

Palladium-Catalyzed Selective Carbonylation Reactions of *Ortho*-Phenylene Dihalides with Bifunctional *N,O*-Nucleophiles

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General considerations

Palladium precursors, phosphine ligands, solvents and other additives were purchased from Sigma-Aldrich Kft., Budapest, Hungary and were used without further purification. The reactions were performed under inert argon atmosphere using Schlenk techniques.

Conversion and selectivity were determined Shimadzu GC- gas chromatograph, using splitless injection and FID detector (column: DB-1MS or DB-5MS (30m x 0.250mm x 0.25 μ m) inlet temperature: 250 °C; starting oven temperature: 50 °C; rate: 15 °C/min; final temperature: 320 °C, carrier gas: N₂ 1.30 mL/min).

For MS measurements Shimadzu GC-MS was used with electron spray ionisation (ESI). The data are given as mass unit per charge (m/z) and intensities are given in brackets.

The ¹H- and ¹³C-NMR spectra were recorded on a Bruker Avance-III 500 spectrometer at 500 and 125 MHz, respectively. Chemical shifts δ (ppm) are given relative to solvent: references for CDCl₃ were 7.26 ppm (¹H-NMR) and 77.16 ppm (¹³C-NMR). Multiplets were assigned as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), m (multiplet).

High-resolution mass spectrometry (HRMS) data were obtained using a 6530 Accurate-Mass Quadrupole Time-of-Flight (Q-TOF) LC/MS system (Agilent Technologies, Singapore). The compounds were ionized by an Agilent Jet Stream electrospray ion source.

General atmospheric carbonylation reaction

In a typical experiment, catalyst precursor [Pd(OAc)₂] (2 mol %) and ligand (4 mol % monophosphine, 2 mol % diphosphine) were placed in a three-necked flask, which was refilled with argon gas three times. DMF (10 mL), 2-iodobromobenzene (0.5 mmol), 2-aminoethanol (0.5 mmol) and Et₃N (2.0 mmol) were transferred to the flask, against constant argon flow. Finally, the atmosphere was changed to carbon monoxide (1 bar). The mixture was placed in a heating block (100 °C) and stirred with a magnetic stirrer for 24 hours. After the given reaction time the reaction mixture was cooled, filtered and immediately analyzed by GC and GC-MS.

General high-pressure carbonylation reaction

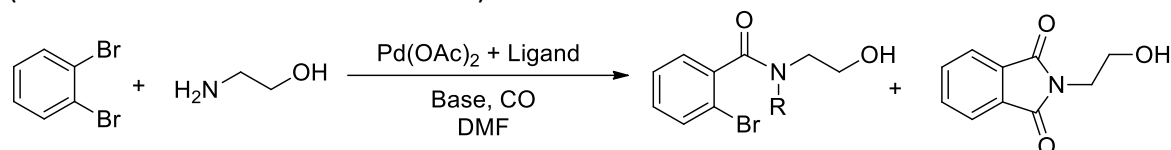
In a typical experiment, catalyst precursor [Pd(OAc)₂] (2 mol %) and ligand (4 mol % monophosphine, 2 mol % diphosphine) were placed in a stainless steel autoclave and the atmosphere was refilled with argon gas three times. DMF (10 mL), iodobenzene (0.5 mmol), 2-aminoethanol (0.5 mmol) and Et₃N (2.0 mmol) were transferred to the autoclave. The reaction vessel was pressurized to 40 bar carbon monoxide, placed in a heating block (100 °C) and stirred with a magnetic stirrer for 24 hours. After cooling and venting the autoclave, the pale yellow solution was removed and immediately analyzed by GC and GC-MS.

Copper-catalyzed C-O coupling reaction

In a typical experiment, catalyst precursor [CuI] (20 mol %) and ligand [R-BINAM] (20 mol %) were placed in a three-necked flask, which was refilled with argon gas three times. DMSO (10 mL), substrate (0.5 mmol) and KOtBu (1.0 mmol) were transferred to the flask, against constant argon flow. The mixture was placed in a heating block (130 °C) and stirred with a magnetic stirrer for 24 hours under argon atmosphere (1 bar). After the given reaction time the reaction mixture was cooled, filtered and immediately analyzed by GC and GC-MS.

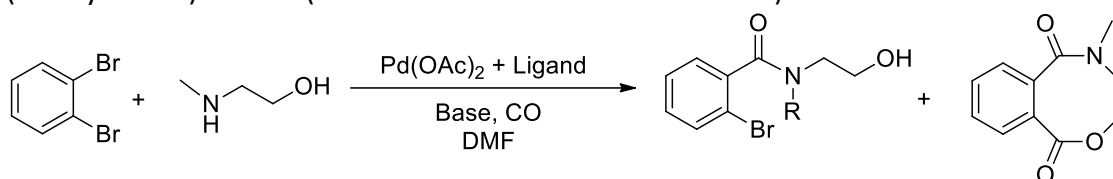
Reaction condition screening

Table S1. Carbonylation of 1,2-dibromobenzene in the presence of 2-aminoethanol (reaction conditions under the table)



#	Ligand [0.002 mmol]		Substrate-Nucleophile ratio	Conv. [%]	Products [%]		
							other
1	Xantphos		1:1	34	25	7	2
2	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene		1:2	37	28	7	2
3	N-XantPhos		1:1	49	29	16	4
4	NiXantphos, 4,6-Bis(diphenylphosphino)-10H-phenoxazine, 4,6-Bis(diphenylphosphino)phenoxazine		1:2	55	40	14	1
5	tBu-XantPhos		1:1	0	-	-	-
6	9,9-Dimethyl-4,5-bis(di-tert-butylphosphino)xanthene		1:2	0	-	-	-
7	DPPF		1:1	0	-	-	-
8	1,1'-Ferrocenediyl-bis(diphenylphosphine)		1:2	0	-	-	-
9	DiPrPF		1:1	18	11	6	1
10	1,1'-Bis(diisopropylphosphino)ferrocene		1:2	23	15	7	1
11	DPEPhos		1:1	8	6	1	1
12	(Oxydi-2,1-phenylene)bis(diphenylphosphine)		1:2	9	7	1	1
Reaction conditions: Pd(OAc) ₂ (0.002 mmol); 1,2-dibromobenzene (0.1 mmol); 2-aminoethanol (1 or 2 eq.); Et ₃ N (0.4 mmol); DMF (2 mL); p _{CO} =1 bar; T=100°C; t=24 h.							

Table S2. Carbonylation of 1,2-dibromobenzene in the presence of 2-(methyamino)ethanol (reaction conditions under the table)



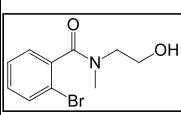
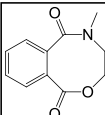
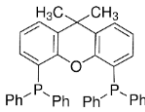
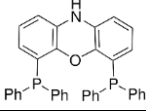
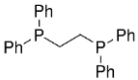
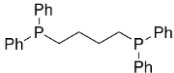
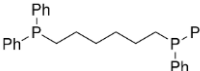
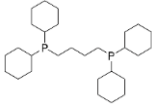
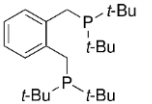
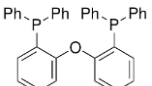
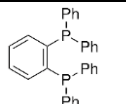
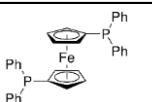
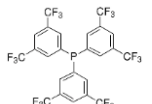
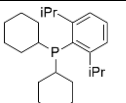
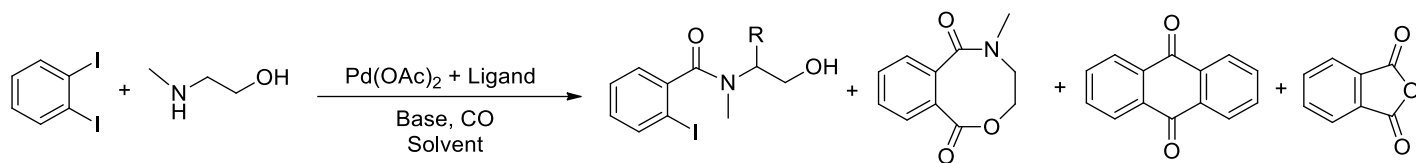
#	Ligand [0.002 mmol]		Conv. [%]	Products [%]	
					
1	Xantphos		30	30	trace
	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene				
2	N-XantPhos		42	41	1
	NiXantphos, 4,6-Bis(diphenylphosphino)-10H-phenoxazine, 4,6-Bis(diphenylphosphino)phenoxazine				
3	DPPE		2	2	-
	1,2-Bis(diphenylphosphino)ethane				
4	DPPB		3	3	-
	1,4-Bis(diphenylphosphino)butane				
5	DPPH		<1	<1	-
	1,6-Bis(diphenylphosphino)hexane				
6	DCyPB		6	6	-
	1,4-Bis(dicyclohexylphosphino)butane				
7	dt BuPB		<1	<1	-
	1,2-Bis(di-tert-butylphosphinomethyl)benzene				
8	DPEPhos		36	36	trace
	(Oxydi-2,1-phenylene)bis(diphenylphosphine)				
9	BPPBenz		<1	<1	-
	1,2-Bis(diphenylphosphino)benzene				
10	DPPF		18	18	trace
	1,1'-Ferrocenediyl-bis(diphenylphosphine)				
11	3,5-CF ₃ -PPh ₃		<1	<1	-
	Tris[3,5-bis(trifluoromethyl)phenyl]phosphine				
12	DCy ₂ (iPr) ₂ Ph		<1	<1	-
	Dicyclohexyl-(2,6-diisopropylphenyl)phosphine				
Reaction conditions: Pd(OAc) ₂ (0.002 mmol); 1,2-dibromobenzene (0.1 mmol); N-methylethanolamine (0.1 mmol); Et ₃ N (0.4 mmol); DMF (2 mL); p _{CO} =1 bar; T=100°C; t=24 h.					

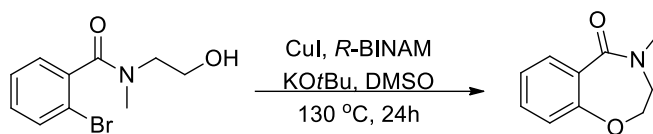
Table S3. Carbonylation of 1,2-diiodobenzene in the presence of 2-(methylamino)ethanol



#	Ligand [mmol]	Base [mmol]	Solvent	T [°C]	t [h]	Conv. [%]	Selectivity [%]				
											Other ^a
1	TPP [0.005]	Et_3N [0.5]	DMF	75	24	84	74	0	6	20	0
2	TPP [0.005]	DABCO [0.5]	DMF	75	24	100	33	16	15	36	0
3	TPP [0.005]	DBU [0.5]	DMF	75	24	0	0	0	0	0	0
4	TPP [0.005]	Na_3PO_4 [0.5]	DMF	75	24	100	8	33	20	39	0
5	Xantphos [0.005]	Et_3N [0.5]	DMF	75	24	95	17	7	0	72	0
6	tBu-Xantphos [0.005]	Et_3N [0.5]	DMF	75	24	7	100	0	0	0	0
7	DPPF [0.005]	Et_3N [0.5]	DMF	75	24	16	100	0	0	0	0
8	$\text{DCy}_2(\text{iPr})_2\text{Ph}$ [0.005]	Et_3N [0.5]	DMF	75	24	100	11	4	26	39	20
9	dtBuPB [0.005]	Et_3N [0.5]	DMF	75	24	24	100	0	0	0	0
10	3,5- CF_3 -PPh ₃ [0.005]	Et_3N [0.5]	DMF	75	24	69	64	9	0	16	11
11	TPP [0.005]	Et_3N [0.5]	DMSO	75	24	71	0	0	0	0	100
12	TPP [0.005]	Na_3PO_4 [0.5]	DMSO	75	24	100	21	14	24	32	9
13	TPP [0.005]	K_2CO_3 [0.5]	DMSO	75	24	100	0	0	0	10	90
14	TPP [0.005]	Et_3N [0.5]	MeCN	75	24	25	94	0	0	0	6
15	TPP [0.005]	Na_3PO_4 [0.5]	MeCN	75	24	40	78	13	0	0	9
16	TPP [0.005]	K_2CO_3 [0.5]	MeCN	75	24	73	27	25	4	21	24
17	TPP [0.005]	Et_3N [0.5]	Dioxane	75	24	12	50	33	0	0	17
18	TPP [0.005]	Na_3PO_4 [0.5]	Dioxane	75	24	40	53	5	0	0	42
19	TPP [0.005]	K_2CO_3 [0.5]	Dioxane	75	24	60	13	37	10	36	10
20	TPP [0.005]	Et_3N [0.5]	THF	75	24	7	0	0	0	0	100
21	TPP [0.005]	Na_3PO_4 [0.5]	THF	75	24	7	0	0	0	0	100
22	TPP [0.005]	K_2CO_3 [0.5]	THF	75	24	7	0	0	0	0	100
23	Xantphos [0.005]	K_2CO_3 [0.5]	DMF	50	24	81	0	0	0	0	100
24	Xantphos [0.005]	K_2CO_3 [0.5]	DMF	75	24	100	0	38	32	30	0
25	Xantphos [0.005]	K_2CO_3 [0.5]	DMF	100	24	100	0	23	44	33	4
26	Xantphos [0.005]	Na_3PO_4 [0.5]	DMF	50	24	100	8	16	13	42	21
27	Xantphos [0.005]	Na_3PO_4 [0.5]	DMF	75	24	100	5	32	14	49	0
28	Xantphos [0.005]	Na_3PO_4 [0.5]	DMF	100	24	100	5	33	15	47	0
29	Xantphos [0.01]	K_2CO_3 [0.5]	DMF (anhydr.)	75	24	100	5	48	47	0	12
30 ^a	Xantphos [0.01]	K_2CO_3 [0.5]	DMF (anhydr.)	75	24	100	0	38	0	31	31
30 ^b	Xantphos [0.01]	K_2CO_3 [0.5]	DMF (anhydr.)	75	24	100	0	38	0	31	31

Reaction conditions: $\text{Pd}(\text{OAc})_2$ (0.0025 mmol), 1,2-diiodobenzene (0.125 mmol), N-methylethanolamine (0.125 mmol), Solvent (5 mL), $p\text{CO}=1$ bar. ^a Unidentified side products. ^a N-methylethanolamine (0.25 mmol). ^b N-methylethanolamine (0.50 mmol).

Table S4. Intramolecular C-O coupling of 2-bromo-N-(2-hydroxyethyl)-N-methylbenzamide (**3b**)

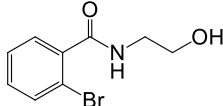


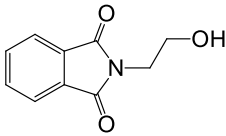
#	precursor [mmol]	ligand [mmol]	substrate (3b) [mmol]	additive [mmol]	base [mmol]	solvent	T [°C]	t [h]	conversion [%]	oxazepine selectivity [%]
1	CuI [0.05]	R-BINAM [0.05]	0.25	-	Cs ₂ CO ₃ [0.5]	DMF [5 ml]	130	24	100	0
2	CuI [0.05]	R-BINAM [0.05]	0.25	-	Cs ₂ CO ₃ [0.5]	dioxane [5 ml]	110	24	100	0
3	Pd(OAc) ₂ [0.025]	-	0.25	Bu ₄ NI [0.375]	Cs ₂ CO ₃ [0.375]	DMF [4 ml]	110	24	100	0
4	CuI [0.05]	R-BINAM [0.05]	0.25	-	Cs ₂ CO ₃ [0.5]	DMF [5 ml]	110	24	100	0
5	Pd(OAc) ₂ [0.025]	-	0.25	Bu ₄ NI [0.375]	Cs ₂ CO ₃ [0.375]	DMF [6 ml]	110	24	100	0
6	CuI [0.05]	R-BINAM [0.05]	0.25	-	Cs ₂ CO ₃ [0.5]	dioxane [5 ml]	100	24	100	0
7	Pd(OAc) ₂ [0.025]	TPP [0.0375]	0.25	Bu ₄ NI [0.375]	Cs ₂ CO ₃ [0.375]	DMF [4 ml]	130	24	100	0
8	PdCl ₂ [0.025]	TPP [0.0375]	0.25	Bu ₄ NI [0.375]	Cs ₂ CO ₃ [0.375]	DMF [4 ml]	130	24	100	0
9	CuI [0.025]	R-BINAM [0.025]	0.125	-	Cs ₂ CO ₃ [0.25]	DMF [2.5 ml]	130	24	100	0
10	CuI [0.025]	R-BINAM [0.025]	0.125	-	Cs ₂ CO ₃ [0.25]	DMSO [2.5 ml]	130	24	100	0
11	CuI [0.025]	R-BINAM [0.025]	0.125	-	Na ₂ CO ₃ [0.25]	DMF [2.5 ml]	130	24	100	0
12	CuI [0.025]	R-BINAM [0.025]	0.125	-	Na ₂ CO ₃ [0.25]	DMSO [2.5 ml]	130	24	100	0
13	CuI [0.025]	R-BINAM [0.025]	0.125	-	KOtBu [0.25]	DMF [2.5 ml]	130	24	100	0
14	CuI [0.025]	R-BINAM [0.025]	0.125	-	KOtBu [0.25]	DMSO [2.5 ml]	130	24	100	24
15	CuI [0.025]	R-BINAM [0.025]	0.125	-	DABCO [0.25]	DMF [2.5 ml]	130	24	100	0
16	CuI [0.025]	R-BINAM [0.025]	0.125	-	DABCO [0.25]	DMSO [2.5 ml]	130	24	100	0
17	CuI [0.025]	R-BINAM [0.025]	0.125	-	Et ₃ N [0.25]	DMF [2.5 ml]	130	24	100	0
18	CuI [0.025]	R-BINAM [0.025]	0.125	-	Et ₃ N [0.25]	DMSO [2.5 ml]	130	24	100	0
19	CuI [0.025]	R-BINAM [0.025]	0.125	-	DBU [0.25]	DMF [2.5 ml]	130	24	100	0
20	CuI [0.025]	R-BINAM [0.025]	0.125	-	DBU [0.25]	DMSO [2.5 ml]	130	24	100	0
21	CuI [0.1]	R-BINAM [0.1]	0.5	-	KOtBu [1.0]	DMSO [10 ml]	130	24	100	35
22	CuI [0.1]	R-BINAM [0.1]	0.5	-	KOtBu [1.0]	DMSO [10 ml]	130	24	100	34

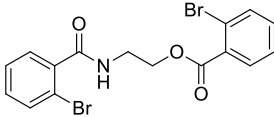
The general procedure of product isolation/purification

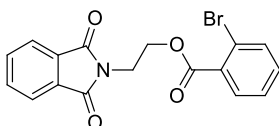
The solvent of the reaction mixture was evaporated under vacuum and the crude product was purified by column chromatography on silica gel (0.063-0.2) using different eluents (given in the characterization) to afford the corresponding products.

Characterization of the prepared compounds

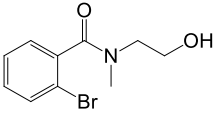
3a 	Isolated yield: 0.0996 g (82%). R_F : 0.46 (on silica gel chloroform:2-propanol=9:1). Yellow high viscosity liquid.
	δ_H (500 MHz, $CDCl_3$) 7.62 (1H, d, 7.5 Hz, <i>Ar</i>), 7.58 (1H, d, 7.5 Hz, <i>Ar</i>), 7.39 (1H, t, 7.6 Hz, <i>Ar</i>), 7.3 (1H, t, 7.6 Hz, <i>Ar</i>), 6.82 (1H, s, <i>NH</i>), 3.77 (2H, t, 4.9 Hz, OCH_2), 3.67 (2H, m, $NHCH_2$).
	δ_C (125.7 MHz, $CDCl_3$) 168.4, 133.4, 131.4, 129.7, 127.6, 119.3, 62.1, 42.8.
	MS m/z (rel int.): 245/243 (1, M^+), 225/227 (7), 200/202 (37), 183/185 (100), 155/157 (25), 146 (15), 77 (11).
	HRMS (ESI-Q-TOF) m/z calcd for $C_9H_{10}BrNO_2$ $[M+H]^+$: 243.9968; found: 243.9970.

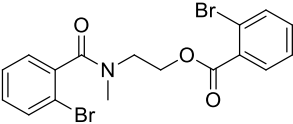
4a 	Isolated yield: 0.0382 g (40%). R_F : 0.40 (on silica gel chloroform:ethyl acetate=7:3). Brownish white crystals.
	δ_H (500 MHz, $CDCl_3$) 7.88-7.86 (2H, m, <i>Ar</i>), 7.75-7.74 (2H, m, <i>Ar</i>), 3.93-3.89 (4H, m, CH_2).
	δ_C (125.7 MHz, $CDCl_3$) 168.8, 134.1, 132.0, 123.4, 61.0, 40.9.
	MS m/z (rel int.): 191 (3, M^+), 160 (100), 148 (48), 133 (27), 104 (20), 77 (26), 50 (9).
	HRMS (ESI-Q-TOF) m/z calcd for $C_{10}H_9NO_3$ $[M+H]^+$: 192.0655; found: 192.0659.

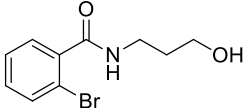
6a 	Isolated yield: 0.1381 g (65%). R_F : 0.49 (on silica gel chloroform:2-propanol=95:5). Yellowish brown high viscosity liquid.
	δ_H (500 MHz, $CDCl_3$) 7.86 (1H, d, 7.6 Hz, <i>Ar</i>), 7.69 (1H, d, 7.6 Hz, <i>Ar</i>), 7.61 (1H, d, 7.9 Hz, <i>Ar</i>), 7.58 (1H, d, 7.9 Hz, <i>Ar</i>), 7.43-7.36 (3H, m, <i>Ar</i>), 7.32 (1H, d, 7.9 Hz, <i>Ar</i>), 6.43 (1H, br s, <i>NH</i>), 4.61 (2H, t, 5.3 Hz, CH_2O), 3.95-3.92 (2H, m, CH_2NH).
	δ_C (125.7 MHz, $CDCl_3$) 167.7, 166.2, 137.5, 134.4, 133.4, 132.8, 131.9, 131.6, 131.4, 129.6, 127.6, 127.3, 121.6, 119.3, 64.3, 39.1.
	MS m/z (rel int.): 244/242 (14), 227/225 (31), 185/183 (100), 157/155 (16), 146 (33), 105 (9), 76 (19), 50 (9).

7a 	Isolated yield: 0.0281 g (12%). R_F : 0.84 (on silica gel chloroform:ethyl acetate=9:1). Brownish white crystals.
	δ_H (500 MHz, $CDCl_3$) 7.91-7.89 (2H, m, <i>Ar</i>), 7.84 (1H, d, 7.9 Hz, <i>Ar</i>), 7.77-7.75 (2H, m, <i>Ar</i>), 7.65 (1H, d, 7.9 Hz, <i>Ar</i>), 7.40-7.37 (1H, m, <i>Ar</i>), 7.35-7.32 (1H, m, <i>Ar</i>), 4.62 (2H, t, 5.4 Hz, CH_2O), 4.15 (2H, t, 5.4 Hz, CH_2N).
	δ_C (125.7 MHz, $CDCl_3$) 168.1, 165.7, 134.3, 134.1, 132.7, 132.1, 131.7, 127.2, 123.5, 122.7, 121.9, 62.6, 37.0.

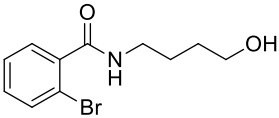
	MS m/z (rel int.): 185/183 (20), 173 (100), 160 (22), 105 (11), 77 (8).
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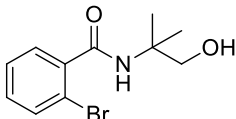
3b 	Isolated yield: 0.1015 g (79%). R _F : 0.56 (on silica gel chloroform:2-propanol=9:1). Yellowish brown high viscosity liquid.
	δ_H (500 MHz, CDCl ₃) 7.60-7.56 (1H, m, Ar), 7.40-7.23 (3H, m, Ar), 3.93 (1H, br s), 3.78 (0.5H, br s), 3.70 (1H, br s), 3.61 (0.5H, br s), 3.33 (1H, br s), 3.17 (1H, s, CH ₃), 2.93 (2H, s, CH ₃)
	δ_C (125.7 MHz, CDCl ₃) 170.6, 169.9, 138.2, 132.8, 132.7, 130.4, 130.2, 128.5, 127.9, 127.7, 127.6, 119.2, 119.0, 60.9, 59.7, 52.6, 50.5, 37.7, 33.1.
	MS m/z (rel int.): 259/257 (M ⁺ , 2), 229/227 (15), 216/214 (15), 185/183 (100), 157/155 (19), 105 (8), 76 (18), 42 (11).
	HRMS (ESI-Q-TOF) m/z calcd for C ₁₀ H ₁₂ BrNO ₂ [M+H] ⁺ : 258.0124; found: 258.0124.

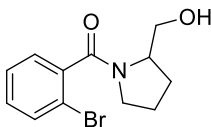
6b 	Isolated yield: 0.0944 g (43%). R _F : 0.76 (on silica gel chloroform:2-propanol=95:5). Colorless high viscosity liquid.
	δ_H (500 MHz, CDCl ₃) 7.86 (0.7H, d, 7.5 Hz, Ar), 7.72 (0.3H, d, 7.5 Hz, Ar), 7.67-7.64 (1H, m, Ar), 7.56-7.53 (1H, m, Ar), 7.34-7.31 (3H, m, Ar), 7.25-7.20 (2H, m, Ar), 4.67 (1.4H, br s, CH ₂), 4.46-4.41 (0.3H, m, CH ₂), 4.39-4.34 (0.3H, m, CH ₂), 4.05 (0.7H, br s, CH ₂), 3.92 (0.7H, br s, CH ₂), 3.67-3.61 (0.3H, m, CH ₂), 3.51-3.47 (0.3H, m, CH ₂), 3.24 (1H, s, CH ₃), 2.96 (2H, s, CH ₃).
	δ_C (125.7 MHz, CDCl ₃) 169.6, 169.5, 165.9, 165.7, 138.3, 137.9, 134.5, 134.4, 133.0, 132.8, 131.8, 131.6, 131.3, 130.4, 130.3, 129.9, 128.3, 127.8, 127.7, 127.6, 127.54, 127.50, 127.3, 127.2, 121.8, 121.7, 119.1, 119.0, 62.8, 62.4, 49.2, 46.3, 37.5, 33.0.
	MS m/z (rel int.): 258/256 (8), 241/293 (15), 228/226 (9), 185/183 (100), 160 (39), 132 (47), 105 (10), 76 (14).

3c 	Isolated yield: 0.0386 g (30%). R _F : 0.26 (on silica gel chloroform:2-propanol=97:3). Reddish brown high viscosity liquid.
	δ_H (500 MHz, CDCl ₃) 7.61 (1H, d, 8.0 Hz, Ar), 7.53 (1H, d, 7.5 Hz, Ar), 7.37 (1H, t, 7.5 Hz, Ar), 7.30 (1H, t, 8.0 Hz, Ar), 6.52 (1H, br s, NH), 3.79 (2H, t, 5.6 Hz, CH ₂ O), 3.66-3.62 (2H, m, CH ₂ N), 2.71 (1H, br s, OH), 1.85-1.81 (2H, m, CH ₂).
	δ_C (125.7 MHz, CDCl ₃) 168.7, 137.6, 133.4, 131.4, 129.5, 127.6, 119.3, 59.6, 37.0, 32.1.
	MS m/z (rel int.): 259/257 (1, M ⁺), 241/239 (6), 228/226 (8), 214/212 (28), 185/183 (100), 157/155 (22), 105 (10), 76 (24), 50 (10).

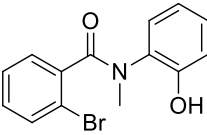
	HRMS (ESI-Q-TOF) m/z calcd for C ₁₀ H ₁₂ BrNO ₂ [M+H] ⁺ : 258.0124; found: 258.0125.
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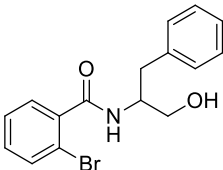
3d 	Isolated yield: 0.0766 g (57%). R _F : 0.35 (on silica gel chloroform:2-propanol=9:1). White crystals.
	δ _H (500 MHz, CDCl ₃) 7.66 (1H, d, 7.9 Hz, Ar), 7.46-7.41 (2H, m, Ar), 7.38-7.34 (1H, m, Ar), 3.64 (2H, t, 8.3 Hz, CH ₂ O), 3.41 (2H, t, 6.5 Hz, CH ₂ N), 1.75-1.65 (4H, m, CH ₂ CH ₂).
	δ _C (125.7 MHz, CDCl ₃) 169.6, 138.8, 132.8, 130.7, 128.3, 127.2, 119.0, 61.2, 39.3, 29.6, 25.4.
	MS m/z (rel int.): 273/271 (3, M ⁺), 255/253 (5), 242/240 (10), 228/226 (12), 214/212 (15), 185/183 (100), 157/155 (15), 105 (10), 88 (19), 76 (16).
	HRMS (ESI-Q-TOF) m/z calcd for C ₁₁ H ₁₄ BrNO ₂ [M+H] ⁺ : 272.0281; found: 272.0277.

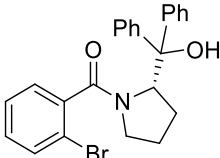
3e 	Isolated yield: 0.1111 g (82%). R _F : 0.58 (on silica gel chloroform:2-propanol=92:8). White crystals.
	δ _H (500 MHz, CDCl ₃) 7.60 (1H, d, 7.7 Hz, Ar), 7.53 (1H, d, 7.7 Hz, Ar), 7.38 (1H, t, 7.7 Hz, Ar), 7.31 (1H, d, 7.7 Hz, Ar), 6.02 (1H, br s, NH), 3.74 (2H, s, CH ₂), 1.44 (6H, s, CH ₃).
	δ _C (125.7 MHz, CDCl ₃) 168.3, 138.1, 133.3, 131.4, 129.4, 127.7, 119.3, 70.3, 57.3, 24.6.
	MS m/z (rel int.): 242/240 (47), 202/200 (11), 185/183 (100), 157/155 (14), 105 (11), 76 (15).
	HRMS (ESI-Q-TOF) m/z calcd for C ₁₁ H ₁₄ BrNO ₂ [M+H] ⁺ : 272.0281; found: 272.0274.

3g 	Isolated yield: 0.1033 g (73%). R _F : 0.58 (on silica gel chloroform:2-propanol=92:8). Yellow high viscosity liquid.
	δ _H (500 MHz, CDCl ₃) 7.58 (1H, d, 7.9 Hz, Ar), 7.37 (1H, t, 7.1 Hz, Ar), 7.30-7.24 (2H, m, Ar), 4.41 (1H, br s, CH ₂ O), 4.35 (1H, br s, CH ₂ O), 3.79 (1H, br s, CH), 3.28-3.23 (2H, m, CH ₂ N), 2.18-2.13 (1H, m, CH ₂ CH ₂), 1.90-1.86 (1H, m, CH ₂ CH ₂), 1.83-1.78 (1H, m, CH ₂ CH ₂), 1.73-1.70 (1H, m, CH ₂ CH ₂).
	δ _C (125.7 MHz, CDCl ₃) 169.6, 139.0, 132.8, 130.5, 127.9, 127.3, 118.6, 66.3, 61.4, 49.6, 28.6, 24.5.

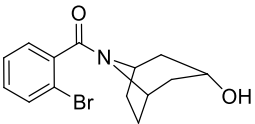
	MS m/z (rel int.): 267/265 (7), 254/252 (44), 185/183 (100), 157/155 (15), 105 (10), 76 (13).
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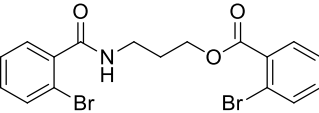
3h 	Isolated yield: 0,0979 g (64%). R _F : 0.53 (on silica gel chloroform:ethyl acetate=8:2). Yellow high viscosity liquid.
	δ_H (500 MHz, CDCl ₃) 7.69 (0.5H, d, 8.1 Hz, Ar), 7.48-7.47 (1H, m, Ar), 7.43-7.41 (0.5H, m, Ar), 7.38-7.35 (0.5H, m, Ar), 7.32-7.27 (1H, m, Ar), 7.22-7.20 (0.5H, m, Ar), 7.18-7.13 (1H, m, Ar), 7.06-7.02 (2H, m, Ar), 6.80 (0.5H, d, 8.1 Hz, Ar), 6.69 (0.5H, t, 7.5 Hz, Ar), 3.42 (1.5H, s, CH ₃), 3.29 (1.5H, s, CH ₃).
	δ_C (125.7 MHz, CDCl ₃) 170.1, 151.7, 151.3, 138.0, 137.8, 133.0, 132.5, 131.1, 131.0, 130.1, 130.0, 129.7, 128.9, 128.4, 128.1, 127.8, 127.6, 126.7, 124.9, 121.4, 120.6, 120.1, 119.5, 119.0, 116.7, 40.4, 36.2.
	MS m/z (rel int.): 307/305 (24, M ⁺), 185/183 (100), 157/155 (15), 122 (11).

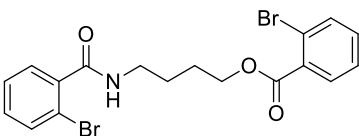
3f 	Isolated yield: 0.1228 g (73%). R _F : 0.14 (on silica gel chloroform:2-propanol=97:3). White crystals.
	δ_H (500 MHz, CDCl ₃) 7.50 (1H, d, 7.8 Hz, Ar), 7.32-7.18 (8H, m, Ar), 6.70 (1H, br s, NH), 4.35-4.32 (1H, m, CH), 3.69 (1H, dd, 10.3 Hz, 3.5 Hz, CH ₂ O), 3.60 (1H, dd, 10.3 Hz, 4.5 Hz, CH ₂ O), 3.43 (1H, br s, OH), 2.96 (2H, d, 7.2 Hz, CHCH ₂).
	δ_C (125.7 MHz, CDCl ₃) 168.2, 137.8, 133.2, 131.2, 129.4, 129.1, 128.6, 127.4, 126.6, 119.3, 63.2, 53.3, 36.8.
	MS m/z (rel int.): 335/333 (1, M ⁺), 304/302 (7), 244/242 (5), 226/224 (10), 202/200 (12), 185/183 (100), 157/155 (16), 134 (12), 105 (18), 91 (25), 76 (15).
	HRMS (ESI-Q-TOF) m/z calcd for C ₁₆ H ₁₆ BrNO ₂ [M+H] ⁺ : 334.0437; found: 334.0426.

3i 	Isolated yield: 0.0435 g (20%). R _F : 0.42 (on silica gel chloroform:ethyl acetate=95:5). Yellow high viscosity liquid.
	δ_H (500 MHz, CDCl ₃) 7.64 (2H, d, 7.5 Hz, Ar), 7.55 (1H, d, 8.0 Hz, Ar), 7.49 (2H, d, 7.5 Hz, Ar), 7.42-7.29 (8H, m, Ar), 7.22 (1H, t, 7.5 Hz, Ar), 5.32 (1H, t, 7.9 Hz, CH), 3.13-3.09 (1H, m, NCH ₂), 2.66 (1H, br s, CH ₂), 2.21 (1H, br s, CH ₂), 2.05 (1H, br s, CH ₂), 1.66 (1H, br s, CH ₂), 1.36 (1H, br s, CH ₂).
	δ_C (125.7 MHz, CDCl ₃) 170.5, 145.3, 143.0, 138.8, 132.7, 130.4, 128.0, 127.8, 127.6, 127.4, 118.1, 81.9, 68.1, 50.8, 30.4, 24.1.

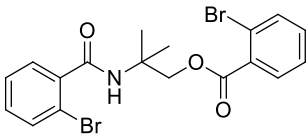
	MS m/z (rel int.): 253/255 (70), 254/252 (64), 183/185 (100), 174 (31), 157/155 (10), 105 (63), 77 (39).
	HRMS (ESI-Q-TOF) m/z calcd for C ₂₄ H ₂₀ BrNO [M+H] ⁺ : 418.0801; found: 418.0786.

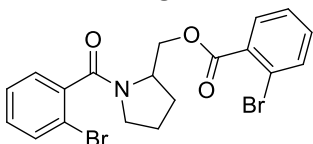
3j 	Isolated yield: 0.1066 g (69%). R _f : 0.54 (on silica gel chloroform:ethyl acetate:2-propanol=70:20:10). Yellowish brown high viscosity liquid.
	δ _H (500 MHz, CDCl ₃) 7.62-7.59 (1H, m, Ar), 7.36 (1H, t, 7.5 Hz, Ar), 7.28-7.25 (2H, m, Ar), 4.85 (1H, br, s, CHO), 4.20-4.18 (1H, m, CHN), 3.67 (1H, br s, CHN), 2.31-1.70 (8H, m, CH ₂).
	δ _C (125.7 MHz, CDCl ₃) 164.2, 138.6, 132.9, 130.2, 128.0, 127.6, 119.0, 64.9, 55.5, 50.7, 40.2, 39.1, 28.7, 27.5.
	MS m/z (rel int.): 311/309 (27), 230 (33), 202 (22), 185/183 (100), 157/155 (24), 126 (69), 110 (32), 68 (53).
	HRMS (ESI-Q-TOF) m/z calcd for C ₁₄ H ₁₆ BrNO ₂ [M+H] ⁺ : 310.0437; found: 310.0429.

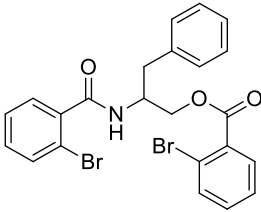
4c 	Isolated yield: 0.0785 g (36%). R _f : 0.56 (on silica gel chloroform:2-propanol=95:5). Reddish brown high viscosity liquid.
	δ _H (500 MHz, CDCl ₃) 7.80 (1H, dd, 7.5 Hz, 2.2 Hz, Ar), 7.66 (1H, dd, 7.5 Hz, 2.2 Hz, Ar), 7.58 (1H, d, 7.5 Hz, Ar), 7.51 (1H, dd, 7.5 Hz, 2.2 Hz, Ar), 7.39-7.33 (3H, m, Ar), 7.29-7.24 (1H, m, Ar), 6.40 (1H, br s, NH), 4.52 (2H, t, 6.0 Hz, CH ₂ O), 3.67-3.63 (2H, m, CH ₂ NH), 2.17-2.12 (2H, CH ₂ CH ₂).
	δ _C (125.7 MHz, CDCl ₃) 167.9, 166.5, 137.9, 134.3, 133.3, 132.7, 132.2, 131.3, 131.2, 129.5, 127.6, 127.3, 121.5, 119.3, 63.2, 37.0, 28.6.
	MS m/z (rel int.): 258/256 (11), 241/239 (37), 185/183 (100), 157/155 (17), 132 (8), 105 (12), 76 (18), 56 (40).
	HRMS (ESI-Q-TOF) m/z calcd for C ₁₇ H ₁₅ Br ₂ NO ₃ [M+H] ⁺ : 439.9491; found: 439.9482.

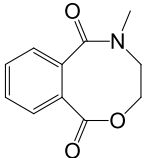
4d 	Isolated yield: 0.1002 g (44%). R _f : 0.58 (on silica gel chloroform:2-propanol=95:5). Reddish brown high viscosity liquid.
	δ _H (500 MHz, CDCl ₃) 7.79 (1H, d, 7.5 Hz, Ar), 7.67 (1H, d, 7.5 Hz, Ar), 7.58 (1H, d, 8.0 Hz, Ar), 7.51 (1H, d, 7.8 Hz, Ar), 7.39-7.32 (3H, m, Ar), 7.27 (1H, t, 7.9 Hz, Ar), 6.24 (1H, br s, NH), 4.40 (2H, t, 6.3 Hz, CH ₂ O), 3.56-3.52 (2H, m, CH ₂ N), 1.95-1.90 (2H, m, CH ₂ CH ₂), 1.85-1.80 (2H, m, CH ₂ CH ₂).

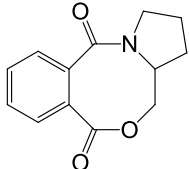
	δ_c (125.7 MHz, $CDCl_3$) 167.8, 166.3, 137.9, 134.3, 133.3, 132.5, 132.4, 131.3, 131.2, 129.5, 127.6, 127.2, 121.5, 119.2, 65.2, 39.6, 26.3, 26.2.
	MS m/z (rel int.): 457/455/453 (5, M^+), 272/270 (26), 255/253 (10), 202/200 (15), 185/183 (100), 157/155 (17), 105 (25), 75 (16), 70 (33).
	HRMS (ESI-Q-TOF) m/z calcd for $C_{18}H_{17}Br_2NO_3$ $[M+H]^+$: 453.9648; found: 453.9635.

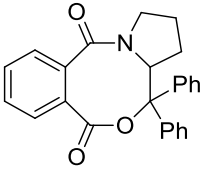
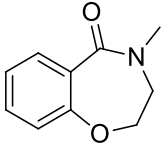
4e 	Isolated yield: 0.1539 g (68%). R_F: 0.74 (on silica gel chloroform:2-propanol=95:5). Reddish brown crystals. δ_H (500 MHz, $CDCl_3$) 7.83 (1H, dd, 7.5 Hz, 2.0 Hz, <i>Ar</i>), 7.66 (1H, d, 7.5 Hz, <i>Ar</i>), 7.55 (1H, d, 7.5 Hz, <i>Ar</i>), 7.49 (1H, d, 7.5 Hz, <i>Ar</i>), 7.40-7.30 (3H, m, <i>Ar</i>), 7.24 (1H, t, 8.0 Hz, <i>Ar</i>), 6.08 (1H, br s, <i>NH</i>), 4.58 (2H, s, CH_2), 1.60 (6H, s, CH_3). δ_c (125.7 MHz, $CDCl_3$) 167.3, 166.2, 138.5, 134.4, 133.2, 132.8, 132.1, 131.6, 131.1, 129.3, 127.5, 127.3, 121.5, 119.1, 70.2, 54.3, 24.2. MS m/z (rel int.): 255/253 (7), 242/240 (73), 185/183 (100), 157/155 (15), 105 (17), 76 (16). HRMS (ESI-Q-TOF) m/z calcd for $C_{18}H_{17}Br_2NO_3$ $[M+H]^+$: 453.9648; found: 453.9642.
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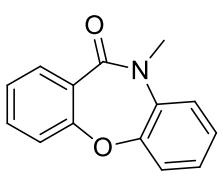
4g 	Isolated yield: 0.0582 g (25%). R_F: 0.65 (on silica gel chloroform:ethyl acetate=8:2). Orange high viscosity liquid. δ_H (500 MHz, $CDCl_3$) 7.86 (1H, d, 7.5 Hz, <i>Ar</i>), 7.69-7.65 (1H, m, <i>Ar</i>), 7.57 (1H, d, 7.9 Hz, <i>Ar</i>), 7.41-7.24 (5H, m, <i>Ar</i>), 4.72-4.62 (2H, m, CH_2O), 4.10-3.68 (1H, m, <i>NCH</i>, <i>NCH</i>), 3.32-3.23 (2H, m, <i>NCH</i>, <i>NCH</i>), 2.21-2.16 (1H, m, CH_2), 2.10-2.02 (2H, m, CH_2), 1.92-1.88 (1H, m, CH_2). δ_c (125.7 MHz, $CDCl_3$) 167.9, 166.1, 139.3, 134.5, 132.8, 132.6, 132.2, 131.5, 131.2, 130.5, 130.3, 127.8, 127.6, 127.3, 121.6, 118.8, 65.7, 64.9, 55.6, 48.7, 46.1, 39.1, 29.1, 27.9, 24.3, 22.5. MS m/z (rel int.): 284/282 (5), 254/252 (50), 185/183 (100), 157/155 (13), 105 (19), 76 (11). HRMS (ESI-Q-TOF) m/z calcd for $C_{19}H_{17}Br_2NO_3$ $[M+H]^+$: 465.9648; found: 465.9634.
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4f 	Isolated yield: 0.0953 g (37%). R_f: 0.72 (on silica gel chloroform:ethyl acetate=9:1). Brownish white crystals. δ_H (500 MHz, $CDCl_3$) 7.87 (1H, dd, 7.5 Hz, 1.8 Hz, Ar), 7.70 (1H, d, 7.8 Hz, Ar), 5.57 (1H, d, 7.8 Hz, Ar), 7.43-7.40 (2H, m, Ar), 7.38-7.31 (6H, m, Ar), 7.29-7.25 (2H, m, Ar), 6.32 (1H, s, NH), 4.86-4.80 (1H, m, NCH_2), 4.50 (1H, dd, 11.0 Hz, 4.0 Hz, CH_2O), 4.46 (1H, dd, 11.0 Hz, 4.7 Hz, CH_2O), 3.16 (1H, dd, 13.7 Hz, 6.7 Hz, $ArCH_2$), 3.09 (1H, dd, 13.7 Hz, 8.0 Hz, $ArCH_2$). δ_C (125.7 MHz, $CDCl_3$) 167.3, 166.1, 137.6, 136.8, 134.4, 133.4, 132.9, 131.8, 131.3, 129.44, 129.36, 128.8, 127.6, 127.4, 127.0, 121.6, 119.2, 65.8, 50.2, 37.6. MS m/z (rel int.): 226/224 (100), 198/196 (21), 171/169 (26), 146 (5), 117 (10), 91 (16), 65 (7). HRMS (ESI-Q-TOF) m/z calcd for $C_{23}H_{19}Br_2NO_3$ $[M+H]^+$: 515.9804; found: 515.9789.
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8b 	Isolated yield: 0.0513 g (48%). R_f: 0.69 (on silica gel chloroform:2-propanol=9:1). Yellow high viscosity liquid. δ_H (500 MHz, $CDCl_3$) 7.76 (1H, d, 8.0 Hz, Ar), 7.66 (1H, t, 8.0 Hz, Ar), 7.61-7.56 (2H, m, Ar), 4.43-4.38 (1H, m, OCH_2), 4.17-4.14 (1H, m, OCH_2), 3.72-3.67 (1H, m, NCH_2), 3.34-3.30 (1H, m, NCH_2), 3.22 (3H, s, CH_3). δ_C (125.7 MHz, $CDCl_3$) 170.6, 169.9, 135.9, 132.9, 130.3, 130.1, 129.6, 128.7, 64.7, 48.5, 34.8. MS m/z (rel int.): 205 (6, M^+), 175 (11), 160 (26), 132 (50), 104 (100), 76 (32), 57 (14), 42 (20). HRMS (ESI-Q-TOF) m/z calcd for $C_{11}H_{11}NO_3$ $[M+H]^+$: 206.0812; found: 206.0820.
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8g 	Isolated yield: 0.0294 g (26%). R_f: 0.42 (on silica gel chloroform:2-propanol=95:5). Yellowish brown high viscosity liquid. δ_H (500 MHz, $CDCl_3$) 7.66-7.53 (4H, m, Ar), 4.22 (1H, dd, 5.6 Hz, 13.5 Hz, CH_2O), 4.12-4.09 (1H, m, CH_2O), 3.97-3.92 (1H, m, CH), 3.78-3.74 (1H, m, NCH_2), 3.69-3.65 (1H, m, NCH_2), 2.17-2.03 (3H, m, CH_2CH_2), 1.19-1.88 (1H, m, CH_2CH_2). δ_C (125.7 MHz, $CDCl_3$) 170.6, 167.7, 134.8, 131.8, 130.8, 129.1, 128.8, 128.0, 68.9, 57.0, 47.8, 32.3, 21.8. MS m/z (rel int.): 231 (14, M^+), 201 (40), 163 (39), 145 (20), 1332 (78), 104 (100), 76 (36). HRMS (ESI-Q-TOF) m/z calcd for $C_{13}H_{13}NO_3$ $[M+H]^+$: 232.0890; found: 232.0966.
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8i 	Isolated yield: 0.0349 g (36%). R_f: 0.45 (on silica gel chloroform:ethyl acetate=9:1). Yellowish white high viscosity liquid. δ_H (500 MHz, $CDCl_3$) 7.64 (2H, d, 7.0 Hz, <i>Ar</i>), 7.50 (2H, d, 7.5 Hz, <i>Ar</i>), 7.44-7.35 (5H, m, <i>Ar</i>), 7.32-7.27 (3H, m, <i>Ar</i>), 6.97 (1H, br s, <i>Ar</i>), 6.74-6.72 (1H, m, <i>Ar</i>), 5.26 (1H, t, 8.3 Hz, <i>CH</i>), 3.30 (1H, t, 8.0 Hz, <i>NCH_2</i>), 2.77-2.72 (1H, m, <i>NCH_2</i>), 2.25-2.18 (1H, m, <i>CH_2CH_2</i>), 2.01-1.94 (1H, m, <i>CH_2CH_2</i>), 1.74-1.68 (1H, m, <i>CH_2CH_2</i>), 1.42-1.36 (1H, m, <i>CH_2CH_2</i>). δ_C (125.7 MHz, $CDCl_3$) 172.0, 145.4, 143.1, 135.3, 129.0, 128.06, 128.01, 127.9, 127.5, 127.4, 127.3, 126.2, 82.1, 67.9, 51.8, 30.4, 24.1. HRMS (ESI-Q-TOF) m/z calcd for $C_{25}H_{21}NO_3$ $[M+H]^+$: 384.1594; found: 384.1582.
9b 	Isolated yield: 0.0250 g (28%). R_f: 0.48 (on silica gel chloroform:2-propanol=95:5). Yellowish brown high viscosity liquid. δ_H (500 MHz, $CDCl_3$) 7.84 (1H, d, 7.4 Hz, <i>Ar</i>), 7.43 (1H, t, 7.4 Hz, <i>Ar</i>), 7.18 (1H, t, 7.4 Hz, <i>Ar</i>), 7.02 (1H, d, 7.4 Hz, <i>Ar</i>), 4.42 (2H, t, 5.2 Hz, <i>OCH_2</i>), 3.55 (2H, t, 5.2 Hz, <i>NCH_2</i>), 3.25 (3H, s, <i>CH_3</i>). δ_C (125.7 MHz, $CDCl_3$) 168.6, 153.8, 132.7, 131.1, 127.2, 123.5, 121.3, 72.5, 48.5, 35.5. MS m/z (rel int.): 177 (15, M^+), 162 (100), 120 (81), 92 (46), 56 (34), 42 (21). HRMS (ESI-Q-TOF) m/z calcd for $C_{10}H_{11}NO_2$ $[M+H]^+$: 178.0863; found: 178.0855.

9c 	Isolated yield: 0.0439 g (39%). R_f: 0.78 (on silica gel chloroform:ethyl acetate=9:1). Yellowish brown high viscosity liquid.
	δ_H (500 MHz, $CDCl_3$) 7.91 (1H, d, 8.0 Hz, <i>Ar</i>), 7.48 (1H, t, 7.3 Hz, <i>Ar</i>), 7.32-7.15 (6H, m, <i>Ar</i>), 3.61 (3H, s, CH_3).
	δ_C (125.7 MHz, $CDCl_3$) 166.5, 160.6, 153.7, 136.1, 133.5, 132.3, 126.3, 126.2, 125.8, 125.2, 122.6, 121.5, 119.8, 36.8.
	MS m/z (rel int.): 225 (100, M^+), 208 (15), 196 (20), 182 (23), 168 (25), 127 (9), 77 (10).
	HRMS (ESI-Q-TOF) m/z calcd for $C_{14}H_{11}NO_2$ $[M+H]^+$: 226.0863; found: 226.0859.

Spectroscopic data (^1H , ^{13}C , MS) of prepared compounds

