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RESEARCH ARTICLE

The Synthesis of (Iodobenzyl)oxybenzaldehydes, Useful Intermediates for Biologically Active Targets

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Abstract: The benzyloxy-benzyl moiety is a valuable building block in medicinal chemistry, *e.g.* in case of the voltage gated sodium channel blockers Safinamide and Ralfinamide. To prepare further derivatives a series of (iodobenzyl)oxybenzaldehydes (**3a-3i**) useful intermediates for the synthesis of biologically active compounds were synthesized in high yields by *O*-benzylation of 2-, 3- and 4-hydroxybenzaldehydes (**2a-2c**) with a variety of iodobenzylbromides (**1a-1c**). The title compounds were obtained in 77-100 % yield in 2-5 hours. Longer reaction time or addition of water favoured the formation of aldol-type by-products, mainly 4-hydroxy-4-{[(iodophenyl)methoxy]phenyl}butan-2-one derivatives (**5a-5g**), which contained the iodine group and the 4-hydroxy-butan-2-one moiety in various positions. In one case (3*E*-)-4-{3-[(2-iodophenyl)methoxy]phenyl}but-3-en-2-one (**6c**) with a double bond has been isolated. These side-reactions could be avoided by using acetonitrile as solvent. The structures of the new products were established by high resolution MS and NMR measurements, where ^{1}H-^{1}H, direct ^{1}H-^{13}C, long-range ^{1}H-^{13}C scalar spin-spin connectivities were established from 1D ^{1}H, ^{13}C, 2D gHSQCAD, zTOCSY and gHMBCAD NMR experiments.

Keywords: Alkylation, hydroxybenzaldehyde, iodobenzylbromide, (iodobenzyloxy)benzaldehydes, aldol reaction, aldol condensation.

1. INTRODUCTION

The benzyloxy-benzyl moiety is a common building block in medicinal chemistry as shown by *e.g.* the voltage gated sodium channel blockers Safinamide and Ralfinamide (Fig. **1**). Both of them were obtained by the reductive amination of the corresponding fluor-benzyloxy-benzaldehyde with alanin-amide [1, 2].

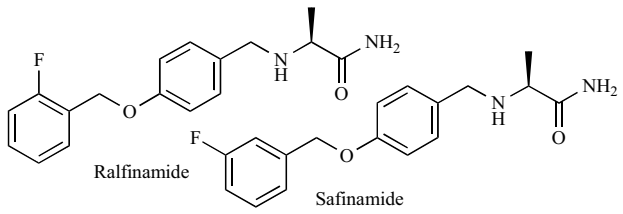

Fig. (1). Molecular structure of Ralfinamide and Safinamide.

In the synthesis of a diverse set of potentially biologically active compounds, we needed several aryl- and heteroaryl-substituted benzyloxybenzaldehydes (**4**) as intermediates**. The synthesis of these compounds (**4**) was planned by the Suzuki-Miyaura coupling reaction of the corresponding halogenated benzyloxybenzaldehyde *e.g.* (**3**), and aryl- and heteroaryl boronic acid (Scheme **1**) [3].

It was expected, that the bromo-derivatives were less active in the Suzuki-Miyaura coupling reaction than the iodo-compounds. Thus, we focused on the preparation of the corresponding iodo-derivatives (**3**). The series of reactions mentioned above leads to the intermediates of potentially biologically active compounds.

The alkylation of phenols is a well-known procedure. It was named after Williamson, who developed this reaction in 1850 [4]. The Williamson ether synthesis was extended in many cases *i.e.* concerning hydroxybenzaldehydes [5]. Katritzky *et al.* isolated 2-alkoxy-5-methoxy-benzaldehydes with alkylbromides or iodides in acetone in the presence of potassium carbonate [6]. Chang *et al.* alkylated substituted hydroxybenzaldehydes with benzyl chloride in the presence of potassium-carbonate and potassium iodide in acetone [7]. Lu *et al.* used dimethylformamide as the solvent at a higher temperature (120 °C) in course of the alkylation of 4-bromo-2-hydroxy-benzaldehyde with 4-chloro-benzyl chloride [8].

Heating benzylchloride with 2-hydroxy-benzaldehyde and potassium carbonate in acetone for 3 hours, Majhi *et al.*

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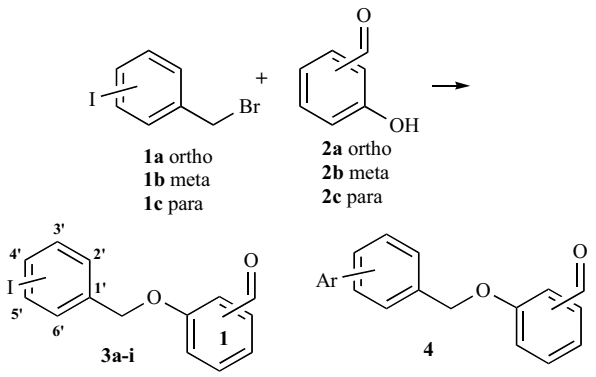

Reagents		Product
1	**2**	
ortho	ortho	3a
meta	ortho	3b
para	ortho	3c
ortho	meta	3d
meta	meta	3e
para	meta	3f
ortho	para	3g
meta	para	3h
para	para	3i

Scheme 1. The planned synthetic protocol: alkylation followed by Suzuki-Miyaura reaction.

prepared 2-[(2-iodobenzyl)oxy]benzaldehyde, which is one of our target compounds [9].

Potassium carbonate was used in most of the cases, but cesium carbonate or cesium hydroxide can also promote O-alkylation in the presence of tetrabutylammonium iodide and molecular sieves [10]. Voelter *et al.* published that CsF-celite combinations in acetonitrile provided an efficient method for the alkylation of phenols with benzyl halogenides [11]. Keglevich and his coworkers studied the benzylation of cresols using phase transfer catalysis and microwave irradiation. Benzylation of phenols led mostly to O-alkylation, but modification of the reaction conditions resulted in C-alkylation [12]. Using acetonitrile as the solvent, the benzylations were fully selective, but complete conversions were obtained only in the presence of cesium carbonate [13].

2. RESULTS AND DISCUSSIONS

Starting from the corresponding iodobenzyl bromide, we applied the Chang's conditions [7] (acetone, potassium carbonate) for the iodobenzylation of our o-, m-, p-hydroxybenzaldehydes. In this way, a series of iodo-benzyloxybenzaldehydes (**3a-i**) was synthesized in high yields, eight of which (except 2-[(2-iodobenzyl)oxy]benzaldehyde **3a**) are new compounds according to the databases Reaxys and SciFinder.

Our results were summarized in Table **1**.

In a few cases, when we applied longer heating in course of the reaction to reach the complete consumption of the starting material, aldol addition and aldol condensation were observed with the participation of acetone used as solvent as side reactions. The general scheme of the aldol condensation is shown in Scheme **2**.

The conditions of the alkylation (acetone, potassium carbonate, etc.) are often used, and it is rare that aldol-type reaction occurs simultaneously. The by-products of aldol-type

Table 1. Products obtained by alkylation (3a-i).

Reagents		Reaction Time (h)	Yield (%)	Product
1	**2**			
1a	**2a**	2.5	99	**3a**[a]
1a	**2a**	2.0	100	**3a**[b]
1b	**2a**	2.5	98	**3b**[a]
1c	**2a**	2.0	99	**3c**[a]
1a	**2b**	3.3	77	**3d**[a]
1a	**2b**	2.0	100	**3d**[b]
1b	**2b**	2.0	98	**3e**[a]
1c	**2b**	3.0	93	**3f**[a]
1a	**2c**	2.0	100	**3g**[a]
1a	**2c**	2.0	100	**3g**[b]
1b	**2c**	5.0	87	**3h**[a]
1c	**2c**	1.75	100	**3i**[a]

[a]Acetone was the solvent, see general procedure
[b]Acetonitrile was the solvent, see general procedure.

Table 2. Formation of Aldol-products 5a-e and 5g.

Reagents		Reaction time (h)	Yield (%)[a]	Aldol Product
1a	**2a**	25	20	**5a**[b]
1b	**2a**	25	72	**5b**[b]
1a	**2b**	25	99	**6c**[c]
1b	**2b**	16	15	**5d**[b]
1c	**2b**	16	30	**5e**[b]
1c	**2c**	25	99	**5g**[b]

[a]Area percentage of the aldol-type products in the crude mixtures as determined by LC-MS.
[b]aldol adduct
[c]dehydrated aldol product

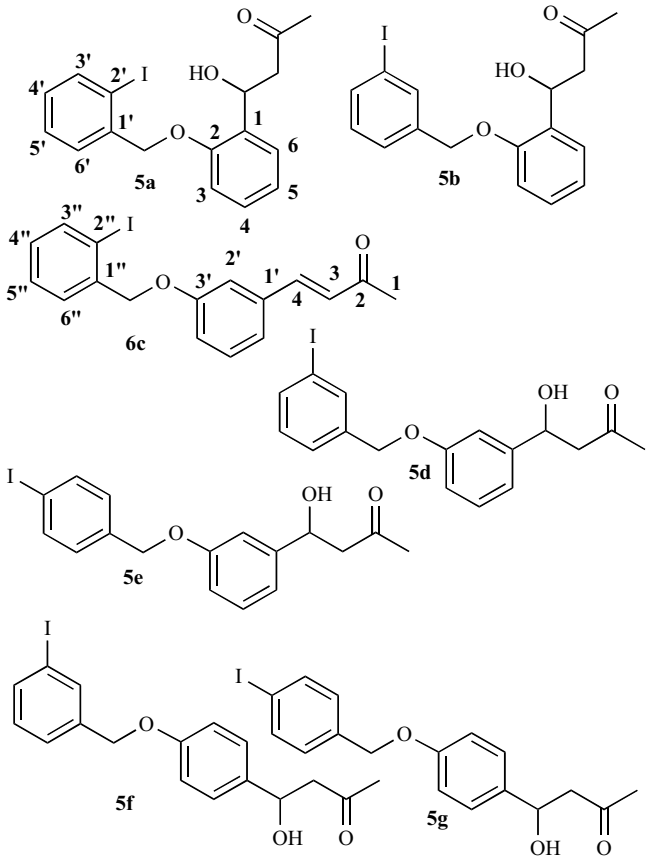

Fig. (2). Aldol-type by-products.

shown in Figure **2** were formed in reaction times of 16-25 hours. Applying a reaction time of 16 hours, starting from **1b** and **2b** or **1c** and **2b**, the relative amount of aldol-type products beside the desired product was only 15% and 30% respectively. The relative amount of the side products in most cases was increased by the reaction time (Table **2**). Using acetonitrile as the solvent, these side reactions could be avoided.

Several examples are known in the literature, when aldol reaction took place between acetone and benzaldehyde using various types of catalysts improving the selectivity of the reaction, *e.g.* [14,15,16]. Sometimes, the aldol reaction occurred in water, or in the presence of water [17,18]. In our model reactions, the addition of water shifted the reaction to the direction of formation of the aldol adduct (see Table **3**).

Table 3. Product composition of the reaction starting from 1b and 2c.

Solvents		Composition [%]*	
		3f	**5f**
acetone	1ekv H_2O	82	18
acetone	5ekv H_2O	62	27

*Determined on the basis of the area percentage in the LC-MS spectrum.

3. CONCLUSION

A complete set of iodobenzyloxybenzaldehydes (**3a-i**) was prepared, eight of which are new compounds. They can be valuable building blocks in the synthesis of biologically active compounds. In course of the O-benzylation allowing longer reaction times, aldol type by-products were formed and isolated. All of the new products were identified by NMR spectroscopy and mass spectrometry.

4. EXPERIMENTAL SECTION

4.1. LC-MS Analysis

LC-MS experiments were carried out on an Agilent 1200 liquid chromatography system coupled with 6120 MSD (Agilent Technologies, Palo Alto, CA, USA), equipped with vacuum degasser, binary pump, autosampler, column temperature controller and diode array detector. Analysis was done at 40°C on Kinetex C_{18} column (5 cm x 2.1 mm, 2.6 μm) (Phenomenex, Torrance, CA, USA) with a mobile phase flow rate of 0.9 mL/min. Composition of eluent A was 0.1% (v/v) trifluoroacetic acid in water (pH 1.9), eluent B was the mixture of acetonitrile and water in 95:5 (v/v) with 0.1% (v/v) trifluoroacetic acid. A fast linear gradient of 0-100% B was applied at a range of 0-4 min, then 100% B held for 3 min. This was followed by 2 min equilibration period prior to the next injection. The injection volume was

set at 1 μL and the sample concentration was uniformly 1.0 mg/mL (solved in DMSO). The amount of reaction products (%) were calculated from peak areas (mAU*s) registered at 240 nm. Confirmation of compound identity was based on detection of the appropriate protonated molecular ion $[M+H]^+$ or the $[M+Na]^+$ adduct ion. The MSD operating parameters were as follows: positive ionization mode, scan spectra from *m/z* 100 to 800, drying gas temperature 350°C, nitrogen flow rate 12 L/min, nebuliser pressure 60 psi, quadrupole temperature 100°C, capillary voltage 3000 V, fragmentor voltage 50 V.

4.2. NMR Spectroscopy

NMR measurements were performed on a Varian 800 MHz NMR spectrometer equipped with $^1H\{^{13}C/^{15}N\}$ Triple Resonance ^{13}C Enhanced Salt Tolerant Cold Probe operating at 800 MHz for ^1H and 201 MHz for ^{13}C, and a Varian 500 MHz NMR spectrometer equipped with ^1H $\{^{13}C/^{15}N\}$ 5 mm PFG Triple Resonance ^{13}C Enhanced Cold Probe operating at 500 MHz for ^1H and 125 MHz for ^{13}C and Varian NMR System 400 Spectrometer equipped with 5 mm 400 MHz ATB/PFG Probe operating at 400 MHz for ^1H and 101 MHz for ^{13}C, using DMSO-*d6* as solvent. ^1H-^1H, direct ^1H-^{13}C, long-range ^1H-^{13}C scalar spin-spin connectivities were established from ^1D ^1H, ^{13}C, 2D gHSQCAD, zTOCSY and gHMBCAD NMR experiments.

4.3. MS Spectrometry

High-resolution MS measurements were carried out on a Thermo LTQ FT Ultra mass spectrometer using ESI (electrospray) ionization technique (3.0 kV source voltage, 280°C capillary temperature, solvent: MeOH:H_2O 1:1 + 1 V/V% cc. AcOH). The protonated molecular ion peaks were fragmented by CID at normalized collision energy of 35%. The relative abundance values of the fragment ions in the MS-MS spectra are given in brackets. Part of the high-resolution MS measurements was performed on a Finnigan MAT 95XP mass spectrometer using EI (electron impact) ionization technique (70 eV, 220 °C source temperature, perfluorokerosene or perfluorotributyl amine reference compounds). Melting points given were measured on a hot-stage microscope.

4.4. General Procedure

Alkylation in Acetone. A stirred mixture of the appropriate hydroxy benzaldehyde (2.1 g, 16.8 mmol) was treated with the corresponding iodobenzylbromide (5.0 g, 16.8 mmol) in acetone (60 ml), in the presence of potassium carbonate (4.0g, 29 mmol) and potassium iodide (0.6 g, 3.6 mmol) [#]. The reaction was stirred at the boiling point for 2-5 h, and then cooled to room temperature. The acetone was evaporated, the residue was taken up in ethyl acetate - distilled water (50:50 mL). After drying the organic layer (Na_2SO_4), the solvent was removed, and the residue was purified by column chromatography, with Kieselgel 60 (0.040-0.063 mm) or crystallized to give the compound as a white solid. [#]Studying the formation of side product **5f**, 1 or 5 equivalent of distilled water was also added to the reaction mixture (see Table **3**).

Alkylation in Acetonitrile. The hydroxy-benzaldehyde (2.1 g, 16.8 mmol) was treated with the corresponding iodobenzylbromide (5.0 g, 16.8 mmol) in acetonitrile (60 ml), in the presence of potassium carbonate (4.0 g, 29 mmol) and potassium iodide (0.6 g, 3.6 mmol). The mixture was agitated at 70 °C for 2 h, and cooled to room temperature. The reaction mixture was then diluted with 100 ml of distilled water, and 5 ml of brine was added, then the product was filtered off as a white solid.

2-[(2-Iodophenyl)methoxy]benzaldehyde (3a). Separated by column chromatography with cyclohexane: ethyl acetate 9:1 eluent. M.p. 81 °C. ^1H NMR (400 MHz, DMSO): δ = 5.23 (s, 2H, OCH_2), 7.13 (t, 1H, $J_{5,6}$= 7.6 Hz, $J_{5,4}$=7.6 Hz, H-5,), 7.15 (td, 1H, $J_{3',4'}$=7.7 Hz, $J_{;4',5'}$=7.7 Hz, $J_{4',6'}$=1.6 Hz, H-4'), 7.35 (d, 1H, $J_{3,4}$= 8.3 Hz, H-3), 7.47 (td, 1H, $J_{5',4'}$ =7.7 Hz, $J_{;5',6'}$ =7.7 Hz, $J_{5',3'}$=1.2 Hz, H-5'), 7.64 (dd, 1H, $J_{5',6'}$=7.7 Hz, $J_{4',6'}$=1.6 Hz, H-6'), 7.70 (ddd, 1H, $J_{4,5}$=7.6 Hz, $J_{4,3}$=8.3 Hz, $J_{4,6}$=1.8 Hz, H-4), 7.74 (dd, 1H, $J_{6,5}$=7.6 Hz, $J_{6,4}$=1.8 Hz, H-6), 7.95 (dd, 1H, $J_{3',4'}$=7.7 Hz, $J_{3',5'}$=1.2 Hz, H-3'), 10.43 (d, 1H, $J_{CHO,5}$= 0.7 Hz, CHO) ppm; ^{13}C NMR (400 MHz, DMSO): δ = 73.8 (OCH_2), 99.1 (C-2'), 114.1 (C-3), 121.2 (C-5), 124.5 (C-1), 127.9 (C-6), 128.5 (C-5'), 130.2 (C-6'), 130.4 (C-4'), 136.4 (C-4), 138.3 (C-1'), 139.3 (C-3'), 160.4 (C-2), 189.1 (CHO) ppm; MS-EI: *m/z* (%): 338(M^+, 10), 309(14), 217(100), 211(3). M: *m/z* 337.97998, calculated value for $C_{14}H_{11}O_2I$: 337.97982 (delta: 0.5 ppm).

2-[(3-Iodophenyl)methoxy]benzaldehyde (3b). Crystallized from cold ethyl acetate. M.p. 74-77 °C. ^1H NMR (800 MHz, DMSO): δ = 5.27 (s, 2H, OCH_2), 7.10 (tt, 1H, $J_{6,5}$=7.5 Hz, $J_{5,4}$=7.5 Hz, $J_{5,3}$=0.8 Hz, $J_{5,CHO}$=0.8 Hz, H-5), 7.23 (t, 1H, $J_{4',5'}$=7.7 Hz, $J_{5',6}$=7.7 Hz, H-5'), 7.29 (dd, 1H, $J_{3,4}$=8.4 Hz, $J_{3,5}$=0.8 Hz, H-3), 7.55 (d, 1H, $J_{5',6'}$=7.7 Hz, H-6'), 7.66 (ddd, 1H, $J_{4,5}$=7.5 Hz, $J_{4,3}$=8.4 Hz, $J_{4,6}$=1.8 Hz, H-4), 7.72 (d, 1H, $J_{4',5'}$=7.7, H-4'), 7.73 (dd, 1H, $J_{6,5}$=7.5 Hz, $J_{6,4}$=1.8 Hz, H-6), 7.90 (m, 1H, H-2'), 10.42 (d, 1H, $J_{CHO,5}$=0.8 Hz, CHO) ppm; ^{13}C NMR (500 MHz, DMSO) δ 68.8 (OCH_2), 94.9 (C-3'), 114.0 (C-3), 121.1 (C-5), 124.6 (C-1), 126.9 (C-6'), 128.1 (C-6), 130.8 (C-5'), 136.0 (C-2'), 136.3 (C-4), 136.7 (C-4'), 139.2 (C-1'), 160.3 (C-2), 189.2 (CHO) ppm; MS-EI: *m/z* (%): 338(M^+, 14), 309(12), 217(100), 211(1). M: *m/z* 337.97994, calculated value for $C_{14}H_{11}O_2I$: 337.97982 (delta: 0.3 ppm).

2-[(4-Iodophenyl)methoxy]benzaldehyde (3c). Separated by column chromatography with hexane: ethyl acetate 10:1 eluent. M.p. 84-86 °C. ^1H NMR (500 MHz, DMSO): δ = 5.26 (s, 2H, OCH_2), 7.10 (tt, 1H, $J_{5,4}$=7.6 Hz, $J_{5,6}$=7.6 Hz, $J_{5,CHO}$=0.7 Hz, $J_{5,3}$=0.7 Hz, H-5), 7.29 (dd, 1H, $J_{3,4}$=8.4 Hz, $J_{3,5}$=0.7 Hz, H-3), 7.34 (m, 2H, H-2',H-6'), 7.65 (ddd, 1H, $J_{4,6}$=1.8 Hz, $J_{4,3}$=8.4 Hz, $J_{4,5}$=7.6 Hz, H-4), 7.72 (dd, 1H, $J_{6,5}$=7.6 Hz, $J_{4,6}$=1.8 Hz, H-6), 7.78 (m, 2H, H-3', H-5'), 10.42 (d, 1H, $J_{CHO,5}$=0.7 Hz, CHO) ppm; ^{13}C NMR (500 MHz, DMSO): δ = 69.2 (OCH_2), 94.1 (C-4'), 114.1 (C-3), 121.1 (C-5), 124.5 (C-1), 127.9 (C-6), 129.8 (C-2', C-6'), 136.3 (C-1'), 136.4 (C-4), 137.3 (C-3', C-5'), 160.4 (C-2), 189.2 (CHO) ppm; MS-EI: *m/z* (%): 338(M^+, 9), 309(8), 217(100), 211(1). M: *m/z* 337.97973, calculated value for $C_{14}H_{11}O_2I$: 337.97982 (delta: -0.3 ppm).

3-[(2-Iodophenyl)methoxy]benzaldehyde (3d). Separated by column chromatography with hexane: ethyl acetate 10:1 eluent. M.p. 74-76 °C. ^1H NMR (500 MHz, DMSO): δ

= 5.13 (s, 2H, OCH_2), 7.14 (td, 1H, $J_{4',3'}$=7.6 Hz, $J_{4',5'}$=7.6 Hz, $J_{4',6'}$=1.7 Hz, H-4'), 7.38 (m, 1H, H-4), 7.45 (td, 1H, $J_{5',4'}$=7.6 Hz, $J_{5',6'}$=7.6 Hz, $J_{5',3'}$=1.1 Hz, H-5'), 7.53 (m, 1H, H-2), 7.55-7.59 (m, 3H, H-5, H-6, H-6'), 7.94 (dd, 1H, $J_{3',4'}$=7.6 Hz, $J_{3',5'}$=1.1 Hz, H-3'), 9.99 (s, 1H, CHO) ppm; ^{13}C NMR (500 MHz, DMSO): δ = 73.5 (OCH_2), 99.4 (C-2'), 113.8 (C-2), 121.6 (C-4), 123.0 (C-6), 128.5 (C-5'), 130.0 (C-6'), 130.3 (C-4'), 130.5 (C-5), 137.7 (C-1), 138.5 (C-1'), 139.2 (C-3'), 158.7 (C-3), 192.9 (CHO) ppm; MS-ESI: MS-MS of *m/z* 339 (M+H): *m/z* 217. M+H: *m/z* 338.98798, calculated value for $C_{14}H_{12}O_2I$: 338.98766 (delta: 0.9 ppm).

3-[(3-Iodophenyl)methoxy]benzaldehyde (3e). Separated by column chromatography with hexane: ethyl acetate 10:1 eluent. ^{1}H NMR (500 MHz, DMSO): δ = 5.18 (s, 2H, OCH_2), 7.22 (t, 1H, $J_{5',6'}$=7.8 Hz, $J_{5',4'}$=7.8 Hz, H-5'), 7.37 (m, 1H, H-4), 7.50 (d, 1H, $J_{5',6'}$=7.8 Hz, H-6'), 7.52 (m, 1H, H-2), 7.53-7.57 (m, 2H, H-5, H-6), 7.72 (d, 1H, $J_{4',5'}$=7.8 Hz, H-4'), 7.86 (s br, 1H, H-2'), 9.98 (s, 1H, CHO) ppm; ^{13}C NMR (500 MHz, DMSO): δ = 68.4 (OCH_2), 94.8 (C-3'), 113.9 (C-2), 121.6 (C-4), 122.9 (C-6), 127.0 (C-6'), 130.4 (C-5), 130.7 (C-5'), 136.1 (C-2'), 136.6 (C-4'), 137.6 (C-1), 139.3 (C-1'), 158.6 (C-3), 192.9 (CHO) ppm; MS-ESI: MS-MS of *m/z* 339 (M+H): *m/z* 311(2), 217(100), 135(2). M+H: *m/z* 338.98786, calculated value for $C_{14}H_{12}O_2I$: 338.98766 (delta: 0.6 ppm).

3-[(4-Iodophenyl)methoxy]benzaldehyde (3f). Separated by column chromatography with hexane: ethyl acetate 30:1 eluent. ^{1}H NMR (400 MHz, DMSO): δ = 5.17 (s, 2H, OCH_2), 7.28 (m, 2H, H-2', H-6'), 7.49 (m, 1H, H-2), 7.53 (m, 2H, H-5, H-6), 7.55 (m, 1H, H-4), 7.77 (m, 2H, H-3', H-5'), 9.97 (s, 1H, CHO) ppm; ^{13}C NMR (500 MHz, DMSO): δ = 68.7 (OCH_2), 94.0 (C-4'), 113.9 (C-2), 121.7 (C-4), 122.9 (C-6), 129.9 (C-2', C-6'), 130.5 (C-5), 136.5 (C-1'), 137.3 (C-3', C-5'), 137.6 (C-1), 158.6 (C-3), 192.9 (CHO) ppm; MS-ESI: MS-MS of *m/z* 339 (M+H): *m/z* 311(1), 217(100), 135(2). M+H: *m/z* 338.98786, calculated value for $C_{14}H_{12}O_2I$: 338.98766 (delta: 0.6 ppm).

4-[(2-Iodophenyl)methoxy]benzaldehyde (3g). Separated by column chromatography with hexane: ethyl acetate 5:2 eluent. M.p. 71.4-74.8 °C . ^{1}H NMR (500 MHz, DMSO): δ = 5.18 (s, 2H, OCH_2), 7.15 (td, 1H, $J_{4',3'}$=7.7 Hz, $J_{4',5'}$=7.7 Hz, $J_{4',6'}$=1.6 Hz, H-4'), 7.23 (m, 2H, H-3, H-5), 7.46 (td, 1H, $J_{5',4'}$=7.7 Hz, $J_{5',6'}$=7.7 Hz, $J_{5',3'}$=1.1 Hz, H-5'), 7.57 (dd, 1H, $J_{6',5'}$=7.7 Hz, $J_{6',4'}$=1.6 Hz, H-6'), 7.90 (m, 2H, H-2, H-6), 7.95 (dd, 1H, $J_{3',4'}$=7.7 Hz, $J_{3',5'}$=1.1 Hz, H-3'), 9.89 (s, 1H, CHO) ppm; ^{13}C NMR (500 MHz, DMSO): δ = 73.7 (OCH_2), 99.5 (C-2'), 115.2 (C-3, C-5), 128.6 (C-5'), 130.0 (C-1), 130.2 (C-6'), 130.5 (C-4'), 131.9 (C-2, C-6), 138.2 (C-1'), 139.3 (C-3'), 163.2 (C-4), 191.4 (CHO) ppm; MS-ESI: MS-MS of *m/z* 339 (M+H): *m/z* 311(3), 217(100). M+H: *m/z* 338.98786, calculated value for $C_{14}H_{12}O_2I$: 338.98766 (delta: 0.6 ppm).

4-[(3-Iodophenyl)methoxy]benzaldehyde (3h). Separated by column chromatography with hexane: ethyl acetate 5:2 eluent. M.p. 51 °C. ^{1}H NMR (500 MHz, DMSO): δ = 5.21 (s, 2H, OCH_2), 7.21 (m, 2H, H-3, H-5), 7.22 (m, 1H, H-5'), 7.49 (d, 1H, $J_{6',5'}$=7.8 Hz, H-6'), 7.72 (d, 1H, $J_{4',5'}$=8.0 Hz, H-4'), 7.86 (s, 1H, H-2'), 7.88 (m, 2H, H-2, H-6), 9.88 (s, 1H, CHO) ppm; ^{13}C NMR (500 MHz, DMSO): δ = 68.6 (OCH_2), 94.9 (C-3'), 115.3 (C-3, C-5), 127.1 (C-6'), 129.9 (C-1), 130.7 (C-5'), 131.8 (C-2,C-6), 136.2 (C-2'), 136.8 (C-4'), 139.0 (C-1'), 163.1 (C-4), 191.4 (CHO) ppm; MS-ESI: MS-MS of *m/z* 339 (M+H): *m/z* 311(5), 217(100). M+H: *m/z* 338.98793, calculated value for $C_{14}H_{12}O_2I$: 338.98766 (delta: 0.8 ppm).

4-[(4-Iodophenyl)methoxy]benzaldehyde (3i). Separated by column chromatography with hexane: ethyl acetate 5:2 eluent. M.p. about 130 °C (subl.). ^{1}H NMR (500 MHz, DMSO): δ = 5.20 (s, 2H, OCH_2), 7.20 (m, 2H, H-3, H-5), 7.29 (m, 2H, H-2',H-6'), 7.78 (m, 2H, H-3', H-5'), 7.87 (m, 2H, H-2, H-6), 9.87 (s, 1H, CHO) ppm; ^{13}C NMR (500 MHz, DMSO): δ = 69.0 (OCH_2), 94.2 (C-4'), 115.3 (C-3,C-5), 129.9 (C-1), 130.0 (C-2', C-6'), 131.8 (C-2, C-6), 136.2 (C-1'), 137.3 (C-3', C-5'), 163.1 (C-4), 191.3 (CHO) ppm; MS-ESI: MS-MS of *m/z* 339 (M+H): *m/z* 311(1), 217(100). M+H: *m/z* 338.98790, calculated value for $C_{14}H_{12}O_2I$: 338.98766 (delta: 0.7 ppm).

By-products Formed by Aldol Reactions

4-Hydroxy-4-{2-[(2-iodophenyl)methoxy]phenyl}butan-2-one (5a). Separated by column chromatography with hexane: acetone 3:1 eluent. ^{1}H NMR (500 MHz, DMSO) δ 2.04 (s, 3H, CH_3), 2.51-2.58 (m, 1H, butan-2-one CH_2), 2.70-2.75 (m, 1H, butan-2-one CH_2), 5.05 (s, 2H, OCH_2), 5.30 (d, 1H, *J*=4.9 Hz, OH), 5.36-5.41 (m, 1H, butan-2-one CH), 7.00 (td, 1H, $J_{5,4}$=7.5 Hz, $J_{5,6}$=7.5 Hz, $J_{5,3}$=0.9 Hz, H-5), 7.04 (dd, 1H, $J_{3,4}$=8.2 Hz, $J_{3,5}$=0.9 Hz, H-3), 7.14 (ddd, 1H, $J_{4',3'}$=7.8 Hz, $J_{4',5'}$=7.5 Hz, $J_{4',6'}$=1.6 Hz, H-4'), 7.25 (ddd, 1H, $J_{4,3}$=8.2 Hz, $J_{4,5}$=7.5 Hz, $J_{4,6}$=1.8 Hz, H-4), 7.45 (td, 1H, $J_{5',4'}$= 7.5Hz, $J_{5',6'}$= 7.5Hz, $J_{5',3'}$=1.1 Hz, H-5'), 7.47 (dd, 1H, $J_{6,5}$=7.5 Hz, $J_{6,4}$=1.8 Hz, H-6), 7.58 (dd, 1H, $J_{6',5'}$=7.5 Hz, $J_{6',4'}$=1.6 Hz, H-6'), 7.94 (dd, 1H, $J_{3',4'}$=7.8 Hz, $J_{3',5'}$=1.1 Hz, H-3') ppm; MS-ESI: MS-MS of *m/z* 419 (M+Na): *m/z* 361(100), 333(1), 202(2). M+Na: *m/z* 419.01168, calculated value for $C_{17}H_{17}O_3INa$: 419.01146 (delta: 0.5 ppm).

4-Hydroxy-4-{2-[(3-iodophenyl)methoxy]phenyl}butan-2-one (5b). Separated by column chromatography with hexane: acetone 5:1 eluent. ^{1}H NMR (500 MHz, DMSO) δ 2.12 (s, 3H, CH_3, 2.53-2.60 (m, 1H, butan-2-one CH_2), 2.65-2.71 (m, 1H, butan-2-one CH_2), 5.07-5.14 (m, 2H, OCH_2), 5.33 (d, 1H, *J*=4.9 Hz, OH), 5.36-5.41 (m, 1H, butan-2-one CH), 6.98 (td, 1H, $J_{5,4}$=7.4 Hz, $J_{5,6}$=7.4 Hz, $J_{5,3}$=0.8 Hz, H-5), 7.02 (dd, 1H, $J_{3,4}$=8.2 Hz, $J_{3,5}$=0.8 Hz, H-3), 7.21 (t, 1H, $J_{5',4'}$=7.8 Hz, $J_{5',6'}$=7.8 Hz, H-5'), 7.22 (ddd, 1H, $J_{4,3}$=8.2 Hz, $J_{4,5}$=7.4 Hz, $J_{4,6}$=1.7 Hz, H-4), 7.46 (dd, 1H, $J_{6,5}$=7.4 Hz, $J_{6,4}$=1.7 Hz, H-6), 7.49 (ddd, 1H, $J_{6',5'}$=7.8 Hz, $J_{6',2'}$=1.6 Hz, $J_{6',4'}$=1.0 Hz, H-6'), 7.70 (ddd, 1H, $J_{4',5'}$=7.8 Hz, $J_{4',2'}$=1.6 Hz, $J_{4',6'}$=1.0 Hz, H-4'), 7.89 (t, 1H, $J_{2',4'}$=1.6 Hz, $J_{2',6'}$=1.6 Hz, H-2') ppm; MS-ESI: MS-MS of *m/z* 419 (M+Na): *m/z* 361(100), 333(1>), 202(1). M+Na: *m/z* 419.01109, calculated value for $C_{17}H_{17}O_3INa$: 419.01146 (delta: -0.9 ppm).

(3*E*-)-4-{3-[(2-Iodophenyl)methoxy]phenyl}but-3-en-2-one (6c). Crystallized from hexane:ethyl acetate 1:1. ^{1}H NMR (400 MHz, DMSO) δ 2.34 (s, 3H, CH_3); 5.10 (s, 2H, OCH_2), 6.85 (d, 1H, $J_{3,4}$=16.4 Hz, but-3-en-2-one C(3)H), 7.08 (ddd, 1H, $J_{4',5'}$=7.8 Hz, $J_{4',2'}$=2.7 Hz, $J_{4',6'}$=1.0 Hz, H-4'), 7.14 (td, 1H, $J_{4'',3''}$= 7.6 Hz, $J_{4'',5''}$= 7.6 Hz, $J_{4'',6''}$= 1.7 Hz, H-4''), 7.32 (dt, 1H, $J_{6',5'}$= 7.8 Hz, $J_{6',2'}$= 1.1 Hz, $J_{6',4'}$=

1.1 Hz, H-6'), 7.38 (t, 1H, $J_{5',4'}$= 7.8 Hz, $J_{5,'6'}$= 7.8 Hz, H-5'), 7.39-7.42 (m, 1H, H-2'), 7.45 (td, 1H, $J_{5",4"}$= 7.6 Hz, $J_{5",6"}$= 7.6 Hz, $J_{5",3"}$= 1.2 Hz, H-5"), 7.57 (dd, 1H, $J_{6",5"}$= 7.6 Hz, $J_{6",4"}$= 1.7 Hz, H-6"), 7.61 (d, 1H, $J_{4,3}$=16.4 Hz, but-3-en-2-one C(4)H), 7.93 (dd, 1H, $J_{3",4"}$= 7.6 Hz, $J_{3",5"}$= 1.2 Hz, H-3") ppm; MS-ESI: MS-MS of *m/z* 379 (M+H): *m/z* 361(15), 321(11), 252(12), 234(33), 217(100), 194(25), 145(4). M+H: *m/z* 379.01933, calculated value for $C_{17}H_{16}O_2I$: 379.01895 (delta: 1.0 ppm).

4-Hydroxy-4-{3-[(3-iodophenyl)methoxy]phenyl}butan-2-one (5d). Separated by column chromatography with hexane: ethyl acetate 1:1 eluent. ^{1}H NMR (400 MHz, DMSO) δ 2.11 (s, 3H, CH_3), 2.61-2.75 (m, 2H, butan-2-one CH_2), 4.94-5.00 (m, 1H, butan-2-one CH), 5.07 (s, 2H, OCH_2), 5.38 (d, 1H, *J*=4.8 Hz, OH), 6.86 (ddd, 1H, $J_{4,5}$=8.0 Hz, $J_{4,2}$=2.7 Hz, $J_{4,6}$=1.0 Hz, H-4), 6.94 (m, 1H, H-6), 7.00-7.02 (m, 1H, H-2), 7.20 (t, 1H, $J_{5',4'}$=7.8 Hz, $J_{5',6'}$=7.8 Hz, H-5'), 7.23 (t, 1H, $J_{5,4}$=8.0 Hz, $J_{5,6}$=8.0 Hz, H-5), 7.47 (ddd, 1H, $J_{6',5'}$=7.8 Hz, $J_{6',2'}$=1.7 Hz, $J_{6',4'}$=1.0 Hz, H-6'), 7.71 (ddd, 1H, $J_{4',5'}$=7.8 Hz, $J_{4',2'}$=1.7 Hz, $J_{4',6'}$=1.0 Hz, H-4'), 7.83 (t, 1H, $J_{2',4'}$=1.7 Hz, $J_{2',6'}$=1.7 Hz, H-2') ppm; MS-EI: *m/z* (%): 396(M^+, 4), 378(4), 338(12), 217(100), 90(26). M: *m/z* 396.01953, calculated value for $C_{17}H_{17}O_3I$: 396.02170 (delta: -2.2 ppm).

4-Hydroxy-4-{3-[(4-iodophenyl)methoxy]phenyl}butan-2-one (5e). Separated by column chromatography with hexane: ethyl acetate 1:1 eluent. ^{1}H NMR (400 MHz, DMSO) δ 2.11 (s, 3H, CH_3), 2.61-2.75 (m, 2H, butan-2-one CH_2), 4.94-5.00 (m, 1H, butan-2-one CH), 5.06 (s, 2H, O-CH_2), 5.37 (d, 1H, *J*=4.7 Hz, OH), 6.85 (ddd, 1H, $J_{4,5}$=7.9 Hz, $J_{4,2}$=2.6 Hz, $J_{4,6}$=1.0 Hz, H-4), 6.93 (d, 1H, $J_{6,5}$=7.9 Hz, H-6), 6.98-7.01 (m, 1H, H-2), 7.23 (t, 1H, $J_{5,4}$=7.9 Hz, $J_{5,6}$=7.9 Hz, H-5), 7.26 (m, 2H, H-2', H-6'), 7.76 (m, 2H, H-3', H-5') ppm; MS-EI: *m/z* (%): 396(M^+, 2), 378(2), 338(4), 217(100), 90(13). M: *m/z* 396.02223, calculated value for $C_{17}H_{17}O_3I$: 396.02170 (delta: 0.5 ppm).

4-Hydroxy-4-{4-[(3-iodophenyl)methoxy]phenyl}butan-2-one (5f). Separated by column chromatography with hexane: ethyl acetate 3:1 eluent. ^{1}H NMR (800 MHz, DMSO) δ 2.10 (s, 3H, CH_3), 2.62 (dd, 1H, *J*=15.0 Hz, 3.6 Hz, butan-2-one CH_2), 2.71 (dd, 1H, *J*=15.0 Hz, 9.1 Hz, butan-2-one CH_2), 5.07 (s, 2H, OCH_2), 5.26 (d, 1H, *J*=4.2 Hz, OH), 4.94 (ddd, 1H, *J*=9.1 Hz, 4.2 Hz, 3.6 Hz, butan-2-one CH), 6.95 (m, 2H, H-3, H-5), 7.20 (t, 1H, $J_{5',4'}$=7.7 Hz, $J_{5',6'}$=7.7 Hz, H-5'), 7.26 (m, 2H, H-2, H-6), 7.45 (d, 1H, $J_{6',5'}$=7.7 Hz, H-6'), 7.69 (d, 1H, $J_{4',6'}$=7.7 Hz, H-4'), 7.81 (s br, 1H, H-2') ppm. ^{13}C NMR (800 MHz, DMSO): δ = 30.4 (CH_3), 53.0 (butan-2-one CH_2), 68.1 (OCH_2), 68.5 (butan-2-one CH), 94.8 (C-3'), 114.4 (C-3, C-5), 126.86 (C-6'), 126.93 (C-2,C-6), 130.6 (C-5'), 135.9 (C-2'), 136.4 (C-4'), 137.7 (C-1), 139.9(C-1'), 157.0 (C-4), 206.9 (CO) ppm; MS-ESI: MS-MS of *m/z* 419 (M+Na): *m/z* 361. M+Na: *m/z* 419.01148, calculated value for $C_{17}H_{17}O_3INa$: 419.01146 (delta: 0.1 ppm).

4-Hydroxy-4-{4-[(4-iodophenyl)methoxy]phenyl}butan-2-one (5g). Separated by column chromatography with hexane: ethyl acetate 3:1 eluent. ^{1}H NMR (800 MHz, DMSO) δ 2.10 (s, 3H, CH_3), 2.61-2.65 (m, 1H, butan-2-one CH_2), 2.70-2.75 (m, 1H, butan-2-one CH_2), 4.92-4.95 (m, 1H, butan-2-one CH), 5.05 (s, 2H, OCH_2), 5.33 (d, 1H, *J*=4.6 Hz, OH), 6.92-6.95 (m, 2H, H-3, H-5), 7.24-7.27 (m, 4H, H-2, H-6, H-2', H-6'), 7.74-7.76 (m, 2H, H-3', H-5') ppm; MS-ESI: MS-MS of *m/z* 419 (M+Na): *m/z* 361. M+Na: *m/z* 419.01176, calculated value for $C_{17}H_{17}O_3INa$: 419.01146 (delta: 0.7 ppm).

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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