Supporting Information

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The Nickel/Copper-Catalyzed Direct Alkylation of Heterocyclic C–H Bonds**

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Experimental Section

Chemicals and Reagents

All manipulations were carried out under an inert N₂(g) atmosphere using glovebox techniques. Solvents were purified using a two-column solid-state purification system (Innovative Technology, NJ, USA) and transferred to the glove box without exposure to air. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc., and were degassed and stored over activated 3 Å molecular sieves. Unless noted, all other reagents were purchased from commercial sources and used without further purification. Liquid compounds were degassed by standard freeze-pump-thaw procedures prior to use in the glovebox. Complex [(^{Mc}NN₂)Ni-Cl] was prepared as described previously.¹ The following starting materials were prepared according to literature procedures: 2-(3-iodopropyl)furan², 6-iodohexyl benzoate from 6-chlorohexyl benzoate³ and NaI in acetone by standard method, 1-chloro-4-(2-chloroethyl)benzene⁴, 9-(3-chloropropyl)-9H-carbazole⁵, [(3-bromopropyl)sulfanyl]benzene⁶, (3-bromopropoxy)benzene⁷, tert-butyl 4-(iodomethyl)piperidine-1-carboxylate⁸, lithium 3-ethylpentan-3-olate⁹. Substrates 5-phenyloxazole, 5-(4-methoxyphenyl)oxazole and 5-(4-bromophenyl)oxazole were prepared according to a general procedure¹⁰. Synthesis of 1-(4-(3-chloropropyl)phenyl)propan-1-one, 1-

¹ Z. Csok, O. Vechorkin, S. B. Harkins, R. Scopelliti, X. L. Hu, *J. Am. Chem. Soc.* **2008**, *130*, 8156-8157.

² G. Gomez, H. Rivera, I. Garcia, L. Estevez, Y. Fall, *Tetrahedron Letters* **2005**, *46*(35), 5819-5822.

³ Ian H. Gilbert et al., *J. Med. Chem.* **2006**, *49*, 4183-4195.

⁴ M. Yus et al., *Journal of Organometallic Chemistry* **2002**, *663*, 21-31.

⁵ J. W. Hulshof et al., *Bioorg. Med. Chem.* **2006**, *14*, 7213-7230.

⁶ X. Zhou, R. G. Carter, *Angew. Chem., Int. Ed.* **2006**, *45*(11), 1787-1790.

⁷ A. Kakefuda et al., *J. Med. Chem.* **2003**, *46*, 4728-4740.

⁸ J. C. Sutton et al., *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2233-2239.

⁹ H. Do, R. M. Kashif Khan, O. Daugulis, *J. Am. Chem. Soc.* **2008**, *130*, 15185-15192.

¹⁰ F. Besselièvre, F. Mahuteau-Betzer, D. Grierson, S. Pigue, *J. Org. Chem.* **2008**, *73*, 3278-3280.

(3-chloropropyl)-2-methyl-1H-indole, 2-(5-chloropentyl)-1,3-dioxane and 6-chloro-2,2-diphenylhexanenitrile was described in our previous work.¹¹ 2-Deuteriobenzoxazole was made following literature method.¹²

Physical methods

The ¹H and ¹³C NMR spectra were recorded at 293 K on a Bruker Avance 400 spectrometer. ¹H NMR chemical shifts were referenced to residual solvent as determined relative to Me₄Si (δ = 0 ppm). The ¹³C{¹H} chemical shifts were reported in ppm relative to the carbon resonance of CDCl₃ (77.00 ppm). GC-MS measurements were conducted on a Perkin-Elmer Clarus 600 GC equipped with Clarus 600T MS. GC measurement was conducted on a Perkin-Elmer Clarus 400 GC with a FID detector. HRESI-MS measurements were conducted at the EPFL ISIC Mass Spectrometry Service at Micro Mass QTOF Ultima. Elemental analyses were performed on a Carlo Erba EA 1110 CHN instrument at EPFL.

General procedure for coupling reactions

A mixture of [(^{Me}NN₂)Ni-Cl] (26 mg, 0.075 mmol), CuI (14 mg, 0.075mmol), ^tBuOLi (168mg, 2.1mmol) or Et₃COLi (256mg, 2.1mmol), Alkyl-X (1.8 mmol) and heteroarene (1.5 mmol) was placed in a vial and 5 mL of dioxane was added. Additional NaI (45 mg, 0.3 mmol) was added for coupling of Alkyl-Br or Alkyl-Cl. The mixture was heated under N₂ during 16h at 140⁰C.

¹¹ O. Vechorkin, D. Barmaz, V. Proust, X. L. Hu, *J. Am. Chem. Soc.* **2009**, *131*, 12078–12079.

¹² F. Mongin et al., *J. Org. Chem.* **2005**, *70*, 5190-5196.

The reaction mixture was then cooled to room temperature, quenched with 15 mL of water and 1 mL of 1M HCl, extracted with CH₂Cl₂ (3 times, 20 mL each), dried over Na₂SO₄, filtered, and finally evaporated under a reduced pressure. The residue was purified by flash chromatography on silica-gel.

Exploration of reaction conditions

Table S1. Investigation of conditions for coupling of Alkyl-I^a

Entry	CuI	Base	Solvent	Catalyst	Temp.	Time	Yield ^b
1	7.5mol%	CS ₂ CO ₃	Dioxane	[(^{Me} NN ₂)Ni-Cl]	100	16h	12
2	7.5mol%	CS ₂ CO ₃	Dioxane	[(^{Me} NN ₂)Ni-Cl]	140	16h	20
3	7.5mol%	tBuOK	Dioxane	[(^{Me} NN ₂)Ni-Cl]	100	16h	22
4	7.5mol%	tBuOK	Toluene	[(^{Me} NN ₂)Ni-Cl]	100	16h	29
5	7.5mol%	tBuONa	Dioxane	[(^{Me} NN ₂)Ni-Cl]	120	16h	68
6	7.5mol%	tBuONa	Toluene	[(^{Me} NN ₂)Ni-Cl]	120	16h	67

7	7.5mol%	tBuONa	Toluene	[(^{Me}NN₂)Ni-Cl]	140	16h	75
8	7.5mol%	tBuOLi	Toluene	[(^{Me} NN ₂)Ni-Cl]	120	16h	29
9	7.5mol%	tBuOLi	Dioxane	[(^{Me} NN ₂)Ni-Cl]	120	16h	76
10	7.5mol%	tBuOLi	Dioxane	[(^{Me}NN₂)Ni-Cl]	140	16h	78
11	7.5mol%	MeONa	Dioxane	[(^{Me} NN ₂)Ni-Cl]	140	16h	65
12	7.5mol%	K ₃ PO ₄	Dioxane	[(^{Me} NN ₂)Ni-Cl]	140	16h	35
13	0 mol%	tBuONa	Toluene	[(^{Me} NN ₂)Ni-Cl]	140	16h	54
14	0 mol%	tBuONa	Toluene	-	140	16h	0
15	0 mol%	tBuOLi	Dioxane	[(^{Me} NN ₂)Ni-Cl]	140	16h	18
16	7.5mol%	Et ₃ N	Dioxane	[(^{Me} NN ₂)Ni-Cl]	140	16h	0
17	7.5mol%	DBU	Dioxane	[(^{Me} NN ₂)Ni-Cl]	140	16h	0
18	7.5mol%	4Me-guanidine	Dioxane	[(^{Me} NN ₂)Ni-Cl]	140	16h	0
19	7.5mol%	tBuONa	Toluene	Ni(dme)Cl ₂	140	16h	36
20	7.5mol%	tBuONa	Toluene	Ni(PPh ₃) ₂ Cl ₂	140	16h	37

^a Reactions were performed with 0.5 mmol of butyl-I. ^b GC yields relative to butyl iodide

Table S2. Investigation of conditions for coupling of Alkyl-Br and Alkyl-Cl^a

Entry	X	Additive	Base	Solvent	Temp.	Time	Yield ^b
1	Br	-	tBuONa	Toluene	140	16h	22
2	Br	0.2 equiv. NaI	tBuONa	Toluene	140	16h	35
3	Br	0.2 equiv. Bu ₄ NI	tBuONa	Toluene	140	16h	27
4	Br	0.2 equiv. NaI	tBuOLi	Dioxane	140	16h	85
5	Br	-	tBuOLi	Dioxane	140	16h	83
6	Cl	0.2 equiv. NaI	tBuOLi	Dioxane	140	16h	72
7	Cl	-	tBuOLi	Dioxane	140	16h	66
8	Cl	0.2 equiv. Bu ₄ NI	tBuOLi	Dioxane	140	16h	68
9	Cl	-	tBuONa	Toluene	140	16h	0
10	Cl	0.2 equiv. NaI	tBuONa	Toluene	140	16h	0
11	Cl	0.2 equiv. Bu ₄ NI	tBuONa	Toluene	140	16h	5

^a Reactions were performed with 0.5 mmol of octyl-X, 0.65 mmol benzoxazole, 5 mol% $[(^{\text{Me}}\text{NN}_2)\text{Ni-Cl}]$ catalyst, 7.5 mol% CuI. ^b GC yields relative to octyl halides

Examples of substrates that suffer from elimination:

Comments: Styrene could be detected by GC (17%) in addition to 47% coupling product.

Comments: some elimination product can be isolated and characterized.

N,N-diethylhex-5-enamide (elimination product):

Eluated from the column with hexane-diethyl ether (1:1) in 71% yield as a colorless liquid:

¹H NMR (400MHz, CDCl₃): 5.84 – 5.68 (m, 1H), 4.95 (m, 2H), 3.33 (q, *J* = 7.1 Hz, 2H), 3.25 (q, *J* = 7.1 Hz, 2H), 2.25 (t, *J* = 7.5 Hz, 2H), 2.06 (q, *J* = 7.0 Hz, 2H), 1.71 (p, *J* = 7.4 Hz, 2H), 1.12 (t, *J* = 7.1 Hz, 3H), 1.06 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): 171.83, 138.14, 114.90, 41.81, 39.93, 33.23, 32.09, 24.35, 14.26, 12.99.

HR-MS: calculated for (C₁₀H₂₀NO, M+H), 170.1545; found, 170.1550.

Mechanistic investigations

1. Hg-test experiment

Conditions: [(^{Me}NN₂)Ni-Cl] (9 mg, 0.025 mmol), CuI (5 mg, 0.025mmol), ^tBuOLi (56mg, 0.7mmol), Hg (501mg, 2.5mmol), Bu-I (57.1μl, 0.5 mmol) and Benzoxazole (77mg, 0.65 mmol) were placed in a vial and 2 mL of dioxane was added. After addition the mixture was heated in absence of oxygen during 16h at 140⁰C. After this time the reaction mixture was cooled to r.t., quenched with 10 mL of water and 1 mL of 1M HCl. The resulting solution mixture was then extracted with CH₂Cl₂ (3 times, 10 mL each), dried over Na₂SO₄, filtered, and subjected to GC analysis. 60 μL of dodecane was used as an internal standard. The yield of coupling product is 19% (instead of ca. 80% in the absence of Hg).

Comments: Hg poisoned the active catalyst, suggesting that metal particles are responsible for the catalysis.

2. Filtration experiment

Conditions: [^{13}C MeNN₂)Ni-Cl] (9 mg, 0.025 mmol), CuI (5 mg, 0.025mmol), ^tBuOLi (56mg, 0.7mmol), Bu-I (57.1μl, 0.5 mmol) and Benzoxazole (77mg, 0.65 mmol) were placed in a vial and 2 mL of dioxane was added. After addition the mixture was heated in absence of oxygen during 1h at 140⁰C. Then the reaction mixture was cooled to r.t. and filtered in absence of oxygen to a new vial. CuI (5 mg, 0.025mmol) and ^tBuOLi (56mg, 0.7mmol) were added again and the mixture was heated during 16h at 140⁰C. After this time the reaction mixture was cooled to r.t., quenched with 10 mL of water and 1 mL of 1M HCl. The resulting solution mixture was then extracted with CH₂Cl₂ (3 times, 10 mL each), dried over Na₂SO₄, filtered, and subjected to GC analysis. 60 μL of dodecane was used as an internal standard. The yield of coupling product is ca. 30% (instead of ca. 80% in without filtration of heterogeneous mixture after 1 h).

Comments: Filtration of insoluble solids during the reaction decreased the yield of coupling, suggesting that the active catalyst is insoluble.

3. D₂O quenching experiment

Conditions: [^{13}C MeNN₂)Ni-Cl] (9 mg, 0.025 mmol), CuI (5 mg, 0.025mmol), ^tBuOLi (56mg, 0.7mmol), Bu-I (57.1μl, 0.5 mmol) and Benzoxazole (77mg, 0.65 mmol) were placed in a vial and 1.5 mL of dioxane-D₈ was added. After addition the mixture was heated in absence of oxygen during 1h at 140⁰C. After this time the reaction mixture was cooled to r.t., filtered and its NMR-spectrum was recorded. Then D₂O (91μl, 5mmol, 99.9% D) was added and the NMR-spectrum was recorded again after 15 minutes and overnight (ca. 12h).

Results: 2-D-benzoxazole was produced. This can be seen from the relative intensities of the ¹H NMR signals corresponding to the 2-H and the protons on the phenyl ring. As shown in Figure

S2, after 1 hour of reaction and before D₂O quenching, the ratio of integrations is ca. 1 to 3.7, which is close to the theoretical ratio of 1 to 4 within experimental errors (Figure S1, top). 15 minute after D₂O quenching, the ratio turned into ca. 1 to 5.5 (Figure S1, middle), which was due to the formation of 2-D-benzoxazole (ca. 40% relative to unreacted starting materials). When compared to an internal standard (e.g., from proton residue of d₈-dioxane), the intensity of the ¹H signal from 2-H remained the same after D₂O quenching, suggesting that 2-H-benzoxazole did not undergo H/D exchange during the 15-minute time period. This H/D exchange did occur when the same mixture was allowed to stay at room temperature overnight, as shown in Figure S1, bottom.

Comments: These results suggest that anionic azole intermediates exist during the catalysis. These intermediates might exist in the 2-metallated cyclic azole form, or in the ring-opened isocyano phenolate/enolate form, or as an equilibrium mixture. Addition of D₂O converted these anionic species back to 2-D-azoles. For a discussion of equilibrium between metallated oxazole(thiazole) derivatives and their acyclic isomers, see Hiff et al. Chem. Ber./Recueil 1997, 130, 1213-1221.

Figure S1. NMR spectra before, 15 minutes after, and 12 hours after the D₂O quenching experiment as described in the previous paragraphs.

4. H/D isotopic effect measurement

Conditions: Identical reactions conditions including the reaction scale and time were employed. Two independent runs were carried out. To ensure a relatively high conversion in 1 hour, 20% catalyst loading was used. [$(^{\text{Me}}\text{NN}_2)\text{Ni-Cl}$] (36 mg, 0.1 mmol), CuI (5 mg, 0.025mmol), $^t\text{BuOLi}$ (56mg, 0.7mmol), Bu-I (68.6 μl , 0.6 mmol) and Benzoxazole-H (60mg, 0.5 mmol) or Benzoxazole-D (60mg, 0.5 mmol, contains 89.4% D) were placed in a vial and 1.5 mL of dioxane was added. After addition the mixture was heated in absence of oxygen during 1h at 140 $^{\circ}\text{C}$. After this time the reaction mixture was cooled to r.t., quenched with 10 mL of water and 1 mL of 1M HCl. The resulting solution mixture was then extracted with CH_2Cl_2 (3 times, 10

mL each), dried over Na₂SO₄, filtered, and subjected to GC analysis. 60 µL of dodecane was used as an internal standard.

Results: Two trials were made. For the coupling of 2-H benzoxazole, the yields were 49% and 50%, respectively. For the coupling of 2-D benzoxazole, the yields were 46% and 44%, respectively. The difference in yields is very small and almost no isotopic effect is detected.

5. Following the catalysis by NMR

Experimental conditions: [(^{Me}NN₂)Ni-Cl] (36 mg, 0.1 mmol), CuI (5 mg, 0.025mmol), ^tBuOLi (56mg, 0.7mmol), Bu-I (57.1µl, 0.5 mmol) and Benzoxazole (77mg, 0.65 mmol) were placed in a vial and 1.5 mL of dioxane-D8 was added. After addition the mixture was heated in absence of oxygen during 1h or 16h at 140⁰C. After this time the reaction mixture was cooled to r.t., filtered and its NMR-spectrum was measured.

Results: free ligand H^{Me}NN₂ was the only ligand-containing species observed after 1h (ca. 50% conversion) and after completion of reaction (16h).

Figure S2. Comparison of NMR spectra of ligand $\text{H}^{\text{Me}}\text{NN}_2$ (top) and catalysis mixture (bottom).

Detail descriptions for products

2-butylbenzo[d]oxazole:

Eluated from the column with hexane-diethyl ether (20:1) in 78% yield as a slightly yellow liquid:

¹H NMR (400MHz, CDCl₃): 7.67 (m, 1H), 7.47 (m, 1H), 7.29 (m, 2H), 2.93 (t, *J* = 7.6 Hz, 2H), 1.87 (m, 2H), 1.46 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): 167.3, 150.7, 141.3, 124.3, 123.9, 119.4, 110.2, 28.8, 28.3, 22.2, 13.6.

HR-MS: calculated for (C₁₁H₁₄NO, M+H), 176.1075; found, 176.1067.

2-(cyclohexylmethyl)benzo[d]oxazole (table 1, entry 1):

Eluated from the column with hexane-diethyl ether (10:1) in 79% yield as a slightly yellow liquid:

¹H NMR (400MHz, CDCl₃): 7.67 (m, 1H), 7.47 (m, 1H), 7.29 (m, 2H), 2.81 (d, *J* = 7.0 Hz, 2H), 1.97 (m, 1H), 1.72 (m, 5H), 1.15 (m, 5H).

¹³C NMR (100 MHz, CDCl₃): 166.4, 150.7, 141.3, 124.2, 123.9, 119.4, 110.1, 36.5, 36.2, 33.0, 26.0, 25.9.

HR-MS: calculated for (C₁₄H₁₈NO, M+H), 216.1388; found, 216.1386.

2-(3-phenylpropyl)benzo[d]oxazole (table 1, entry 2):

Eluated from the column with hexane-diethyl ether (10:1) in 70% yield as a slightly yellow liquid:

¹H NMR (400MHz, CDCl₃): 7.70 (m, 1H), 7.49 (m, 1H), 7.26 (m, 7H), 2.96 (t, *J* = 7.6 Hz, 2H), 2.78 (t, *J* = 7.3 Hz, 2H), 2.24 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): 166.9, 150.7, 141.1, 141.0, 128.4, 128.3, 126.0, 124.4, 124.0, 119.4, 110.2, 35.0, 28.1, 27.9.

HR-MS: calculated for (C₁₆H₁₆NO, M+H), 238.1232; found, 238.1241.

2-(4-chlorophenethyl)benzo[d]oxazole (table 1, entry 3):

Eluated from the column with hexane-diethyl ether (10:1) in 75% yield as a white solid:

¹H NMR (400MHz, CDCl₃): 7.68 (m 1H), 7.48 (m 1H), 7.31 (m 2H), 7.25 (m 2H), 7.17 (m 2H), 3.20 (s 4H).

¹³C NMR (100 MHz, CDCl₃): 165.7, 150.6, 141.1, 138.4, 132.2, 129.5, 128.6, 124.5, 124.1, 119.5, 110.2, 32.0, 30.2.

HR-MS: calculated for (C₁₅H₁₃NOCl, M+H), 258.0686; found, 258.0695.

2-(3-phenoxypropyl)benzo[d]oxazole (table 1, entry 4):

Eluated from the column with hexane-diethyl ether (4:1) in 84% yield as a slightly yellow liquid:

¹H NMR (400MHz, CDCl₃): 7.70 (m, 1H), 7.50 (m, 1H), 7.28 (m, 4H), 6.92 (m, 3H), 4.12 (t, *J* = 5.9 Hz, 2H), 3.17 (t, *J* = 7.3 Hz, 2H), 2.40 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): 166.4, 158.6, 150.7, 141.2, 129.4, 124.5, 124.0, 120.7, 119.5, 114.4, 110.2, 66.3, 26.3, 25.3.

HR-MS: calculated for ($\text{C}_{16}\text{H}_{16}\text{NO}_2$, $\text{M}+\text{H}$), 254.1181; found, 254.1169.

2-(3-(phenylthio)propyl)benzo[d]oxazole (table 1, entry 5):

Eluated from the column with hexane-diethyl ether (4:1) in 65% yield as a slightly yellow liquid:

^1H NMR (400MHz, CDCl_3): 7.68 (m, 1H), 7.48 (m, 1H), 7.31 (m, 6H), 7.18 (m, 1H), 3.08 (q, $J = 7.3$ Hz, 4H), 2.23 (quint, $J = 7.0$ Hz, 2H).

^{13}C NMR (100 MHz, CDCl_3): 166.0, 150.6, 141.1, 135.7, 129.3, 128.8, 126.0, 124.5, 124.0, 119.4, 110.2, 32.8, 27.2, 25.9.

HR-MS: calculated for ($\text{C}_{16}\text{H}_{16}\text{NOS}$, $\text{M}+\text{H}$), 270.0953; found, 270.0953.

6-(benzo[d]oxazol-2-yl)-2,2-diphenylhexanenitrile (table 1, entry 6):

Eluated from the column with hexane-diethyl ether (2:1) in 56% yield as a yellow oil:

¹H NMR (400MHz, CDCl₃): 7.67 (m, 1H), 7.37 (m, 13H), 2.92 (t, *J* = 7.6 Hz, 2H), 2.46 (m, 2H), 1.98 (m, 2H), 1.60 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): 166.4, 150.6, 141.1, 139.9, 128.8, 127.8, 126.7, 124.4, 124.0, 122.2, 119.4, 110.2, 51.5, 39.1, 28.1, 26.4, 25.1.

HR-MS: calculated for (C₂₅H₂₃N₂O, M+H), 367.1810; found, 367.1794.

2-(5-(1,3-dioxan-2-yl)pentyl)benzo[d]oxazole (table 1, entry 7):

Eluated from the column with hexane-diethyl ether (2:1) in 86% yield as a yellow oil:

¹H NMR (400MHz, CDCl₃): 7.65 (m, 1H), 7.46 (m, 1H), 7.28 (m, 2H), 4.49 (t, *J* = 5.0 Hz, 1H), 4.07 (dd, *J*₁ = 11.7 Hz, *J*₂ = 5.0 Hz, 2H), 3.73 (m, 2H), 2.92 (t, *J* = 7.9 Hz, 2H), 2.06 (m, 1H), 1.88 (m, 2H), 1.59 (m, 2H), 1.40 (m, 5H).

¹³C NMR (100 MHz, CDCl₃): 167.1, 150.7, 141.3, 124.3, 123.9, 119.4, 110.1, 102.1, 66.8, 34.9, 28.9, 28.4, 26.6, 25.7, 23.5.

HR-MS: calculated for (C₁₆H₂₂NO₃, M+H), 276.1600; found, 276.1601.

2-(pent-4-enyl)benzo[d]oxazole (table 1, entry 8):

Eluated from the column with hexane-diethyl ether (10:1) in 70% yield as a slightly yellow liquid:

¹H NMR (400MHz, CDCl₃): 7.67 (m, 1H), 7.47 (m, 1H), 7.28 (m, 2H), 5.82 (m, 1H), 5.04 (m, 2H), 2.93 (t, *J* = 7.6 Hz, 2H), 2.20 (q, *J* = 7.0 Hz, 2H), 1.99 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): 166.9, 150.7, 141.3, 137.3, 124.3, 123.9, 119.4, 115.5, 110.1, 32.9, 27.8, 25.7.

HR-MS: calculated for (C₁₂H₁₄NO, M+H), 188.1075; found, 188.1083.

6-(benzo[d]oxazol-2-yl)hexyl benzoate (table 1, entry 9):

Eluated from the column with hexane-diethyl ether (3:1) in 71% yield as a yellow oil:

¹H NMR (400MHz, CDCl₃): 8.03 (d, *J* = 7.6 Hz, 2H), 7.67 (m, 1H), 7.54 (t, *J* = 6.7 Hz, 1H), 7.44 (m, 3H), 7.29 (m, 2H), 4.32 (t, *J* = 6.5 Hz, 2H), 2.94 (t, *J* = 7.3 Hz, 2H), 1.93 (m, 2H), 1.79 (m, 2H), 1.54 (m, 4H).

¹³C NMR (100 MHz, CDCl₃): 167.0, 166.5, 150.7, 141.3, 132.7, 130.3, 129.4, 128.2, 124.3, 124.0, 119.4, 110.2, 64.8, 28.7, 28.5, 28.4, 26.5, 25.6.

HR-MS: calculated for (C₂₀H₂₂NO₃, M+H), 324.1600; found, 324.1588.

1-(4-(3-(benzo[d]oxazol-2-yl)propyl)phenyl)propan-1-one (table 1, entry 10):

Eluated from the column with hexane-diethyl ether (3:1) in 44% yield as a yellow oil:

¹H NMR (400MHz, CDCl₃): 7.89 (d, *J* = 8.2 Hz, 2H), 7.67 (m, 1H), 7.47 (m, 1H), 7.30 (m, 4H), 2.97 (m, 4H), 2.82 (t, *J* = 7.3 Hz, 2H), 2.25 (m, 2H), 1.22 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): 200.4, 166.4, 150.7, 146.5, 141.2, 135.0, 128.6, 128.2, 124.5, 124.1, 119.5, 110.2, 35.0, 31.6, 27.8, 27.7, 8.2.

HR-MS: calculated for (C₁₉H₂₀NO₂, M+H), 294.1494; found, 294.1483.

2-(3-(2-methyl-1H-indol-1-yl)propyl)benzo[d]oxazole (table 1, entry 11):

Eluated from the column with hexane-diethyl ether (2:1) in 74% yield as a yellow oil:

¹H NMR (400MHz, CDCl₃): 7.74 (m, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.51 (m, 1H), 7.34 (m, 3H), 7.17 (t, *J* = 7.0 Hz, 1H), 7.11 (m, 1H), 6.29 (s, 1H), 4.27 (t, *J* = 7.3 Hz, 2H), 2.97 (t, *J* = 7.0 Hz, 2H), 2.45 (s, 3H), 2.41 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): 165.8, 150.6, 141.1, 136.5, 136.1, 128.0, 124.6, 124.1, 120.5, 119.6, 119.5, 119.2, 110.2, 108.8, 100.2, 41.9, 26.6, 25.6, 12.6.

HR-MS: calculated for (C₁₉H₁₉N₂O, M+H), 291.1497; found, 291.1483.

2-(3-(9H-carbazol-9-yl)propyl)benzo[d]oxazole (table 1, entry 12):

Eluated from the column with hexane-diethyl ether (10:1 to 3:1) in 75% yield as a yellow solid:

¹H NMR (400MHz, CDCl₃): 8.11 (d, *J* = 7.6 Hz, 2H), 7.73 (m, 1H), 7.44 (m, 5H), 7.29 (m, 4H), 4.54 (t, *J* = 7.0 Hz, 2H), 2.97 (t, *J* = 7.3 Hz, 2H), 2.53 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): 165.9, 150.6, 140.9, 140.2, 125.7, 124.7, 124.2, 122.9, 120.3, 119.5, 118.9, 110.2, 108.5, 41.8, 25.8, 25.6.

HR-MS: calculated for (C₂₂H₁₉N₂O, M+H), 327.1497; found, 327.1497.

2-(3-(furan-2-yl)propyl)benzo[d]oxazole (table 1, entry 13):

Eluated from the column with hexane-diethyl ether (10:1) in 73% yield as a slightly yellow liquid:

¹H NMR (400MHz, CDCl₃): 7.68 (m, 1H), 7.48 (m, 1H), 7.30 (m, 3H), 6.28 (m, 1H), 6.05 (m, 1H), 2.98 (t, *J* = 7.3 Hz, 2H), 2.80 (t, *J* = 7.0 Hz, 2H), 2.25 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): 166.6, 154.7, 150.7, 141.0, 124.5, 124.1, 119.4, 110.2, 110.0, 105.4, 27.8, 27.2, 25.0.

HR-MS: calculated for (C₁₄H₁₄NO₂, M+H), 228.1024; found, 228.1022.

2-(3-(9H-carbazol-9-yl)propyl)-5-phenyloxazole (table 2, entry 1):

Eluated from the column with hexane-diethyl ether (1:1) in 74% yield as a yellow solid:

¹H NMR (400MHz, CDCl₃): 8.18 (d, *J* = 7.6 Hz, 2H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.49 (m, 6H), 7.34 (m, 4H), 4.49 (t, *J* = 6.7 Hz, 2H), 2.88 (t, *J* = 7.0 Hz, 2H), 2.47 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): 163.0, 151.0, 140.1, 128.7, 128.0, 127.8, 125.6, 123.8, 122.7, 121.6, 120.2, 118.8, 108.4, 41.6, 25.6, 25.3.

HR-MS: calculated for (C₂₄H₂₁N₂O, M+H), 353.1654; found, 353.1653.

5-(4-methoxyphenyl)-2-octyloxazole (table 2, entry 2):

Eluated from the column with hexane-diethyl ether (2:1) in 86% yield as a yellow solid:

¹H NMR (400MHz, CDCl₃): 7.51 (d, *J* = 8.8 Hz, 2H), 7.07 (s, 1H), 6.91 (d, *J* = 8.5 Hz, 2H), 3.80 (s, 3H), 2.78 (t, *J* = 7.6 Hz, 2H), 1.79 (m, 2H), 1.22-1.42 (m, 10H), 0.86 (t, *J* = 6.2 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): 163.9, 159.3, 150.6, 125.3, 121.0, 120.0, 114.1, 55.1, 31.7, 29.1, 29.06, 29.05, 28.1, 26.9, 22.5, 14.0.

HR-MS: calculated for (C₁₈H₂₆NO₂, M+H), 288.1964; found, 288.1977.

5-(4-methoxyphenyl)-2-(3-phenoxypropyl)oxazole (table 2, entry 3):

Eluated from the column with hexane-diethyl ether (1:1) in 81% yield as a yellow solid:

¹H NMR (400MHz, CDCl₃): 7.52 (d, *J* = 7.6 Hz, 2H), 7.28 (t, *J* = 7.3 Hz, 2H), 7.11 (s, 1H), 6.93 (m, 5H), 4.08 (t, *J* = 6.2 Hz, 2H), 3.82 (s, 3H), 3.04 (t, *J* = 7.3 Hz, 2H), 2.31 (quint, *J* = 7.0 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃): 162.9, 159.4, 158.7, 150.9, 129.3, 125.4, 120.9, 120.6, 120.1, 114.3, 114.1, 66.3, 55.2, 26.6, 24.8.

HR-MS: calculated for (C₁₉H₂₀NO₃, M+H), 310.1443; found, 310.1427.

5-(4-bromophenyl)-2-(cyclohexylmethyl)oxazole (table 2, entry 4):

Eluted from the column with hexane-diethyl ether (3:1) in 76% yield as a dark red oil:

¹H NMR (400MHz, CDCl₃): 7.52 (m, 2H), 7.46 (m, 2H), 7.23 (s, 1H), 2.69 (d, *J* = 7.0 Hz, 2H), 1.75 (m, 6H), 1.24 (m, 3H), 1.04 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): 164.3, 149.8, 131.9, 127.1, 125.3, 122.2, 121.7, 36.7, 35.8, 32.9, 26.1, 26.0.

HR-MS: calculated for (C₁₆H₁₉NOBr, M+H), 320.0650 and 322.0631; found, 320.0640 and 322.0630.

2-butylbenzo[d]thiazole (table 2, entry 5):

Eluated from the column with hexane-diethyl ether (15:1) in 79% yield as a yellow oil:

¹H NMR (400MHz, CDCl₃): 7.97 (d, *J* = 7.9 Hz, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.44 (m, 1H), 7.34 (m, 1H), 3.12 (t, *J* = 7.6 Hz, 2H), 1.87 (m, 2H), 1.47 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): 172.3, 153.2, 135.1, 125.7, 124.5, 122.4, 121.4, 34.0, 31.7, 22.2, 13.7.

HR-MS: calculated for (C₁₁H₁₄NS, M+H), 192.0847; found, 192.0844.

2-(pent-4-enyl)benzo[d]thiazole (table 2, entry 6):

Eluated from the column with hexane-diethyl ether (10:1) in 74% yield as a yellow oil:

¹H NMR (400MHz, CDCl₃): 7.97 (d, *J* = 7.9 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.33 (m, 1H), 5.82 (m, 1H), 5.05 (m, 2H), 3.11 (m, 2H), 2.20 (q, *J* = 7.0 Hz, 2H), 1.98 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): 171.7, 153.1, 137.4, 135.0, 125.7, 124.5, 122.4, 121.3, 115.4, 33.5, 32.9, 28.6.

HR-MS: calculated for ($\text{C}_{12}\text{H}_{14}\text{NS}$, $\text{M}+\text{H}$), 204.0847; found, 204.0842.

6-(benzo[d]thiazol-2-yl)hexyl benzoate (table 2, entry 7):

Eluted from the column with hexane-diethyl ether (4:1) in 72% yield as a yellow solid:

^1H NMR (400MHz, CDCl_3): 8.04 (d, $J = 7.3$ Hz, 2H), 7.97 (d, $J = 7.6$ Hz, 1H), 7.83 (d, $J = 7.9$ Hz, 1H), 7.55 (t, $J = 7.0$ Hz, 1H), 7.44 (m, 3H), 7.34 (m, 1H), 4.32 (t, $J = 6.5$ Hz, 2H), 3.13 (t, $J = 7.6$ Hz, 2H), 1.92 (m, 2H), 1.79 (m, 2H), 1.53 (m, 4H).

^{13}C NMR (100 MHz, CDCl_3): 172.0, 166.6, 153.1, 135.0, 132.7, 130.3, 129.4, 128.2, 125.8, 124.6, 122.4, 121.4, 64.8, 34.1, 29.5, 28.7, 28.5, 25.7.

HR-MS: calculated for ($\text{C}_{20}\text{H}_{22}\text{NO}_2\text{S}$, $\text{M}+\text{H}$), 340.1371; found, 340.1369.

4,5-dimethyl-2-(3-phenylpropyl)thiazole (table 2, entry 8):

Eluated from the column with hexane-diethyl ether (5:1) in 76% yield as a yellow liquid:

¹H NMR (400MHz, CDCl₃): 7.28 (m, 2H), 7.19 (d, *J* = 7.0 Hz, 3H), 2.92 (t, *J* = 7.6 Hz, 2H), 2.71 (t, *J* = 7.6 Hz, 2H), 2.30 (s, 6H), 2.07 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): 166.0, 147.1, 141.4, 128.3, 128.2, 125.7, 124.8, 35.1, 32.7, 31.6, 14.5, 11.1.

HR-MS: calculated for (C₁₄H₁₈NS, M+H), 232.1160; found, 232.1161.

4,5-dimethyl-2-(3-(2-methyl-1H-indol-1-yl)propyl)thiazole (table 2, entry 9):

Eluated from the column with hexane-diethyl ether (2:1) in 85% yield as a yellow oil:

¹H NMR (400MHz, CDCl₃): 7.53 (d, *J* = 7.6 Hz, 1H), 7.27 (m, 1H), 7.14 (t, *J* = 6.7 Hz, 1H), 7.07 (m, 1H), 6.25 (s, 1H), 4.17 (t, *J* = 7.3 Hz, 2H), 2.96 (t, *J* = 7.6 Hz, 2H), 2.42 (s, 3H), 2.32 (m, 6H), 2.22 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): 164.7, 147.4, 136.5, 136.1, 128.0, 125.2, 120.3, 119.6, 119.1, 108.9, 100.0, 42.2, 30.5, 29.9, 14.5, 12.6, 11.2.

HR-MS: calculated for (C₁₇H₂₁N₂S, M+H), 285.1425; found, 285.1411.

tert-butyl 4-((4,5-dimethylthiazol-2-yl)methyl)piperidine-1-carboxylate (table 2, entry 10):

Eluated from the column with hexane-diethyl ether (1:1) in 79% yield as a yellow oil:

¹H NMR (400MHz, CDCl₃): 4.06 (br., 2H), 2.78 (d, *J* = 7.0 Hz, 2H), 2.65 (br., 2H), 2.28 (m, 6H), 1.86 (m, 1H), 1.68 (d, *J* = 12.9 Hz, 2H), 1.43 (s, 9H), 1.21 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): 163.9, 154.7, 147.5, 125.1, 79.2, 43.6, 39.8, 37.2, 31.7, 28.3, 14.6, 11.1.

HR-MS: calculated for (C₁₆H₂₇N₂O₂S, M+H), 311.1793; found, 311.1798.

2-(4-bromophenethyl)thiazole (table 2, entry 11):

Eluated from the column with hexane-diethyl ether (3:1) in 60% yield as a slightly yellow liquid:

¹H NMR (400MHz, CDCl₃): 7.69 (d, *J* = 3.2 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 3.2 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 2H), 3.30 (t, *J* = 7.6 Hz, 2H), 3.08 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): 169.4, 142.3, 139.2, 131.5, 130.1, 120.1, 118.2, 35.2, 34.6.

HR-MS: calculated for (C₁₁H₁₁NSBr, M+H), 267.9796 and 269.9775; found, 267.9779 and 269.9764.

2-chloro-5-octylthiophene (table 2, entry 12):

Eluated from the column with hexane-diethyl ether (30:1) in 81% yield as a colorless oil:

¹H NMR (400MHz, CDCl₃): 6.70 (d, *J* = 3.8 Hz, 1H), 6.53 (d, *J* = 3.8 Hz, 1H), 2.71 (t, *J* = 7.3 Hz, 2H), 1.62 (m, 2H), 1.30 (m, 10H), 0.88 (t, *J* = 6.5 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): 144.7, 126.4, 125.5, 123.1, 31.8, 31.4, 30.3, 29.2, 29.1, 28.9, 22.6, 14.0.

Elemental analysis: Anal. Calcd for C₁₂H₁₉ClS: C, 62.45; H, 8.30. Found: C, 62.25; H, 8.43.

tert-butyl 4-((5-chlorothiophen-2-yl)methyl)piperidine-1-carboxylate (table 2, entry 13):

Eluated from the column with hexane-diethyl ether (10:1) in 62% yield as a colorless oil:

¹H NMR (400MHz, CDCl₃): 6.71 (d, *J* = 3.5 Hz, 1H), 6.52 (d, *J* = 3.2 Hz, 1H), 4.10 (br., 2H), 2.65 (m, 4H), 1.70 (m, 3H), 1.45 (s, 9H), 1.11 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): 154.7, 141.6, 125.6, 124.5, 79.3, 43.1, 38.3, 37.2, 31.7, 28.4.

HR-MS: calculated for (C₁₅H₂₃ClNO₂S, M+H), 316.1138; found, 316.1128.

2-butylbenzo[b]thiophene (table 2, entry 14):

Eluated from the column with hexane in 78% yield as a colorless liquid:

¹H NMR (400MHz, CDCl₃): 7.80 (d, *J* = 8.2 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.35 (m, 2H), 7.28 (m, 1H), 2.94 (t, *J* = 7.3 Hz, 2H), 1.78 (m, 2H), 1.47 (m, 2H), 1.01 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): 146.7, 140.1, 139.2, 123.9, 123.2, 122.5, 122.0, 120.3, 33.1, 30.4, 22.1, 13.8.

Elemental analysis: Anal. Calcd for C₁₂H₁₄S: C, 75.45; H, 7.42. Found: C, 75.14; H, 7.43.

2-(cyclohexylmethyl)benzo[b]thiophene (table 2, entry 15):

Eluated from the column with hexane-diethyl ether (100:1) in 72% yield as a colorless liquid:

¹H NMR (400MHz, CDCl₃): 7.77 (d, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.28 (m, 2H), 6.98 (s, 1H), 2.78 (d, *J* = 7.0 Hz, 2H), 1.73 (m, 6H), 1.23 (m, 3H), 1.00 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): 145.2, 140.1, 139.4, 123.9, 123.2, 122.5, 122.0, 121.3, 39.7, 38.6, 33.0, 26.4, 26.1.

Elemental analysis: Anal. Calcd for C₁₅H₁₈S: C, 78.21; H, 7.88. Found: C, 77.94; H, 7.59.

1-(3-(5-ethylthiophen-2-yl)propyl)-2-methyl-1H-indole (table 2, entry 16):

Eluated from the column with hexane-diethyl ether (100:1) in 66% yield as a colorless liquid:

¹H NMR (400MHz, CDCl₃): 7.53 (d, *J* = 7.3 Hz, 1H), 7.24 (m, 1H), 7.14 (t, *J* = 7.0 Hz, 1H), 7.07 (m, 1H), 6.61 (s, 2H), 6.25 (s, 1H), 4.12 (t, *J* = 7.3 Hz, 2H), 2.83 (m, 4H), 2.41 (s, 3H), 2.13 (m, 2H), 1.30 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): 145.4, 141.1, 136.5, 136.2, 128.0, 123.9, 122.7, 120.3, 119.6, 119.1, 108.9, 99.9, 42.3, 31.6, 27.5, 23.4, 15.9, 12.7.

HR-MS: calculated for (C₁₈H₂₂NS, M+H), 284.1473; found, 284.1468.

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