Abstract: A series of 2-arylbenzofurans and 2-arylbenzothiophenes was synthesized carrying three different side chains in position five. The synthesized compounds were tested for NF-κB inhibition to establish a structure activity relationship. It was found that both, the side chain in position five and the substitution pattern of the aryl moiety in position two have a significant influence on the inhibitory activity.

Keywords: NF-κB inhibition; natural product; lignans; cross-coupling; C-H activation; direct arylation

1. Introduction

Inflammation is a protective host response to infection or tissue damage (including stress or dyshomeostasis) [1,2]. Whereas an acute response resulting in the elimination of the noxious agent is beneficial, long lasting chronic inflammatory states contribute to the development of many pathologies like autoimmune, metabolic, cardiovascular and neurodegenerative diseases or cancer [2,3]. PAMPs (pathogen-associated molecular patterns) as well as DAMPs (damage-associated molecular patterns) activate pattern recognition receptors (PRR) that transduce signals to NF-κB signaling pathways [2], which play a pivotal role in chronic and acute inflammation [4]. Thus, dampen NF-κB signaling will interfere with an inflammatory response.

Krameria lappacea (Dombey), Krameriacae, is a tropical perennial shrub growing across South America. The extract of the Rhatany root was introduced into European medicine over 200 years ago as a remedy against stomach aches, diarrhea, menstrual problems, nose bleeds and oropharyngeal inflammation [5,6]. In a study on constituents of the Rhatany root, the group of Stuppner isolated eleven lignan derivatives from the dichloromethane extract of the root (Figure 1) [7].

These isolated lignan derivatives were pharmacologically characterized in topical anti-inflammatory in vivo experiments [8]. Two of the most potent compounds, 2-(2-hydroxy-4-methoxyphenyl)-5-(3-hydroxypropyl)benzofuran 1 and (+)-conocarpan 3 (Figure 1) inhibited edema development and infiltration by neutrophils time-dependently and comparably to indomethacin. In addition, all lignans were tested in vitro for their potential to inhibit the activation of the NF-κB signaling pathway and the activity of the pro-inflammatory enzymes COX-1, COX-2, 5-LO and mPGES-1. Determination of the IC50 values for all compounds showed that inhibition of NF-κB is the most relevant mechanism likely contributing to the observed in vivo activity [8].
2. Materials and Methods

2.1. Chemical Synthesis

2.1.1. Synthesis of 5-Allylbenzo[b]furan (14)

From 5-bromobenzo[b]furan 12: Compound 12 (98 mg, 0.5 mmol), allyl-B(pin) (140 µL, 0.75 mmol, 1.5 equiv.), K$_2$CO$_3$ (138 mg, 1.0 mmol, 2.0 equiv.) and Pd(PPh$_3$)$_2$Cl$_2$ (18 mg, 0.025 mmol, 5 mol %) was mixed in 2 mL DMAc and at 100 °C and stirred for 6 h. The reaction mixture was then cooled to room temperature and filtered through celite. The organic phase was washed with saturated aq. NH$_4$Cl and then diluted with 15 mL diethyl ether or ethyl acetate (depending on the polarity of the product) and stirred at 140 °C and SPhos (16.4 mg, 0.08 mmol, 0.08 equiv.) was mixed in 2 mL of degassed DMAc. The mixture was washed with saturated aq. NH$_4$Cl and a last time with 10 mL brine and then dried over Na$_2$SO$_4$ and the solvent was evaporated under reduced pressure to obtain coupling product 14 (67 mg, colorless oil), 85% yield.

From 5-chlorobenzo[b]furan 17: Compound 17 (76 mg, 0.5 mmol), allyl-B(pin) (126 mg, 140 µL, 0.75 mmol, 1.5 equiv.), Cs$_2$CO$_3$ (326 mg, 1.0 mmol, 2.0 equiv.), SPhos (21 mg, 0.05 mmol, 10 mol %) and Pd$_2$(dba)$_3$ (23 mg, 0.025 mmol, 5 mol %) was mixed in 2 mL DMAc and at 100 °C and stirred for 6 h. The reaction mixture was then cooled to room temperature and filtered through celite and washed with EtOAc. The product was washed with saturated aq. NH$_4$Cl and a last time with 10 mL brine. Then dried over Na$_2$SO$_4$ and the solvent was evaporated under reduced pressure to obtain coupling product 14 (54 mg, colorless oil), 68% yield.

$^1$H-NMR (200 MHz, CDCl$_3$) δ (ppm) 3.51 (d, $J = 6.7$ Hz, 2H), 5.08–5.17 (m, 2H), 5.95–6.15 (m, 2H), 6.73–6.75 (m, 1H), 7.16 (d, $J = 8.6$ Hz, 1H), 7.44–7.48 (m, 2H), 7.62 (d, $J = 2.1$ Hz, 1H). $^{13}$C-NMR (50 MHz, CDCl$_3$) δ (ppm) 40.1, 106.4, 111.1, 115.6, 120.7, 125.1, 127.6, 134.5, 138.0, 145.1, 153.7. MS analyst, m/z (Int.) 158(100), 157(46), 129(82), 128(50), 115(18), 102(10), 89(10), 77(22), 63(15).

2.1.2. General Procedure of C-H Activation Reaction on 5-Chlorobenzo[b]furan (17)

Procedure A: Benzo-fused starting material (1.0 mmol, 1.0 equiv.), aryl bromide (1.5 mmol, 1.5 equiv.), cesium pivalate (350 mg, 1.5 mmol, 1.5 equiv.), Pd(OAc)$_2$ (9 mg, 0.04 mmol, 0.04 equiv.) and SPhos (16.4 mg, 0.08 mmol, 0.08 equiv.) was mixed in 2 mL of degassed DMAc. The mixture was stirred at 140 °C for 24 h in argon atmosphere. The reaction mixture was cooled to room temperature and then diluted with 15 mL diethyl ether or ethyl acetate (depending on the polarity of the product) and filtered through a pad of celite. The organic phase was washed with saturated NH$_4$Cl solution, once with brine and then dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure.
Purification was performed on silica gel eluting with LP or LP/EtOAc mixtures (depending on the polarity of the product).

2.1.3. 5-Chloro-2-(4-(methoxymethoxy)phenyl)benzo[\(b\)]furan (18a)

Prepared according to the general procedure A. mp 138–141 °C. \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 3.50 (s, 3H), 5.22 (s, 2H), 6.82 (s, 1H), 7.09–7.13 (m, 2H), 7.19 (dd, \(J = 8.7, 2.1\) Hz, 1H), 7.39 (d, \(J = 8.7\) Hz, 1H), 7.50 (d, \(J = 2.1\) Hz, 1H), 7.76 (m, 2H). \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 56.1, 94.3, 99.5, 111.9, 116.5 (2C), 120.1, 123.8, 123.9, 126.5 (2C), 128.4, 130.8, 153.1, 157.4, 157.9. HR-MS analyst [M + H]\(^+\) m/z (predicted) = 289.0631, m/z (measured) = 289.0636, difference = –1.90 ppm.

2.1.4. 5-Chloro-2-(4-methoxyphenyl)benzo[\(b\)]furan (18c)

Prepared according to the general procedure A. mp 144–146 °C. \(^1\)H-NMR (200 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 3.86 (s, 3H), 6.81 (s, 1H), 6.95–7.00 (m, 2H), 7.18 (dd, \(J = 8.7, 2.1\) Hz, 1H), 7.39 (d, \(J = 8.4\) Hz, 1H), 7.50 (d, \(J = 2.1\) Hz, 1H), 7.76–7.80 (m, 2H). \(^{13}\)C-NMR (50 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 55.4, 99.2, 111.9, 114.3 (2C), 120.1, 122.8, 123.8, 126.6 (2C), 128.3, 130.9, 153.1, 157.5, 160.3.

2.1.5. 5-Chloro-2-(3,5-dimethoxyphenyl)benzo[\(b\)]furan (18d)

Prepared according to the general procedure A. \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 3.68 (s, 6H), 6.48 (t, \(J = 2.3\) Hz, 1H), 6.93 (d, \(J = 0.8\) Hz, 1H), 6.99 (d, \(J = 2.3\) Hz, 2H), 7.23 (dd, \(J = 8.7, 2.1\) Hz, 1H), 7.42 (d, \(J = 8.7\) Hz, 1H), 7.53 (d, \(J = 2.1\) Hz, 1H). \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 55.5 (2C), 101.3, 101.4 (2C), 103.2, 112.1, 120.5, 124.5, 128.5, 130.5, 131.7, 153.2, 157.2, 161.2 (2C).

2.1.6. 5-Chloro-2-phenylbenzo[\(b\)]furan (18e)

Prepared according to the general procedure A. mp 125–128 °C. \(^1\)H-NMR (200 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 6.96 (s, 1H), 7.20–7.55 (m, 6H), 7.81–7.87 (m, 2H). \(^{13}\)C-NMR (50 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 100.8, 112.1, 120.4, 124.4, 125.0 (2C), 128.5, 128.8 (2C), 129.0, 130.0, 130.6, 153.2, 157.4.

2.1.7. 5-Chloro-2-(4-fluorophenyl)benzo[\(b\)]furan (18f)

Prepared according to the general procedure A. mp 119–122 °C. \(^1\)H-NMR (200 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 6.86 (s, 1H), 7.09–7.24 (m, 3H), 7.38–7.52 (m, 2H), 7.76–7.83 (m, 2H). \(^{13}\)C-NMR (50 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 100.5, 112.1, 116.0 (d, \(J_{C-F} = 21.9\) Hz), 120.4, 124.4, 126.3 (d, \(J_{C-F} = 3.4\) Hz), 126.9 (d, \(J_{C-F} = 8.3\) Hz, 2C), 128.6, 130.5, 153.2, 156.5, 163.1 (d, \(J_{C-F} = 247.9\) Hz).

2.1.8. 5-Chloro-2-(4-(difluoromethyl)phenyl)benzo[\(b\)]furan (18g)

Prepared according to the general procedure A. mp 121–124 °C. \(^1\)H-NMR (200 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 6.69 (t, \(J_{H,F} = 56.4\) Hz, 1H), 7.02 (s, 1H), 7.26 (dd, \(J = 8.7, 2.1\) Hz, 1H), 7.44 (d, \(J = 8.7\) Hz, 1H), 7.55–7.62 (m, 3H), 7.90–7.93 (m, 2H). \(^{13}\)C-NMR (50 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 102.1, 112.2, 114.4 (t, \(J_{C-F} = 237.6\) Hz), 120.7, 125.0, 125.2 (2C), 126.1 (t, \(J_{C-F} = 6.1\) Hz), 128.7, 130.3, 132.2, 134.6 (t, \(J_{C-F} = 22.5\) Hz), 153.4, 156.1. HR-MS analyst [M + H]\(^+\) m/z (predicted) = 279.0388, m/z (measured) = 279.0392, difference = –1.62 ppm.

2.1.9. 5-Chloro-2-(2-chlorophenyl)benzo[\(b\)]furan (18h)

Prepared according to the general procedure A. \(^1\)H-NMR (200 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 7.26–7.54 (m, 6H), 7.61 (d, \(J = 1.9\) Hz, 1H), 8.04 (dd, \(J = 7.7, 1.8\) Hz, 1H). \(^{13}\)C-NMR (50 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 106.8, 112.0, 120.9, 125.1, 127.0, 128.4, 128.5, 129.0, 129.5, 130.4, 130.9, 131.5, 152.5, 153.4.

2.1.10. 5-Chloro-2-(4-(methoxymethoxy)phenyl)benzo[\(b\)]thiophene (22a)

Prepared according to the general procedure A. mp 175–177 °C. \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 3.51 (s, 3H), 5.22 (s, 2H), 7.09–7.12 (m, 2H), 7.25 (dd, \(J = 8.7, 2.0\) Hz, 1H), 7.34 (s, 1H), 7.60–7.63 (m, 2H), 7.69–7.71 (m, 2H). \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 56.1, 94.4, 116.7 (2C),
2.1.11. 5-Allyl-2-(4-methoxyphenyl)benzo[b]thiophene (22c)

Prepared according to the general procedure A. mp 163–165 °C. \(^1\)H-NMR (200 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 3.86 (s, 3H), 6.96 (d, \(J = 8.8\) Hz, 2H), 7.21–7.26 (m, 1H), 7.34 (s, 1H), 7.63 (d, \(J = 8.7\) Hz, 2H), 7.68–7.72 (m, 2H), \(^{13}\)C-NMR (100 MHz, benzene-d\(_6\)) \(\delta\) (ppm) = 54.6, 114.5 (2C), 118.6, 122.3, 123.4, 124.5, 127.7, 127.9 (2C), 130.6, 137.4, 141.3, 146.4, 160.1. HR-MS analyst \([M + H]^+\) \(m/z\) (predicted) = 275.0297, \(m/z\) (measured) = 275.0300, difference = 0.02 ppm.

2.1.12. General Procedure of the Suzuki-Miyaura Coupling of Chloro Benzo-Fused Derivatives

Procedure B: 5-chloro benzo-fused (1.0 mmol, 1.0 equiv.), allylboronic acid pinacol ester (1.5 mmol, 1.5 equiv.) and SPhos (41 mg, 0.1 mmol, 0.1 equiv.) was mixed in 2 mL of dried dioxane. The mixture was stirred at 100 °C for 5 h in argon atmosphere. The reaction mixture was cooled to room temperature and then diluted with 15 mL diethyl ether or ethyl acetate (depending on the polarity of the product) and filtered through a pad of celite. The organic phase was washed with saturated NH\(_4\)Cl solution, once with brine and then dried over Na\(_2\)SO\(_4\). The solvent was removed under reduced pressure. Purification was performed on silica gel eluting with LP or LP/EtOAc mixtures (depending on the polarity of the product).

2.1.13. 5-Allyl-2-(4-(methoxymethoxy)phenyl)benzo[b]furan (16a)

Prepared according to the general procedure B. mp 126–129 °C. \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 3.47–3.51 (m, 5H), 3.76 (s, 6H), 4.96–5.03 (m, 2H), 5.92 (ddt, \(J = 8.4, 1.7\) Hz, 1H), 7.01 (dd, \(J = 8.4, 1.7\) Hz, 1H), 7.27–7.34 (m, 2H). \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 40.2, 55.4, 99.6, 110.7, 114.3 (2C), 115.5, 120.2, 123.5, 124.6, 126.4 (2C), 129.7, 134.6, 138.1, 153.5, 156.3, 160.0. HR-MS analyst \([M + H]^+\) \(m/z\) (predicted) = 295.1329, \(m/z\) (measured) = 295.1323, difference = 0.17 ppm.

2.1.14. 5-Allyl-2-(4-methoxyphenyl)benzo[b]furan (16c)

Prepared according to the general procedure B. mp 130–132 °C. \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 3.49 (d, \(J = 6.6\) Hz, 2H), 3.86 (s, 3H), 5.07–5.17 (m, 2H), 6.05 (d, \(J = 16.8, 10.1, 6.7\) Hz, 1H), 6.84 (s, 1H), 6.93–7.00 (m, 2H), 7.09 (dd, \(J = 8.4, 1.7\) Hz, 1H), 7.34–7.40 (m, 2H), 7.77–7.82 (m, 2H). \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 40.2, 55.4, 99.6, 110.7, 114.3 (2C), 115.5, 120.2, 123.5, 124.6, 126.4 (2C), 129.7, 134.6, 138.1, 153.5, 156.3, 160.0. HR-MS analyst \([M + H]^+\) \(m/z\) (predicted) = 265.1223, \(m/z\) (measured) = 265.1221, difference = 0.02 ppm.

2.1.15. 5-Allyl-2-(3,5-dimethoxyphenyl)benzo[b]furan (16d)

Prepared according to the general procedure B. \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 3.37 (d, \(J = 6.7\) Hz, 2H), 3.76 (s, 6H), 4.98–5.03 (m, 2H), 5.92 (ddt, \(J = 16.8, 10.1, 6.7\) Hz, 1H), 6.37 (t, \(J = 2.3\) Hz, 1H), 6.84 (d, \(J = 0.8\) Hz, 1H), 6.91 (d, \(J = 2.3\) Hz, 2H), 7.00 (dd, \(J = 8.4, 1.7\) Hz, 1H), 7.27–7.34 (m, 2H). \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 40.2, 55.5, 101.2, 101.8, 103.0 (2C), 110.9, 115.6, 120.5, 125.3, 129.3, 132.3, 134.8, 138.0, 153.7, 155.0, 161.1 (2C). HR-MS analyst \([M + H]^+\) \(m/z\) (predicted) = 295.1329, \(m/z\) (measured) = 295.1328, difference = 0.01 ppm.

2.1.16. 5-Allyl-2-phenylbenzo[b]furan (16e)

Prepared according to the general procedure B. mp 118–120 °C. \(^1\)H-NMR (200 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 3.37 (d, \(J = 6.5\) Hz, 2H), 4.96–5.04 (m, 2H), 5.92 (ddt, \(J = 16.8, 10.1, 6.7\) Hz, 1H), 6.83 (s, 1H), 7.00 (d, \(J = 8.4\) Hz, 1H), 7.21–7.35 (m, 5H), 7.72–7.75 (d, \(J = 7.2\) Hz, 2H). \(^{13}\)C-NMR (50 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 40.2, 101.2, 110.9, 115.6, 120.5, 124.9 (2C), 125.1, 128.5, 128.8 (2C), 129.5, 130.6, 134.7,
138.1, 153.8, 156.2. HR-MS analyst [M + H]^+ m/z (predicted) = 235.1117, m/z (measured) = 235.1119, difference = −0.8 ppm.

2.1.17. 5-Allyl-2-(4-fluorophenyl)benzo[b]furan (16f)

Prepared according to the general procedure B. mp 113–115 °C. ^1H-NMR (400 MHz, CDCl3) δ (ppm) = 3.50 (d, J = 6.6 Hz, 2H), 5.08–5.17 (m, 2H), 6.04 (ddt, J = 16.8, 10.1, 6.7 Hz, 1H), 6.90 (s, 1H), 7.11–7.16 (m, 3H), 7.39–7.45 (m, 2H), 7.81–7.84 (m, 2H). ^13C-NMR (100 MHz, CDCl3) δ (ppm) = 40.2, 100.9, 110.9, 115.6, 115.9 (d, J_{C,F} = 21.9 Hz), 120.5, 125.2, 126.7 (d, J_{C,F} = 8.5 Hz), 126.9 (d, J_{C,F} = 3.0), 129.4, 134.8, 138.0, 153.7, 155.3, 162.9 (d, J_{C,F} = 248.7). HR-MS analyst [M + H]^+ m/z (predicted) = 253.1023, m/z (measured) = 253.1034, difference = −4.1 ppm.

2.1.18. 5-Allyl-2-(4-(difluoromethyl)phenyl)benzo[b]furan (16g)

Prepared according to the general procedure B. mp 116–118 °C. ^1H-NMR (400 MHz, CDCl3) δ (ppm) = 3.50 (d, J = 6.6 Hz, 2H), 5.08–5.17 (m, 2H), 6.04 (ddt, J = 17.0, 10.4, 6.7 Hz, 1H), 6.68 (t, J_{H-F} = 56.4 Hz, 1H), 7.04 (s, 1H), 7.15 (dd, J = 8.4, 1.6 Hz, 1H), 7.41–7.60 (m, 4H), 7.90–7.94 (m, 2H). ^13C-NMR (100 MHz, CDCl3) δ (ppm) = 40.1, 102.6, 111.0, 114.5 (t, J_{C,F} = 238.8 Hz), 115.7, 120.7, 125.0 (2C), 125.8, 126.1 (t, J_{C,F} = 6.1 Hz), 129.2, 132.8, 134.1 (t, J_{C,F} = 22.4 Hz), 135.0, 137.9, 153.9, 154.9. HR-MS analyst [M + H]^+ m/z (predicted) = 285.1091, m/z (measured) = 285.1088, difference = 0.0 ppm.

2.1.19. 5-Allyl-2-(2-chlorophenyl)benzo[b]furan (16h)

Prepared according to the general procedure B. 1H-NMR (200 MHz, CDCl3) δ (ppm) = 3.57 (d, J = 6.2 Hz, 2H), 4.90–5.03 (m, 2H), 5.95 (ddt, J = 17.0, 10.4, 6.7 Hz, 1H), 6.74 (d, J = 0.7 Hz, 1H), 7.17–7.67 (m, 6H), 7.76 (d, J = 8.1 Hz, 1H). ^13C-NMR (50 MHz, CDCl3) δ (ppm) = 38.3, 104.5, 112.1, 116.3, 120.5, 124.4, 126.9, 129.1, 129.2, 129.5 (2C), 130.4, 130.7, 136.8, 138.0, 153.0, 157.1. HR-MS analyst [M + H]^+ m/z (predicted) = 269.0733, m/z (measured) = 269.0730, difference = 0.0 ppm.

2.1.20. 5-Allyl-2-(4-(methoxymethoxy)phenyl)benzo[b]thiophene (23a)

Prepared according to the general procedure B. mp 164–166 °C. ^1H-NMR (400 MHz, CDCl3) δ (ppm) = 3.46–3.48 (m, 5H), 5.07–5.13 (m, 2H), 5.19 (s, 2H), 6.01 (ddt, J = 16.8, 10.1, 6.7 Hz, 1H), 7.06–7.13 (m, 3H), 7.35 (s, 1H), 7.53 (d, J = 0.7 Hz, 1H), 7.59–7.61 (m, 2H), 7.70 (d, J = 8.2 Hz, 1H). ^13C-NMR (100 MHz, CDCl3) δ (ppm) = 40.2, 56.1, 94.4, 115.8, 116.7 (2C), 118.4, 122.1, 123.0, 125.3, 127.7 (2C), 128.3, 136.5, 137.2, 137.7, 141.3, 144.3, 157.4. HR-MS analyst [M + H]^+ m/z (predicted) = 311.1100, m/z (measured) = 311.1108, difference = −0.02 ppm.

2.1.21. 5-Allyl-2-(4-methoxyphenyl)benzo[b]thiophene (23c)

Prepared according to the general procedure B. mp 146–147 °C. ^1H-NMR (200 MHz, CDCl3) δ (ppm) = 3.49 (d, J = 6.7 Hz, 2H), 3.80 (s, 3H), 5.06–5.16 (m, 2H), 6.02 (ddt, J = 16.8, 10.2, 6.7 Hz, 1H), 6.90–6.98 (m, 2H), 7.13 (dd, J = 8.2, 1.6 Hz, 1H), 7.36 (s, 1H), 7.54 (s, 1H), 7.63 (d, J = 8.8 Hz, 2H), 7.71 (d, J = 8.2 Hz, 1H). ^13C-NMR (50 MHz, CDCl3) δ (ppm) = 40.2, 55.4, 114.3 (2C), 115.8, 118.0, 122.0, 122.9, 125.1, 127.2, 127.7 (2C), 136.4, 137.1, 137.7, 141.3, 144.4, 159.8. HR-MS analyst [M + H]^+ m/z (predicted) = 281.0995, m/z (measured) = 281.1000, difference = −0.008 ppm.

2.1.22. General Procedure for Hydroboration-Oxidation on Allyl Benzo-Fused Heterocycles

Procedure C: 5-allyl benzo-fused derivatives (0.5 mmol, 1.0 equiv.) was dissolved in 0.5 mL dry THF then the solution was cooled to 0 °C. A 1M solution of BH₃ THF (0.5 mL, 0.5 mmol, 1.0 equiv.) was added slowly. Afterwards, the reaction solution was warmed to room temperature and stirred for 24 h. On the other hand, a solution of 3M NaOH and H₂O₂ 30% was mixed in ratio of 2:3 and then cooled to 0 °C. After 24 h of reaction time, the reaction was cooled again to 0 °C and then the prepared solution of NaOH and H₂O₂ (1.20 mL, 1.2 mmol NaOH and 7.8 mmol H₂O₂) was added.
slowly. The reaction mixture was stirred at room temperature for 4 more hours, then diluted with 5 mL diethyl ether. The organic phase was washed with a saturated NH₄Cl solution for 3 times, once with brine and dried over Na₂SO₄. The solvent was removed under reduced pressure. Purification was performed on silica gel eluting with LP/EtOAc mixtures.

2.1.23. 3-(2-(4-(Methoxymethoxy)phenyl)benzo[b]furan-5-yl)propan-1-ol (19a)

Prepared according to the general procedure C. mp 155–156 °C. ¹H-NMR (200 MHz, CDCl₃) δ (ppm) = 1.33 (s, 1H), 1.88–2.01 (m, 2H), 2.81 (t, J = 7.3 Hz, 2H), 3.51 (s, 3H), 3.70 (s, J = 6.4 Hz, 2H), 5.23 (s, 2H), 6.85 (s, 1H), 7.08–7.13 (m, 3H), 7.38–7.43 (m, 2H), 7.78 (d, J = 8.7 Hz, 2H). ¹³C-NMR (50 MHz, CDCl₃) δ (ppm) = 32.0, 34.8, 56.1, 62.3, 94.4, 99.8 110.7, 116.5 (2C), 120.0, 124.4, 124.5, 126.3 (2C), 129.6, 136.3, 153.4, 156.1, 157.5. HR-MS analyst [M + H]⁺ m/z (predicted) = 313.1434, m/z (measured) = 313.1431, difference = 0.93 ppm.

2.1.24. 3-(2-(4-Methoxyphenyl)benzo[b]furan-5-yl)propan-1-ol (19c)

Prepared according to the general procedure C. mp 150–152 °C. ¹H-NMR (400 MHz, CDCl₃) δ (ppm) = 1.41 (s, 1H), 1.94 (ddt, J = 12.9, 8.9, 6.4 Hz, 2H), 2.80 (t, J = 7.2 Hz, 2H), 3.70 (t, J = 6.4 Hz, 2H), 3.86 (s, 3H), 6.83 (d, J = 0.8 Hz, 1H), 6.95–7.00 (m, 2H), 7.09 (dd, J = 8.4, 1.8 Hz, 1H), 7.36–7.41 (m, 2H), 7.76–7.80 (m, 2H). ¹³C-NMR (100 MHz, CDCl₃) δ (ppm) = 32.0, 34.8, 55.4, 62.3, 99.5, 110.7, 114.2 (2C), 119.9, 123.5, 124.4, 126.4 (2C), 129.7, 136.3, 153.4, 156.3, 159.9. HR-MS analyst [M + H]⁺ m/z (predicted) = 283.1329, m/z (measured) = 283.1339, difference = –3.63 ppm.

2.1.25. 3-(2-(3,5-Dimethoxyphenyl)benzo[b]furan-5-yl)propan-1-ol (19d)

Prepared according to the general procedure C. mp 66–68 °C. ¹H-NMR (400 MHz, CDCl₃) δ (ppm) = 1.43 (s, 1H), 1.94 (ddt, J = 12.9, 8.9, 6.4 Hz, 2H), 2.80 (t, J = 7.4 Hz, 2H), 3.70 (t, J = 6.4 Hz, 2H), 3.87 (s, 6H), 6.47 (t, J = 2.2 Hz, 1H), 6.95 (s, 1H), 7.01 (d, J = 2.2 Hz, 2H), 7.12 (dd, J = 8.4, 1.6 Hz, 1H), 7.39–7.44 (m, 2H). ¹³C-NMR (100 MHz, CDCl₃) δ (ppm) = 32.0, 34.7, 55.5 (2C), 62.2, 101.0, 101.7, 103.0 (2C), 110.9, 120.3, 125.1, 129.5, 132.3, 136.5, 153.5, 155.9, 161.1 (2C). HR-MS analyst [M + H]⁺ m/z (predicted) = 313.1434, m/z (measured) = 313.1430, difference = 1.32 ppm.

2.1.26. 3-(2-Phenylbenzo[b]furan-5-yl)propan-1-ol (19e)

Prepared according to the general procedure C. mp 128–129 °C. ¹H-NMR (400 MHz, CDCl₃) δ (ppm) = 1.39 (s, 1H), 1.95 (ddt, J = 12.9, 8.9, 6.4 Hz, 2H), 2.81 (t, J = 7.6 Hz, 2H), 3.71 (t, J = 6.4 Hz, 2H), 6.97 (d, J = 0.8 Hz, 1H), 7.13 (dd, J = 8.4, 1.8 Hz, 1H), 7.33–7.47 (m, 5H), 7.84–7.87 (m, 2H). ¹³C-NMR (100 MHz, CDCl₃) δ (ppm) = 32.0, 34.8, 62.3, 101.1, 110.9, 120.2, 124.9 (2C), 125.0, 128.5, 128.8 (2C), 129.4, 130.6, 136.5, 153.6, 156.2. HR-MS analyst [M + H]⁺ m/z (predicted) = 253.1223, m/z (measured) = 253.1220, difference = 1.05 ppm.

2.1.27. 3-(2-(4-Fluorophenyl)benzo[b]furan-5-yl)propan-1-ol (19f)

Prepared according to the general procedure C. mp 124–126 °C. ¹H-NMR (400 MHz, CDCl₃) δ (ppm) = 1.41 (s, 1H), 1.94 (ddt, J = 12.9, 8.9, 6.4 Hz, 2H), 2.81 (t, J = 7.6 Hz, 2H), 3.72 (t, J = 6.4 Hz, 2H), 6.89 (d, J = 0.4 Hz, 1H), 7.11–7.15 (m, 3H), 7.33 (m, 2H), 7.80–7.84 (m, 2H). ¹³C-NMR (100 MHz, CDCl₃) δ (ppm) = 32.0, 34.8, 62.3, 100.9, 110.9, 115.9 (d, 2f/C-F = 22.0 Hz, 2C), 120.2, 125.0, 126.7 (d, 3f/C-F = 8.2 Hz, 2C), 126.9 (d, 4f/C-F = 3.4 Hz), 129.4, 136.6, 153.6, 155.3, 162.9 (d, 5f/C-F = 248.6 Hz). HR-MS analyst [M + H]⁺ m/z (predicted) = 295.1329, m/z (measured) = 295.1327, difference = 0.69 ppm.

2.1.28. 3-(2-(4-(Difluoromethyl)phenyl)benzo[b]furan-5-yl)propan-1-ol (19g)

Prepared according to the general procedure C. mp 127–129 °C. ¹H-NMR (400 MHz, CDCl₃) δ (ppm) = 1.59 (s, 1H), 1.95 (ddt, J = 12.9, 8.9, 6.4 Hz, 2H), 2.82 (t, J = 7.6 Hz, 2H), 3.71 (t, J = 6.4 Hz, 2H), 6.68 (t, J = 5.6 Hz, 1H), 7.04 (s, 1H), 7.16 (dd, J = 8.4, 1.8 Hz, 1H), 7.41–7.45 (m, 2H), 7.58 (d, J = 8.2 Hz,
2H), 7.92 (d, J = 8.5 Hz, 2H). 13C-NMR (100 MHz, CDCl3) δ (ppm) = 32.0, 34.7, 62.2, 102.5, 111.0, 114.5 (t, 1JCF = 238.8 Hz), 120.5, 125.0 (2C), 125.6, 126.1 (t, 1JCF = 6.1 Hz), 129.1, 132.8, 134.1 (t, 2JCF = 22.4 Hz), 136.8, 153.8, 154.9. HR-MS analyst [M + H]+ m/z (predicted) = 303.1191, m/z (measured) = 303.1185, difference = 2.17 ppm.

2.1.29. 3-(2-(2-Chlorophenyl)benzo[b]furan-5-yl)propan-1-ol (19h)

Prepared according to the general procedure C. 1H-NMR (400 MHz, CDCl3) δ (ppm) = 1.39 (s, 1H), 1.95 (ddt, J = 12.9, 8.9, 6.4 Hz, 2H), 2.81 (t, J = 7.6 Hz, 2H), 3.71 (t, J = 6.4 Hz, 2H), 6.61 (d, J = 1.9 Hz, 1H), 7.26–7.54 (m, 6H), 7.83 (dd, J = 7.7, 1.8 Hz, 1H). 13C-NMR (100 MHz, CDCl3) δ (ppm) = 31.8, 36.0, 64.2, 104.1, 113.3, 120.4, 124.0, 127.4, 127.8, 128.4, 129.1, 129.1, 131.9, 132.5, 134.3, 151.8, 153.5. HR-MS analyzer [M + H]+ m/z (predicted) = 287.0833, m/z (measured) = 287.0826, difference = 2.71 ppm.

2.1.30. 3-(2-(4-Methoxyphenyl)phenyl)benzo[b]thiophen-5-yl)propan-1-ol (24a)

Prepared according to the general procedure C. mp 170–172 °C. 1H-NMR (400 MHz, CDCl3) δ (ppm) = 1.44 (s, 1H), 1.95 (ddt, J = 12.9, 8.9, 6.4 Hz, 2H), 2.82 (t, J = 7.4 Hz, 2H), 3.50 (s, 3H), 3.71 (t, J = 6.4 Hz, 2H), 5.22 (s, 2H), 7.07–7.16 (m, 3H), 7.38 (s, 1H), 7.57 (d, J = 0.9 Hz, 1H), 7.57–7.64 (m, 2H), 7.72 (d, J = 8.2 Hz, 1H). 13C-NMR (100 MHz, CDCl3) δ (ppm) = 32.0, 34.5, 56.1, 62.2, 94.4, 116.6 (2C), 118.3, 122.1, 122.8, 125.1, 127.7 (2C), 128.3, 137.0, 138.2, 141.2, 144.3, 157.4. HR-MS analyzer [M + H]+ m/z (predicted) = 329.1206, m/z (measured) = 329.1211, difference = −0.91 ppm.

2.1.31. 3-(2-(4-Methoxyphenyl)phenyl)benzo[b]thiophen-5-yl)propan-1-ol (24c)

Prepared according to the general procedure C. mp 151–153 °C. 1H-NMR (200 MHz, CDCl3) δ (ppm) = 1.29 (s, 1H), 1.96 (ddt, J = 12.9, 8.9, 6.4 Hz, 2H, H-2′′), 2.82 (t, J = 7.4 Hz, 2H, H-1′′′), 3.71 (t, J = 6.4 Hz, 2H), 3.85 (s, 3H), 6.94–6.96 (m, 2H), 7.08–7.16 (m, 1H), 7.36–7.38 (m, 1H), 7.57 (s, 1H), 7.62–7.64 (m, 2H), 7.71 (d, J = 8.2 Hz, 1H). 13C-NMR (50 MHz, CDCl3) δ (ppm) = 32.0, 34.5, 55.4, 62.3 (C-3′′′), 114.4 (2C), 118.0, 122.1, 122.7, 125.0, 127.71, 127.72 (2C), 136.9, 138.2, 141.2, 144.4, 159.8. HR-MS analyzer [M + H]+ m/z (predicted) = 299.1100, m/z (measured) = 299.1072, difference = 9.57 ppm.

2.1.32. General Procedure for Isomerization on Allyl Benzo-Fused Heterocycles

Procedure D: 5-allyl benzo-fused derivatives (0.5 mmol, 1.0 equiv.), Pd(dbach)2 (5.8 mg, 0.01 mmol, 0.02 equiv.), P(η5C5H4B)2HBF4 (5.8 mg, 0.02 mmol, 0.04 equiv.) and 1PrCOCI (10 µL, 10.6 mg, 0.1 mmol, 0.2 equiv.) was mixed in 1 mL of degassed DMAc. The mixture was stirred at 100 °C for 6 h in argon atmosphere. The reaction mixture was cooled to room temperature and then diluted with 15 mL ethylacetate and filtered through a pad of celite. The organic phase was washed with a saturated NH4Cl solution for 3 times, once with brine and dried over Na2SO4. The solvent was removed under reduced pressure. Purification was performed on silica gel eluting with LP or LP/EtOAc mixtures (depending on the polarity of the product).

2.1.33. (E)-2-(4-(Methoxymethoxy)phenyl)-5-(prop-1-en-1-yl)benzo[b]furan (20a)

Prepared according to the general procedure D. mp 151–153 °C. 1H-NMR (200 MHz, CDCl3) δ (ppm) = 1.90 (dd, J = 6.6, 1.5 Hz, 3H), 3.50 (s, 3H), 5.22 (s, 2H), 6.20 (dq, J = 15.6, 6.5 Hz, 1H), 6.48 (dd, J = 15.7, 1.3 Hz, 1H), 6.85 (s, 1H), 7.09–7.12 (m, 2H), 7.25–7.27 (m, 1H), 7.39–7.47 (m, 2H), 7.76–7.79 (m, 2H). 13C-NMR (50 MHz, CDCl3) δ (ppm) = 18.5, 56.1, 94.4, 100.1, 110.9, 116.5 (2C), 117.7, 122.1, 124.4, 124.5, 126.3 (2C), 129.7, 131.2, 133.2, 154.1, 156.3, 157.6. HR-MS analyzer [M + H]+ m/z (predicted) = 295.1329, m/z (measured) = 295.1328, difference = 0.22 ppm.

2.1.34. (E)-2-(4-Methoxyphenyl)-5-(prop-1-en-1-yl)benzo[b]furan (20c)

Prepared according to the general procedure D. mp 145–147 °C. 1H-NMR (400 MHz, CDCl3) δ (ppm) = 1.91 (dd, J = 6.6, 1.5 Hz, 3H), 3.86 (s, 3H), 6.22 (dq, J = 15.6, 6.5 Hz, 1H), 6.50 (dd, J = 15.7, 1.3 Hz,
1H), 6.83 (d, J = 0.6 Hz, 1H), 6.96–6.99 (m, 2H), 7.25–7.28 (m, 1H), 7.40–7.47 (m, 2H), 7.77–7.79 (m, 2H). 

13C-NMR (100 MHz, CDCl3) δ (ppm) = 18.5, 55.4, 99.7, 110.9, 114.3 (2C), 117.7, 122.0, 123.4, 123.4, 126.4 (2C), 129.8, 131.2, 133.2, 154.1, 156.4, 160.0. HR-MS analyst [M + H]+ m/z (predicted) = 265.1223, m/z (measured) = 265.1223, difference = −0.01 ppm.

2.1.35. (E)-2-(3,5-Dimethoxyphenyl)-5-(prop-1-en-1-yl)benzofuran (20d)

Prepared according to the general procedure D. 1H-NMR (200 MHz, CDCl3) δ (ppm) = 1.91 (d, J = 6.4 Hz, 3H), 3.85 (s, 6H), 6.26 (dq, J = 15.9, 6.5 Hz, 1H), 6.47–6.55 (m, 2H), 6.97–7.03 (m, 3H), 7.27–7.50 (m, 3H). 13C-NMR (50 MHz, CDCl3) δ (ppm) = 18.5, 55.5 (2C), 101.0, 101.9, 102.9 (2C), 111.0, 118.0, 122.6, 124.6, 129.4, 131.1, 132.2, 133.3, 154.1, 156.1, 161.1 (2C). HR-MS analyst [M + H]+ m/z (predicted) = 313.1434, m/z (measured) = 313.1430, difference = 1.32 ppm.

2.1.36. (E)-2-Phenyl-5-(prop-1-en-1-yl)benzofuran (20e)

Prepared according to the general procedure D. mp 126–128 ºC. 1H-NMR (200 MHz, CDCl3) δ (ppm) = 1.92 (dd, J = 6.4, 1.8 Hz, 3H), 6.22 (dq, J = 15.9, 6.5 Hz, 1H), 6.51 (d, J = 15.9 Hz, 1H), 7.00 (s, 1H), 7.27–7.52 (m, 6H), 7.87 (m, 2H). 13C-NMR (50 MHz, CDCl3) δ (ppm) = 18.5, 101.3, 111.0, 118.0, 122.5, 124.5, 124.9 (2C), 128.5, 128.8 (2C), 129.5, 130.5, 131.1, 133.3, 154.2, 156.3. HR-MS analyst [M + H]+ m/z (predicted) = 235.1117, m/z (measured) = 235.1123, difference = −2.28 ppm.

2.1.37. (E)-2-(4-Fluorophenyl)-5-(prop-1-en-1-yl)benzofuran (20f)

Prepared according to the general procedure D. mp 123–125 ºC. 1H-NMR (400 MHz, CDCl3) δ (ppm) = 1.91 (dd, J = 6.6, 1.5 Hz, 3H), 6.22 (dq, J = 15.6, 6.5 Hz, 1H), 6.50 (dd, J = 15.7, 1.3 Hz, 1H), 6.89 (s, 1H), 7.11–7.16 (m, 2H), 7.29–7.31 (dd, J = 8.6, 1.7 Hz, 1H), 7.41–7.49 (m, 2H), 7.80–7.83 (m, 2H). 13C-NMR (100 MHz, CDCl3) δ (ppm) = 18.5, 101.1, 111.0, 119.5 (d, J1,C-F = 11.8 Hz), 118.0, 122.6, 124.6, 126.7 (d, J2,C-F = 8.3 Hz), 126.8 (d, J3,C-F = 3.2 Hz), 129.5, 133.4, 136.5, 154.2, 155.4, 161.3 (d, J1,C-F = 247.2 Hz, 1C). HR-MS analyst [M + H]+ m/z (predicted) = 253.1023, m/z (measured) = 253.1027, difference = −0.41 ppm.

2.1.38. (E)-2-(4-(Difluoromethyl)phenyl)-5-(prop-1-en-1-yl)benzofuran (20g)

Prepared according to the general procedure D. mp 125–128 ºC. 1H-NMR (200 MHz, CDCl3) δ (ppm) = 1.91 (dd, J = 6.6, 1.5 Hz, 3H), 6.23 (dq, J = 15.6, 6.5 Hz, 1H), 6.50 (dd, J = 15.7, 1.3 Hz, 1H), 6.89 (s, 1H), 7.07 (s, 1H), 7.32–7.34 (m, 2H), 7.51–7.59 (m, 3H), 7.92 (d, J = 8.4 Hz, 2H). 13C-NMR (50 MHz, CDCl3) δ (ppm) = 18.5, 102.7, 111.2, 114.5 (t, J1,C-F = 237.3 Hz), 118.2, 123.1, 124.8, 125.0 (2C), 126.1 (t, J3,C-F = 6.2 Hz), 129.2, 131.0, 132.7, 133.5, 134.1 (t, J2,C-F = 22.4 Hz), 154.4, 155.1. HR-MS analyst [M + H]+ m/z (predicted) = 285.1091, m/z (measured) = 285.1084, difference = 2.13 ppm.

2.1.39. (E)-2-(2-Chlorophenyl)-5-(prop-1-en-1-yl)benzofuran (20h)

Prepared according to the general procedure D. mp 66–68 ºC. 1H-NMR (200 MHz, CDCl3) δ (ppm) = 1.94 (d, J = 6.5 Hz, 3H), 6.33 (dq, J = 15.6, 6.5 Hz, 1H), 6.55 (dd, J = 15.7, 1.3 Hz, 1H), 6.67–6.77 (m, 2H), 7.42–7.54 (m, 5H), 7.77–7.83 (m, 1H). 13C-NMR (50 MHz, CDCl3) δ (ppm) = 18.7, 105.6, 112.1, 120.4, 124.4, 125.1, 127.0, 127.4, 128.3, 128.5, 128.9, 129.0, 129.1, 130.0, 130.6, 153.0, 153.3. HR-MS analyst [M + H]+ m/z (predicted) = 269.0728, m/z (measured) = 269.0730, difference = −0.08 ppm.

2.1.40. (E)-2-(2-(Methoxymethoxy)phenyl)-5-(prop-1-en-1-yl)benzothiophene (25a)

Prepared according to the general procedure D. mp 173–174 ºC. 1H-NMR (400 MHz, CDCl3) δ (ppm) = 1.91 (dd, J = 6.6, 1.5 Hz, 3H), 3.50 (s, 3H), 5.21 (s, 2H), 6.28 (dq, J = 15.6, 6.5 Hz, 1H), 6.50 (dd, J = 15.8, 1.5 Hz, 1H), 7.08–7.10 (m, 2H), 7.32 (dd, J = 8.4, 2.6 Hz, 1H), 7.39 (s, 1H), 7.61–7.64 (m, 3H), 7.70 (d, J = 8.4 Hz, 1H). 13C-NMR (100 MHz, CDCl3) δ (ppm) = 18.5, 56.1, 94.4, 116.6 (2C), 118.5, 120.6,
122.1 (2C), 125.3, 127.7 (2C), 128.2, 131.1, 134.7, 137.7, 141.3, 144.4, 157.4. HR-MS analyst [M + H]^+ m/z (predicted) = 310.1022, m/z (measured) = 310.1025, difference = -1.01 ppm.

2.1.41. (E)-2-(4-Methoxyphenyl)-5-(prop-1-en-1-yl)benzo[b]thiophene (25c)

Prepared according to the general procedure D. mp 154–156 °C. 1H-NMR (200 MHz, CDCl3) δ (ppm) = 1.93 (d, J = 6.5 Hz, 3H), 3.86 (s, 3H), 6.29 (dq, J = 15.6, 6.5 Hz, 1H), 6.51 (d, J = 15.6 Hz, 1H), 6.96 (d, J = 8.6 Hz, 2H), 7.27–7.39 (m, 2H), 7.62–7.74 (m, 4H). 13C-NMR (50 MHz, CDCl3) δ (ppm) = 18.5, 55.4, 114.3 (2C), 118.2, 120.6, 122.0, 122.1, 125.2, 127.1, 127.7 (2C), 131.1, 134.6, 137.6, 141.3, 144.5, 159.8. HR-MS analyst [M + H]^+ m/z (predicted) = 281.0995, m/z (measured) = 281.1004, difference = -3.48 ppm.

2.1.42. General Procedure for De-Protection of MOM Group

Procedure D: MOM protected substrate (0.1 mmol, 1.0 equiv.) was dissolved in 0.5 mL MeOH. A 1N solution of HCl (50 µL, 0.05 mol, 0.5 equiv.) was added subsequently. The mixture was stirred at 65 °C for 30 min. The reaction mixture was cooled to room temperature and then diluted with 15 mL Et2O. The organic phase was washed with a saturated NH4Cl solution for 3 times, once with brine and dried over Na2SO4. The solvent was removed under reduced pressure. Purification was performed on silica gel eluting with LP/EtOAc 3:1 to obtain the desired product.

2.1.43. 4-(5-Allylbenzo[b]furan-2-yl)phenol (16b)

Prepared according to the general procedure E. mp 165–168 °C. 1H-NMR (400 MHz, acetone-d6) δ (ppm) = 3.33 (d, J = 6.7 Hz, 2H, H-1′′), 4.88–4.99 (m, 2H, H-3′′), 5.88 (ddt, J = 16.8, 10.4, 6.7 Hz, 1H, H-2′′), 6.82–6.84 (m, 2H), 6.89 (s, 1H), 6.96 (dd, J = 8.5, 1.2 Hz, 1H), 7.26–7.31 (m, 2H), 7.63–7.65 (m, 2H), 8.60 (s, 1H, ArOH). 13C-NMR (100 MHz, acetone-d6) δ (ppm) = 39.8 (C-1′′), 99.1, 110.4, 114.7, 115.8 (2C), 120.2, 122.2, 124.5, 126.4 (2C), 129.9, 134.8, 138.3, 153.4, 156.6, 158.2. HR-MS analyst [M + H]^+ m/z (predicted) = 251.1067, m/z (measured) = 251.1062, difference = 1.82 ppm.

2.1.44. 4-(5-(3-Hydroxypropyl)benzo[b]furan-2-yl)phenol (19b)

Prepared according to the general procedure E. mp 194–196 °C. 1H-NMR (200 MHz, acetone-d6) δ (ppm) = 1.89 (ddt, J = 12.9, 8.9, 6.4 Hz, 2H), 2.80 (t, J = 7.2 Hz, 2H), 2.95 (s, 1H), 3.62 (t, J = 6.4 Hz, 2H), 6.95–6.97 (m, 3H), 7.10–7.13 (m, 1H), 7.39–7.40 (m, 2H), 7.75–7.77 (m, 2H), 8.66 (s, 1H). 13C-NMR (50 MHz, acetone-d6) δ (ppm) = 31.9, 35.1, 60.8, 115.9, 117.8, 121.8, 122.7, 125.1, 125.9, 127.6 (2C), 129.7, 137.0, 153.2, 156.5, 158.0. HR-MS analyst [M + H]^+ m/z (predicted) = 269.1172, m/z (measured) = 269.1183, difference = -3.87 ppm.

2.1.45. (E)-4-(5-(Prop-1-en-1-yl)benzo[b]furan-2-yl)phenol (6)

Prepared according to the general procedure E. mp 198–199 °C. 1H-NMR (200 MHz, acetone-d6) δ (ppm) = 1.87 (dd, J = 6.6, 1.2 Hz, 3H), 6.26 (dq, J = 15.6, 6.6 Hz, 1H), 6.51 (d, J = 15.8 Hz, 1H), 6.98–7.02 (m, 3H), 7.32 (dd, J = 8.6, 1.1 Hz, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.54 (s, 1H), 7.78–7.80 (m, 2H), 8.76 (s, 1H). 13C-NMR (50 MHz, acetone-d6) δ (ppm) = 17.7, 99.3, 110.6, 115.8 (2C), 117.7, 121.9, 122.1, 123.9, 126.5 (2C), 130.0, 131.2, 133.3, 153.9, 156.8, 158.2. HR-MS analyst [M + H]^+ m/z (predicted) = 251.1067, m/z (measured) = 251.1057, difference = 3.71 ppm.

2.1.46. 4-(5-(3-Hydroxypropyl)benzo[b]thiophen-2-yl)phenol (24b)

Prepared according to the general procedure E. mp 217–219 °C. 1H-NMR (400 MHz, acetone-d6) δ (ppm) = 1.74 (tt, J = 7.5, 6.2 Hz, 2H), 2.67 (t, J = 7.6 Hz, 2H), 2.73 (s, 1H), 3.46 (t, J = 5.8 Hz, 2H), 6.79–6.81 (m, 2H), 7.06 (dd, J = 8.2, 1.6 Hz, 1H), 7.38 (s, 1H), 7.47–7.65 (m, 4H), 8.54 (s, 1H). 13C-NMR (100 MHz, acetone-d6) δ (ppm) = 31.9, 34.9, 60.8, 115.9, 117.8, 121.8, 122.7, 125.1, 125.9, 127.6 (2C), 136.3, 139.0.
141.5, 144.4, 157.9. HR-MS analyst [M + H]⁺ m/z (predicted) = 285.0944, m/z (measured) = 285.0934, difference = 3.56 ppm.

2.1.47. (E)-4-(5-(Prop-1-en-1-yl)benzo[b]thiophen-2-yl)phenol (25b)

Prepared according to the general procedure E. mp 212–213 °C. ¹H-NMR (200 MHz, CDCl₃) δ (ppm) = 1.74 (dd, J = 6.6, 1.6 Hz, 3H), 6.21 (dq, J = 15.7, 6.6 Hz, 1H), 6.38 (dd, J = 15.8, 1.5 Hz, 1H), 6.79–6.81 (m, 2H), 7.23 (dd, J = 8.4, 1.7 Hz, 1H), 7.37 (s, 1H), 7.47–7.49 (m, 2H), 7.56 (d, J = 1.2 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 8.54 (s, 1H). ¹³C-NMR (50 MHz, CDCl₃) δ (ppm) = 17.8, 115.9 (2C), 117.9, 120.6, 122.0, 124.8, 125.7, 127.6 (2C), 127.6, 131.1, 134.8, 137.3, 141.6, 144.8, 158.0. HR-MS analyst [M + H]⁺ m/z (predicted) = 267.0838, m/z (measured) = 267.0830, difference = 3.22 ppm.

2.2. NF-κB Transactivation Activity

Measurement of the NF-κB transactivation activity was essentially performed as described previously [9]. Briefly, HEK-293 cells stably transfected with a NF-κB luciferase reporter (HEK293/NF-κB-lac cells, Panomics, RC0014) were loaded with CTG CMFDA (5-chloromethylfluorescein diacetate, Invitrogen) to stain living cells. 4 x 10⁴ cells were seeded in 96-well plates and incubated at 37 °C and 5% CO₂ overnight. On the next day, the medium was exchanged with a serum-free DMEM and cells were treated with the respective test compounds dissolved in dimethyl sulfoxide (DMSO). To avoid nonspecific effects of the solvent, the final concentration of DMSO was always adjusted to 0.1%. One hour after the treatment, cells were stimulated with 2 ng/mL human recombinant TNF-α for 4 h. Then cells were lysed by a reporter lysis buffer (Promega, Madison, WI, USA). The luminescence of the firefly luciferase and the CTG fluorescence were quantified on a GeniosPro plate reader (Tecan, Grödig, Austria). The luciferase signal derived from the NF-κB reporter was normalized by the CTG-derived fluorescence to account for differences in the cell number or transfection efficiency.

3. Results and Discussion

Based on the results presented in the introduction, we were interested to synthesize and evaluate benzofuran-based lignans of general structure I (Figure 2). The synthetic strategy should be modular, efficient, and applicable to the synthesis of a wide range of derivatives, ideally from common intermediates. Breaking the strategic bonds as indicated in Figure 2, three fragments A, B, and C, are obtained which suggest the application of a direct arylation/cross coupling strategy, which introduces the aryl moiety in position two of general structure II via direct arylation and the alkyl or alkenyl chain in position five of the same fragment via a cross-coupling methodology, e.g., with an allyl boronic acid ester such as IV. For the direct arylation protocol we had previously developed an efficient protocol optimized for benzo-fused heterocyclic systems [10]. Hence, the main synthetic task was developing a suitable cross-coupling method introducing the desired residues in position five of building block II and subsequent elaboration of the olefin function towards the substituents identified for the naturally occurring compounds. Naturally, there are many ways to synthesize substituted benzofurans [11], and also the type of structure we are aiming for has been synthesized previously. For example, Duan et al. used a strategy in which the benzofuran core was constructed individually for each derivative synthesized [12]. This strategy is conveniently applicable for a small set of compounds, however, when a larger library of derivatives is targeted, it is lacking the modularity we were aiming for.

Consequently, fragment B was designed as a 5-halo-benzo[b]furan (general structure II, Figure 2). This building block offers two possibilities: Initial allylation at C5 and subsequent C2 arylation, or, alternatively, initial C2 arylation followed by C5-allylation. Since the direct arylation protocol uses aryl bromides as coupling partners, the allylation reaction should be carried out first to avoid homo-coupling between two 5-bromobenzofuran entities. The resulting 5-allyl benzofuran should then be arylated in position two, however it has to be considered that the terminal double bond could react in an undesired Mizoroki-Heck reaction. In case the order of events should be reversed,
5-chlorobenzofuran would need to be applied to avoid or at least suppress the aforementioned problem. To develop the most efficient protocol, it was decided to investigate both approaches. For introducing the side chain in position five, introduction of an allyl substituent is the ideal option, since the allyl substituent can be further transformed into 3-hydroxyl-propyl by a hydroboration-oxidation sequence [13–15] or to a 2-propenyl residue by an isomerization reaction [16–23].

![Chemical structure](image)

**Figure 2.** Retrosynthetic analysis.

Initially, 5-bromobenzofuran 12 was tested as starting material (Scheme 1) [24–27]. The subsequent allylation reaction with 13 worked well using a Suzuki-Miyaura protocol with Pd(PPh₃)₂Cl₂ as catalyst, K₂CO₃ as base and in DMAC solvent. Product 14 was obtained in 58% yield. Next, a direct arylation should introduce the aryl residue in position two, giving rise to 16. Unfortunately, the direct arylation reaction did not take place and only product 15 derived from competing Mizoroki-Heck coupling was found, instead.

![Scheme 1](image)

**Scheme 1.** Allylation and attempted direct arylation of 5-bromobenzofuran 12.
Hence, the alternative approach using 5-chlorobenzo[b]furan \(17\) as starting material was investigated (Scheme 2) [24,28]. In our previous publication [10], it was observed that aryl chlorides were unreactive as coupling partners under the reaction conditions and, hence, homo-coupling of the benzo[bfuran starting material should not be an issue.

Before direct arylation was tested on this substrate, the allylation in position five had to be established. Using the same allylation conditions as for 5-bromobenzo[b]furan 12 did not lead to any conversion towards 14 and, hence, the Suzuki-Miyaura reaction had to be optimized. Several conditions for Suzuki-Miyaura reactions on chloride substrates have been reported [29–32], mainly using elaborate catalyst/ligand systems. However, the method of Thimmaiah et al. used common catalysts and ligands and was therefore very appealing for our purposes of an efficient and simple protocol [30]. After a quick optimization, 5-allylbenzo[b]furan 14 could be synthesized using Pd(\(\text{dba}\)) as catalyst, SPhos as ligand, Cs\(\text{CO}_3\) as base in dioxane, 100 \(^\circ\)C and for 5 h giving an isolated yield of 14 of 68\% (Scheme 2).

Subsequently, the direct arylation protocol was tested on 5-chlorobenzo[b]furan 17 using our previously developed protocol [10]. Gratifyingly, 17 reacted selectively with 1-bromo-4-(methoxymethoxy) benzene giving product \(18a\) as sole compound in 60\% yield after only three hours reaction time. Compound \(18a\) was subsequently submitted to the optimized Suzuki-Miyaura conditions to obtain product 16a in 69\% yield (Scheme 2).

Product 16a represents a key compound for the synthetic route. From 16a, a hydroboration-oxidation sequence [13–15] using BH\(\text{THF}\), NaOH, H\(\text{O}_2\) in THF for the second step was utilized in situ to obtain alcohol 19a with 42\% isolated yield. The MOM protecting group was cleaved in methanol with traces of concentrated HCl subsequently to obtain the final product 19b (Scheme 3).

For the isomerization of 16a several different methods are reported using transition metal catalyst [16–23]. Only Gauthier et al. [23] used palladium catalyst with bulky ligand [23] to migrate the double bond into conjugation with the aryl ring with very good stereoselectivity. Using Pd(\(\text{dba}\)) as catalyst and P(\(\text{Bu}\))\text{HBF}_4 as ligand product 20a was obtained in \(E\) configuration with 75\% yield. De-protection by concentrated HCl in methanol removed the MOM protective group to get final product 6 (Scheme 3).

For structure activity relationship studies, the developed synthetic sequence should also be applied for the synthesis of bioisosteric benzo[b]thiophene derivatives. Required 5-chlorobenzo[b]thiophene 21 was synthesized according to a literature protocol [33]. The direct arylation reaction on 21 was also selective giving 22a in 58\% yield. Allylation via Suzuki-Miyaura coupling on 22a worked under the identical conditions as developed for the benzo[bfuran series, albeit in somewhat lower yield giving 23a in 46\% (Scheme 4).
The reactions for side chain modification were carried out again under identical conditions as in the benzofuran series. The hydroboration-oxidation sequence of 23a gave 46% isolated yield of 24a while isomerization to 25a gave 71% yield. De-protection reaction on 24a and 25a proceeded in very good yield of 89% toward 24b and 90% towards 25b, respectively (Scheme 5).

![Scheme 3](image3.png)

**Scheme 3.** Overview of double bond isomerization, hydroboration-oxidation, and MOM-deprotection of 16a.

![Scheme 4](image4.png)

**Scheme 4.** Direct arylation and allylation of 5-chlorobenzofuran 21.

The reactions for side chain modification were carried out again under identical conditions as in the benzofuran series. The hydroboration-oxidation sequence of 23a gave 46% isolated yield of 24a while isomerization to 25a gave 71% yield. De-protection reaction on 24a and 25a proceeded in very good yield of 89% toward 24b and 90% towards 25b, respectively (Scheme 5).

![Scheme 5](image5.png)

**Scheme 5.** Overview of double bond isomerization, hydroboration-oxidation, and MOM-deprotection of 23a.
With a practical synthesis route for benzo[b]furan and benzo[b]thiophene compounds at hand, a group of lignan-like compounds based on those heterocyclic rings was prepared to evaluate their biological properties as anti-inflammatory agents.

Initially, a series of direct arylation reactions was conducted (Table 1) with aryl moieties carrying electron donating and electron withdrawing substituents. The nature of the substituent had only a minor influence on the yield of this transformation. In the benzo[2,1-g]furane series, aryl bromides carrying electron donating substituents such as OMOM or methoxy gave 10–15% higher yields in the arylation step (see Table 1 examples 18a, 18c and 18d) as compared to substituents with no or an electron withdrawing effect (see Table 1 examples 18e–h). In the benzo[b]thiophene series only two examples were synthesized and hence a general trend cannot be deduced.

### Table 1. Direct arylation and subsequent allylation.

| Entry | X     | R¹     | Product | Yield (%) | Product | Yield (%) |
|-------|-------|--------|---------|-----------|---------|-----------|
| 1     | O     | 4-OMOM | 18a     | 60%       | 16a     | 69%       |
| 2     | O     | 4-OH   | 18b     | n.s.      | 16b     | 91%       |
| 3     | O     | 4-OMe  | 18c     | 58%       | 16c     | 70%       |
| 4     | O     | 3,5-dimethoxy | 18d | 51% | 16d | 66% |
| 5     | O     | H      | 18e     | 44%       | 16e     | 74%       |
| 6     | O     | 4-F    | 18f     | 41%       | 16f     | 72%       |
| 7     | O     | 4-CHF₂ | 18g     | 45%       | 16g     | 69%       |
| 8     | O     | 2-Cl   | 18h     | 44%       | 16h     | 51%       |
| 9     | S     | 4-OMOM | 22a     | 58%       | 23a     | 46%       |
| 10    | S     | 4-OMe  | 22c     | 31%       | 23c     | 58%       |

n.s. not synthesized; ¹ via MOM-deprotection from 16a; the yield refers only to the deprotection step.

The subsequent allylation reactions worked well on all benzo[2,1-g]furan substrates giving yields in the range of 66–74%. Only the 2-Cl product 16h was obtained in somewhat lower yield of 51%. Important to note: compound 16b was obtained via MOM-deprotection of 16a in 91% yield rather than via allylation of the corresponding 4-OH-aryl precursor 18b. The direct arylation procedure turned out not to tolerate a free OH group, hence, requiring this alternate approach to 18b.

The hydroboration-oxidation sequence towards the terminal alcohol products 19a–h (benzo[2,1-g]furan series) and 24a–c (benzo[b]thiophene series) proceeded with similar efficiency (40–53% yield) independent of the substituents present on the aryl ring (Table 2, left). Again, it should be noted that the 4-OH products 19b and 24b were obtained in excellent yield via MOM-deprotection of 19a and 24a respectively. The same is true for the double bond isomerization (Table 2, right). Benzo[2,1-g]furane products 20a–h and benzo[b]thiophene compounds 25a–c were obtained in yields between 57–77% yield. Also, in this case the 4-OH products 6 and 25b were obtained in excellent yield via MOM-deprotection of 20a and 25a, respectively.

Since the pharmacological characterization of the lignan derivatives isolated from Krameria lappaceae revealed as most relevant in vitro anti-inflammatory activity inhibition of the NF-κB signaling pathway, we decided to use again a luciferase reporter model to quantify the transactivation activity of NF-κB [8]. For this, we used HEK293 cells stably transfected with a NF-κB-driven luciferase reporter gene that were loaded with fluorescent Cell Tracker Green to allow luciferase-derived signal normalization to the amount of viable cells. Cells were then treated with test compounds at the indicated concentration or vehicle for 30 min and then stimulated with TNF-α (2 ng/mL) for four hours. Luminescence and fluorescence was quantified in cell lysates by a Genios Pro plate reader (Tecan) [34].
Table 2. Hydroboration-oxidation and isomerization.

| Entry | X   | R\(^1\) | Product | Yield (%) | Product | Yield (%) |
|-------|-----|---------|---------|-----------|---------|-----------|
| 1     | O   | 4-OMOM  | 19a     | 42%       | 20a     | 75%       |
| 2     | O   | 4-OH    | 19b     | 89%\(^1\) | 6       | 93%\(^3\) |
| 3     | O   | 4-OMe   | 19c     | 46%       | 20c     | 62%       |
| 4     | O   | 3,5-dimethoxy | 19d   | 40%       | 20d     | 77%       |
| 5     | O   | H       | 19e     | 52%       | 20e     | 75%       |
| 6     | O   | 4-F     | 19f     | 53%       | 20f     | 77%       |
| 7     | O   | 4-CHF\(_2\) | 19g   | 49%       | 20g     | 74%       |
| 8     | O   | 2-Cl    | 19h     | 50%       | 20h     | 65%       |
| 9     | S   | 4-OMOM  | 24a     | 46%       | 25a     | 71%       |
| 10    | S   | 4-OH    | 24b     | 89%\(^2\) | 25b     | 90%\(^4\) |
| 11    | S   | 4-OMe   | 24c     | 45%       | 25c     | 57%       |

\(^1\) the yield refers to the MOM-deprotection step of 19a; \(^2\) the yield refers to the MOM-deprotection step of 24a; \(^3\) the yield refers to the MOM-deprotection step of 20a; \(^4\) the yield refers to the MOM-deprotection step of 25a.

4. Discussion

The biological data are compiled in Table 3. With the current synthetic route towards target compounds, structural diversity at position five of the benzo-heteroaromatic core could be further extended regarding the location of the olefinic system. Initially, 2-phenyl benzofurans were tested carrying an allyl group (entry 1, 16e), a 1-propenyl group (entry 2, 20e), or a 1-hydroxy-propan-3-yl group (entry 3, 19e) in position five of the benzofuran scaffold. NF-κB inhibition was measured initially at concentrations of 10 \(\mu\)M and/or at 20 \(\mu\)M. IC\(_{50}\) values were determined for compounds with a significant and concentration-dependent inhibitory activity at these concentrations. Within this initial series, it was found that the propanol substituted derivative 19e (entry 3) showed the highest inhibition (0.1-fold activation at 10 \(\mu\)M and 0.03-fold activation at 20 \(\mu\)M) and already a low IC\(_{50}\) value of 1.42 \(\mu\)M. The 5-allyl substituted derivative 16e as well as the 5-(1-propenyl) derivative 20e showed significantly lower inhibition, whereas the latter one gave the lowest activity (0.36 at 10 \(\mu\)M entry 1 vs. 0.66 at 10 \(\mu\)M entry 2).

Table 3. Pharmacological data.

| Entry | Compound | Structure         | Fold Activation NF-κB (10 \(\mu\)M) | Fold Activation NF-κB (20 \(\mu\)M) | IC\(_{50}\) (NF-κB, \(\mu\)M) |
|-------|----------|-------------------|-------------------------------------|-------------------------------------|-----------------------------|
| 1     | 16e      | ![Structure](#)  | 0.36                                | 0.27                                | n.d.                        |
| 2     | 20e      | ![Structure](#)  | 0.66                                | 0.68                                | n.d.                        |
| 3     | 19e      | ![Structure](#)  | 0.10                                | 0.03                                | 1.46                        |
| 4     | 16b      | ![Structure](#)  | 0.06                                | 0.02                                | 2.12                        |
The 5-allyl substituted derivative (entry 2). Pharmacological data.

Table 3. Cont.

| Entry | Compound | Structure | Fold Activation NF-κB (10 μM) | Fold Activation NF-κB (20 μM) | IC₅₀ (NF-κB, μM) |
|-------|----------|-----------|-------------------------------|-------------------------------|------------------|
| 5     | 6        | ![Structure](image) | 0.15                          | 0.04                          | 2.86             |
| 6     | 19b      | ![Structure](image) | 0.12                          | 0.007                         | 1.24             |
| 7     | 16c      | ![Structure](image) | 0.60                          | 0.28                          | 3.60             |
| 8     | 20c      | ![Structure](image) | n.d.                          | 0.78                          | n.d.             |
| 9     | 19c      | ![Structure](image) | 0.12                          | 0.04                          | 3.82             |
| 10    | 16a      | ![Structure](image) | 0.31                          | 0.147                         | 1.31             |
| 11    | 20a      | ![Structure](image) | 0.77                          | 0.83                          | n.d.             |
| 12    | 19a      | ![Structure](image) | 0.57                          | 0.03                          | 9.22             |
| 13    | 16d      | ![Structure](image) | 0.54                          | n.d.                          | n.d.             |
| 14    | 20d      | ![Structure](image) | 0.94                          | n.d.                          | n.d.             |
| 15    | 19d      | ![Structure](image) | 0.20                          | 0.003                         | 1.92             |
| 16    | 19g      | ![Structure](image) | 0.52                          | 0.08                          | 8.52             |
| 17    | 19f      | ![Structure](image) | 0.32                          | 0.02                          | 2.20             |
| 18    | 19h      | ![Structure](image) | 1.08                          | 0.61                          | n.d.             |
| 19    | 24b      | ![Structure](image) | 0.21                          | 0.05                          | 4.74             |
entry 6) showed the lowest IC$_{50}$ value. Biomolecules are largely inactive and were excluded in further biological evaluation. 

That steric bulk in the phenyl ring influences the IC$_{50}$ value with 0.31 µM (vs. 1.42 entry 3, and 1.24 entry 6). Naturally, the methoxy group in position five was substituted for a MOM group, which further increases the steric bulk. 

In this set of compounds (entries 10–12, compounds 16a, 20a, and 19a respectively), significant inhibitory effects were found with the 5-allyl (entry 7, compound 16c) and 5-propenyl (entry 8, compound 20c) is clearly reestablished. Compound 19c (entry 9) shows a similar inhibitory effect as the other two propanol substituted derivatives (entries 3 and 6 compounds 19e and 19b) but with a significantly higher IC$_{50}$ value of 3.82 µM (vs. 1.42 entry 3, and 1.24 entry 6). Naturally, the methoxy group in 19c is significantly larger than a proton (as in 19e) or a hydroxy group (as in 19b) and it was speculated that this size difference might have an influence on the IC$_{50}$ values. Hence, in a next set of compounds, the methoxy group was substituted for a MOM group, which further increases the steric bulk.

In this set of compounds (entries 10–12), compounds 16a, 20a, and 19a respectively, significant inhibitory effects were found with the 5-allyl- and 5-propanol substituted derivatives 16a and 19a, but only at the higher concentration of 20 µM. The 0.03-fold NF-kB activation of 19a matches however the best values obtained so far. However, as hypothesized, the IC$_{50}$ value is significantly higher with 9.22 µM (entry 12). Interestingly, 16a gave a very low IC$_{50}$ value of 1.31 µM. This supports the argument that steric bulk in the phenyl ring influences the IC$_{50}$ values.

Since naturally occurring benzofuran lignans often carry two oxygen functionalities (OH or OMe), it was tried to access such compounds synthetically. Unfortunately, our synthetic method allowed us only access to 3,5-dimethoxy substituted derivatives 16d, 20d, and 19d (entries 13-15). Again, the 5-propanol substituted derivative 19d (entry 15) showed highest NF-kB inhibition (0.20 at 10 µM) and the overall highest NF-kB inhibition of 0.003 at 20 µM. The IC$_{50}$ value for this compound was surprisingly low (1.92 µM, entry 15), which is contradicting the steric argument previously considered. However, this compound is the only one carrying a 3,5-disubstituted phenyl ring and additional derivatives incorporation this substitution pattern would be required to further establish structure-activity relationship. The two oxygen moieties might lead to favorable interactions, which predominate over steric effects.

At this point it is safe to say that a propanol substituent in position five usually gives highest NF-kB inhibition, which is sometimes matched by 5-allyl substituted derivatives. The propenyl derivatives are largely inactive and were excluded in further biological evaluation.

So far only electron donating substituents on the phenyl ring were considered, in line with the substituion pattern of the natural products. Since fluorine substituents often beneficially influence factors such as lipophilicity and hence also biological activity, two fluorine containing derivatives were tested as

| Entry | Compound | Structure | Fold Activation NF-κB (10 µM) | Fold Activation NF-κB (20 µM) | IC$_{50}$ (NF-kB, µM) |
|-------|----------|-----------|-------------------------------|-------------------------------|-----------------------|
| 20    | 24c      | ![Structure](image) | 0.37                          | 0.12                          | 6.59                  |
| 21    | 24a      | ![Structure](image) | 0.96                          | 1.08                          | n.d.                  |

Compounds were tested at 10 µM and/or at 20 µM in a luciferase-based cell model (HEK293/NF-kB-luc cells) for NF-kB Inhibition. Values display residual fold activation after treatment with the indicated compounds (n = 3; with TNF-α-induced activation set to 1); for selected compounds an IC$_{50}$ value was determined; n.d.: not determined.

Naturally occurring benzofuran lignans contain at least one oxygen functionality (OH or OMe) in the aryl ring in position two, compounds 16b, 19b, and 6 with a 4-hydroxyphenyl group in that position and the three different side chains in position five were tested (entries 4–6). Obviously, the hydroxyl group is very important for NF-kB inhibition since all three derivatives show significant inhibition at both, 10 and 20 µM concentration. Due to the small differences in the inhibitory effect, a trend between the three derivatives cannot be deduced, however, again the propanol substituted derivative 19b (entry 6) showed the lowest IC$_{50}$ value with 1.24 µM, which is also the lowest value of all tested compounds.

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So far only electron donating substituents on the phenyl ring were considered, in line with the substitution pattern of the natural products. Since fluorine substituents often beneficially influence factors such as lipophilicity and hence also biological activity, two fluorine containing derivatives were tested as
well (19g entry 16 and 19f entry 17), both carrying the 5-propanol residue. NF-κB inhibition was mediocre in both compounds (entries 16 and 17) at 10 μM concentration, however at 20 μM, especially 19f showed significant inhibition. The IC$_{50}$ values again showed the trend that the larger 4-CHF$_2$ substituent gave a significantly higher IC$_{50}$ value (19g, entry 16, 8.52 μM) as compared to the 4-F substituted derivative (19f, entry 17, 2.20 μM).

In one example (19h), ortho substitution in the phenyl ring was tested as well, but no significant NF-κB inhibition was obtained (entry 18).

In a next series of compounds, we tested whether the benzofuran core could be substituted by other benzoathiopeine. Hence, several benzoathiopeine derivatives were synthesized and the 4-hydroxyphenyl- (24b, entry 19), 4-methoxyphenyl- (24c, entry 20) and 4-MOM-phenyl- (24a, entry 21) derivatives were tested. In all three examples position five was substituted by the propanol side-chain. The MOM substituted derivative did not show NF-κB inhibition (entry 21), which is surprising since the corresponding benzofuran derivative (entry 9) was amongst the most active ones. The 4-OH (entry 19) and 4-MeO (entry 20) derivative showed NF-κB inhibition, especially at the higher concentration of 20 μM, however the corresponding IC$_{50}$ values were significantly higher as compared to their benzofuran counterparts (see entry 6 vs entry 19 and entry 9 vs. entry 20).

A comparison of the pharmacological data of our synthesized compounds and the benzofuran lignans isolated from krameria lappacea roots (Figure 1, compounds 1, 2, and 5–9) shows that the IC$_{50}$ values of several compounds are in the same range (or even lower) as the most active natural product 6. For compound 6 an IC$_{50}$ of 1.4 μM was reported in literature for the natural product isolate and we measured a similar value of 2.86 μM in our assay with a synthetic sample of 6. Compound 19b, which differs from 6 only in the sidechain (19b: 3-hydroxypropyl, 6: prop-1-en-1-yl) gave an IC$_{50}$ value of 1.24 μM. The difference between synthetic and natural 6 should not be overinterpreted, since the values stem from different measurement series carried out by different researchers.

5. Conclusions

It was found that the propanol side chain in position five is required for good inhibitory activity, independent of the underlying scaffold (benzofuran or benzoathiopeine). Some 5-allyl compounds do show activity as well, however those are the exception, and 5-propenyl derivatives are basically inactive. The IC$_{50}$ values seem to correlate with steric bulk in the aryl-moiety in position two, a finding which we want to confirm further in subsequent studies. The larger the substituents get in this ring, the higher the IC$_{50}$ values become. It can be speculated that there is a certain size restriction in the active site in this position. One examples does not follow this trend, however, in comparison to other compounds, the aryl ring is disubstituted in this example: the 3,5-dimethoxy compounds shows a low IC$_{50}$ value, but other interactions induced by the two methoxy groups might be responsible for this. Here, more examples with different substitution patterns are required to complete the picture. With the established synthetic route towards this compound class, further elaboration of this scaffold has been enabled and additional studies to establish refined structure activity relationship will be conducted in our laboratories. The focus will lie on benzofurans carrying multiple oxygen-functionalities in the aromatic ring in position two. Additionally, further substitution in the benzofuran system besides a side chain in position five is not explored yet and will be investigated.

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