Full Paper

Structural Modifications of Salicylates: Inhibitors of Human CD81-Receptor HCV-E2 Interaction

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Starting point of the present paper was the result of a virtual screening using the open conformation of the large extracellular loop (LEL) of the CD81-receptor (crystal structure: PDB-ID: 1G8Q). After benzyl salicylate had been experimentally validated to be a moderate inhibitor of the CD81-LEL–HCV-E2 interaction, further optimization was performed and heterocyclic-substituted benzyl salicylate derivatives were synthesized. The compounds were tested for their ability to inhibit the interaction of a fluorescence-labeled antibody to CD81-LEL using HUH7.5 cells. No compound showed an increase concerning the inhibition of the protein-protein interaction compared to benzyl salicylate.

Keywords: Benzyl salicylates / CD81-receptor / Hepatitis C Virus / Large extracellular loop / Virtual screening

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Introduction

Hepatitis C Virus (HCV), a positive-stranded RNA virus, infects approximately 170 million people worldwide [1]. The majority of those infected fail to clear the virus under current therapy and in many cases the chronic infection with HCV leads to cirrhosis or liver cancer [2]. Recently, the large extracellular loop (LEL) of the human cell surface protein CD81, a member of the tetraspanin family, was identified as a binding partner for the HCV envelope glycoprotein E2 (HCV-E2) [3]. Inhibition of this interaction prevents infection of HCV target cells, mainly human hepatocytes. This has been demonstrated using several methods including a small molecule LEL-D-helix mimetic that binds to HCV-E2 [4]. Following our aim to synthesize compounds which inhibit the CD81-LEL–HCV-E2 interaction by binding to CD81-LEL, a virtual screening using the crystal structure of the latter protein was performed.

More than 400 000 compounds obtained from the Available Chemicals Directory, the National Cancer Institute Database, the Maybridge Database, and the inhouse-substance library of our group were used. Subsequently, reactive compounds were excluded as well as compounds which do not follow Lipinski's Rule-of-Five. Approximately 100 000 compounds were then docked into the CD81-LEL crystal structure (PDB-ID: 1G8Q) by means of GOLD, DOCK, and FlexX software. The docking site within the 1G8Q structure was a superficial cleft that is localized between two alpha-helical parts of the LEL with pronounced conformational flexibility [5]. There are indications that this part of the LEL is involved in the virus binding process [6] and we hypothesized that conformational changes – which can possibly be blocked by small-molecular ligands – in that area may be linked to virus binding and internalization. Moreover, the cleft-like region in 1G8Q appeared as a more promising binding site for small-molecular ligands than other, purely superficial regions of LEL. About 200 virtual hits were identified. Selected compounds (criterions were commercial availability or easy synthetic route) were tested using the assay developed by Pileri *et al.* [7]. The best compound

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Abbreviations: Hepatitis C Virus (HCV); HCV envelope glycoprotein E2 (HCV-E2); large extracellular loop (LEL)

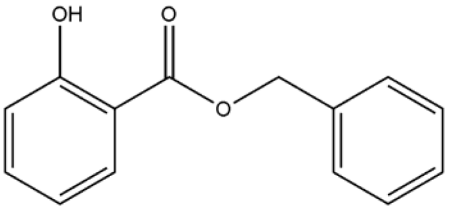


Figure 1. Benzyl salicylate.

found was benzyl salicylate (Fig. 1), which was capable to inhibit the CD81-LEL–HCV-E2 interaction by 25% at 50 μM.

Structure modification

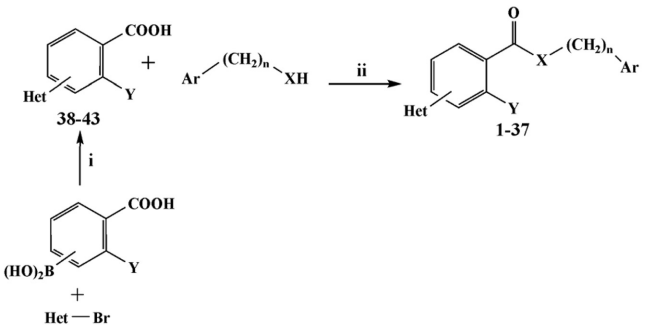
After experimental validation of benzyl salicylate as a hit compound, structural optimizations were performed to increase inhibition of protein-protein interaction. The aim was to synthesize compounds with a core structure similar to benzyl salicylate in which the aromatic ring containing the carboxyl function should be coupled to variable heterocycles to improve drug-likeness. Furthermore, a few compounds with heterocyclic substitution at the benzyl alcohol moiety were prepared.

Syntheses and biological testing

The desired compounds were obtained by connecting substituted benzoic acids to alcohols and amines, respectively. The synthetic pathway and a general structure of the synthesized benzyl salicylate derivatives are shown in Scheme 1, the compounds prepared are outlined in Table 1. Formation of the amides and esters was accomplished by activating the carboxylic acids with thionyl chloride followed by addition of the corresponding alcohols or amines.

The carboxylic acids needed for the formation of the target compounds were prepared using commercially available reagents. Starting from the bromo-substituted aromatic heterocycle and the corresponding boronic acid, Suzuki coupling was performed with tetrakis-(triphenylphosphine) palladium(0) as catalyst and the desired compounds **38**–**43** obtained in satisfactory yields (Scheme 1).

The alcohols and amines used for the formation of the target compounds were commercially available with the exception of **44**–**46** (Table 1). These had to be prepared starting from the bromo-substituted heterocycle and the boronic acid of the corresponding alcohol or amine via Suzuki coupling, performed as mentioned above.



Reagents and conditions: (i) 10 mL EtOH + 15 mL 10% Na_2CO_3-solution, $Pd(PPh_3)_4$, O_2-free, 90°C over night; (ii-1) $SOCl_2$, rt, 2 h; (ii-2) NEt_3, dry CH_2Cl_2, 0°C 30 min, rt 2 h (Het = heterocycle, X = -O-, -NH-, Y = -H, -OH, Ar = aromat, n = 0, 1).

Scheme 1. Synthetic pathway and a general structure of the synthesized benzyl salicylate derivatives.

Biological testing of the synthesized compounds **1**–**37** was performed by means of a medium-throughput assay developed in our group [8] which is based on the procedure of Pileri *et al*. [7]. Briefly, the inhibition of the interaction of the fluorescence-labeled CD81 antibody JS81 with HUH7.5 cells caused by our compounds is determined by FACS. No synthesized compound showed an increase concerning the inhibition of the CD81-LEL–HCV-E2 interaction compared to the original hit benzyl salicylate. The probable point of contact of our compounds should be the cleft-like region of the LEL as shown in the above mentioned docking studies. However, it can not be excluded that our compounds in addition also interact with the E2-mimicking epitope of the antibody.

A possible explanation for the low activity of the compounds might be an unfavorable substitution pattern of the core structure that diminishes binding affinity to the LEL compared to the original hit. Therefore, we are currently looking for an appropriate substitution pattern to solve this problem.

We thank the Deutsche Forschungsgemeinschaft (DFG) for the grants given to M.H., S.Z. and A.N. (KFO129) and the Fonds der Chemischen Industrie for financial support.

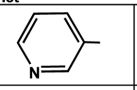
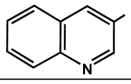
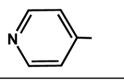
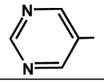
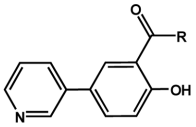
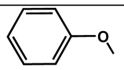
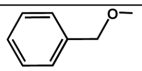
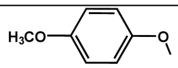
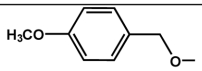
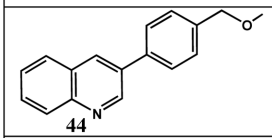
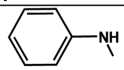
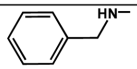
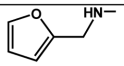
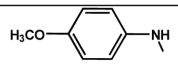
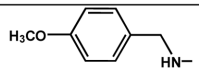
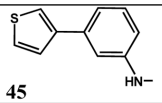
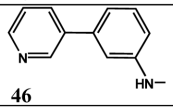
The authors have declared no conflict of interest.

Experimental

General procedure

Solvents and reagents were used as received from commercial distributors without further purification. Anhydrous reactions were conducted under a nitrogen atmosphere. Proton and car-

Table 1. Synthesized compounds **1–37**.

R \ Het						
	1	2	3	4	5	
	6	7	8	9	10	11
				12	13	
				14	15	
 44			16		17	
	18	19		20	21	
	22	23	24		25	26
		27	28	29	30	
				31	32	
				33		
 45		34				
 46		35		36	37	

bon NMR spectra were recorded at a Bruker AM 500 (Bruker Bioscience, Billerica, MA, USA). The proton NMR spectra were recorded at 500 MHz, the carbon NMR spectra at 125 MHz. Chemical shifts δ are reported in ppm units. Molecular mass was determined by liquid chromatography – tandem mass spectrometry (LC-MS/MS) using a TSQ Quantum from Thermo Finnigan equipped with an electro spray interface and connected to a Surveyor HPLC (Thermo Finnigan, Bremen, Germany). Positive and negative ion mass spectra were recorded (mass range m/z 150–1500) in normal scan mode. Melting points were determined using a Stuart Scientific SMP3 melting point apparatus (Stuart Scientific Stone, Staffordshire, UK). IR measurements were performed on a Bruker Vector 33 at a frequency range from 4000–250 cm^{-1} (Bruker). Wave numbers ν are reported in cm^{-1}. Flash chromatography was performed using Merck silica gel 35/40-63/70 (Merck, Germany).

Biological test system

HUH7.5 cells (1×10^5) were incubated with 100 µL of the potential inhibitor (50 µM + 1% DMSO) in 96 transwell plates for 10 minutes at room temperature. Next 4 µL of the fluorescence-labeled CD81 antibody JS81 and 21 µL of PBS were added. After 10 minutes at room temperature 125 µL of PBS were added and the resulting cell suspension was left to incubate in darkness for 5 hours. After addition of 250 µL of PBS FACS analyses followed.

General procedure for the Suzuki coupling

The boronic acid (1 equivalent) and the bromo-substituted heterocycle (1 equivalent) were added to a mixture of 10 mL ethanol and 15 mL sodium carbonate solution (10%). This solution was freed from oxygen by evacuating and flushing with nitrogen several times. After addition of 4 mol% of tetrakis-(triphenylphosphine) palladium(0) under nitrogen the mixture was stirred at 90°C over night.

Work-up for the carboxylic acids

The remaining solid was filtered off at that temperature. Subsequently, half of the solvent was removed. The product precipitated after acidifying to pH = 2 using formic acid. It was then filtered off and dried under high vacuum.

Work-up for the alcohol and amines

After extracting the aqueous phase two times with ethyl acetate, the organic layer was dried and the solvent removed. Flash column chromatography (ethyl acetate / n-hexane mixture) led to the purified product.

General procedure for the formation of the amides and esters

The carboxylic acid (1 equivalent) was stirred with an excess of thionyl chloride for 2 hours at room temperature. The resulting clear solution was freed from remaining thionyl chloride under reduced pressure. The acid chloride was dissolved in dry dichloromethane and added drop wise at 0°C to a solution consisting of the corresponding alcohol or amine (1 equivalent) and an equimolar amount of triethylamine in dry dichloromethane. After stirring for 30 minutes at 0°C the mixture was warmed to room temperature and stirred for 2 hours. The precipitated solid was filtered off. The solvent was removed and the raw product was purified by column flash chromatography using an ethyl acetate / n-hexane mixture.

Phenyl 4-(thiophen-3-yl)benzoate ***1***

Yield 43%, m. p. 155°C; IR ν cm^{-1}: 1719, 1605, 1487, 1278, 1195, 1160, 1079; ^{1}H-NMR ($CDCl_3$) δ: 8.23 (d, 2H, *J* = 8.51), 7.73 (d, 2H, *J* = 8.83), 7.62 – 7.61 (m, 1H), 7.48 – 7.43 (m, 4H), 7.30 – 7.28 (m, 1H), 7.26 – 7.24 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ: 164.95, 151.02, 141.08, 140.70, 130.83, 129.49, 128.01, 127.50, 126.81, 126.37, 126.19, 125.86, 122.15, 121.74; LC/MS-MS:280.96 [M + H^+].

Phenyl 4-(pyridin-3-yl)benzoate ***2***

Yield 45%, m. p 110°C; IR ν cm^{-1}: 2925, 2360, 1730, 1266, 1190, 1073; ^{1}H-NMR ($CDCl_3$) δ: 8.69 (s, 1H), 8.57 (dd, 1H, *J* = 4.73), 8.23 (d, 2H, *J* = 8.51), 7.84 (dt, 1H, *J* = 7.88), 7.63 (d, 2H, *J* = 8.51), 7.37 – 7.30 (m, 3H), 7.21 – 7.16 (m, 3H); ^{13}C-NMR ($CDCl_3$) δ: 164.77, 150.93, 149.43, 148.39, 42.90, 135.41, 134.50, 130.94, 129.52, 129.19, 127.27, 125.97, 123.68, 121.67; LC/MS-MS: 276.20 [M + H^+].

Phenyl 4-(quinolin-3-yl)benzoate ***3***

Yield 43%, m. p. 137°C; IR ν cm^{-1}: 3057, 2924, 1728, 1608, 1492, 1269, 1197, 1082; ^{1}H-NMR ($CDCl_3$) δ: 9.15 (s, 1H), 8.31 (s, 1H), 8.27 (d, 2H, *J* = 8.51), 8.01 (d, 1H, *J* = 8.51), 7.85 (d, 1H, J = 6.94), 7.78 (d, 2H, *J* = 8.51), 7.71 – 7.68 (m, 1H), 7.56 – 7.52 (m, 1H), 7.39 – 7.36 (m, 2H), 7.23 – 7.17 (m, 3H); ^{13}C-NMR (CDCl3) δ: 164.83, 150.96, 149.47, 147.82, 142.99, 133.86, 131.04, 130.00, 129.53, 129.36, 129.16, 128.17, 127.85, 127.52, 127.32, 125.98, 121.69; LC/MS-MS: 326.17 [M + H^+].

Phenyl 4-(pyridin-4-yl)benzoate ***4***

Yield 39%, m. p. 146°C; IR ν cm^{-1}: 3043, 2928, 1725, 1592, 1486, 1401, 1272, 1185, 1085; ^{1}H-NMR ($CDCl_3$) 8.65 (s, 2H), 8.24 (d, 2H, *J* = 8.51), 7.70 (d, 2H, *J* = 8.51), 7.48 (s, 2H), 7.39 – 7.36 (m, 2H), 7.23 – 7.20 (m, 1H), 7.18 – 7.16 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ: 164.67, 150.89, 150.50, 147.06, 143.18, 130.95, 130.06, 129.55, 127.24, 126.03, 121.75, 121.64; LC/MS-MS: 276.27 [M + H^+].

Phenyl 4-(pyrimidin-5-yl)benzoate ***5***

Yield 59%, m. p. 141°C; IR ν cm^{-1}: 3064, 2926, 1726, 1610, 1554, 1489, 1414, 1268, 1183, 1077; ^{1}H-NMR ($CDCl_3$) δ: 9.28 (s, 1H), 9.03 (s, 2H), 8.35 (d, 2H, *J* = 8.83), 7.73 (d, 2H, *J* = 8.51), 7.47 – 7.43 (m, 2H), 7.31 – 7.28 (m, 1H), 7.26 – 7.23 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ: 164.52, 158.25, 155.06, 150.85, 139.27, 133.28, 131.23, 130.13, 129.56, 127.17, 126.08, 121.61; LC/MS-MS: 277.25 [M + H^+].

Benzyl 4-(thiophen-3-yl)benzoate ***6***

Yield 58%, m. p. 138°C; IR ν cm^{-1}: 1705, 1607, 1267, 1105; ^{1}H-NMR ($CDCl_3$) δ: 8.11 (d, 2H, *J* = 8.51), 7.66 (d, 2H, *J* = 8.51), 7.57 – 7.56 (m, 1H), 7.48 – 7.47 (m, 2H), 7.43 – 7.36 (m, 5H), 5.39 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ: 164.50, 139.47, 138.47, 134.42, 128.64, 126.89, 126.53, 126.45, 124.98, 124.51, 124.47, 120.22, 64.96; LC/MS-MS: 294.18 [M + H^+].

Benzyl 4-(pyridin-3-yl)benzoate ***7***

Yield 44%, m. p. 98°C; IR ν cm^{-1}: 2925, 1708, 1455, 1379, 1272, 1097; ^{1}H-NMR ($CDCl_3$) δ: 8.88 (s, 1H), 8.65 (s, 1H), 8.18 (d, 2H, *J* = 8.51), 7.90 (dt, 1H, *J* = 7.88), 7.65 (d, 2H, *J* = 8.83), 7.48 – 7.46 (m, 2H), 7.42 – 7.34 (m, 4H), 4.67 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ: 166.03, 149.29, 148.37, 142.37, 135.97, 134.45, 130.48, 129.76, 128.63, 128.19, 127.10, 123.64, 66.85; LC/MS-MS: 290.19 [M + H^+].

Benzyl 4-(quinolin-3-yl)benzoate ***8***

Yield 15%, m. p. 125°C; IR ν cm^{-1}: 3034, 2963, 1707, 1610, 1454, 1266, 1100; ^{1}H-NMR ($CDCl_3$) δ: 9.19 (s, 1H), 8.35 (s, 1H), 8.22 (d, 2H, *J* = 8.51), 8.15 (d, 1H, *J* = 8.51), 7.91 – 7.90 (m, 1H), 7.80 – 7.74 (m, 3H), 7.62 – 7.59 (m, 1H), 7.49 – 7.48 (m, 2H), 7.43 – 7.35 (m, 3H), 5.42 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ: 166.08, 149.49, 147.71, 142.43, 135.99, 133.78, 132.70, 130.58, 129.91, 129.74, 129.31, 128.65, 128.32, 128.20, 128.13, 127.85, 127.64, 127.36, 127.27, 126.98, 66.88; LC/MS-MS: 340.31 [M + H^+].

Benzyl 4-(pyridin-4-yl)benzoate ***9***

Yield 20%; IR ν cm^{-1}: 3035, 2926, 1716, 1595, 1401, 1268, 1101; ^{1}H-NMR ($CDCl_3$) δ: 8.61 (d, 2H, *J* = 5.68), 8.10 (d, 2H, *J* = 8.51), 7.60 (d, 2H, *J* = 8.51), 7.42 (d, 2H, *J* = 5.99), 7.39 (m, 2H), 7.33 – 7.26 (m, 3H), 5.31 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ: 164.87, 149.42, 146.12, 134.87, 129.46, 127.62, 127.20, 126.84, 126.02, 124.77, 120.66, 65.90; LC/MS-MS: 290.19 [M + H^+].

Benzyl 4-(pyrimidin-5-yl)benzoate ***10***

Yield 36%, m. p. 78°C; IR ν cm^{-1}: 2924, 2855, 1716, 1611, 1554, 1418, 1375, 1268; ^{1}H-NMR ($CDCl_3$) δ: 9.25 (s, 1H), 8.98 (s, 1H), 8.21 (d, 2H, *J* = 8.51), 7.65 (d, 2H, *J* = 8.83), 7.48 – 7.46 (m, 2H), 7.42 – 7.34 (m, 2H), 5.40 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ: 165.73, 158.11,

154.98, 138.69, 135.78, 133.35, 130.75, 128.63, 128.37, 128.23, 126.97, 67.00; LC/MS-MS: 291.24 [M + H$^+$].

Benzyl 2-hydroxy-5-(pyridin-3-yl)benzoate ***11***

Yield 46%; IR ν cm^{-1}: 3033, 2926, 2855, 1675, 1594, 1472, 1387, 1203; ^{1}H-NMR ($CDCl_3$) δ: 10.87 (s, 1H), 8.82 (s, 1H), 8.59 (s, 1H), 8.10 (s, 1H), 7.83–7.81 (m, 1H), 7.68 (dd, 1H, *J* = 8.51), 7.50–7.46 (m, 2H), 7.44–7.34 (m, 4H), 7.11 (d, 1H, *J* = 8.83), 5.44 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ: 169.71, 161.81, 148.26, 147.90, 135.11, 134.41, 133.91, 129.09, 128.79, 128.70, 128.44, 128.39, 127.88, 125.81, 123.59, 123.56, 118.60, 112.92, 67.32; LC/MS-MS: 306.15 [M + H$^+$].

4-Methoxyphenyl 4-(pyridin-4-yl)benzoate ***12***

Yield 48%, m. p. 171°C; IR ν cm^{-1}: 2964, 1724, 1592, 1504, 1460, 1277, 1177, 1081; ^{1}H-NMR ($CDCl_3$) δ: 8.85 (d, 2H, *J* = 6.67), 8.43 (d, 2H, *J* = 8.39), 8.15 (d, 2H, *J* = 6.65), 7.89 (d, 2H, *J* = 8.38), 7.16 (d, 2H, *J* = 9.04), 6.97 (d, 2H, *J* = 9.08), 3.84 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ: 167.07, 157.07, 148.78, 138.18, 136.10, 130.09, 129.00, 127.91, 126.16, 121.50, 55.54; LC/MS-MS: 306.01 [M + H$^+$].

4-Methoxyphenyl 4-(pyrimidin-5-yl)benzoate ***13***

Yield 29%, m. p. 156°C; IR ν cm^{-1}: 2934, 1725, 1607, 1555, 1504, 1420, 1339, 1248, 1180, 1069; ^{1}H-NMR ($CDCl_3$) δ: 9.27 (s, 1H), 9.02 (s, 2H), 8.34 (d, 2H, *J* = 8.49), 7.73 (d, 2H, *J* = 8.49), 7.16 (d, 2H, *J* = 9.03), 6.96 (d, 2H, *J* = 9.04), 3.84 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ: 164.85, 161.28, 157.14, 154.29, 146.36, 134.52, 130.89, 130.42, 124.78, 123.56, 114.29, 55.49; LC/MS-MS: 307.97 [M + H$^+$].

4-Methoxybenzyl 4-(pyridin-4-yl)benzoate ***14***

Yield 13%, m. p. 162°C; IR ν cm^{-1}: 2925, 1629, 1548, 1512, 1417, 1297, 1255, 1178, 1024; ^{1}H-NMR ($CDCl_3$) δ: 8.62 (d, 2H, *J* = 6.03), 8.10 (d, 2H, *J* = 8.52), 7.61 (d, 2H, *J* = 8.53), 7.45 (d, 2H, *J* = 6.15), 7.34 (d, 2H, *J* = 8.68), 6.86 (d, 2H, *J* = 8.70), 5.26 (s, 2H), 3.75 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ: 167.16, 160.45, 149.89, 148.65, 138.14, 131.19, 130.82, 130.34, 129.08, 126.08, 121.46, 113.75, 67.15, 55.39; LC/MS-MS: 320.14 [M + H$^+$].

4-Methoxybenzyl 4-(pyrimidin-5-yl)benzoate ***15***

Yield 50%, m. p. 165°C; IR ν cm^{-1}: 1709, 1610, 1513, 1414, 1276, 1241, 1184, 1097, 1028; ^{1}H-NMR ($CDCl_3$) δ: 9.61 (s, 1H), 8.89 (s, 2H), 8.53 (d, 2H, *J* = 8.53), 7.56 (d, 2H, *J* = 8.54), 7.32 (d, 2H, *J* = 8.69), 6.84 (d, 2H, *J* = 8.70), 5.25 (s, 2H), 3.74 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ: 167.07, 161.32, 160.65, 154.31, 133.61, 131.19, 130.88, 130.28, 129.02, 126.25, 123.35, 113.65, 67.16, 55.48; LC/MS-MS: 321.00 [M + H$^+$].

4-(Quinolin-3-yl)benzyl 4-(quinolin-3-yl)benzoate ***16***

Yield 20%, m. p. 190°C; IR ν cm^{-1}: 2925, 1718, 1608, 1494, 1273, 1116; ^{1}H-NMR ($CDCl_3$) δ: 9.21–9.19 (m, 2H), 8.36 (s, 1H), 8.32 (s, 1H), 8.25 (d, 2H, *J* = 8.22), 8.17–8.14 (m, 2H), 7.90 (t, 2H, *J* = 7.61), 7.81 (d, 2H, *J* = 8.22), 7.78–7.72 (m, 4H), 7.66–7.56 (m, 4H), 5.50 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ: 166.09, 149.50, 147.74, 147.45, 142.56, 137.98, 135.98, 133.53, 133.30, 132.64, 130.61, 129.95, 129.53, 129.33, 128.14, 128.03, 127.84, 127.71, 127.41, 127.29, 66.48; LC/MS-MS: 467.40 [M + H$^+$].

4-(Quinolin-3-yl)benzyl 4-(pyrimidin-5-yl)benzoate ***17***

Yield 29%, m. p. 166°C; IR ν cm^{-1}: 3031, 1713, 1611, 1555, 1417, 1265, 1185, 1094; ^{1}H-NMR ($CDCl_3$) δ: 9.25 (s, 1H), 9.18 (s, 1H), 8.99 (s, 2H), 8.31 (s, 1H), 8.24 (d, 2H, *J* = 8.22), 8.13 (d, 1H, *J* = 8.53), 7.88 (d, 1H, *J* = 7.92), 7.76–7.72 (m, 3H), 7.67 (d, 2H, *J* = 7.92), 7.62 (d, 2H, *J* = 8.22), 7.60–7.57 (m, 1H), 5.48 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ: 165.78, 158.15, 155.02, 149.74, 147.42, 138.82, 138.04, 135.78, 133.30, 133.24, 130.81, 130.52, 129.58, 129.25, 129.13, 128.02, 127.96, 127.72, 127.05, 66.63; LC/MS-MS: 418.27 [M + H$^+$].

N-phenyl-4-(thiophen-3-yl)benzamide ***18***

Yield 19%, m. p. 165°C; IR ν cm^{-1}: 3341, 2926, 1637, 1600, 1413; ^{1}H-NMR ($CDCl_3$) δ: 8.51–8.46 (m, 2 H), 8.24–8.18 (m, 4H), 7.95 (s, 1H), 7.89–7.86 (m, 2H), 7.73 (d, 1H, *J* = 5.68), 7.67–7.61 (m, 2H); LC/MS-MS: 280.19 [M + H$^+$].

N-phenyl-4-(pyridin-3-yl)benzamide ***19***

Yield 29%, m. p. 222°C; IR ν cm^{-1}: 3240, 2924, 1674, 1597, 1533, 1438, 1317; ^{1}H-NMR (d_6-DMSO) δ: 10.31 (s, 1H), 8.99 (s, 1H), 8.62 (dd, 1H, *J* = 4.73), 8.19 (dt, 1H, *J* = 7.88), 8.10 (d, 2H, *J* = 8.20), 7.91 (d, 2H, *J* = 8.20), 7.81 (d, 2H, *J* = 7.57), 7.55-7.52 (m, 1H), 7.36 (t, 2H, *J* = 7.25), 7.11 (t, 1H, *J* = 7.25); ^{13}C-NMR (d_6-DMSO) δ: 164.96, 149.04, 147.78, 139.97, 139.09, 134.55, 134.33, 128.56, 128.43, 126.77, 123.91, 123.67, 120.36; LC/MS-MS: 275.15 [M + H$^+$].

N-phenyl-4-(pyridin-4-yl)benzamide ***20***

Yield 23%, m. p. 225°C; IR ν cm^{-1}: 3305, 2925, 2443, 1632, 1595, 1494, 1412, 1316; ^{1}H-NMR ($CDCl_3$) δ: 8.12 (d, 2H, *J* = 5.99), 7.57 (d, 2H, *J* = 8.20), 7.36 (d, 2H, *J* = 8.51), 7.25–7.23 (m, 2H), 7.19 (d, 2H, *J* = 7.57), 6.87 (m, 2H), 7.67-6.64 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ: 166.22, 148.91, 147.71, 140.20, 137.79, 135.16, 128.03, 127.77, 126.45, 123.97, 121.47, 120.57; LC/MS-MS: 272.91 [M − H$^+$].

N-phenyl-4-(pyrimidin-5-yl)benzamide ***21***

Yield 49%, m. p. 220°C; IR ν cm^{-1}: 3316, 2361, 1677, 1599, 1538, 1400, 1326; ^{1}H-NMR ($CDCl_3$) δ: 9.19 (s, 1H), 8.96 (s, 2H), 8.02 (d, 2H, *J* = 8.20), 7.68–7.64 (m, 4H), 7.34 (m, 2H), 7.15–7.11 (m, 1H), 7.89 (dt, 1H, *J* = 7.92), 7.72–7.68 (m, 3H), 7.47 (t, 1H, *J* = 7.92), 7.37–7.34 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ: 165.36, 157.66, 154.94, 137.84, 137.18, 135.53, 133.51, 129.01, 128.40, 127.14, 124.75, 120.52; LC/MS-MS: 273.96 [M − H$^+$].

N-benzyl-4-(thiophen-3-yl)benzamide ***22***

Yield 62%, m. p. 180°C; IR ν cm^{-1}: 3346, 2928, 1635, 1521, 1278; ^{1}H-NMR ($CDCl_3$) δ: 7.82 (d, 2H, *J* = 8.83), 7.65 (d, 2H, *J* = 8.51), 7.53 (t, 1H, *J* = 2.21), 7.42 (d, 2H, *J* = 2.21), 7.38–7.37 (m, 4H), 7.33–7.29 (m, 1H), 4.67 (d, 2H, *J* = 5.68); ^{13}C-NMR ($CDCl_3$) δ: 166.89, 141.17, 138.88, 138.20, 132.75, 128.81, 127.95, 127.65, 127.57, 127.64, 126.64, 126.15, 121.53, 44.18; LC/MS-MS: 294.11 [M + H$^+$].

N-benzyl-4-(pyridin-3-yl)benzamide ***23***

Yield 50%, m. p. 108°C; IR ν cm^{-1}: 3324, 2925, 2359, 1636, 1541, 1313, 1260, 1027; ^{1}H-NMR ($CDCl_3$) δ: 8.69 (s, 1H), 8.48 (dd, 1H, *J* = 5.04), 7.82 (d, 2H, *J* = 8.20), 7.77 (dt, 1H, *J* = 7.88), 7.50 (d, 2H, *J* = 8.83), 7.29–7.23 (m, 4H), 7.21–7.18 (m, 1H), 6.94–6.92 (m, 1H), 4.57 (d, 2H, *J* = 5.68); ^{13}C-NMR ($CDCl_3$) δ: 165.89, 148.03, 147.20, 139.78, 137.23, 134.52, 133.38, 127.74, 126.87, 126.56, 126.17, 122.63, 43.12; LC/MS-MS: 289.22 [M + H$^+$].

N-benzyl-4-(quinolin-3-yl)benzamide ***24***

Yield 51%, m. p. 190°C; IR ν cm^{-1}: 3280, 3306, 2926, 2430, 1625, 1551, 1437, 1303; ^{1}H-NMR ($CDCl_3$) δ: 8.63 (s, 1H), 8.47 (s, 1H), 8.07

(s, 1H), 7.57 – 7.50 (m, 4H), 7.37 (d, 2H, *J* = 8.51), 7.15 – 7.08 (m, 3H), 7.03 – 7.00 (m, 2H), 6.87 – 6.85 (m, 2H), 4.10 (s, 2H); LC/MS-MS: 339.26 [M + H$^+$].

N-benzyl-4-(pyrimidin-5-yl)benzamide ***25***

Yield 90%, m. p. 171°C; IR ν cm^{-1}: 3314, 3056, 2229, 1641, 1533, 1418, 1313; ^{1}H-NMR ($CDCl_3$) δ: 9.23 (s, 1H), 8.96 (s, 2H), 7.94 (d, 2H, *J* = 8.51), 7.64 (d, 2H, *J* = 8.51), 7.38 – 7.30 (m, 5H), 6.55 (s, 1H), 4.67 (d, 2H, *J* = 5.68); ^{13}C-NMR ($CDCl_3$) δ: 166.46, 158.03, 154.94, 137.96, 137.35, 134.85, 133.34, 128.87, 128.13, 127.97, 127.78, 127.18, 44.30; LC/MS-MS: 290.19 [M + H$^+$].

N-benzyl-2-hydroxy-5-(pyridin-3-yl)benzamide ***26***

Yield 11%; IR ν cm^{-1}: 3349, 2926, 1732, 1642, 1543, 1474, 1290, 1230; ^{1}H-NMR ($CDCl_3$) δ: 8.81 (s, 1H), 8.51 (s, 1H), 7.84 (s, 1H), 7.66 (s, 1H), 7.55 (d, 1H, *J* = 8.51), 7.37 – 7.29 (m, 7H), 7.08 (d, 2H, *J* = 8.51), 4.66 (d, 2H, *J* = 5.68); LC/MS-MS: 303.19 [M – H$^+$].

N-(furan-2-ylmethyl)-4-(pyridin-3-yl)benzamide ***27***

Yield 23%, m. p. 137°C; IR ν cm^{-1}: 3313, 2934, 1630, 1544, 1310, 1190, 1154; ^{1}H-NMR ($CDCl_3$) δ: 8.84 (s, 1H), 8.61 (s, 1H), 7.91 – 7.86 (m, 3H), 7.63 (d, 2H, *J* = 8.51), 7.40 – 7.37 (m, 2H), 6.61 (s, 1H), 6.36 – 6.31 (m, 2H), 4.66 (d, 2H, *J* = 5.36); ^{13}C-NMR ($CDCl_3$) δ: 166.31, 151.10, 149.12, 148.28, 142.36, 141.01, 135.54, 134.42, 133.75, 127.85, 127.27, 123.64, 110.56, 107.80, 37.09; LC/MS-MS: 279.21 [M + H$^+$].

N-(furan-2-ylmethyl)-4-(quinolin-3-yl)benzamide ***28***

Yield 76%, m. p. 176°C; IR ν cm^{-1}: 2962, 1728, 1649, 1546, 1495, 1377, 1272, 1122, 1073; ^{1}H-NMR ($CDCl_3$) δ: 9.10 (s, 1H), 8.25 (s, 1H), 8.07 (d, 1H, *J* = 8.20), 7.87 (d, 2H, *J* = 8.51), 7.81 (d, 1H, *J* = 8.20), 7.71 – 7.64 (m, 3H), 7.54 – 7.51 (m, 1H), 7.32 (s, 1H), 6.53 (s, 1H), 6.29 – 6.26 (m, 2H), 4.61 (d, 2H, *J* = 5.36); ^{13}C-NMR ($CDCl_3$) δ: 166.24, 151.10, 149.49, 147.66, 142.38, 141.10, 133.68, 133.61, 129.83, 129.30, 128.84, 128.09, 127.87, 127.93, 127.53, 127.24, 110.57, 107.81, 37.11; LC/MS-MS: 329.04 [M + H$^+$].

N-(furan-2-ylmethyl)-4-(pyridin-4-yl)benzamide ***29***

Yield 77%, m. p. 158°C; IR ν cm^{-1}: 3254, 1635, 1596, 1554, 1486, 1414, 1315, 1189, 1070; ^{1}H-NMR ($CDCl_3$) δ: 8.66 – 8.65 (m, 2H), 7.90 (d, 2H, *J* = 8.51), 7.56 (d, 2H, *J* = 8.83), 7.50 – 7.48 (m, 2H), 7.37 – 7.36 (m, 1H), 6.82 (s, 1H), 6.34 – 6.33 (m, 1H), 6.30 – 6.29 (m, 1H), 4.65 (d, 2H, *J* = 5.36); ^{13}C-NMR ($CDCl_3$) δ: 166.55, 151.11, 150.34, 147.21, 142.32, 141.18, 134.66, 132.10, 128.55, 128.46, 127.91, 127.17, 121.63, 110.54, 107.78, 37.08; LC/MS-MS: 279.21 [M + H$^+$].

N-(furan-2-ylmethyl)-4-(pyrimidin-5-yl)benzamide ***30***

Yield 73%, m. p. 165°C; IR ν cm^{-1}: 3343, 1634, 1544, 1415, 1307, 1190; ^{1}H-NMR ($CDCl_3$) δ: 9.14 (s, 1H), 8.87 (s, 2H), 7.87 (d, 2H, d, *J* = 8.51), 7.55 (d, 2H, *J* = 8.51), 7.30 – 7.29 (m, 1H), 6.72 (s, 1H), 6.28 – 6.27 (m, 1H), 6.26 – 6.24 (m, 1H), 4.59 (d, 2H, *J* = 5.36); ^{13}C-NMR ($CDCl_3$) δ: 166.37, 157.99, 154.91, 151.02, 142.36, 137.34, 134.68, 133.32, 128.20, 127.11, 110.57, 107.84, 37.11; LC/MS-MS: 280.12 [M + H$^+$].

N-(4-methoxyphenyl)-4-(pyridin-4-yl)benzamide ***31***

Yield 26%; IR ν cm^{-1}: 2987, 1715, 1598, 1515, 1453, 1402, 1365, 1249, 1182, 1026; ^{1}H-NMR ($CDCl_3$) δ: 9.16 (s, 1H), 8.89 (s, 2H), 8.12 (d, 2H, *J* = 8.53), 7.56 (d, 2H, *J* = 8.54), 7.32 (d, 2H, *J* = 8.69), 6.84 (d, 2H, *J* = 8.70), 3.74 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ: 167.35, 156.56, 153.45, 150.07, 135.30, 134.71, 131.58, 130.62, 129.47, 123.17, 121.48, 114.35, 55.44; LC/MS-MS: 306.01 [M + H$^+$].

N-(4-methoxyphenyl)-4-(pyrimidin-5-yl)benzamide ***32***

Yield 22%; IR ν cm^{-1}: 3046, 1645, 1514, 1410, 1325, 1246, 1175, 1118; ^{1}H-NMR ($CDCl_3$) δ: 9.26 (s, 1H), 9.00 (s, 2H), 8.03 (d, 2H, *J* = 8.06), 7.76 (s, 1H), 7.71 (d, 2H, *J* = 8.17), 7.57 (d, 2H, *J* = 8.48), 6.94 (d, 2H, *J* = 8.86), 3.83 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ: 167.35, 161.21, 156.48, 155.84, 137.86, 135.35, 134.54, 131.71, 130.69, 128.05, 121.25, 114.37, 55.43; LC/MS-MS: 306.27 [M + H$^+$].

N-(4-methoxybenzyl)-4-(pyridin-4-yl)benzamide ***33***

Yield 19%, m. p. 174°C; IR ν cm^{-1}: 3298, 1635, 1594, 1556, 1511, 1414, 1316, 1242, 1174, 1033; ^{1}H-NMR ($CDCl_3$) δ: 8.75 (d, 2H, *J* = 5.67), 7.89 (d, 2H, *J* = 8.13), 7.91 (d, 2H, *J* = 5.63), 7.76 (d, 2H, *J* = 7.63), 7.29 (d, 2H, *J* = 8.33), 6.88 (d, 2H, *J* = 8.53), 6.43 (s, 1H), 4.60 (d, 2H, *J* = 5.55), 3.79 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ: 166.58, 160.28, 153.34, 150.11, 135.41, 132.57, 130.18, 129.86, 128.68, 123.07, 113.88, 55.14, 44.20; LC/MS-MS: 319.58 [M + H$^+$].

N-(3-(thiophen-3-yl)phenyl)-4-(pyridin-3-yl)benzamide ***34***

Yield 24%, m. p. 175°C; IR ν cm^{-1}: 3270, 2924, 1650, 1601, 1480, 1304; ^{1}H-NMR ($CDCl_3$) δ: 8.81 (s, 1H), 8.58 (s, 1H), 7.95-7.93 (m, 3H), 7.90 (s, 1H), 7.85 (dt, 1H, *J* = 7.88), 7.63 (d, 2H, *J* = 8.51), 7.53 – 7.50 (m, 1H), 7.43 – 7.42 (m, 1H), 7.34 – 7.31 (m, 3H), 7.19 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ: 165.17, 149.24, 148.30, 141.79, 141.31, 138.35, 136.89, 134.46, 129.55, 127.88, 127.50, 126.33, 126.28, 123.70, 122.81, 120.80, 118.90, 118.27; LC/MS-MS: 357.24 [M + H$^+$].

N-(3-(pyridin-3-yl)phenyl)-4-(pyridin-3-yl)benzamide ***35***

Yield 3%, m. p. 70°C; IR ν cm^{-1}: 2963, 1655, 1594, 1545, 1425, 1260; ^{1}H-NMR ($CDCl_3$) δ: 8.90 – 8.88 (m, 2H), 8.67 – 8.65 (m, 1H), 8.62 – 8.61 (m, 1H), 8.05 – 7.99 (m, 4H), 7.94 – 7.92 (m, 2H), 7.72 (d, 2H, *J* = 8.51), 7.69 – 7.67 (m, 1H), 7.51 (t, 1H, *J* = 7.88), 7.43 – 7.38 (m, 3H); LC/MS-MS: 350.91 [M – H$^+$].

N-(3-(pyridin-3-yl)phenyl)-4-(pyridin-4-yl) benzamide ***36***

Yield 6%; IR ν cm^{-1}: 3265, 3039, 1665, 1595, 1547, 1471, 1401, 1295, 1259; ^{1}H-NMR ($CDCl_3$) δ: 8.88 (s, 1H), 8.72 – 8.71 (m, 2H), 8.61 – 8.60 (m, 1H), 8.24 (s, 1H), 8.04 (d, 2H, *J* = 8.51), 8.00 (s, 1H), 7.94 – 7.92 (m, 1H), 7.76 (d, 2H, *J* = 8.83), 7.70 (s, 1H), 7.55 – 7.54 (m, 2H), 7.50 (t, 1H, *J* = 7.88), 7.40 – 7.37 (m, 2H); LC/MS-MS: 349.98 [M – H$^+$].

N-(3-(pyridin-3-yl)phenyl)-4-(pyrimidin-5-yl) benzamide ***37***

Yield 24%, m. p. 155°C; IR ν cm^{-1}: 3287, 3045, 1677, 1597, 1554, 1399, 1294; ^{1}H-NMR ($CDCl_3$) δ: 9.24 (s, 1H), 8.96 (s, 2H), 8.84 (s, 1H), 8.57 – 8.53 (m, 2H), 8.07 (d, 2H, *J* = 8.53), 7.97 (s, 1H), 7.89 (dt, 1H, *J* = 7.92), 7.72 – 7.68 (m, 3H), 7.47 (t, 1H, *J* = 7.92), 7.37 – 7.34 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ: 165.20, 158.09, 154.95, 148.63, 148.16, 138.78, 138.69, 137.69, 136.21, 135.24, 134.57, 129.87, 128.36, 127.31, 123.65, 123.46, 120.04, 119.11; LC/MS-MS: 353.25 [M + H$^+$].

4-(Thiophen-3-yl)benzoic acid ***38***

Yield 94%, m. p. 280°C (Lit.: 281–282°C) [9]; ^{1}H-NMR (d_6-DMSO) δ: 8.05–8.04 (m, 1H), 7.96 (d, 2H, *J* = 8.51), 7.85 (d, 2H, *J* = 8.20), 7.63–7.68 (m, 1H), 7.64–7.63 (m, 1H); ^{13}C-NMR (d_6-DMSO) δ: 167.02, 140.31, 139.09, 129.92, 129.07, 127.46, 126.14, 125.99, 122.79.

4-(Pyridin-3-yl)benzoic acid ***39***

Yield 62%, m. p. 215°C (Lit.: 215°C) [10]; ^{1}H-NMR (D_2O / TFA) δ: 7.80 (s, 1H), 7.61–7.56 (m, 2H), 7.00 (d, 2H, *J* = 8.51), 6.96–6.93 (m, 1H), 6.56 (d, 2H, *J* = 8.51).

4-(Chinolin-3-yl)benzoic acid ***40***

Yield 92%; ^{1}H-NMR (d_6-DMSO / TFA : 1 / 0.1) δ: 9.66 (s, 1H), 9.51 (s, 1H), 7.80–7.78 (m, 1H), 8.38 (d, 1H, *J* = 7.88), 8.27 (d, 1H, *J* = 8.51), 8.15–8.08 (m, 5H), 7.98–7.95 (m, 1H); (Lit.: 250 MHz, d_6-DMSO: 13.09 (br s, 1H), 9.32 (d, 1H), 8.76 (d, 1H), 8.07 (m, 5H), 7.83 (m, 2H), 7.67 (m, 1H)) [11]; ^{13}C-NMR (d_6-DMSO + TFA) δ: 166.79, 144.39, 132.64, 131.15, 130.18, 127.61, 129.76, 129.47, 118.44, 116.15, 113.85, 111.56.

5-(Pyridin-3-yl)salicylic acid ***41***

Yield 46%, m. p. 260°C (Lit.: 263°C) [12]; ^{1}H-NMR (D_2O / TFA : 1 / 1) δ: 7.61 (s, 1H), 7.42–7.40 (m, 1H), 7.36–7.35 (m, 1H), 6.93 (d, 1H, *J* = 2.52), 6.78–6.75 (m, 1H), 6.49 (dd, 1H, *J* = 8.51), 5.84 (d, 1H, *J* = 8.83); ^{13}C-NMR had no expressiveness because of the TFA.

4-(Pyrimidin-5-yl)benzoic acid ***42***

Yield 60%, m. p. 218°C (Lit. 220°C) [13]; ^{1}H-NMR (d_6-DMSO) δ: 9.17 (s, 1H), 9.15 (s, 2H), 8.01 (d, 2H, *J* = 8.20), 7.74 (d, 2H, *J* = 8.20); ^{13}C-NMR (d_6-DMSO) δ: 169.60, 157.11, 154.60, 140.35, 133.92, 133.18, 131.47, 131.39, 129.85, 128.75, 125.81.

4-(Pyridin-4-yl)benzoic acid ***43***

Yield 98%, m. p. 208°C (Lit.: 210°C) [14]; due to the insolubility of the compound, it was impossible to measure NMR. Further reactions showed it to be the desired product.

3-(Thiophen-3-yl)aniline ***44***

Yield 82%, m. p. 85°C (Lit.: 86–88°C) [15]; ^{1}H-NMR ($CDCl_3$) δ: 7.44–7.43 (m, 1H), 7.40–7.39 (m, 2H), 7.22 (t, 1H, *J* = 7.88), 7.07–7.05 (m, 1H), 6.94–6.93 (m, 1H), 6.66–6.64 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ: 146.89, 142.58, 136.96, 129.81, 126.51, 126.04, 120.28, 117.04, 114.12, 113.21.

3-(Pyridin-3-yl)-aniline ***45***

Yield 54%, m. p. 75°C (Lit.: 72–74°C) [16]; ^{1}H-NMR ($CDCl_3$) δ: 8.80 (s, 1H), 8.54 (s, 1H), 7.80–7.78 (m, 1H), 7.30–7.28 (m, 1H), 7.23–7.22 (m, 1H), 6.93–6.91 (m, 1H), 6.83 (s, 1H), 6.69–6.67 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ: 148.33, 134.28, 132.11, 132.03, 131.93, 129.98, 128.46, 123.44, 117.30, 114.78, 113.57.

4-(Chinolin-3-yl)benzyl alcohol ***46***

Yield 48%; ^{1}H-NMR ($CDCl_3$) δ: 9.06 (s, 1H), 8.28 (s, 1H), 8.12 (d, 1H, *J* = 8.53), 7.87–7.85 (m, 1H), 7.73–7.67 (m, 3H), 7.58–7.55 (m, 1H), 7.50 (d, 2H, *J* = 8.53), 7.24 (s, 1H), 4.77 (s, 2H); (Lit.: d_6-DMSO: 8.88 (d, 1H, *J* = 2.00), 8.56 (dd, 1H, *J* = 5, 20), 8.07 (dt, 1H, *J* = 8, 20), 7.68 (d, 2H, *J* = 8.00), 7.48 (dd, 1H, *J* = 8, 50), 7.44 (d, 2H, *J* = 8.00), 5.25 (t, 1H, *J* = 6.00), 4.55 (d, 2H, *J* = 6.00)) [17]; ^{13}C-NMR ($CDCl_3$) δ: 149.82, 147.27, 142.30, 141.03, 140.36, 140.31, 137.16, 133.52, 133.19, 129.46, 129.16, 127.99, 127.81, 127.56, 127.05, 64.31.

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