, 1H, J=7.3, H_{arom}), 7.46 (t, 1H, J=7.9, H_{arom}), 7.53 (d, 1H, J=4.6, H_{arom}), 7.73 (s, 1H, H_{arom}), 7.89 (s, 1H, H_{arom}), 7.97 (d, 1H, J=8.2, H_{arom}), 8.25 (s, 1H, NH_{urea}), 10.49 (bs, 1H, NH_{urea}), 11.99 (bs, 2H, NH_{Py}). ^{13}C-NMR δ: 55.5, 103.3, 103.9, 110.6, 114.0, 117.8, 121.8, 122.4, 123.2, 129.3, 129.7, 135.8, 138.4, 140.3, 140.7, 141.0, 141.4, 144.6, 146.7, 151.3, 152.6. LC-MS: *m/z* 460 ($[M+H]^+$, 100). HRMS: *m/z* calcd for $C_{21}H_{16}F_3N_5O_4$ ($[M+H]^+$): 460.1230; found: 460.1233.

1-(4-(2-Oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-7-yl-oxy)-2-fluorophenyl)-3-(3-(trifluoromethyl) phenyl)urea (21q). 7-(4-amino-3-fluorophenoxy)-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one (**2d**) (26 mg, 0.1 mmol) and 3-(trifluoromethyl)phenyl isocyanate (18 μL, 0.13 mmol) afforded the title compound as an light brown solid (30 mg, 67%) following procedure B. ^{1}H-NMR δ: 6.46 (d, 1H, J=6.0, H_{Py}), 6.98 (d, 1H, J=7.5, H_{arom}), 7.21 (d, 1H, J=8.5, H_{arom}), 7.33 (d, 1H, J=6.5, H_{arom}), 7.50-7.56 (m, 2H, H_{arom}), 7.79 (d, 1H, J=6.0, H_{Py}), 8.02 (s, 1H, H_{arom}), 8.10 (t, 1H, J=8.8, H_{arom}), 8.63 (s, 1H, NH_{urea}), 9.36 (s, 1H, NH_{urea}), 11.16 (s, 1H, NH_{Py3}), 11.37 (s, 1H, NH_{Py2}). LC-MS: *m/z* 448 ($[M+H]^+$, 100). HRMS: *m/z* calcd for $C_{20}H_{14}F_4N_5O_3$ ($[M+H]^+$): 448.1033; found: 448.1031.

1-(4-(2-Oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-7-yl-oxy)-2-fluorophenyl)-3-(5-fluoro-3-(trifluoro methyl)phenyl)urea (21r). 7-(4-amino-3-fluorophenoxy)-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one (**2d**) (26 mg, 0.1 mmol) and 5-fluoro-3-(trifluoromethyl)phenyl isocyanate (19 μL, 0.13 mmol) afforded the title compound as an light brown solid (41 mg, 88%) following procedure B. ^{1}H-NMR δ: 6.46 (d, 1H, H_{Py}, J=6.0 Hz), 6.99 (d, 1H, H_{arom} , J=8.0 Hz), 7.23 (d, 1H, J=6.5, H_{arom}), 7.40-7.42 (m, 1H, H_{arom}), 7.50 (t, 1H, J=9.8, H_{arom}), 7.79 (d, 1H, J=6.0, H_{Py}), 8.17 (t, 1H, J=8.8, H_{arom}), 8.63 (d, 1H, J=7.0, H_{arom}), 9.14 (s, 1H, NH_{urea}), 9.46 (s, 1H, NH_{urea}), 11.16 (s, 1H, NH_{Py}), 11.37 (s, 1H, NH_{Py}). LC-MS: *m/z* 466 ($[M+H]^+$, 100). HRMS: *m/z* calcd for $C_{20}H_{13}F_5N_5O_3$ ($[M+H]^+$): 466.0939; found: 466.0935.

1-(4-(2-Oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-7-yl-oxy)-2-fluorophenyl)-3-(3-(trifluoromethylthio) phenyl)urea (21s). 7-(4-amino-3-fluorophenoxy)-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one (**2d**) (26 mg, 0.1 mmol) and 3-(trifluoromethyl)phenyl isocyanate (19 μL, 0.13 mmol) afforded the title compound as an light brown solid (41 mg, 86%) following procedure B. ^{1}H-NMR δ: 6.46 (d, 1H, J=6.0, H_{Py}), 6.99 (d, 1H, J=9.0, H_{arom}), 7.22 (d, 1H, J=8.0, H_{arom}), 7.32 (d, 1H, J=6.5, H_{arom}), 7.46 (t, 1H, J=10.5, H_{arom}), 7.54 (d, 1H, J=8.5, H_{arom}), 7.79 (d, 1H, J=6.0, H_{Py}), 7.90 (s, 1H, H_{arom}), 8.10

(t, 1H, J=9.3, H_{arom}), 8.60 (s, 1H, NH_{urea}), 9.31 (s, 1H, NH_{urea}), 11.17 (s, 1H, NH_{Py}), 11.37 (s, 1H, NH_{Py}). LC-MS: *m/z* 480 ([M+H]$^+$, 100). HRMS: *m/z* calcd for $C_{20}H_{14}F_4N_5O_3S$ ([M+H]$^+$): 480.0753; found: 480.0751.

1-(4-(2-Oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-7-yl-oxy)naphthalen-1-yl)-3-(3-(trifluoromethyl)phenyl)urea (21t). 7-(4-Aminonaphthalen-1-yl-oxy)-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one **2e** (30 mg, 0.10 mmol) and 1-isocyanato-3-(trifluoromethyl)benzene (21 mg, 0.11 mmol) afforded the title compound as a brown solid (31 mg, 65%) following procedure B. ^{1}H-NMR δ: 6.21 (d, 1H, J = 5.5, H_{Py}), 7.32 (m, 2H, H_{arom}), 7.53 – 7.71 (m, 5H, H_{arom}), 7.96 (t, 2H, H_{arom}), 8.09 (s, 1H, H_{arom}), 8.19 (d, 1H, J = 5.5, H_{Py}), 8.96 and 9.46 (bs, 2H, NH_{urea}), 11.39 (s, NH, NH_{Py}), 11.44 (s, NH, NH_{Py}). LC-MS: *m/z* 480 ([M + H]$^+$, 100). HRMS: *m/z* calcd for $C_{24}H_{16}F_3N_5O_3$ ([M+H]$^+$): 480.1289; found: 480.1283.

1-(2-Fluoro-5-trifluoromethylphenyl)-3-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-7-yl-oxy)naphthalen-1-yl)urea (21u). 2-Fluoro-5-trifluoromethylphenylisocyanate (24 µL, 0.16 mmol) and 7-(4-aminonaphthalen-1-yl-oxy)-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one **2e** (40 mg, 0.14 mmol) afforded the title compound (39 mg, 57%) as a solid following procedure B. ^{1}H-NMR δ: 6.23 (d, 1H, J=6.0, H_{Py}), 7.31 (d, 1H, J=8.4, H_{arom}), 7.40-7.42 (m, 1H, H_{arom}), 7.53 (t, 1H, J=9.8, H_{arom}), 7.62 (t, 1H, J=7.6, H_{arom}), 7.70 (m, 2H, J=6.0, H_{arom} +H_{Py}), 7.99 (d, 1H, J=8.4, H_{arom}), 8.02 (d, 1H, J=8.4, H_{arom}), 8.23 (d, 1H, J=8.6, H_{arom}), 8.68 (d, 1H, J=5.6, H_{arom}), 9.31 (s, 1H, NH_{urea}), 9.37 (s, 1H, NH_{urea}), 11.33 (s, 1H, NH_{Py}), 11.39 (s, 1H, NH_{Py}). LC MS: *m/z* 498 ([M+H]$^+$, 100). HRMS: *m/z* calcd for $C_{24}H_{15}F_4N_5O_3$ ([M+H]$^+$) 498.1189; found 498.1186.

1-(3-Fluorophenyl)-3-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-7-yl-oxy)naphthalen-1-yl)urea (21v). 3-Fluorophenylisocyanate (18 µL, 0.16 mmol) and 7-(4-aminonaphthalen-1-yl-oxy)-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one **2e** (40 mg, 0.14 mmol) afforded the title compound (58 mg, 97%) as an off-white solid following procedure B. ^{1}H-NMR δ: 6.23 (d, 1H, J=6.0, H_{Py}), 6.80 (m, 1H, H_{arom}), 7.17 (d, 1H, J=7.9, H_{arom}), 7.30 (d, 1H, J=8.3, H_{arom}), 7.32-7.35 (m, 1H, H_{arom}), 7.55 (d, 1H, J=11.0, H_{arom}), 7.61 (t, 1H, J=7.4, H_{arom}), 7.70 (d, 1H, J=6.0, H_{Py}), 7.96 (t, 1H, J=7.9, H_{arom}), 8.18 (d, 1H, J=8.5, H_{arom}), 8.67 (s, 1H, NH_{urea}), 9.27 (s, 1H, NH_{urea}), 11.33 (s, 1H, NH_{Py}), 11.38 (s, 1H, NH_{Py}). LC-MS: *m/z* 429 [(M+H)$^+$, 100]. HRMS: *m/z* calcd for $C_{23}H_{16}FN_5O_3$ ([M+H]$^+$): 430.1315; found 430.1314.

1-(3,4-Difluoro-phenyl)-3-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-7-yl-oxy)naphthalen-1-

yl)urea (21w). 3,4-Difluorophenylisocyanate (24 μL, 0.16 mmol) and 7-(4-aminonaphthalen-1-yl-oxy)-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one **2e** (40 mg, 0.14 mmol) afforded the title compound (57 mg, 91%), as a solid following procedure B. ^{1}H-NMR δ: 6.23 (d, 1H, J=6.0, H_{Py}), 6.16-6.19 (m, 1H, H_{arom}), 7.30 (d, 1H, J=8.3, H_{arom}), 7.32-7.39 (m, 1H, H_{arom}), 7.59-7.68 (m, 2H, H_{arom}), 7.70 (d, 1H, J= 6.0, H_{Py}), 7.70-7.75 (m, 1H, H_{arom}), 7.93 (d, 1H, J=8.3, H_{arom}), 7.97 (d, 1H, J=8.4, H_{arom}), 8.17 (d, 1H, J=8.5, H_{arom}), 8.86 (s, 1H, NH_{urea}), 9.25 (s, 1H, NH_{urea}), 11.33 (s, 1H, NH_{Py}), 11.39 (s, 1H, NH_{Py}). LC-MS: *m/z* 448 ([M+H]$^+$, 100). HRMS: *m/z* calcd for $C_{23}H_{15}F_2N_5O_3$ ([M+H]$^+$, 100): 448.1221; found 448.1220.

1-(3-*Tert*-butyl-phenyl)-3-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-7-yl-oxy)naphthalen-1-yl)urea (21x). 3-*Tert*-butylphenylisocyanate (0.20 mmol) and 7-(4-aminonaphthalen-1-yl-oxy)-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one **2e** (40 mg, 0.14 mmol) afforded the title compound (46 mg, 70%) as a solid following procedure B. ^{1}H-NMR δ: 1.29 (s, 9H, *t*Bu), 6.21 (d, 1H, J=6.0, H_{Py}), 7.03 (d, 1H, J= 7.0, H_{arom}), 7.23 (t, 1H, J= 7.9, H_{arom}), 7.31 (d, 1H, J= 8.3, H_{arom}), 7.35 (d, 1H, J= 8.0, H_{arom}), 7.49-7.51 (m, 1H, H_{arom}), 7.60 (t, 1H, J= 7.5, H_{arom}), 7.67-7.70 (m, 1H, H_{arom}), 7.69 (d, 1H, J=6.0, H_{Py}), 7.96 (d, 1H, J= 8.0, H_{arom}), 8.00 (d, 1H, J= 8.3, H_{arom}), 8.20 (d, 1H, J= 8.6, H_{arom}), 9.74 (s, 1H, NH_{urea}), 9.00 (s, 1H, NH_{urea}), 11.28 (s, 1H, NH_{Py}), 11.40 (s, 1H, NH_{Py}). LC-MS: *m/z* 468 ([M+H]$^+$, 100). HRMS: *m/z* calcd for $C_{27}H_{25}N_5O_3$ ([M+H]$^+$): 468.2030; found 468.2036.

1-(2-*N*-morpholyl-5-trifluoromethylphenyl)-3-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-7-yl-oxy)naphthalen-1-yl)urea (21y). 2-*N*-morpholyl-5-trifluoromethylphenylisocyanate (0.21 mmol) and 7-(4-aminonaphthalen-1-yl-oxy)-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one **2e** (40 mg, 0.14 mmol) afforded the title compound (56 mg, 71%) as a solid following procedure B. ^{1}H-NMR δ: 2.88-2.91 (m, 4H, CH_2), 3.82 (m, 4H, CH_2), 6.24 (d, 1H, J=6.0, H_{Py}), 7.30 (d, 1H, J= 8.3, H_{arom}), 7.33-7.37 (m, 2H, H_{arom}), 7.62 (t, 1H, J= 7.6, H_{arom}), 7.69-7.71 (m, 1H, H_{arom}), 7.71 (d, 1H, J=6.0, H_{Py}), 7.90 (d, 1H, J= 8.0, H_{arom}), 8.00 (d, 1H, J= 8.4, H_{arom}), 8.23 (d, 1H, J= 8.6, H_{arom}), 8.44 (s, 1H, H_{arom}), 8.53 (s, 1H, NH_{urea}), 9.58 (s, 1H, NH_{urea}), 11.34 (s, 1H, NH_{Py}), 11.39 (s, 1H, NH_{Py}). LC-MS: *m/z* 565 ([M+H]$^+$, 100). HRMS: *m/z* calcd for $C_{28}H_{23}F_3N_6O_4$ ([M+H]$^+$): 565.1805; found 565.1800.

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(2-fluoro-4-(1-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-7-yloxy)phenyl)urea (22a). 7-(4-Amino-3-fluorophenoxy)-1-methyl-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one **3d** (30 mg, 0.11 mmol) and 4-chloro-3-(trifluoromethyl)phenyl isocyanate (29 μL, 0.13 mmol) afforded the title compound as a light brown solid (6 mg, 11%, purity 90%) following procedure B. ^{1}H-NMR δ: 3.43 (s, 3H, CH_3N), 6.51 (d, 1H, J=6.4, H_{Py}), 7.02 (d, 1H, J=8.3, H_{arom}), 7.24 (d, 1H, J=12.2, H_{arom}), 7.62 (broad s, 2H, H_{arom}), 7.82 (d, 1H, J=5.5, H_{Py}), 8.06 (t, 1H,

J=9.1, H_{arom}), 8.11 (s, 1H, H_{arom}), 8.67 (s, 1H, NH_{urea}), 9.48 (s, 1H, NH_{urea}), 11.22 (s, 1H, NH_{Py}), 11.63 (s, 1H, NH_{Py}). LC-MS: *m/z* 496 ($[M+H]^+$, 100). HRMS: *m/z* calcd for $C_{21}H_{14}ClF_4N_5O_3$ ($[M+H]^+$): 496.0794; found: 496.0793.

1-(3-Trifluoromethyl-4-chlorophenyl)-3-(4-(2-oxo-2,3-dihydro-1*H*-1-*N*-methyl-imidazo[4,5-*b*]pyridin-7-yl-oxy)naphthalen-1-yl)urea (22b). 3-Trifluoromethyl-4-chlorophenylisocyanate (24 μL, 0.16 mmol) and 7-(4-aminonaphthalen-1-yloxy)-1-methyl-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one **3e** (50 mg, 0.16 mmol) afforded the title compound (75 mg, 89%) as a solid following procedure B. ^{1}H-NMR δ: 3.54 (s, 3H, CH_3), 6.30 (d, 1H, J=5.9, H_{Py}), 6.16-6.19 (m, 1H, H_{arom}), 7.26 (d, 1H, J=8.3, H_{arom}), 7.62-7.64 (m, 2H, H_{arom}), 7.68-7.70 (m, 2H, H_{arom}), 7.75 (d, 1H, J= 5.9, H_{Py}), 7.88 (d, 1H, J=8.3, H_{arom}), 8.10 (d, 1H, J=8.3, H_{arom}), 8.15-8.17 (m, 1H, H_{arom}), 8.93 (s, 1H, NH_{urea}), 9.49 (s, 1H, NH_{urea}), 11.62 (s, 1H, NH_{Py}). LC-MS: *m/z* 528 ($[M+H]^+$, 100). HRMS: *m/z* calcd for $C_{25}H_{17}ClF_3N_5O_3$ ($[M+H]^+$): 528.1050; found 528.1052.

1-(2-Fluoro-5-trifluoromethylphenyl)-3-(4-(2-oxo-2,3-dihydro-1*H*-1-*N*-methyl-imidazo[4,5-*b*]pyridin-7-yloxy)naphtyhalen-1-yl)urea (22c). 2-Fluoro-5-trifluoromethylphenylisocyanate (24 μL, 0.16 mmol) and 7-(4-aminonaphthalen-1-yloxy)-1-methyl-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one **3e** (50 mg, 0.16 mmol) afforded the title compound (55 mg, 67%) as a solid following procedure B. ^{1}H-NMR δ: 3.56 (s, 3H, CH_3), 6.31 (d, 1H, J=5.9, H_{Py}), 7.28 (d, 1H, J=8.4, H_{arom}), 7.39-7.42 (m, 1H, H_{arom}), 7.53 (t, 1H, J= 9.7, H_{arom}), 7.62-7.65 (m, 1H, H_{arom}), 7.70-7.73 (m, 1H, H_{arom}), 7.75 (d, 1H, J= 5.9, H_{Py}), 8.01 (d, 1H, J=8.4, H_{arom}), 8.11 (d, 1H, J=8.3, H_{arom}), 8.23 (d, 1H, J= 8.6, H_{arom}), 8.67-8.69 (m, 1H, H_{arom}), 9.29 (s, 1H, NH_{urea}), 9.36 (s, 1H, NH_{urea}), 11.65 (s, 1H, NH_{Py}). LC-MS: *m/z* 512 ($[M+H]^+$, 100). HRMS: *m/z* calcd for $C_{25}H_{17}ClF_3N_5O_3$ ($[M+H]^+$): 512.1346; found 512.1348.

1-(3-*Tert*-butylphenyl)-3-(4-(2-oxo-2,3-dihydro-1-*N*-methyl-imidazo[4,5-*b*]pyridin-7-yl-oxy)naphthalen-1-yl)urea (22d). 3-*Tert*-butylphenylisocyanate (0.20 mmol) and 7-(4-aminonaphthalen-1-yloxy)-1-methyl-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one **3e** (40 mg, 0.13 mmol) afforded the title compound (46 mg, 73%) as a solid following procedure B. ^{1}H-NMR δ: 1.29 (s, 9H, *t*Bu), 3.54 (s, 3H, CH_3), 6.28 (d, 1H, J=5.9, H_{Py}), 7.02 (d, 1H, J= 7.8, H_{arom}), 7.15-7.23 (m, 1H, H_{arom}), 7.25 (d, 1H, J= 8.3, H_{arom}), 7.36 (d, 1H, J= 8.0, H_{arom}), 7.50-7.54 (m, 1H, H_{arom}), 7.61 (t, 1H, J= 7.5, H_{arom}), 7.69 (t, 1H, J=7.1, H_{arom}), 7.73 (d, 1H, J=5.9, H_{Py}), 7.97 (d, 1H, J= 8.0, H_{arom}), 8.09 (d, 1H, J= 8.3, H_{arom}), 8.22 (d, 1H, J= 8.6, H_{arom}), 8.87 (s, 1H, NH_{urea}), 9.15 (s, 1H, NH_{urea}), 11.63 (s, 1H, NH_{Py}). LC-MS: *m/z* 482 ($[M+H]^+$, 100). HRMS: *m/z* calcd for $C_{28}H_{27}N_5O_3$ ($[M+H]^+$): 482.2187; found

482.2185.

1-(3-Trifluoromethylphenyl)-3-(4-(2-oxo-2,3-dihydro-1*H*-1-*N*-methyl-imidazo[4,5-*b*]pyridin-7-yl-oxy)naphthalen-1-yl)urea (22e). 3-Trifluoromethylphenylisocyanate (24 μL, 0.18 mmol) and 7-(4-aminonaphthalen-1-yloxy)-1-methyl-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one **3e** (50 mg, 0.16 mmol) afforded the title compound (55 mg, 70%) as a solid following procedure B. ^{1}H-NMR δ: 3.54 (s, 3H, CH_3), 6.31 (d, 1H, J=5.9, H_{Py}), 7.26 (d, 1H, J= 8.3, H_{arom}), 7.36-7.47 (m, 3H, H_{arom}), 7.51-7.56 (m, 1H, H_{arom}), 7.61-7.71 (m, 1H, H_{arom}), 7.81 (d, 1H, J=5.9, H_{Py}), 7.91 (d, 1H, J= 8.3, H_{arom}), 8.09 (m, 2H, H_{arom}), 8.21 (d, 1H, J= 8.6, H_{arom}), 9.09 (s, 1H, NH_{urea}), 9.62 (s, 1H, NH_{urea}), 11.65 (s, 1H, NH_{Py}). LC-MS: *m/z* 494 ($[M+H]^+$, 100). HRMS: *m/z* calcd for $C_{25}H_{18}F_3N_5O_3$ ($[M+H]^+$): 494.1440; found 494.1446.

1-(3-Trifluoromethylthiophenyl)-3-(4-(2-oxo-2,3-dihydro-1*H*-1-*N*-methyl-imidazo[4,5-*b*]pyridin-7-yl-oxy)naphthalen-1-yl)urea (22f). 3-Trifluoromethylthiophenylisocyanate (28 μL, 0.18 mmol) and 7-(4-aminonaphthalen-1-yloxy)-1-methyl-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one **3e** (50 mg, 0.16 mmol) afforded the title compound (58 mg, 69%) as a solid following procedure B. ^{1}H-NMR δ: 3.54 (s, 3H, CH_3), 6.31 (d, 1H, J=5.9, H_{Py}), 7.26 (d, 1H, J= 8.3, H_{arom}), 7.31 (d, 1H, J= 8.0, H_{arom}), 7.46 (t, 1H, J= 7.9, H_{arom}), 7.60-7.63 (m, 2H, H_{arom}), 7.67-7.71 (m, 1H, H_{arom}), 7.74 (d, 1H, J=5.9, H_{Py}), 7.91 (d, 1H, J= 8.3, H_{arom}), 8.04 (s, 1H, H_{arom}), 8.10 (d, 1H, J=8.3, H_{arom}), 8.20 (d, 1H, J= 8.5, H_{arom}), 9.08 (s, 1H, NH_{urea}), 9.56 (s, 1H, NH_{urea}), 11.66 (s, 1H, NH_{Py}). LC-MS: *m/z* 526 ($[M+H]^+$, 100). HRMS: *m/z* calcd for $C_{25}H_{18}F_3N_5O_3SNa$ ($[M+Na]^+$): 548.0974; found 548.0965.

1-(3-Trifluoromethyl-4-chlorophenyl)-3-(4-(2-oxo-2,3-dihydro-3-*N*-methyl-imidazo[4,5-*b*]pyridin-7-yl-oxy)naphthalen-1-yl)urea (23a). 3-Trifluoromethyl-4-chlorophenylisocyanate (35 mg, 0.16 mmol) and 7-(4-aminonaphthalen-1-yloxy)-3-methyl-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one **4** (40 mg, 0.13 mmol) afforded the title compound (55 mg, 80%) as a solid following procedure B. ^{1}H-NMR δ: 3.35 (s, 3H, CH_3), 6.25 (d, 1H, J=5.9, H_{Py}), 7.47-7.58 (m, 1H, H_{arom}), 7.60 (d, 2H, J=8.7, H_{arom}), 7.68-7.83 (m, 4H, H_{arom}+ H_{Py}), 7.87-7.97 (m, 1H, H_{arom}), 8.15 (d, 1H, J=7.4, H_{arom}), 8.20-8.27 (m, 1H, H_{arom}), 9.49 (s, 1H, NH_{urea}), 10.04 (s, 1H, NH_{urea}), 11.59 (s, 1H, NH_{Py}). LC-MS: *m/z* 528 ($[M+H]^+$, 100). HRMS: *m/z* calcd for $C_{25}H_{17}ClF_3N_5O_3$ ($[M+H]^+$): 528.1045; found 528.1046.

1-(2-Fluoro-5-trifluoromethylphenyl)-3-(4-(2-oxo-2,3-dihydro-3-*N*-methyl-imidazo[4,5-*b*]pyridin-7-yloxy)naphthalen-1-yl)urea (23b). 2-Fluoro-5-trifluoromethylphenylisocyanate (24 μL, 0.16 mmol) and 7-(4-aminonaphthalen-1-yloxy)-3-methyl-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one **4** (40 mg, 0.13 mmol) afforded the title compound (59 mg, 72%) as a solid following procedure B. ^{1}H-NMR δ: 3.33 (s,

3H, CH_3), 6.28 (d, 1H, J=5.9, H_{Py}), 7.25 (d, 1H, J= 8.0, H_{arom}), 7.39-7.41 (m, 1H, H_{arom}), 7.52 (t, 1H, J= 9.8, H_{arom}), 7.60 (t, 1H, J= 7.3, H_{arom}), 7.75 (t, 1H, J= 8.0, H_{arom}), 7.75 (d, 1H, J= 5.9, H_{Py}), 7.97-8.10 (m, 2H, H_{arom}), 8.22 (d, 1H, J= 8.5, H_{arom}), 8.67-8.70 (m, 1H, H_{arom}), 9.38 (s, 1H, NH_{urea}), 9.42 (s, 1H, NH_{urea}), 11.60 (s, 1H, NH_{Py}). LC-MS: *m/z* 512 ($[M+H]^+$, 100). HRMS: *m/z* calcd for $C_{25}H_{17}F_4N_5O_3$ ($[M+H]^+$): 512.1340; found 512.1339.

1-(3-*Tert*-butylphenyl)-3-(4-(2-oxo-2,3-dihydro-3-*N*-methylimidazo[4,5-*b*]pyridin-7-yloxy)naphthalen-1-yl)urea (23c). 3-*Tert*-butylphenylisocyanate (0.20 mmol) and 7-(4-aminonaphthalen-1-yloxy)-3-methyl-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one **4** (40 mg, 0.13 mmol) afforded the title compound (42 mg, 67%) as a solid following procedure B. ^{1}H-NMR δ: 1.29 (s, 9H, *t*Bu), 3.33 (s, 3H, CH_3), 6.25 (d, 1H, J=5.9, H_{Py}), 7.02 (d, 1H, J=8.3, H_{arom}), 7.22 (t, 1H, J= 7.9, H_{arom}), 7.31-7.34 (m, 1H, H_{arom}), 7.36 (d, 1H, J= 8.0, H_{arom}), 7.51-7.54 (m, 1H, H_{arom}), 7.58 (t, 1H, J= 7.6, H_{arom}), 7.66 (t, 1H, J= 7.9, H_{arom}), 7.74 (d, 1H, J= 5.9, H_{Py}), 7.93-8.01 (m, 2H, H_{arom}), 8.20 (d, 1H, J=8.6, H_{arom}), 8.93 (s, 1H, NH_{urea}), 9.16 (s, 1H, NH_{urea}), 11.57 (s, 1H, NH_{Py}). LC-MS: *m/z* 481.2 ($[M+H]^+$, 100). HRMS: *m/z* calcd for $C_{28}H_{27}N_5O_3$ ($[M+H]^+$): 482.2187; found 482.2187.

3. Compounds **24b; 25a, b** following Procedure C

***N*-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-7-yl-oxy)naphthalen-1-yl)-aminocarbonylmethylene-(3-trifluoromethyloxy-phenyl) (24b).** 7-(4-aminonaphthalen-1-yloxy)-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one **2e** (50 mg, 0.17 mmol) and 2-(3-(trifluoromethoxy)phenyl)acetyl chloride (0.20 mmol) afforded the title compound (56 mg, 67%) following procedure C. ^{1}H-NMR δ: 3.91 (s, 2H, CH_2), 6.24 (d, 1H, J=5.9, H_{Py}), 7.27 (t, 2H, J= 9.9, H_{arom}), 7.45-7.52 (m, 3H, H_{arom}), 7.58-7.68 (m, 3H, H_{arom}), 7.70 (d, 1H, J=5.9, H_{Py}), 7.98 (d, 1H, J=8.0, H_{arom}), 8.10 (d, 1H, J= 8.3, H_{arom}), 10.26 (s, 1H, NH_{amide}), 11.38 (s, 1H, NH_{Py}), 11.44 (s, 1H, NH_{Py}). LC-MS: *m/z* 495 ($[M+H]^+$, 100). HRMS: *m/z* calcd for $C_{25}H_{17}F_3N_4O_4$ ($[M+H]^+$): 495.1280; found 495.1266.

***N*-(4-(2-oxo-2,3-dihydro-1-*N*-methyl-imidazo[4,5-*b*]pyridin-7-yl-oxy)naphthalen-1-yl)-aminocarbonylmethylene-(3-trifluoromethyloxy-phenyl) (25a).** 7-(4-aminonaphthalen-1-yloxy)-1-methyl-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one **3e** (50 mg, 0.16 mmol) and 3-trifluoromethyloxybenzoyl chloride (19 µL, 0.19 mmol) afforded the title compound (38 mg, 48%) following procedure C. ^{1}H-NMR δ: 3.51 (s, 3H, CH_3), 6.43 (d, 1H, J=5.9, H_{Py}), 7.26 (d, 1H, J= 8.1, H_{arom}), 7.61-7.68 (m, 3H, H_{arom}), 7.73 (t, 1H, J= 8.1, H_{arom}), 7.81 (d, 1H, J=5.9, H_{Py}), 8.03 (s, 1H, H_{arom}), 8.06-8.08 (m, 2H, H_{arom}),

8.15-8.19 (m, 2H, H_{arom}), 10.60 (s, 1H, NH_{amide}), 11.69 (s, 1H, NH_{Py}). LC-MS: *m/z* 495 ($[M+H]^+$, 100). HRMS: *m/z* calcd for $C_{25}H_{17}F_3N_4O_4$ ($[M+H]^+$): 495.1280; found 495.1284.

***N*-(4-(2-oxo-2,3-dihydro-1-*N*-methyl-imidazo[4,5-*b*]pyridin-7-yl-oxy)naphthalen-1-yl)-aminocarbonylmethylene-(3-trifluoromethylthiophenyl) (25b).** 7-(4-aminonaphthalen-1-yloxy)-1-methyl-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one **3e** (50 mg, 0.17 mmol) and 3-trifluoromethylthiobenzoyl chloride (24 µL, 0.18 mmol) afforded the title compound (36 mg, 44%) following procedure C. ^{1}H-NMR δ: 3.51 (s, 3H, CH_3), 6.43 (d, 1H, J=5.9, H_{Py}), 7.27 (d, 1H, J= 8.1, H_{arom}), 7.61-7.67 (m, 3H, H_{arom}), 7.77 (t, 1H, J= 7.9, H_{arom}), 7.81 (d, 1H, J=5.9, H_{Py}), 7.99 (d, 1H, J=7.9, H_{arom}), 8.06-8.08 (m, 1H, H_{arom}), 8.17-8.19 (m, 1H, H_{arom}), 8.33 (d, 1H, J= 7.7, H_{arom}), 8.40 (s, 1H, H_{arom}), 10.64 (s, 1H, NH_{amide}), 11.69 (s, 1H, NH_{Py}). LC-MS: *m/z* 511 ($[M+H]^+$, 100). HRMS: *m/z* calcd for $C_{25}H_{17}F_3N_4O_3S$ ($[M+H]^+$): 511.1052; found 511.1053.

II. Chemistry-Synthesis and chemical data of intermediates

3-(Methylthio)-4-nitrophenol (6a). To a solution of 3-fluoro-4-nitrophenol (2 g, 12.7 mmol) in dry DMF (67 mL) was added by aliquots 2 equivalents of sodium thiomethoxide (1.78 g, 25.5 mmol) followed by 3 equivalents of potassium carbonate (5.27 g, 38.2 mmol). The mixture was stirred at room temperature for 23 hrs and then water (100 mL) was added. The mixture was extracted with EtOAc, and the combined organic layers washed successively with water (60 mL) and brine (60 mL) and then dried over $MgSO_4$. The solvent was evaporated under vacuum to provide the title compound (2.12 g, 90%) as a yellow powder. ^{1}H-NMR δ: 2.44 (s, 3H, H_{Me}), 6.72 (d, 1H, J=9.0, H_{arom}), 6.79 (s, 1H, H_{arom}), 8.19 (d, 1H, J=9.1, H_{arom}), 11.20 (bs, 1H, OH). ^{13}C-NMR δ: 15.2, 111.3, 112.0, 128.7, 136.7, 142.0, 162.9.

3-Methoxy-4-nitrophenol (6f). A mixture of 3-fluoro-4-nitrophenol and freshly prepared sodium methoxide (12 equiv) in anhydrous MeOH (4.7 mL/mmol) was heated at refluxed for a week. After cooling to room temperature, water was added and the mixture extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and evaporated under powerful vacuum to afford the title compound as a yellow solid (1.5 g) in a quantitative yield. ^{1}H-NMR δ: 3.38 (s, 3H, H_{Me}), 6.46 (dd, 1H, J=8.9, J=2.2, H_{arom}), 6.61 (d, 1H, J=2.2, H_{arom}), 7.86 (d, 1H, J=8.9, H_{arom}). ^{13}C-NMR δ: 52.9, 100.4, 107.6, 128.3, 130.8, 155.7, 164.0.

3-(Dimethylamino)-4-nitrophenol (6g). To a solution of 3-fluoro-4-nitrophenol in a mixture of

DMSO:H_2O (2.5:1, 2.4 mL/mmol), K_2CO_3 (1 equiv) and dimethylamine hydrochloride (1.4 equiv) were added. The reaction mixture was heated overnight at 100°C. An orange color appeared quickly. After cooling at room temperature, the mixture was diluted in water (6.3 mL/mmol) and extracted with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated to dryness to provide the expected compound as a dark red solid (94% yield). ^{1}H-NMR δ: 2.68 (s, 6H, H_{Me}), 6.21 (dd, 1H, J=9.0 and J=2.4, H_{arom}), 6.32 (d, 1H, J=2.4, H_{arom}), 7.68 (d, 1H, J=9.0, H_{arom}), 10.41 (bs, 1H, OH). ^{13}C-NMR δ: 42.2 (2), 102.9, 106.3, 129.3, 131.1, 149.0, 162.4.

4-Amino-3-phenylphenol (7j). This material was synthesized according to a literature procedure.[21] ^{1}H-NMR δ: 6.60-6.73 (m, 3H, H_{arom}), 7.30-7.48 (m, 5H, H_{arom}). ^{13}C-NMR δ: 115.4, 117.1, 117.2, 127.2, 128.7, 128.9, 129.0, 129.1, 139.0, 148.5.

Procedure A: Compounds 7a; 11a; 12a. 4-Amino-3-(methylthio)phenol (7a). A suspension of iron powder (4 equiv), NH_4Cl (5.8 equiv) in a mixture EtOH:H_2O (1 mL:310 µL, 1 mL of ethanol/mmol of Fe) was heated to reflux for 10 minutes. Then, the reactant **6a** was added and the mixture stirred 5 hrs. After cooling at room temperature, the dark slurry was filtered over celite and washed with MeOH. After removing the solvent, EtOAc was added and the mixture filtered once again. The filtrate was washed successively with water and brine, and then dried over $MgSO_4$. Removal of the solvent under vacuum provided the title compound as a green-grey powder (53% yield). ^{1}H-NMR δ: 2.29 (s, 3H, H_{Me}), 4.48 (bs, 2H, NH_2), 6.44 (d, 1H, J=8.5, H_{arom}), 6.54 (d, 1H, J=8.5, H_{arom}), 6.61 (s, 1H, H_{arom}), 8.58 (bs, 1H, OH). ^{13}C-NMR δ: 15.9, 114.7, 115.4, 116.5, 120.1, 139.5, 148.7.

1-(4-(2,3-Diaminopyridin-4-yloxy)-2-(methylthio)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (11a). 1-(4-(2-Amino-3-nitropyridin-4-yloxy)-2-(methyltio)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea **5a** (180 mg, 0.35 mmol) to provide the title compound as a sticky dark oil (100 mg, 59%) as described in procedure A but after 24 hrs reflux. ^{1}H-NMR δ: 2.41 (s, 3H, CH_3), 5.61 (s, 2H, $NH_{2,Py}$), 6.06 (d, 1H, J=5.6, H_{Py}), 6.79 (d, 1H, J=8.7, H_{arom}), 7.01 (s, 1H, H_{arom}), 7.26 (d, 1H, J=5.6, H_{Py}), 7.58-7.69 (m, 4H, H_{arom}), 8.12 (s, 2H, $NH_{2,Py}$), 8.27 (s, 1H, NH_{urea}), 10.02 (s, 1H, NH_{urea}). ^{13}C-NMR δ: 15.6, 103.8, 115.6, 116.3, 117.6, 119.9, 122.5, 122.6, 124.9, 131.7, 131.9, 132.4, 134.7, 139.5, 139.6, 144.1, 147.0, 149.9, 152.3, 152.8. LC-MS: *m/z* 484 ($[M+H]^+$, 100).

***Tert*-butyl 4-(2,3-diaminopyridin-4-yloxy)-2-(methylthio)phenylcarbamate (12a).** *Tert*-butyl-4-(2-amino-3-nitropyridin-4-yloxy)-2-(methylthio)phenylcarbamate **10a** (12.5 g, 31.8 mmol) to provide the title compound (2.07 g, 18%) after purification by chromatography on silica gel (EtOAc:DCM 1:1, then

EtOAc:MeOH 95:5) as a powder (R_f 0.16, EtOAc-DCM, 1:1) as described in procedure A but after 24 hrs reflux. ^{1}H-NMR δ: 1.44 (s, 9H, *t*Bu), 2.39 (s, 3H, CH_3), 5.56 (bs, 2H, NH_2), 6.29 (d, 1H, J=6.9, H_{Py}), 6.87 (dd, 1H, J=8.6 and J=2.7, H_{arom}), 7.06 (d, 1H, J=2.7, H_{arom}), 7.31 (m, 2H, H_{Py} + H_{arom}), 7.56 (bs, 2H, $NH_{2,\ Py}$), 8.44 (s, 1H, $NH_{carbamate}$). ^{13}C-NMR δ: 14.8, 27.9, 78.8, 103.6, 115.9, 117.3, 121.7, 124.6, 127.5, 132.1, 137.1, 146.0, 148.5, 151.7, 153.4. LC-MS: *m/z* 362 ($[M+H]^+$, 100).

Procedure B (general conditions): Compounds 7b-d/f-i; 11f-m; 12b,c. Catalytic reduction using H_2 over Pd/C. The corresponding nitro compound (1 mmol) was dissolved in ethanol:EtOAc (23 mL/mmol, 3:1). Palladium 10% on activated carbon (156 mg/mmol) was added and the reaction mixture was stirred for 5 hrs under hydrogen atmosphere. The catalyst was discarded by filtration over celite and the filtrate evaporated to dryness to afford the title compound.

4-Amino-3-methoxyphenol (7b). 3-Methoxy-4-nitrophenol (790 mg, 5.7 mmol) afforded the title compound (749 mg, 94%) as a dark powder as described in procedure B. ^{1}H-NMR δ: 3.69 (s, 3H, H_{Me}), 4.05 (bs, 2H, NH2), 6.13 (dd, 1H, J=8.2, J=2.5, $H_{arom,}$), 6.30 (d, 1H, J=2.5, H_{arom}), 6.44 (d, 1H, J=8.2 Hz, H_{arom}), 8.47 (bs, 1H, OH).^{13}C-NMR δ: 55.0, 99.6, 106.4, 114.6, 129.2, 147.2, 148.9.

4-Amino-2-methoxyphenol (7c). 2-Methoxy-4-nitrophenol (1.5 g, 8.9 mmol) afforded the title compound (1.21 g, 98%) as a brown powder as described in procedure B. ^{1}H-NMR δ: 3.67 (s, 3H, H_{Me}), 4.41 (bs, 2H, NH_2), 5.99 (dd, 1H, J=8.2, J=2.5, H_{arom}), 6.23 (d, 1H, J=2.4, H_{arom}), 6.46 (d, 1H, J=8.2, H_{arom}), 7.76 (bs, 1H, OH). ^{13}C-NMR δ: 55.2, 100.2, 105.9, 116.1, 137.2, 141.5, 148.0.

4-Amino-3-fluorophenol (7d). 3-Fluoro-4-nitrophenol (10.5 g, 66.8 mmol) afforded the title compound (8.18 g, 96%) as a grey solid as described in procedure B. ^{1}H-NMR δ: 4.36 (br s, 2H, N*H*$_2$), 6.35-6.63 (m, 3H, H_{arom}), 8.77 (s, 1H, O*H*).^{13}C-NMR δ: 102.8 (d, J_{FH}=21.1), 111.0 (d, J_{FH}=2.9), 117.1 (d, J_{FH}=5.7), 127.8 (d, J_{FH}=13.0), 148.5 (d, J_{FH}=10), 150.9 (d, J_{FH}=237).

4-Amino-3-methoxyphenol (7f). 3-Methoxy-4-nitrophenol **6f** (790 mg, 5.7 mmol) afforded the title compound (749 mg, 94%) as described in procedure B as a dark powder. ^{1}H-NMR δ: 3.69 (s, 3H, H_{Me}), 4.05 (bs, 2H, NH_2), 6.13 (dd, 1H, J=8.2, J=2.5, H_{arom}), 6.30 (d, 1H, J=2.5, H_{arom}), 6.44 (d, 1H, J=8.2, H_{arom}), 8.47 (bs, 1H, OH). ^{13}C-NMR δ: 55.0, 99.6, 106.4, 114.6, 129.2, 147.2, 148.9.

4-Amino-3-(dimethylamino)phenol (7g). 3-(Dimethylamino)-4-nitrophenol **6g** (3.26 g, 17.9 mmol)

afforded the title compound (2.50 g, 92%) as a pale brown powder as described in procedure B. ^{1}H-NMR δ: 2.53 (s, 6H, H_{Me}), 4.10 (bs, 2H, NH_2), 6.22 (dd, 1H, J=8.3 and J=2.6, H_{arom}), 6.37 (d, 1H, J=2.6, H_{arom}), 6.46 (d, 1H, J=8.3, H_{arom}), 8.31 (bs, 1H, OH). ^{13}C-NMR δ: 42.8 (2), 106.1, 109.6, 115.1, 133.9, 140.4, 148.8.

4-Amino-2,3-dimethylphenol (7h). 2,3-Dimethyl-4-nitrophenol (2.0 g, 12.0 mmol) afforded the title compound (1.61 g, 97%) as a brown powder as described in procedure B. ^{1}H-NMR δ: 1.95 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 4.07 (bs, 2H. NH_2), 6.33 (d, 1H, J= 8.3, H_{arom}), 6.40 (d, 1H, J= 8.3, H_{arom}), 8.11 (bs, 1H, OH). ^{13}C-NMR δ: 12.0, 13.1, 112.3, 112.4, 121.4, 122.2, 138.3, 146.4.

4-Amino-3-(trifluoromethyl)phenol (7i). 3-(Trifluoromethyl)-4-nitrophenol (1 g, 5 mmol) afforded the title compound (812 mg, 92%) as a pale brown powder as described in procedure B. ^{1}H-NMR δ: 4.83 (bs, 2H, NH_2), 6.70-6.79 (m, 3H, H_{arom}), 8.88 (bs, 1H, OH). ^{13}C-NMR δ: 111.2, 111.4, 118.6, 120.8, 124.6, 138.5, 147.6. ^{19}F NMR δ: -61.32.

1-(4-(2,3-Diaminopyridin-4-yloxy)-2-methoxyphenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (11f). 1-(4-(2-Amino-3-nitropyridin-4-yloxy)-2-methoxyphenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea **5f** (206 mg, 0.4 mmol) afforded the title compound (173 mg, 90%) as a brown powder as described in procedure B. ^{1}H-NMR δ: 3.86 (s, 3H, CH_3), 4.43 (bs, 2H, $NH_{2,Py}$), 5.57 (s, 2H, $NH_{2,Py}$), 6.03 (d, 1H, J=5.6, H_{Py}), 6.54 (dd, 1H, J= 8.8 and J=2.5, H_{arom}), 6.80 (d, 1H, J=2.5, H_{arom}), 7.25 (d, 1H, J=5.6, H_{Py}), 7.59 (m, 2H, H_{arom}), 8.01 (d, 1H, J=8.8, H_{arom}), 8.10 (s, 1H, H_{arom}), 8.24 (s, 1H, NH_{urea}), 9.76 (s, 1H, NH_{urea}). ^{13}C-NMR δ: 55.9, 102.9, 103.3, 110.0, 116.1, 119.3, 119.5, 121.6, 121.9, 122.4, 123.7, 126.5, 131.9, 135.3, 139.3, 147.6, 149.0, 149.9, 150.7, 152.1. LC-MS: *m/z* 468 ($[M+H]^+$, 100).

1-(4-(2,3-Diaminopyridin-4-yloxy)-2-(dimethylamino)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl) urea (11g). 1-(4-(2-Amino-3-nitropyridin-4-yloxy)-2-(dimethylamino)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea **5g** (200 mg, 0.4 mmol) afforded the title compound (162 mg, 86%) as a pale brown powder as described in procedure B. ^{1}H-NMR δ: 2.61 (s, 6H, CH_3), 4.39 (s, 2H, $NH_{2,Py}$), 5.52 (s, 2H, $NH_{2,Py}$), 6.01 (d, 1H, J=5.6, H_{Py}), 6.68 (dd, 1H, J= 8.8 and J=2.7, H_{arom}), 6.89 (d, 1H, J=2.7, H_{arom}), 7.24 (d, 1H, J=5.6, H_{Py}), 7.58-7.64 (m, 2H, H_{arom}), 8.01 (d, 1H, J=8.8, H_{arom}), 8.11 (d, 1H, J=2.3, H_{arom}), 8.30 (s, 1H, NH_{urea}), 9.90 (s, 1H, NH_{urea}). ^{13}C-NMR δ: 43.8 (2), 103.2, 110.7, 113.6, 116.1, 119.2, 120.0, 121.9, 122.3, 123.7, 126.5, 129.0, 131.9, 135.6,

139.5, 144.1, 147.6, 150.1, 150.6, 152.2. LC-MS: *m/z* 481 ($[M+H]^+$, 100).

1-(4-(2,3-Diaminopyridin-4-yloxy)-2,3-dimethylphenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (11h). 1-(4-(2-Amino-3-nitropyridin-4-yloxy)-2,3-dimethylphenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea **5h** (300 mg, 1.5 mmol) afforded the title compound (67 mg, 24%) after purification by chromatography on silica gel (EtOAc:MeOH 95:5) as a yellow powder (R_f 0.73, EtOAc:MeOH 95:5) as described in procedure B. ^{1}H-NMR δ: 2.10 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 4.41 (bs, 2H, NH_2), 5.49 (bs, 2H, NH_2), 5.75 (d, 1H, J=5.6, H_{Py}), 6.76 (d, 1H, J=8.7, H_{arom}), 7.19 (d, 1H, J=5.6, H_{Py}), 7.41 (d, 1H, J=8.7, H_{arom}), 7.57 (d, 1H, J=8.7, H_{arom}), 7.64 (dd, 1H, J=8.7 and J=2.5, H_{arom}), 8.11 (d, 1H, J=2.5, H_{arom}), 8.13 (s, 1H, NH_{urea}), 9.34 (s, 1H, NH_{urea}). ^{13}C-NMR δ: 12.4, 14.2, 101.7, 116.4, 117.1, 118.2, 121.8, 122.5, 122.6, 123.8, 126.4, 128.3, 131.5, 131.8, 132.7, 135.7, 139.6, 148.5, 149.5, 149.8, 152.9. LC-MS: *m/z* 466 ($[M+H]^+$, 100).

1-(4-(2,3-Diaminopyridin-4-yloxy)-2-(trifluoromethyl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (11i). 1-(4-(2-Amino-3-nitropyridin-4-yloxy)-2-(trifluoromethyl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea **5i** (72 mg, 0.13 mmol) afforded the title compound (47 mg, 60%) after purification by chromatography on silica gel (EtOAc:MeOH 95:5) as a pink powder as described in procedure B. ^{1}H-NMR δ: 4.58 (s, 2H, NH_2), 5.68 (s, 2H, NH_2), 6.14 (d, 1H, J=5.5, H_{Py}), 7.24 (s, 2H, H_{arom}), 7.29 (d, 1H, J=5.6, H_{Py}), 7.62 (s, 2H, H_{arom}), 7.75 (d, 1H, J=8.5, H_{arom}), 8.10 (s, 1H, H_{arom}), 8.17 (s, 1H, NH_{urea}), 9.63 (s, 1H, NH_{urea}). ^{13}C-NMR δ: 104.7, 114.7, 116.6, 120.7, 121.6, 122.4, 122.7, 122.9, 123.7, 124.3, 126.7, 129.3, 130.4, 131.9, 135.6, 139.1, 145.5, 150.6, 152.7, 152.8. LC-MS: *m/z* 506 ($[M+H]^+$, 100).

1-(4-(2,3-Diaminopyridin-4-yloxy)-2-(phenyl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (11j). 1-(4-(2-Amino-3-nitropyridin-4-yloxy)-2-phenylphenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea **5j** (400 mg, 1.5 mmol) afforded the title compound (377 mg, 99%) as a pale brown powder as described in procedure B. ^{1}H-NMR δ: 4.52 (bs, 2H, $NH_{2,Py}$), 6.22 (d, 1H, J=5.9, H_{Py}), 6.85 (s, 1H, H_{arom}), 6.99 (m, 1H, H_{arom}), 7.40 (m, 4H, H_{arom}), 7.46 (m, 3H, H_{arom}), 7.55 (bs, 2H, $NH_{2,Py}$), 7.72 (d,1H, J=8.8, H_{arom}), 7.88 (s, 1H, H_{arom}), 8.02 (s, 1H, NH_{urea}), 9.41 (s, 1H, NH_{urea}). ^{13}C-NMR δ: 104.3, 116.4, 116.5, 117.4, 119.3, 120.2, 121.7, 122.6, 126.2, 127.6, 128.7, 128.8, 130.4, 131.9, 135.3, 135.6, 136.1, 138.0, 139.6, 146.6, 146.7, 147.9, 150.4, 152.5, 153.0. LC-MS: *m/z* 513 ($[M+H]^+$, 100).

1-(4-(2,3-Diaminopyridin-4-yl-oxy)-3-fluorophenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl) urea

(11k). 1-(4-(2-Amino-3-nitropyridin-4-yl-oxy)-3-fluorophenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea **5k** (181 mg, 0.37 mmol) afforded the title compound (163 mg, 96%) as described in procedure B. ^{1}H-NMR δ: 4.48 (s, 2H, $NH_{2,Py}$), 5.56 (s, 2H, $NH_{2,Py}$), 5.89 (t, 1H, J=4.8), 7.10 (dt, 1H, J=8.8 and J=4.1), 7.16-7.18 (m, 1H), 7.21 (t, 1H, J=5.0), 7.60-7.66 (m, 3H), 8.09 (s, 1H), 9.06 (s, 1H, NH_{urea}), 9.22 (s, 1H, NH_{urea}). LC-MS: *m/z* 456 ($[M+H]^+$, 100).

1-(4-(2,3-Diaminopyridin-4-yloxy)-2-chlorophenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (11l). 1-(4-(2-Amino-3-nitropyridin-4-yloxy)-2-chlorophenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea **5l** (350 mg, 0.7 mmol) afforded the title compound (199 mg, 60%) as described in procedure B after purification by chromatography on silica gel (EtOAc:EtOH 95:5) as a brown powder (R_f 0.44, EtOAc:EtOH 8:2). ^{1}H-NMR δ: 4.51 (s, 2H, NH_2), 5.65 (s, 2H, NH_2), 6.10 (d, 1H, J=5.6, H_{Py}), 6.97 (dd, 1H, J= 8.9 and J= 2.7, H_{arom}), 7.11 (d, 1H, J=2.7, H_{arom}), 7.26 (d, 1H, J=5.6, H_{Py}), 7.62 (broad s, 2H, H_{arom}), 7.99 (d, 1H, J=9.0, H_{arom}), 8.10 (s, 1H, H_{arom}), 8.35 (s, 1H, NH_{urea}), 9.71 (s, 1H, NH_{urea}). ^{13}C-NMR δ: 104.3, 116.5, 116.6, 117.3, 118.5, 120.2, 122.4, 122.8, 123.8, 124.1, 126.7, 130.8, 132.0, 135.5, 139.1, 146.3, 150.3, 151.7, 152.2. LC-MS: *m/z* 472 ($[M+H]^+$, 100).

1-(4-(2,3-Diaminopyridin-4-yloxy)-2-methylphenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (11m). 1-(4-(2-Amino-3-nitropyridin-4-yloxy)-2-methylphenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea **5m** (350 mg, 0.7 mmol) afforded the title compound (247 mg, 75%) as a dark brown powder (R_f 0.73, EtOAc:DCM 1:1) as described in procedure B. ^{1}H-NMR δ: 2.22 (s, 3H, CH_3), 4.42 (broad s, 2H, NH_2), 5.58 (broad s, 2H, NH_2), 6.03 (d, 1H, J=5.6, H_{Py}), 6.83 (dd, 1H, J=8.7 and J=2.7, H_{arom}), 6.88 (d, 1H, J=2.7, H_{arom}), 7.27 (d, 1H, J=5.6, H_{Py}), 7.52 (d, 1H, J=8.7, H_{arom}), 7.62 (dd, 1H, J=8.7 and J=2.3, H_{arom}), 7.67 (d, 1H, J=8.7, H_{arom}), 8.04 (s, 1H, H_{arom}), 8.09 (s, 1H, NH_{urea}), 9.37 (s, 1H, NH_{urea}). ^{13}C-NMR δ: 17.8, 103.9, 116.3, 116.6, 119.8, 120.2, 122.2, 122.7, 123.9, 124.1, 126.8, 131.4, 131.9, 132.5, 135.8, 139.5, 147.8, 150.3, 151.7, 152.8. LC-MS: *m/z* 452 ($[M+H]^+$, 100).

***Tert*-butyl-4-(2,3-diaminopyridin-4-yloxy)-3-methoxyphenylcarbamate (12b).** *Tert*-butyl-4-(2-amino-3-nitropyridin-4-yloxy)-3-methoxyphenylcarbamate **10b** (640 mg, 1.7 mmol) afforded the title compound (549 mg, 93%) as a brown powder as described in procedure B.^{1}H-NMR δ: 1.48 (s, 9H, *t*Bu), 3.69 (s, 3H, CH_3), 5.42 (bs, 2H, NH_2), 5.71 (d, 1H, J=5.6, H_{Py}), 6.91 (d, 1H, J=8.6, H_{arom}), 6.99 (dd, 1H, J=8.6 and J=1.8, H_{arom}), 7.15 (d, 1H, J=5.6, H_{Py}), 7.36 (m, 3H, H_{arom} + $NH_{2,\ Py}$), 9.36 (bs, 1H, $NH_{carbamate}$). ^{13}C-NMR δ: 28.0, 55.4, 78.9, 100.8, 103.5, 110.1, 117.5, 121.8, 135.5, 137.2, 137.4, 149.4, 149.6, 151.1, 152.6. LC-MS: *m/z* 346 ($[M+H]^+$, 100).

***Tert*-butyl-4-(2,3-diaminopyridin-4-yl-oxy)-3-methylphenylcarbamate (12c).** *Tert*-butyl-4-(2-amino-3-nitropyridin-4-yl-oxy)-3-methylphenylcarbamate **10c** (133 mg, 0.37 mmol) afforded the title compound (115 mg, 94%) as described in procedure B. ^{1}H-NMR δ: 1.47 (s, 9H, *t*Bu), 2.08 (s, 3H, CH_3), 4.38 (s, 2H, $NH_{2,Py}$), 5.45 (s, 2H, $NH_{2,Py}$), 5.73 (d, 1H, J=5.5, H_{Py}), 6.83 (d, 1H, J=8.7, H_{arom}), 7.18 (d, 1H, J=5.5, H_{Py}), 7.25 (d, 1H, J=8.6, H_{arom}), 7.41 (s, 1H, H_{arom}), 9.26 (s, 1H, $NH_{carbamate}$). ^{13}C-NMR δ: 15.8, 28.1, 78.9, 101.4, 117.1, 118.0, 120.2, 120.8, 129.4, 135.8, 135.9, 147.7, 148.6, 149.8, 152.8. LC-MS: *m/z* 331 ($[M+H]^+$, 100).

Procedure C: Compounds 8a; 10a. *Tert*-butyl-4-hydroxy-2-(methylthio)phenylcarbamate (8a). 4-Amino-3-(methylthio)phenol **7a** (3.0 g, 19 mmol) was added to a magnetically stirred mixture of Boc_2O (1.05 equiv) and $InCl_3$ (1 mol%) at 30-35°C and stirred 5 hrs. EtOAc was then added, and the mixture washed with water, dried over $MgSO_4$ and filtered. Solvent was evaporated and the crude mixture purified by chromatography on silica gel (DCM then EtOAc:DCM 1:1), to provide the expected compound as a brown powder (61%, R_f 0.17, DCM). ^{1}H-NMR δ: 1.41 (s, 9H, *t*Bu), 2.33 (s, 3H, CH_3), 6.51 (dd, 1H, J=8.4 and J=2.6, H_{arom}), 6.62 (d, 1H, J=2.6, H_{arom}), 6.97 (d, 1H, J=8.4, H_{arom}), 8.06 (s, 1H, $NH_{carbamate}$), 9.41 (s, 1H, OH). ^{13}C-NMR δ: 14.4, 28.0, 78.2, 111.5, 111.9, 126.4, 128.2, 136.7, 153.9, 155.7.

***Tert*-butyl-4-(2-amino-3-nitropyridin-4-yloxy)-2-(methylthio)phenylcarbamate (10a).** 4-(4-Amino-3-(methylthio)phenoxy)-3-nitropyridin-2-amine **9a** (2 g, 6.8 mmol) afforded the title compound (2.42 g, 90%) as described in procedure C after purification by chromatography on silica gel (pure DCM then DCM:EtOAc 95:5) as a powder (R_f 0.83, EtOAc:DCM 1:1). ^{1}H-NMR δ: 1.46 (s, 9H, *t*Bu), 2.81 (s, 3H, CH_3), 6.07 (d, 1H, J=5.6, H_{Py}), 7.19 (m, 1H, H_{arom}), 7.35 (m, 1H, H_{arom}), 7.53 (d, 1H, J=2.8, H_{arom}), 8.05 (d, 1H, J=5.6, H_{Py}), 9.32 (s, 1H, $NH_{carbamate}$). ^{13}C-NMR δ: 14.8, 27.9, 78.8, 103.6, 115.9, 117.3, 121.7, 124.6, 127.5, 132.1, 137.1, 146.0, 148.5, 151.7, 153.4. LC-MS: *m/z* 393 ($[M+H]^+$, 100).

***Tert*-butyl-2-fluoro-4-hydroxyphenylcarbamate (8d).** 4-Amino-3-fluorophenol **7d** (10.61 g, 83.5 mmol) was added to a molten mixture of Boc_2O (18.29 g, 83.8 mmol) and $InCl_3$ (188 mg, 0.85 mmol) at 35 °C. The black mixture was stirred at 35 °C for 2 h, during which time it turned into a thick black oil. The mixture was then diluted with EtOAc (200 mL) and H_2O (200 mL) and stirring was continued for 10 min. The layers were separated and the organic layer was washed with H_2O (3 × 200 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The resulting black oil was redissolved in DCM (50 mL) and loaded onto a silica gel column. Elution with 5→7% EtOAc in DCM furnished the title compound

as a light yellow, crystalline solid (16.7 g, 90%). ^{1}H-NMR δ: 1.46 (s, 9H, C(C*H*$_3$)$_3$), 6.08 (d, 1H, $^{3}J_{HH}$=5.5, H_{Pyr}), 7.01 (m, 1H, H_{arom}), 7.18 (br s, 2H, N*H*$_2$), 7.22 (m, 1H, H_{arom}), 7.67 (m, 1H, H_{arom}), 8.04 (d, 1H, $^{3}J_{HH}$=5.5, H_{Pyr}), 9.03 (s, 1H, N*H*Boc). ^{13}C-NMR δ: 28.0, 78.6, 102.7 (d, J_{FC}=22.2), 110.8 (d, J_{FC}=2.7), 117.1 (d, J_{FC}=12.6), 127.2, 153.7, 155.5 (d, J_{FC}=11.3), 156.1 (d, J_{FC}=246). ^{19}F-NMR δ: -121.6. LC-MS: *m/z* 172 [M-C(CH$_3$)$_3$]$^{+}$, 100).

4-(4-*N*-(*tert*-butoxycarbonyl)amino-3-fluorophenoxy)-2,3-diamino-pyridine (12d). Pd/C (1.09 g) was added to a yellow solution of 4-(4-*N*-(*tert*-butoxycarbonyl)amino-3-fluorophenoxy)-3-nitro-2-amino-pyridine **10b** (6.20 g, 17.0 mmol) in EtOAc/EtOH (90/150 mL) and the black mixture was stirred under a nitrogen atmosphere for 5hrs and filtered over Celite. The dark brown filtrate was concentrated to dryness, redissolved in DCM (20 mL) and loaded onto a silicagel column. The products were eluted with EtOAc and the fractions containing the title compound were gathered and evaporated to dryness. The orange oil was dissolved in DCM and an equal amount of hexane was added. The solution was concentrated to dryness to give the title compound as an orange foam. Yield: 4.30 g (76%). ^{1}H-NMR δ: 1.46 (s, 9H, *t*Bu), 4.47 (s, 2H, NH$_2$), 5.61 (s, 2H, NH$_2$), 6.09 (d, 1H, J=5.5, H_{Py}), 6.76 (m, 1H, H_{arom}), 6.87 (m, 1H, H_{arom}), 7.28 (d, 1H, , J=5.5, H_{Py}), 7.47 (vt, 1H, $^{3}J_{HH}$=8.5, H_{arom}), 8.82 (br s, 1H, NHBoc). LC-MS: *m/z* 335 ([M+H]$^{+}$, 100).

***Tert*-butyl-4-(2,3-diaminopyridin-4-yl-oxy)naphthalen-1-yl-carbamate (12e).** *Tert*-butyl-4-(2-amino-3-nitropyridin-4-yl-oxy)naphthalen-1-yl-carbamate **10e** (0.50 g, 1.26 mmol) was dissolved in ethanol (20 mL). Palladium 10% on activated carbon (139 mg) was added, followed by ammonium formate finely grounded (926 mg, 14.8 mmol). The reaction mixture was stirred for 1.5 hrs, then filtered over Celite and concentrated. The brown solid was dissolved in an EtOAc:H_2O mixture (10:10 mL) and the layers were separated. The organic layers was washed with saturated $NaHCO_3$ (aq) (10 mL), dried ($MgSO_4$) and concentrated to afford the title compound as a brown solid (0.38 g, 82%). ^{1}H-NMR δ: 1.55 (s, 9H, *t*Bu), 4.63 (s, 2H, NH$_2$), 5.66 (s, 2H, NH$_2$), 5.92 (d, 1H, J = 5.6, H_{Py}), 7.05 (d, 1H, J = 8.3, $H_{arom,naph}$), 7.24 (d, 1H, H_{Py}), 7.54 (d, 1H, J = 8.3, $H_{arom,naph}$), 7.60 – 7.65 (m, 2H, $H_{arom,naph}$), 8.07 – 8.12 (m, 2H, $H_{arom,naph}$), 9.22 (s, 1H, $NH_{carbamate}$). LC-MS: *m/z* 339 ([M]$^{+}$, 100).

Procedure D: Compounds 10b,c/e. Boc protection. To a solution of the appropriate 4-(4-aminophenoxy)-3-nitropyridin-2-amine (1 mmol) in THF (5 mL/mmol) was added 2.2 equivalents of di-*tert*-butyl dicarbonate and the solution stirred for 16 hrs at room temperature. The solvent was evaporated and the residue purified by column chromatography (eluent gradient DCM to DCM:EtOAc 1:1), to afford the title compound.

***Tert*-butyl-4-(2-amino-3-nitropyridin-4-yloxy)-3-methoxyphenylcarbamate (10b).** 4-(4-Amino-2-methoxyphenoxy)-3-nitropyridin-2-amine **9b** (500 mg, 1.8 mmol) afforded the title compound (640 mg, 94%) as described in procedure D after purification by chromatography on silica gel (DCM then DCM:EtOAc 1:1) as a yellow powder. ^{1}H-NMR δ: 1.49 (s, 9H, *t*Bu), 3.70 (s, 3H, CH_3), 5.80 (d, 1H, J=5.7, H_{Py}), 7.02-7.10 (m, 4H, $2H_{arom}$+ $NH_{2,\ Py}$), 7.44 (d, 1H, J=1.6 Hz, H_{arom}), 7.92 (d, 1H, J=5.7, H_{Py}), 9.47 (bs, 1H, $NH_{carbamate}$). ^{13}C-NMR δ: 27.9, 55.5, 79.2, 99.1, 103.3, 110.2, 121.0, 122.2, 135.2, 138.7, 150.6, 152.6, 152.7, 153.6, 159.3. LC-MS: *m/z* 376 ($[M+H]^+$, 100).

***Tert*-butyl-4-(2-amino-3-nitropyridin-4-yl-oxy)-3-methylphenylcarbamate (10c).** 4-(4-Amino-2-methylphenoxy)-3-nitropyridin-2-amine **9c** (0.160 g, 0.615 mmol) to afford the title compound (0.143 g, 65%) as described in procedure D. ^{1}H-NMR δ: 1.48 (s, 9H, *t*Bu), 2.05 (s, 3H, CH_3), 5.76 (d, 1H, J=5.4, H_{Py}), 7.03 (d, 1H, J=8.5, H_{arom}), 7.15 (s, 2H, $NH_{2,\ Py}$), 7.33 (d, 1H, J=8.9, H_{arom}), 7.48 (s, 1H, H_{arom}), 7.94 (d, 1H, J=5.7, H_{Py}), 9.46 (bs, 1H, NH_{Boc}). ^{13}C-NMR δ: 15.5, 28.0, 79.1, 99.1, 117.3, 120.7, 121.2, 121.4, 129.8, 137.6, 145.4, 152.7, 153.0, 153.7, 158.9. LC-MS: *m/z* 362 ($[M+H]^+$, 100).

***Tert*-butyl-4-(2-amino-3-nitropyridin-4-yl-oxy)naphthalen-1-ylcarbamate (10e).** 4-(4-Aminonaphthalen-1-yl-oxy)-3-nitropyridin-2-amine **9e** (1.10 g, 3.7 mmol) afforded the title compound (0.50 g, 34%) as described in procedure D. ^{1}H-NMR δ: 1.52 (s, 9H, *t*Bu), 5.80 (d, 1H, J = 5.7, H_{Py}), 7.26 (s, 2H, NH_2), 7.38 (d, 1H, J = 8.3, $H_{arom,naph}$), 7.58 – 7.69 (m, 3H, $H_{arom,naph}$), 7.86 – 7.89 (m, 1H, $H_{arom,naph}$), 7.93 (d, 1H, H_{Py}), 8.14 – 8.17 (m, 1H, $H_{arom,naph}$), 9.36 (s, 1H, $NH_{carbamate}$).

Procedure E: Compounds 9a-c/e-m; 10a,d. Coupling of 2-amino-3-nitro-4-chloropyridine with functionalized protected or not aminophenols and aminonaphthol.

a) with tBuOK: A 4-hydroxyaniline or *tert*-butyl-4-hydroxyphenylcarbamate (1 mmol) was dissolved in dry DMF (5 mL/mmol) and the solution was degassed by argon bubbling for 10 minutes. Potassium *tert*-butoxide (1.1 mmol) was added, and the stirring and argon bubbling continued for 1 hr. 4-Chloro-3-nitropyridin-2-amine (1 mmol) was dissolved in 5 mL dry DMF and added to the reaction mixture. The reaction mixture was heated and stirred at 70°C for 20 hrs under argon. The solvent was evaporated and the residue was partitioned between DCM and aqueous Na_2CO_3 containing 5% KOH. The extraction was repeated twice; the organic layer was dried over $MgSO_4$, and evaporated to afford the title compound.

b) with NaH: Sodium hydride (60 wt% in mineral oil, 40 mg/mmol) was added to dry DMSO (39

µl/mg) and the mixture was stirred at room temperature for 20 minutes under Ar atmosphere. The 4-hydroxyaniline or *tert*-butyl-4-hydroxyphenylcarbamate (1 mmol) was added thereto, and the mixture was stirred for 10 more minutes. Next, 4-chloro-3-nitropyridin-2-amine (1 mmol) was added, and the mixture temperature raised to 100°C and stirred 3 hrs. After cooling down to room temperature, water was added, and the mixture was extracted three times with EtOAc. The combined organic layers were washed first with a saturated aqueous $NaHCO_3$ solution then water, dried over $MgSO_4$ and evaporated to afford the title compound.

4-(4-Amino-3-(methylthio)phenoxy)-3-nitropyridin-2-amine (9a). Using method Eb with 4-amino-3-(methylthio)phenol **7a** (3.28 g, 21 mmol), the title compound (6.18 g, 94%) was obtained after purification by chromatography on silica gel (EtOAc:DCM 1:1) as a red brown solid (R_f 0.56, EtOAc:DCM 1:1). ^{1}H-NMR δ: 2.36 (s, 3H, CH_3), 5.18 (s, 2H, $NH_{2,Ph}$), 5.92 (d, 1H, J=5.8, H_{Py}), 6.75 (d, 1H, J= 8.6, H_{arom}), 6.81 (dd, 1H, J= 8.6 and J=2.6, H_{arom}), 6.98 (d, 1H, J=2.6, H_{arom}), 7.07 (bs, 2H, $NH_{2,Py}$), 7.95 (d, 1H, J=5.7, H_{Py}). ^{13}C-NMR δ: 15.6, 99.8, 114.7, 119.7, 120.7, 121.4, 121.5, 143.2, 145.1, 152.8, 153.6, 159.9. LC-MS: *m/z* 293 ($[M+H]^+$, 100).

4-(4-Amino-2-methoxyphenoxy)-3-nitropyridin-2-amine (9b). Using method Ea with 4-amino-2-methoxyphenol **7b** (1 g, 7.2 mmol), the title compound (1.13 g, 57%) was obtained without any purification as a brown solid. ^{1}H-NMR δ: 3.62 (s, 3H, CH_3), 5.17 (s, 2H, $NH_{2,Ph}$), 5.80 (d, 1H, J=5.7, H_{Py}), 6.14 (dd, 1H, J= 8.5 and J=2.4, H_{arom}), 6.35 (d, 1H, J= 2.4, H_{arom}), 6.77 (d, 1H, J=8.5, H_{arom}), 6.98 (bs, 2H, $NH_{2,Py}$), 7.88 (d, 1H, J=5.7, H_{Py}). ^{13}C-NMR δ: 55.2, 98.9, 99.2, 105.5, 121.0, 122.4, 130.7, 148.3, 151.1, 152.5, 153.5, 160.1. LC-MS: *m/z* 276 ($[M+H]^+$, 100).

4-(4-Amino-2-methylphenoxy)-3-nitropyridin-2-amine (9c). Using method Ea with 4-amino-*o*-cresol (642 mg, 5.2 mmol) afforded the title compound (0.57 g, 42%). ^{1}H-NMR δ: 1.95 (s, 3H, CH_3), 5.08 (s, 2H, NH_2), 5.79 (d, 1H, J=5.7, H_{Py}), 6.44 (dd, 1H, J=8.5 and J=2.8, H_{arom}), 6.49 (d, 1H, J=2.7, H_{arom}), 6.77 (d, 1H, J=8.4, H_{arom}), 7.04 (s, 2H, $NH_{2,Py}$), 7.92 (d, 1H, J=5.7, H_{Py}). ^{13}C-NMR δ: 15.3, 99.0, 112.5, 116.0, 121.1, 121.6, 129.7, 140.8, 147.0, 152.8, 153.6, 159.7. LC-MS: *m/z* 261 ($[M+H]^+$, 100).

4-(4-Aminonaphthalen-1-yl-oxy)-3-nitropyridin-2-amine (9e). Using method Ea with 4-aminonaphthalen-1-ol **7e** (0.92 g, 5.8 mmol) afforded the title compound as a brown solid (1.10 g, 64%). ^{1}H-NMR δ: 5.75 (d, 1H, J = 5.4, H_{Py}), 5.90 (s, 2H, NH_2), 6.69 (d, 1H, J = 7.98, $H_{arom,naph}$), 7.13 (m, 3H, NH_2 + $H_{arom,naph}$), 7.48 (m, 2H, $H_{arom,naph}$), 7.67 (m, 1H, $H_{arom,naph}$), 7.86 (d, 1H, H_{Py}), 8.16 (m, 1H, $H_{arom,naph}$). LC-MS: *m/z* 297 ($[M + H]^+$, 100).

4-(4-Amino-3-methoxy-phenoxy)-3-nitro-pyridin-2-ylamine (9f). Using method Eb with 4-amino-3-methoxyphenol **7f** (0.85 g, 6.1 mmol), the title compound (1.08 g, 64%) was obtained without any purification as a dark solid. ^{1}H-NMR δ: 3.75 (s, 3H, CH_3), 4.82 (s, 2H, $NH_{2,Ph}$), 5.93 (d, 1H, J=5.7, H_{Py}), 6.52 (dd, 1H, J= 8.5 and J=2.5, H_{arom}), 6.68 (d, 1H, J= 2.5, H_{arom}), 7.04 (bs, 2H, $NH_{2,\ Py}$), 7.42 (d, 1H, J=8.5, H_{arom}), 7.94 (d, 1H, J=5.7, H_{Py}). ^{13}C-NMR δ: 55.5, 99.8, 104.2, 112.5, 113.2, 121.7, 123.8, 149.4, 149.7, 152.6, 153.7, 158.4. LC-MS: *m/z* 277 ([M+H]$^+$, 100).

5-(2-Amino-3-nitropyridin-4-yloxy)-*N*1,*N*1-dimethylbenzene-1,2-diamine (9g). Using method Eb with 4-amino-3-(dimethylamino)phenol **7g** (489 mg, 3.2 mmol), the title compound (930 mg, 98%) was obtained without any purification as a dark solid. ^{1}H-NMR δ: 2.57 (s, 6H, CH_3), 4.80 (s, 2H, $NH_{2,Ph}$), 5.92 (d, 1H, J=5.7, H_{Py}), 6.61 (dd, 1H, J= 8.5 and J=2.5, H_{arom}), 6.70 (m, 2H, H_{arom}), 7.04 (s, 2H, $NH_{2,Py}$), 7.94 (d, 1H, J=5.7, H_{Py}). ^{13}C-NMR δ: 42.5 (2), 99.7, 111.5, 114.5, 115.3, 121.4, 140.2, 140.3, 143.1, 152.7, 153.5, 160.0. LC-MS: *m/z* 290 ([M+H]$^+$, 100).

4-(4-Amino-2,3-dimethylphenoxy)-3-nitropyridin-2-amine (9h). Using method Ea with 4-amino-2,3-dimethylphenol **7h** (682 mg, 5 mmol) afforded the title compound (866 mg, 70%) after purification by chromatography on silica gel (EtOAc:DCM 1:1) as a yellow solid (R_f 0.40, EtOAc:DCM 1:1). ^{1}H-NMR δ: 1.96 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 4.93 (s, 2H, NH_2), 5.74 (d, 1H, J=5.7, H_{Py}), 6.56 (d, 1H, J=8.6, H_{arom}), 6.67 (d, 1H, J=8.6, H_{arom}), 7.02 (s, 2H, $NH_{2,\ Py}$), 7.90 (d, 1H, J=5.7, H_{Py}). ^{13}C-NMR δ: 12.2, 13.1, 99.2, 112.5, 118.5, 121.1, 123.5, 125.3, 127.9, 134.7, 152.3, 152.7, 156.1. LC-MS: *m/z* 275 ([M+H]$^+$, 100).

4-(4-Amino-3-(trifluoromethyl)phenoxy)-3-nitropyridin-2-amine (9i). Using method Ea with 4-amino-3-(trifluoromethyl)phenol **7i** (812 mg, 4.6 mmol) afforded the title compound (946 mg, 72%) after purification by chromatography on silica gel (EtOAc:DCM 1:1) as a yellow solid (R_f 0.62, EtOAc:DCM 1:1). ^{1}H-NMR δ: 5.68 (s, 2H, NH_2), 5.88 (d, 1H, J=5.7, H_{Py}), 7.12 (m, 5H, H_{arom} + $NH_{2,Py}$), 7.95 (d, 1H, J=5.7, H_{Py}). ^{13}C-NMR δ: 99.7, 118.1, 118.3, 121.4, 123.1, 125.3, 126.1, 141.8, 144.4, 153.0, 153.7, 159.6. LC-MS: *m/z* 315 ([M+H]$^+$, 100).

4-(4-Amino-3-phenylphenoxy)-3-nitropyridin-2-amine (9j). Using method Ea with 4-amino-3-phenylphenol **7j** (0.76 g, 0.4 mmol), the title compound (1.26 g, 95%) was obtained without any purification as a red brown solid. ^{1}H-NMR δ: 4.89 (bs, 2H, $NH_{2,Ph}$), 6.02 (d, 1H, J=5.7, H_{Py}), 6.81 (d, 1H, J=2.8, H_{arom}), 6.84 (d, 1H, J=8.7, H_{arom}), 6.92 (dd, 1H, J=8.7 and J=2.8, H_{arom}), 7.05 (bs, 2H,

$NH_{2,Py}$), 7.36 (m, 1H, H_{arom}), 7.45 (m, 4H, H_{arom}), 7.96 (d, 1H, J=5.7, H_{Py}). ^{13}C-NMR δ: 99.9, 116.1, 120.5, 121.5, 121.8, 126.5, 127.0, 128.4, 128.7, 138.3, 143.1, 143.4, 152.7, 153.6, 159.9. LC-MS: *m/z* 322 ($[M+H]^+$, 100).

4-(4-Amino-2-fluorophenoxy)-3-nitropyridin-2-amine (9k). Using method Ea with 4-amino-2-fluorophenol (0.58 g, 4.5 mmol) afforded the title compound (0.35 g, 29%). ^{1}H-NMR δ: 5.53 (s, 2H, NH_2), 5.92 (d, 1H, J=5.7, H_{Py}), 6.41 (dd, J=8.7 and J=2.5, $1H_{arom}$), 6.50 (dd, 1H, J=13.1 and J=2.5, H_{arom}), 7.00 (t, 1H, J=9.0, H_{arom}), 7.15 (s, 2H $NH_{2,\ Py}$), 7.97 (d, 1H, J=5.8, H_{Py}). LC-MS: *m/z* 265 ($[M+H]^+$, 100).

4-(4-Amino-3-chlorophenoxy)-3-nitropyridin-2-amine (9l). Using method Ea with 4-amino-3-chlorophenol hydrochloride (1.03 g, 5.7 mmol) afforded the title compound (0.66 g, 46%) after purification by chromatography on silica gel (EtOAc:DCM 8:2 to 5:5) as a yellow solid (R_f 0.48, EtOAc:DCM 1:1). ^{1}H-NMR δ: 4.57 (s, 2H, NH_2), 5.09 (d, 1H, J=5.7, H_{Py}), 6.03 (s, 1H, H_{arom}), 6.05 (d, 1H, J=2.5, H_{arom}), 6.25 (s, 2H, $NH_{2,Py}$), 6.29 (d, 1H, J=2.5, H_{arom}), 7.13 (d, 1H, J=5.7, H_{Py}). ^{13}C-NMR δ: 99.9, 115.8, 116.9, 120.6, 121.4, 121.5, 142.6, 143.1, 153.0, 153.7, 159.8. LC-MS: *m/z* 281 ($[M+H]^+$, 100).

4-(4-Amino-3-methylphenoxy)-3-nitropyridin-2-amine (9m). Using method Ea with 4-amino-*m*-cresol (701 mg, 5.7 mmol) afforded the title compound (1.083 g, 80%) after purification by chromatography on silica gel (EtOAc:DCM 5:5 to 6:4) as a yellow solid (R_f 0.51, EtOAc:DCM 1:1). ^{1}H-NMR δ: 1.23 (s, 3H, CH_3), 4.08 (s, 2H, NH_2), 5.05 (d, 1H, J=5.7, H_{Py}), 5.83 (s, 1H, H_{arom}), 5.87 (d, 1H, J=2.7, H_{arom}), 5.94 (d, 1H, J=2.7, H_{arom}), 6.19 (s, 2H, $NH_{2,\ Py}$), 7.10 (d, 1H, J=5.7, H_{Py}). ^{13}C-NMR δ: 17.3, 99.8, 114.5, 118.6, 121.5, 122.0, 122.7, 142.8, 144.8, 152.7, 153.6, 160.1. LC-MS: *m/z* 261 ($[M+H]^+$, 100).

***Tert*-butyl-4-(2-amino-3-nitropyridin-4-yloxy)-2-(methylthio)phenylcarbamate (10a).** Using method Eb with *tert*-butyl-4-hydroxy-2-(methylthio)phenylcarbamate **8a** (2.98 g, 11.7 mmol) afforded the title compound (3.90 g, 86%). ^{1}H-NMR δ: 1.46 (s, 9H, *t*Bu), 2.81 (s, 3H, CH_3), 6.07 (d, 1H, J=5.6, H_{Py}), 7.19 (m, 1H, H_{arom}), 7.35 (m, 1H, H_{arom}), 7.53 (d, 1H, J=2.8, H_{arom}), 8.05 (d, 1H, J=5.6, H_{Py}), 9.32 (s, 1H, $NH_{carbamate}$). ^{13}C-NMR δ: 14.8, 27.9, 78.8, 103.6, 115.9, 117.3, 121.7, 124.6, 127.5, 132.1, 137.1, 146.0, 148.5, 151.7, 153.4. LC-MS: *m/z* 393 ($[M+H]^+$, 100).

4-(4-*N*-(*tert*-butoxycarbonyl)amino-3-fluorophenoxy)-3-nitro-2-amino-pyridine (10d). 4-*N*-Boc-

amino-3-fluorophenol **8d** to afford the title compound as a glassy yellow solid (1.9 g, 96%) as described in procedure Ea. ^{1}H-NMR δ: 1.46 (s, 9H, *t*Bu), 6.08 (d, 1H, $^{3}J_{HH}$=5.5, H_{Pyr}), 7.01 (m, 1H, H_{arom}), 7.18 (br s, 2H, NH_2), 7.22 (m, 1H, H_{arom}), 7.67 (m, 1H, H_{arom}), 8.04 (d, 1H, $^{3}J_{HH}$=5.5, H_{Pyr}), 9.03 (s, 1H, N*H*Boc). ^{13}C-NMR δ: 28.0, 79.5, 100.7, 108.8 (d, J_{FH}=23.1), 116.2 (d, J_{FH}=3.1), 121.7, 124.3 (d, J_{FH}=12.2), 125.4, 149.4 (d, J_{FH}=10.1), 153.0, 153.3, 153.9, 154.1 (d, J_{FH}=249), 158.6. ^{19}F-NMR δ: -120.7. LC-MS: *m/z* 365 ([M+H]$^{+}$,100).

Procedure F: Compounds 13a-d. 1*H*-imidazo[4,5-*b*]pyridine-2(3*H*)-one Ring A formation: The corresponding 2,3-diaminopyridin-4-yl-oxy-compound (1.5 mmol) was dissolved in dry THF (20 mL), pyridine (1 mL) was added and the solution was cooled at 0°C. Triphosgene (1.5 mmol) in dry THF (10 mL) was added dropwise. The reaction mixture was stirred at room temperature for 16 hrs. The solvent was evaporated and the residue washed with water to provide the title compound which was recovered by filtration.

***Tert*-butyl-4-(2,3-dihydro-2-oxo-1*H*-imidazo[4,5-*b*]pyridin-7-yloxy)-2-(methylthio)phenylcarbamate (13a).** *Tert*-butyl-4-(2,3-diaminopyridin-4-yloxy)-2-(methylthio)phenylcarbamate **12a** (810 mg, 2.2 mmol) afforded the title compound (594 mg, 69%) as described in procedure F as a brown solid. ^{1}H-NMR δ: 1.44 (s, 9H, *t*Bu), 2.38 (s, 3H, CH_3), 6.40 (d, 1H, J=5.9, H_{Py}), 6.89 (dd, 1H, J=8.5 and J=2.5, H_{arom}), 7.08 (d, 1H, J=2.5, H_{arom}), 7.31 (d, 1H, J=8.5, H_{arom}), 7.78 (d, 1H, J=5.9, H_{Py}), 11.21 (s, 1H, $NH_{carbamate}$), 11.39 (bs, 1H, NH_{Py}), 12.16 (bs, 1H, NH_{Py}). ^{13}C-NMR δ: 14.8, 27.9, 78.8, 105.7, 113.2, 115.9, 117.2, 124.5, 127.5, 131.9, 138.0, 145.0, 146.9, 151.9, 153.5, 154.1. LC-MS: *m/z* 389 ([M+H]$^{+}$, 100).

***Tert*-butyl-4-(2,3-dihydro-2-oxo-1*H*-imidazo[4,5-b]pyridin-7-yloxy)-3-methoxyphenylcarbamate (13b).** *Tert*-butyl-4-(2,3-diaminopyridin-4-yloxy)-3-methoxyphenylcarbamate **12b** (534 mg, 1.5 mmol) afforded the title compound (287 mg, 51%) as described in procedure F as a grey powder. ^{1}H-NMR δ: 1.48 (s, 9H, *t*Bu), 3.94 (s, 3H, CH_3), 6.38 (d, 1H, J=6.1, H_{Py}), 7.06 (dd, 1H, J=8.7 and J=2.0, H_{arom}), 7.13 (d, 1H, J=8.7, H_{arom}), 7.49 (m, 1H, H_{arom}), 7.87 (d, 1H, J=6.1, H_{Py}), 9.50 (bs, 1H, $NH_{carbamate}$), 12.02 (bs, 1H, NH_{urea}). ^{13}C-NMR δ: 28.0, 55.5, 79.2, 103.5, 106.2, 110.3, 111.9, 122.3, 135.3, 136.9, 138.7, 148.9, 149.3, 149.8, 150.8, 152.7. LC-MS: *m/z* 373 ([M+H]$^{+}$, 100).

***Tert*-butyl-3-methyl-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-7-yl-oxy)phenyl-carbamate (13c).** *Tert*-butyl-4-(2,3-diaminopyridin-4-yl-oxy)-3-methylphenylcarbamate **12c** (396 mg, 1.20 mmol)

produced the title compound (153 mg, 36%) as described in procedure F. ^{1}H-NMR δ: 1.48 (s, 9H, *t*Bu), 2.08 (s, 3H, CH_3), 6.13 (d, 1H, J=6.0, H_{Py}), 7.01 (d, 1H, J=8.8, H_{arom}), 7.31 (d, 1H, J=8.8, H_{arom}), 7.47 (s, 1H, H_{arom}), 7.70 (d, 1H, J=6.0, H_{Py}), 9.35 (s, 1H, $NH_{carbamate}$), 11.15 (s, 1H, NH_{urea}), 11.30 (s, 1H, NH_{urea}). ^{13}C-NMR δ: 15.7, 28.1, 79.0, 104.0, 112.1, 117.3, 120.9, 121.1, 129.8, 136.9, 141.3, 146.1, 146.2, 146.7, 152.8, 154.1. LC-MS: *m/z* 357 ([M+H]$^+$, 100).

***Tert*-butyl-2-fluoro-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-7-yloxy)phenylcarbamate (13d).** *Tert*-butyl-4-(2,3-diaminopyridin-4-yloxy)-2-(fluoro)phenylcarbamate **12d** (670 mg, 2 mmol) afforded the title compound (490 mg, 94%) as described in procedure F as a solid. ^{1}H-NMR δ: 1.50 (s, 9H, *t*Bu), 6.49 (d, 1H, J=6.0, H_{Py}), 6.96 (m, 1H), 7.17 (d, 1H, J=11.3 and J=2.7, H_{arom}), 7.62 (t, 1H, J=9, H_{arom}), 7.83 (d, 1H, J=6.0, H_{Py}), 8.99 (s, 1H, $NH_{carbamate}$), 11.21 (bs, 1H, NH_{Py}), 11.42 (bs, 1H, NH_{Py}).

***Tert*-butyl-4-(2-Oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-7-yl-oxy)naphthalen-1-yl-carbamate (13e).** *Tert*-butyl 4-(2,3-diaminopyridin-4-yl-oxy)naphthalen-1-yl-carbamate **12e** (191 mg, 0.51 mmol) was dissolved in dry THF (5 mL, 10 mL/mmol). The solution was cooled in an ice bath under nitrogen. Pyridine (95 µL, 1.17 mmol) was added, followed by dropwise addition of a phosgene solution 1.93 M in toluene (322 µL, 0.61 mmol) under vigourous stirring. The ice bath was removed and the mixture was stirred at room temperature overnight, then at 60°C during 2 hrs. The solvent was evaporated under reduced pressure and the solid residue was washed with water and dried to afford to afford the title compound as a solid (0.17 g, 83%). ^{1}H-NMR δ: 1.51 (s, 9H, *t*Bu), 6.26 (d, 1H, J = 6.1, H_{Py}), 7.29 (d, 1H, J = 8.2, $H_{arom,naph}$), 7.55 – 7.66 (m, 3H, $H_{arom,naph}$), 7.73 (d, 1H, H_{Py}), 7.92 – 7.97 (m, 1H, $H_{arom,naph}$), 8.06 – 8.15 (m, 1H, $H_{arom,naph}$), 9.28 (s, 1H, NHBoc), 11.48 (s, NH, NH_{Py}). LC-MS: *m/z* 392 ([M]$^+$, 100).

Procedure G: Compounds 2a-e. Boc Deprotection : Substituted *tert*-butyl-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-7-yl-oxy)phenyl-carbamate was dissolved in TFA (4.7 mL/mmol) and the solution was stirred at room temperature for 1.5 hrs. TFA was evaporated in vacuo and the resulting viscous oil was taken up in water (230 µL/mL TFA). A saturated aqueous solution of Na_2CO_3 was added until pH 7. The resulting precipitate was recovered by filtration, washed with water and dried to afford the title compound.

7-(4-Amino-3-(methylthio)phenoxy)-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one (2a). *Tert*-butyl-4-(2,3-dihydro-2-oxo-1*H*-imidazo[4,5-*b*]pyridin-7-yloxy)-2-(methylthio)phenylcarbamate **13a** (300 mg, 0.77 mmol) afforded the title compound (142 mg, 63%) as described in procedure G as a powder. ^{1}H-NMR δ: 2.09 (s, 3H, CH_3), 4.87 (bs, 2H, NH_2), 6.01 (d, 1H, J=5.7, H_{Py}), 6.50 (d, 1H, J=8.5, H_{arom}), 6.56 (d,

1H, J=8.3, H_{arom}), 6.74 (s, 1H, H_{arom}), 7.45 (d, 1H, J=5.7, H_{Py}), 10.84 (bs, 1H, NH_{Py}), 11.01 (bs, 1H, NH_{Py}). ^{13}C-NMR δ: 15.7, 104.4, 112.2, 114.8, 119.6, 120.6, 121.6, 141.2, 144.1, 144.6, 146.5, 146.9, 154.1. LC-MS: *m/z* 288 ($[M+H]^+$, 100).

7-(4-Amino-2-methoxyphenoxy)-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one (2b). *Tert*-butyl-4-(2,3-dihydro-2-oxo-1*H*-imidazo[4,5-*b*]pyridin-7-yloxy)-3-methoxyphenylcarbamate **13b** (262 mg, 0.7 mmol) afforded the title compound (34 mg, 18%) as described in procedure G as a pale pink powder. ^{1}H-NMR δ: 3.63 (s, 9H, CH_3), 5.18 (bs, 2H, NH_2), 6.08 (d, 1H, J=5.9, H_{Py}), 6.16 (dd, 1H, J=8.4 and J=2.4, H_{arom}), 6.39 (d, 1H, J=2.4, H_{arom}), 6.83 (d, 1H, J=8.4, H_{arom}), 7.65 (d, 1H, J=5.9, H_{Py}), 11.15 (bs, 2H, NH_{urea}). ^{13}C-NMR δ: 55.2, 99.1, 103.2, 105.7, 111.7, 122.8, 131.3, 141.1, 147.6, 147.9, 151.7, 154.1, 154.5. LC-MS: *m/z* 272 ($[M+H]^+$, 100).

7-(4-Amino-2-methylphenoxy)-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one (2c). *Tert*-Butyl-3-methyl-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-7-yl-oxy)phenyl-carbamate **13c** (135 mg, 0.38 mmol) afforded the title compound (61 mg, 63%) as described in procedure G. ^{1}H-NMR δ: 1.95 (s, 3H, CH_3), 5.05 (s, 2H, NH_2), 6.08 (d, 1H, J=6.0, H_{Py}), 6.45 (d, 1H, J=8.2, H_{arom}), 6.50 (s, 1H, H_{arom}), 6.79 (d, 1H, J=8.4, H_{arom}), 7.68 (d, 1H, J=6.0, H_{Py}), 11.15 (s, 1H, NH_{Py}), 11.29 (s, 1H, NH_{Py}). ^{13}C-NMR δ: 15.6, 103.5, 111.7, 112.6, 116.1, 121.8, 129.9, 141.3, 141.6, 146.5, 146.6, 147.1, 154.1. LC-MS: *m/z* 257 ($[M+H]^+$, 100).

7-(4-Amino-3-fluorophenoxy)-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one (2d). *Tert*-butyl-2-fluoro-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-7-yloxy) **13d** (490 mg, 1.36 mmol) afforded the title compound (290 mg, 82%) as described in procedure G. ^{1}H-NMR δ: 5.16 (s, 2H, NH_2), 6.28 (d, 1H, J=5.8, H_{Py}), 6.72-6.81 (m, 2H, H_{arom}), 6.99 (d, 1H, H_{arom}), 7.72 (d, 1H, H_{Py}), 11.16 (s, 1H, NH_{Py}), 11.33 (s, 1H, NH_{Py}).

7-(4-Aminonaphthalen-1-yl-oxy)-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one (2e). *Tert*-butyl-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-7-yloxy)naphthalen-1-yl-carbamate **13e** (170 mg, 0.43 mmol) afforded the title compound as an off-white solid (94 mg, 74%) as described in procedure G. ^{1}H-NMR δ: 5.96 (d, 1H, J = 5.9, H_{Py}), 6.61 (d, 1H, J = 8.1, $H_{arom,naph}$), 7.03 (d, 3H, J = 8.1, $H_{arom,naph}$), 7.33 – 7.37 (m, 2H, $H_{arom,naph}$), 7.52 (d, 1H, H_{Py}), 7.58 – 7.62 (m, 1H, $H_{arom,naph}$), 8.05 – 8.11 (m, 1H, $H_{arom,naph}$), 11.21 (s, NH, NH_{Py}). LC-MS: *m/z* 293 ($[M + H]^+$, 100).

Procedure H: Compounds 5a/f-m. Urea linker formation. The (4-aminophenoxy)-3-nitropyridin-2-amine and the appropriate phenyl isocyanate (1 equivalent) were dissolved in dry DCM or THF (30 mL/mmol) and stirred for 20 hrs under argon at room temperature. The resulting precipitate was recovered by filtration, washed with more DCM and dried, to afford the title compound.

1-(4-(2-Amino-3-nitropyridin-4-yloxy)-2-(methyltio)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (5a). 4-(4-Amino-3-(methylthio)phenoxy)-3-nitropyridin-2-amine **9a** (150 mg, 0.5 mmol) afforded the title compound (247 mg, 93%) as described in procedure H as a orange powder. ^{1}H-NMR δ: 2.47 (s, 3H, CH_3), 6.02 (d, 1H, J=5.7, H_{Py}), 7.04 (d, 1H, J=8.8, H_{arom}), 7.16 (s, 2H, $NH_{2,Py}$), 7.21 (m, 1H, J=8.8, H_{arom}), 7.62 (m, 2H, H_{arom}), 7.85 (m, 1H, H_{arom}), 8.01 (d, 1H, J=8.8, H_{arom}), 8.11 (d, 1H, J=5.7, H_{Py}), 8.20 (s, 1H, NH_{urea}), 9.75 (s, 1H, NH_{urea}). ^{13}C-NMR δ: 15.6, 100.4, 116.5, 118.0, 119.8, 121.6, 122.7, 123.8, 124.0, 126.5, 126.8, 131.7, 132.0, 133.9, 139.2, 149.3, 152.4, 153.1, 153.7, 158.9. LC-MS: *m/z* 514 ([M+H]$^+$, 100). HRMS: *m/z* calcd for $C_{20}H_{15}ClF_3N_5O_4S$ ([M+H]$^+$): 514.0561; found: 514.0564.

1-(4-(2-Amino-3-nitropyridin-4-yloxy)-2-methoxyphenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (5f). 4-(4-Amino-3-methoxy-phenoxy)-3-nitro-pyridin-2-ylamine **9f** (1.83 g, 6.6 mmol) afforded the title compound (0.225 g, 7%) as described in procedure H after purification by chromatography on silica gel (EtOAc:DCM 1:1) as a dark red powder (Rf 0.43, EtOAc:DCM 1:1). ^{1}H-NMR δ: 3.89 (s, 3H, CH_3), 6.01 (d, 1H, J=5.7, H_{Py}), 6.75 (dd, 1H, J= 8.8 and J=2.5, H_{arom}), 6.97 (d, 1H, J=2.5, H_{arom}), 7.12 (s, 2H, $NH_{2,Py}$), 7.60 (s, 2H, H_{arom}), 7.99 (d, 1H, J=5.7, H_{Py}), 8.10 (m, 1H, H_{arom}), 8.16 (d, 1H, J= 8.8, H_{arom}), 8.34 (s, 1H, NH_{urea}), 9.76 (s, 1H, NH_{urea}). ^{13}C-NMR δ: 59.6, 100.1, 104.4, 112.1, 116.2, 119.2, 121.5, 122.1, 122.5, 123.7, 126.5, 131.9, 139.1, 147.7, 148.9, 152.0, 152.9, 153.6, 159.1. LC-MS: *m/z* 498 ([M+H]$^+$, 100).

1-(4-(2-Amino-3-nitropyridin-4-yloxy)-2-(dimethylamino)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (5g). 5-(2-Amino-3-nitropyridin-4-yloxy)-*N*1,*N*1-dimethylbenzene-1,2-diamine **9g** (342 mg, 1.2 mmol) afforded the title compound (200 mg, 33%) as described in procedure H as a green powder. ^{1}H-NMR δ: 2.60 (s, 6H, CH_3), 5.98 (d, 1H, J=5.7, H_{Py}), 6.85 (dd, 1H, J= 8.8, and J=2.5, H_{arom}), 6.99 (d, 1H, J=2.5, H_{arom}), 7.13 (s, 2H, $NH_{2,Py}$), 7.59 (m, 2H, H_{arom}), 7.97 (d, 1H, J=5.7, H_{Py}), 8.08 (m, 2H, H_{arom}), 8.37 (s, 1H, NH_{urea}), 9.89 (s, 1H, NH_{urea}). ^{13}C-NMR δ: 44.0 (2), 100.7, 112.8, 115.9, 116.6, 120.5, 121.9, 122.6, 122.9, 126.9, 131.4, 132.3, 139.5, 144.9, 148.1, 152.6, 153.4, 154.0, 159.6, 170.8. LC-MS: *m/z* 511 ([M+H]$^+$, 100).

1-(4-(2-Amino-3-nitropyridin-4-yloxy)-2,3-dimethylphenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (5h). 4-(4-Amino-2,3-dimethylphenoxy)-3-nitropyridin-2-amine **9h** (400 mg, 1.5 mmol) afforded the title compound (625 mg, 86%) as described in procedure H as a yellow powder. ^{1}H-NMR δ: 2.07 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 5.77 (d, 1H, J=5.7, H_{Py}), 6.98 (d, 1H, J=8.7, H_{arom}), 7.14 (s, 2H, NH_2), 7.57 (d, 1H, J=8.7, H_{arom}), 7.62 (m, 2H, H_{arom}), 7.96 (d, 1H, J=5.7, H_{Py}), 8.12 (m, 1H, H_{arom}), 8.21 (s, 1H, NH_{urea}), 9.38 (s, 1H, NH_{urea}). ^{13}C-NMR δ: 12.4, 14.2, 99.3, 116.6, 118.4, 121.1, 122.1, 122.4, 122.7, 124.9, 126.4, 128.9, 131.4, 131.9, 134.6, 139.5, 147.1, 152.8, 153.1, 153.7, 159.0. LC-MS: *m/z* 496 ([M+H]$^+$, 100). HRMS: *m/z* calcd for $C_{21}H_{17}ClF_3N_5O_4$ ([M+H]$^+$): 496.0996; found: 496.0999.

1-(4-(2-Amino-3-nitropyridin-4-yloxy)-2-(trifluoromethyl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (5i). 4-(4-Amino-3-(trifluoromethyl) phenoxy)-3-nitropyridin-2-amine **9i** (400 mg, 1.3 mmol) afforded the title compound (416 mg, 99%) as described in procedure H as a yellow powder. ^{1}H-NMR δ: 6.06 (d, 1H, J=5.7, H_{Py}), 7.26 (m, 2H, H_{arom}), 7.54 (m, 2H, H_{arom}), 7.64 (s, 2H, NH_2), 7.96 (m, 1H, H_{arom}), 8.05 (d, 1H, J=5.7, H_{Py}), 8.11 (m, 1H, H_{arom}), 8.28 (s, 1H, NH_{urea}), 9.76 (s, 1H, NH_{urea}). ^{13}C-NMR δ: 101.0, 116.8, 118.1, 121.8, 122.4, 122.7, 123.0, 124.8, 125.2, 126.5, 127.0, 128.9, 132.1, 133.2, 138.9, 149.5, 152.6, 153.5, 153.9, 158.4. LC-MS: *m/z* 536 ([M+H]$^+$, 100). HRMS: *m/z* calcd for $C_{20}H_{12}ClF_6N_5O_4$ ([M+H]$^+$): 536.0571; found: 536.0560.

1-(4-(2-Amino-3-nitropyridin-4-yloxy)-2-phenylphenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (5j). 4-(4-Amino-3-phenylphenoxy)-3-nitropyridin-2-amine **9j** (583 mg, 1.8 mmol) afforded the title compound (613 mg, 62%) as described in procedure H as a yellow powder. ^{1}H-NMR δ: 6.11 (d, 1H, J=5.7, H_{Py}), 7.07 (d, 1H, J=2.7, H_{arom}), 7.15 (s, 1H, H_{arom}), 7.21 (dd, 1H, J=8.8 and J=2.7, H_{arom}), 7.40-7.52 (m, 6H, H_{arom}), 7.57 (s, 2H, $NH_{2,Py}$), 7.92 (d, 1H, J=8.8, H_{arom}), 7.99 (s, 1H, NH_{urea}), 8.03 (d, 1H, J=5.7, H_{Py}), 9.75 (s, 1H, NH_{urea}). ^{13}C-NMR δ: 100.7, 116.3, 116.4, 116.5, 119.7, 121.6, 121.8, 121.9, 122.1, 122.7, 123.8, 125.4, 127.8, 128.7, 128.9, 131.8, 132.8, 135.6, 132.7, 139.3, 149.2, 152.7, 153.1, 153.8, 158.9. LC-MS: *m/z* 544 ([M+H]$^+$, 100). HRMS: *m/z* calcd for $C_{25}H_{17}ClF_3N_5O_4$ ([M+H]$^+$): 544.0992; found: 544.0999.

1-(4-(2-Amino-3-nitropyridin-4-yloxy)-3-fluorophenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (5k). 4-(4-Amino-2-fluorophenoxy)-3-nitropyridin-2-amine **9k** (0.25 g, 0.94 mmol) afforded the title compound (0.19 g, 42%) as described in procedure H. ^{1}H-NMR δ: 5.98 (d, 1H, J=5.7, H_{Py}), 7.21 (s, 2H, NH_2), 7.26 (dd, 1H, J=9.1 and J=2.3, H_{arom}), 7.34 (t, 1H, J=8.8, H_{arom}), 7.60-7.73 (m, 3H, H_{arom}), 8.01 (d, 1H, J=5.7, H_{Py}), 8.10 (d, 1H, J=2.1, H_{arom}), 9.19 (s, 1H, NH_{urea}), 9.27

(s, 1 H, NH_{urea}). LC-MS: *m/z* 486 ($[M+H]^+$, 100).

1-(4-(2-Amino-3-nitropyridin-4-yloxy)-2-chlorophenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (5l). 4-(4-Amino-3-chlorophenoxy)-3-nitropyridin-2-amine **9l** (400 mg, 1.4 mmol) afforded the title compound (530 mg, 74%) as described in procedure H as a green powder. ^{1}H-NMR δ: 6.05 (d, 1H, J=5.7, H_{Py}), 7.19 (m, 3H, H_{arom}), 7.43 (d, 1H, J=2.7, H_{arom}), 7.61 (s, 2H, NH_2), 8.01 (d, 1H, J=5.7, H_{Py}), 8.09 (s, 1H, H_{arom}), 8.17 (d, 1H, J=9.1, H_{arom}), 8.49 (s, 1H, NH_{urea}), 9.85 (s, 1H, NH_{urea}). ^{13}C-NMR δ: 100.6, 116.7, 119.8, 121.4, 121.7, 122.6, 122.9, 123.0, 123.6, 126.5, 127.0, 132.1, 133.4, 138.9, 148.4, 152.1, 153.3, 153.9, 158.7. LC-MS: *m/z* 502 ($[M+H]^+$, 100). HRMS: *m/z* calcd for $C_{19}H_{12}Cl_2F_3N_5O_4$ ($[M+H]^+$): 502.0295; found: 502.0297.

1-(4-(2-Amino-3-nitropyridin-4-yloxy)-2-methylphenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (5m). 4-(4-Amino-3-methylphenoxy)-3-nitropyridin-2-amine **9m** (400 mg, 1.5 mmol) afforded the title compound (582 mg, 78%) as described in procedure H as a green powder. ^{1}H-NMR δ: 2.25 (s, 3H, CH_3), 5.95 (d, 1H, J=5.7, H_{Py}), 6.96 (m, 1H, H_{arom}), 7.02 (m, 1H, H_{arom}), 7.12 (s, 2H, NH_2), 7.48-7.68 (m, 2H, H_{arom}), 7.73 (d, 1H, H_{arom}), 7.95 (d, 1H, J=5.7, H_{Py}), 8.13 (m, 1H, H_{arom}), 8.65 (s, 1H, NH_{urea}), 9.99 (s, 1H, NH_{urea}). ^{13}C-NMR δ: 17.7, 100.4, 116.5, 117.9, 120.6, 121.7, 122.0, 122.7, 123.7, 124.9, 126.4, 126.8, 131.6, 134.8, 139.7, 148.5, 152.8, 153.0, 153.8, 159.2. LC-MS: *m/z* 482 ($[M+H]^+$, 100). HRMS: *m/z* calcd for $C_{20}H_{15}ClF_3N_5O_4$ ($[M+H]^+$): 482.0838; found: 482.0843.

Ethyl 4-(4-*N*-(*tert*-butoxycarbonyl)-amino-3-fluorophenoxy)-2-aminopyridin-3-yl-carbamate (14d). 4-(4-*N*-(*tert*-butoxycarbonyl)-amino-3-fluorophenyloxy)-2,3-diaminopyridine **12d** (2.5 g, 7.5 mmol) was dissolved in dry THF (50 mL) under stirring, pyridine (1.2 mL, 15 mmol) was added and the solution was cooled at 0°C. Ethyl chloroformate (0.77 mL, 8.0 mmol) was added at once. After 30 min the reaction mixture was allowed to reach room temperature and stirred for further 24 hrs. The solvent was evaporated under vacuum and the residue partitioned between DCM and saturated aqueous Na_2CO_3. The organic layer was washed with H_2O, dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography (eluent gradient DCM to EtOAc) to afford the title compound as a foam (1.13 g, 37%). ^{1}H-NMR δ: 1.17 (t, 3H, $CH_{3,Et}$, J=7.1 Hz), 1.45 (s, 9H, *t*Bu), 4.02 (q, 2H, J=7.1, $CH_{2,Et}$), 5.89 (s, 2H, $NH_{2,Py2}$), 5.98 (d, 1H, J=5.7, H_{Py}), 6.83 (d, 1H, H_{arom}), 6.96 (d, 1H, H_{arom}), 7.55 (t, 1H, H_{arom}), 7.73 (d, 1H, J=5.7, H_{Py}), 8.29 (br s, 1H, NH_{Py3}), 9.39 (s, 1H, NHBoc).

4-(4-*N*-Boc-aminonaphthalen-1-yl-oxy)-3-*N*-aminocarbamoylethyl-2-amino-pyridine (14e). 4-(4-*N*-

Boc-aminonaphthalen-1-yl-oxy)-2,3-diaminopyridine **12e** (500 mg, 1.4 mmol) and the pyridine (222 µL, 2.7 mmol) were dissolved in dry THF (8 mL) under vigorous stirring at 0°C. To this solution the ethylchloroformate (136 mL, 1.5 mmol) was added at once. The reaction mixture was allowed to reach room temperature and was stirred for an additional 10 hrs. The solvent was evaporated under vacuum and the residue partitioned between EtOAc and Na_2CO_3 solution. The organic layer was washed (20 mL brine), dried ($MgSO_4$) and evaporated to provide a solid residue. After purification by LC (Isolute column, Flash Si II, 50g/170 mL; eluent: EtOAc) the desired compound was obtained (475 mg, 75%). ^{1}H-NMR δ: 1.14-1.21 (m, 3H, CH_3), 1.50 (s, 9H, *t*Bu), 4.04-4.10 (m, 2H, CH_2), 5.66 (d, 1H, J=5.7, H_{Py}), 5.84 (s, 2H, NH_2), 7.15 (d, 1H, J=8.1, H_{arom}), 7.49-7.60 (m, 3H, H_{arom}), 7.62 (d, 1H, J=5.7, H_{Py}), 7.98-8.04 (m, 1H, H_{arom}), 8.07 (d, 1H, J=8.5, H_{arom}), 8.40 (s, 1H, NH_{carb}), 9.22 (s, 1H, NH_{Boc}). LC-MS: *m/z* 440 [$(M + H)^+$, 100]. HRMS: *m/z* calcd for $C_{23}H_{27}N_4O_5$ [$(M + H)^+$]: 439.1981; found 439.1979.

Ethyl 4-(4-amino-3-fluorophenoxy)-2-aminopyridin-3-yl-carbamate (15d). Ethyl 4-(4-*N*-(*tert*-butoxycarbonyl)-amino-3-fluorophenoxy)-2-aminopyridin-3-yl-carbamate **14d** (1.13 g, 2.8 mmol) was dissolved in TFA (8 mL), a few drops of water were added and the reaction mixture was stirred for 2 hrs at room temperature. The TFA was evaporated, the residue dissolved in water (20 mL), neutralized with saturated Na_2CO_3 and extracted with DCM (2x20 mL). The organic layer was dried and evaporated to afford the title compound (730 mg, 86%). ^{1}H-NMR δ: 1.17 (t, 3H, J=7.1, $CH_{3,Et}$), 4.05 (q, 2H, J=7.0, $CH_{2,Et}$), 5.04 (s, 2H, $NH_{2,Ph}$), 5.71 (s, 2H, $NH_{2,Py}$), 5.86 (d, 1H, J=5.7, H_{Py}), 6.64 (d, 1H, H_{arom}), 6.73-6.82 (m, 2H, H_{arom}), 7.68 (d, 1H, J=5.7, H_{Py}), 8.23 (br s, 1H, NH_{Py3}). LC-MS: *m/z* 307 ([M+H]$^+$, 100).

4-(4-Aminonaphthalen-1-yl-oxy)-3-*N*-aminocarbamoylethyl-2-amino-pyridine (15e). 4-(4-*N*-Boc-aminonaphthalen-1-yl-oxy)-3-*N*-aminocarbamoylethyl-2-aminopyridine **14e** (475 mg, 1.05 mmol) was dissolved in dry TFA (10 mL) under vigorous stirring at 0°C. The solution was allowed to reach room temperature and was stirred for an additional 2 hrs. The TFA was evaporated under vacuum and the oily residue partitioned between EtOAc and Na_2CO_3 solution. The organic layer was washed (20 mL brine), dried ($MgSO_4$) and evaporated to a solid residue (346 mg, 97%). ^{1}H-NMR δ: 1.19-1.26 (m, 3H, CH_3), 4.07-4.13 (m, 2H, CH_2), 5.57 (d, 1H, J=5.7, H_{Py}), 5.77 (s, 4H, NH_2), 6.66 (d, 1H, J=8.1, H_{arom}), 6.97 (d, 1H, J=8.1, H_{arom}), 7.37-7.45 (m, 2H, H_{arom}), 7.55 (d, 1H, J=5.7, H_{Py}), 7.76-7.86 (bs, 1H, H_{arom}), 8.09-8.12 (m, 1H, H_{arom}), 8.36 (s, 1H, NH_{carb}). LC-MS: *m/z* 339 [$(M+H)^+$, 100]. HRMS: *m/z* calcd for $C_{18}H_{19}N_4O_3$ [$(M+H)^+$, 100]: 339.1457; found 339.1459.

Ethyl 4-(4-amino-3-fluorophenoxy)-2-aminopyridin-3-yl-methyl-carbamate (16d). Ethyl 4-(4-amino-3-fluorophenoxy)-2-aminopyridin-3-yl-carbamate **15d** (480 mg, 1.6 mmol) was dissolved in dry

THF (8 mL) and cooled at 0°C. Sodium hydride (60% in mineral oil, 80 mg, 2.0 mmol) was added, and the reaction mixture was stirred for 40 min at 0°C. Methyl iodide (130 μL, 1.8 mmol) was added at 0°C. The ice bath was removed, and the mixture was stirred at room temperature for 18 hrs. The solvent was evaporated and the residue partitioned between DCM and distilled water. The organic layer was dried and evaporated, and the residue washed with diethyl ether to afford the title compound as a brown solid (322 mg, 63%). ^{1}H-NMR δ: 1.09 (t, 3H, J=7.0, $CH_{3,Et}$), 3.00 (s, 3H, CH_3N), 3.90-4.10 (m, 2H, $CH_{2,Et}$), 5.07 (s, 2H, $NH_{2,Ph}$), 5.87 (d, 1H, H_{Py}), 6.03 (s, 2H, $NH_{2,Py}$), 6.63 (t, 1H, H_{arom}), 6.77-6.81 (m, 2H, H_{arom}), 7.75 (d, 1H, H_{Py}).

4-(4-Aminonaphthalen-1-yl-oxy)-3-*N*-methyl-*N*-aminocarbamoylethyl-2-amino-pyridine (16e). 4-(4-Aminonaphthalen-1-yl-oxy)-3-*N*-aminocarbamoylethyl-2-amino-pyridine **15e** (350 mg, 1.04 mmol) was dissolved in dry THF (8 mL) under vigorous stirring at 0°C and argon. To this solution NaH (60% dispersed in mineral oil) (45 mg, 1.14 mmol) was added. After 40 min MeI (66 mL, 0.91 mmol) was added at 0°C. The reaction mixture was allowed to reach room temperature and was stirred for further 10 hrs. The solvent was evaporated under vacuum and the residue retaken in 20 mL of EtOAc. The solution was washed with brine (2x20 mL), dried and evaporated to dryness. The residue was triturated with Et_2O and filtered. 238 mg (65%) of the desired compound resulted. ^{1}H-NMR δ: 1.12-1.29 (m, 3H, CH_3), 3.14 (s, 3H, CH_3), 4.05-4.16 (m, 2H, CH_2), 5.53 (d, 1H, J=5.8, H_{Py}), 5.75 (s, 2H, NH_2), 6.01 (s, 2H, NH_2), 6.66 (d, 1H, J=8.1, H_{arom}), 6.96 (d, 1H, J=8.1, H_{arom}), 7.37-7.43 (m, 2H, H_{arom}), 7.57 (d, 1H, J=5.8, H_{Py}), 7.59-7.64 (m, 1H, H_{arom}), 8.11-8.15 (m, 1H, H_{arom}). LC-MS: *m/z* 353 ($[M+H]^+$, 100). HRMS: *m/z* calcd for $C_{19}H_{21}N_4O_3$ ($[M+H]^+$): 353.1614; found 353.1610.

7-(4-Amino-3-fluorophenoxy)-1-methyl-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one (3d). Ethyl 4-(4-amino-3-fluorophenoxy)-2-aminopyridin-3-yl-methyl-carbamate **16d** (320 mg, 1.0 mmol) was suspended in a solution of EtONa in EtOH (4 mL), obtained from dissolving sodium (480 mg, 21 mmol) in ethanol (9 mL). The suspension was heated under microwave irradiation for 1 h (100°C, 100 W). The mixture was cooled at room temperature and the solvent was evaporated. The residue was dissolved in water and was acidified with AcOH to pH 4. The precipitate formed was recovered by filtration, to afford the title compound (188 mg, 67%). ^{1}H-NMR δ: 3.46 (s, 3H, CH_3N), 5.11 (s, 2H, NH_2), 6.35 (d, 1H, J=5.9, H_{Py}), 6.77-6.82 (m, 2H, $H_{arom,}$), 6.99 (d, 1H, H_{arom}), 7.76 (d, 1H, J=6.0, H_{Py}), 11.54 (s, 1H, NH_{Py}).

4-(4-Aminonaphthalen-1-yl-oxy)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridine (3e). 230 mg (0.65 mmol) 4-(4-aminonaphthalen-1-yl-oxy)-3-*N*-methyl-*N*-aminocarbamoylethyl-2-aminopyridine **16e** were

suspended in 5.0 mL solution 1.0 M of EtONa in EtOH. The suspension was submitted to microwave (150 W, 100°C) for 45 min. After cooling the reaction mixture was evaporated to dryness, retaken in 20 mL H_2O, the pH adjusted to 4.5 (AcOH) when the desired compound precipitate (167 mg, 84%). ^{1}H-NMR δ: 3.61 (s, 3H, CH_3), 5.79 (s, 2H, NH_2), 6.10 (d, 1H, J=5.9, H_{Py}), 6.68 (d, 1H, J=8.1, H_{arom}), 7.10 (d, 1H, J=8.1, H_{arom}), 7.43-7.48 (m, 2H, H_{arom}), 7.64 (d, 1H, J=5.8, H_{Py}), 7.74-7.81 (m, 1H, H_{arom}), 8.12-8.17 (m, 1H, H_{arom}), 11.57 (s, 1H, NH_{Py}). LC-MS: *m/z* 307 ([M+H]$^+$, 100). HRMS: *m/z* calcd for $C_{17}H_{25}N_4O_2$ ([M+H]$^+$): 307.1195; found 307.1188.

4-(4-*N*-Boc-aminonaphthalen-1-yl-oxy)-3-nitro-2-*N*-methylaminopyridine (18). 4-*N*-Boc-aminonaphthol (1.38 g, 5.34 mmol) were dissolved in dry DMF (30 mL) under vigorous stirring and Ar at room temperature. To this solution the *t*BuOK (0.76 g, 6.78 mmol) was added at once and stirred for 30 min. To this solution the 4-chloro-3-nitro-2-*N*-methylaminopyridine **17** (1.00 g, 5.34 mmol) was added in one portion and the temperature raised to 85°C. The reaction mixture was stirred for an additional 4 hrs and then allowed to reach room temperature. The solution was partitioned between EtOAc (100 mL) and H_2O (100 mL), the organic layer washed (2x100 mL brine), dried and evaporated under vacuum to give 1.10 g of a yellow solid. The solid was recrystallysed from EtOAc:cyclohexane 1:1 when 432 mg of the desired compound were obtained. The solutions from recrystallysation were purified by LC (Isolute column, Flash Si II, 50g/170 mL; eluent: EtOAc:cyclohexane 1:1) when an additional 510 mg resulted. In total 942 mg (43 %) of the desired compound were obtained. ^{1}H-NMR δ: 1.51 (s, 9H, *t*Bu), 2.94 (d, 3H, J=4.6, CH_3), 5.82 (d, 1H, J=5.7, H_{Py}), 7.34 (d, 1H, J=8.2, H_{arom}), 7.56-7.65 (m, 3H, H_{arom}), 7.62 (d, 1H, J=9.3, H_{arom}), 7.86 (d, 1H, J=5.7, H_{Py}), 8.14 (d, 1H, J=8.7 Hz, H_{arom}), 9.33 (s, 1H, NH_{Boc}). LC-MS: *m/z* 411 ([M + H]$^+$, 100).

4-(4-*N*-Boc-aminonaphthalen-1-yl-oxy)-3-amino-2-*N*-methylaminopyridine (19). 4(4-*N*-Boc-aminonaphthalen-1-yl-oxy)-3-nitro-2-*N*-methylaminopyridine **18** (942 mg, 2.30 mmol) were dissolved in EtOAc:EtOH 1:1 and hydrogenated using the hydrogenation cube (catalyst: Pd/C 10%; flow rate 1.0 mL/min; 30°C). The product was purified by LC (Isolute column, Flash Si II, 50g/170 mL; eluent: EtOAc:EtOH 92:8) when 552 mg (63 %) of the desired compound were obtained. ^{1}H-NMR δ: 1.49 (s, 9H, *t*Bu), 2.88 (d, 3H, J=4.6, CH_3), 4.53 (s, 2H, NH_2), 5.91 (d, 1H, J=5.6, H_{Py}), 6.94 (d, 1H, J=8.2, H_{arom}), 7.32 (d, 1H, J=5.6, H_{Py}), 7.44 (d, 1H, J=9.3, H_{arom}), 7.52-7.64 (m, 2H, H_{arom}), 8.00-8.10 (m, 2H, H_{arom}), 9.12 (s, 1H, NH_{Boc}). HRMS: *m/z* calcd for $C_{21}H_{25}N_4O_3$. ([M+H]$^+$): 381.1921; found 381.1924.

4-(4-*N*-Boc-aminonaphthalen-1-yl-oxy)-pyridin-[2,3]-3-*N*-methyl-imidazolone (20). To a solution of 4-(4-*N*-Boc-aminonaphthalen-1-yl-oxy)-3-amino-2-*N*-methylamino-pyridine **19** (552 mg, 1.45 mmol)

and pyridine (0.937 mL, 11.60 mmol) in dry THF, under vigorous stirring and Ar at 0°C, a solution of triphosgene (431 mg, 1.45 mmol) in dry THF (10 mL) was added slowly (40 min). When the addition was finished the reaction mixture was allowed to reach room temperature and was stirred for an additional 12 hrs. The solvent was evaporated under vacuum and the residue recrystallysed from EtOH. A solid was obtained (536 mg, 91%). ^{1}H-NMR δ: 1.50 (s, 9H, *t*Bu), 3.34 (s, 3H, CH_3), 6.27 (d, 1H, J=5.7, H_{Py}), 7.26 (d, 1H, J=8.2, H_{arom}), 7.55-7.63 (m, 3H, H_{arom}), 7.78 (d, 1H, J=5.7, H_{Py}), 7.92 (d, 1H, J=8.1, H_{arom}), 8.11 (d, 1H, J=8.3, H_{arom}), 9.26 (s, 1H, NH_{Boc}), 11.60 (s, 1H, NH). LC-MS: *m/z* 407 ([M + H]$^+$, 100).

4-(4-Aminonaphthalen-1-yl-oxy)-pyridin-[2,3]-2-*N*-methyl-imidazolone (4). 4-(4-*N*-Boc-aminonaphthalen-1-yl-oxy)-pyridin-[2,3]-2-*N*-methylimidazolone **20** (536 mg, 1.31 mmol) was dissolved, under vigorous stirring and at 0°C, in TFA (10 mL). After 30 min the solution was allowed to reach room temperature and was stirred for another 2 hrs. The reaction mixture was evaporated under vacuum, EtOAc (2x10 mL) added and evaporated again. The red dark oil was dissolved in H_2O, neutralised to pH 7 with $NaHCO_3$ when a precipitate is formed. After filtration and drying 351 mg (88%) of the desired compound resulted. ^{1}H-NMR δ: 3.32 (s, 3H, CH_3), 5.79 (s, 2H, NH_2), 6.09 (d, 1H, J=5.7, H_{Py}), 6.69 (d, 1H, J=8.1, H_{arom}), 7.11 (d, 1H, J=8.1, H_{arom}), 7.42-7.47 (m, 2H, H_{arom}), 7.65-7.70 (m, 2H, H_{arom}), 8.12-8.16 (m, 1H, H_{arom}), 11.52 (s, 1H, NH). HRMS: *m/z* calcd for $C_{17}H_{14}N_4O_2$ ([M+H]$^+$): 307.1190; found 307.1199.

II. ^{V600E}BRAF Kinase Assay and SRB GI_{50} for BRAF Inhibitors.

These assays have been described by Niculescu-Duvaz et al.[15]

III. Phospho-ERK assay.

To determine the effect of compounds on BRAF activity in cells, WM266.4 cells were seeded at a density of 3×10^4 cells per well of a 96 well plate. The following day, test compounds were diluted into growth medium to 2× the desired final concentration and then added directly to the cells. After a 6 hrs incubation, the medium was removed and the cells were fixed and permeabilised in 4% formaldehyde, 0.1% triton X-100 in PBS for 30 minutes. The wells were then blocked with 5% milk in PBS for 30 minutes at room temperature, followed by the addition of an antibody for phospho-ERK1/2 (Sigma,

Dorset, UK) at 3 mg/ml in blocking solution. Plates were incubated for 3 hrs with shaking. Plates were washed three times with 0.1% Tween 20 using an ELx50 plate washer (BioTek, Winooski, USA). 0.5 Mg/ml of a Europium-labelled anti-mouse secondary antibody (Perkin Elmer, Turku, Finland) was added to the wells in DELFIA assay buffer for 1 hr. Plates were washed again and Enhancement solution was added to the wells and time resolved fluorescence was measured as instructed by the manufacturer after 20 minutes using a Spectramax M5 plate reader (Molecular Devices, Berkshire, UK). The plates were washed again and BCA protein assay reagent (Sigma, Dorset, UK) was added to the wells and incubated for 30 minutes at 37°C. The absorbance at 570 nm was measured using a plate reader and used to normalise the fluorescence data. Inhibition of ERK phosphorylation was determined as a percentage of DMSO-treated cells and IC50 values were calculated using Prism (GraphPad Software, San Diego, USA).