

Supporting Info for:

**Demonstration of a Stereospecific Photochemical Meta Effect**

Hoai Pham, Madelyn Hunsley, Chou-Hsun Yang, Haobin Wang, Scott M. Reed

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## Section 1. Synthetic details

All the solvents and chemicals were from Sigma Aldrich and used without further purification. Mass spectrometry was performed on an Agilent 6200 Series TOF and 6500 Series Q-TOF LC/MS System. The  $^1\text{H}$ -NMR and  $^{13}\text{C}$ -NMR spectra were obtained using a Bruker AV-III 400 MHz spectrometer. The NMR samples were prepared in  $\text{CDCl}_3$  with tetramethylsilane as an internal standard. The FTIR spectra were obtained with a Nicolet iS5 FTIR spectrometer and all measurements were in  $\text{cm}^{-1}$ .

### Synthesis of (2-(benzyloxy)phenyl)(3-methoxyphenyl)methanone (1).

2-Benzyloxybenzonitrile (2.09 g, 10 mmol) was dissolved in 10 mL of THF in a 100 mL flask charged with a stir bar, reflux condenser, drying tube, and addition funnel. Grignard reagent solution from *m*-bromoanisole (10 mmol in 10 mL THF) was added dropwise to the apparatus via addition funnel. The solution was heated at reflux for 4 hours. HCl (0.5 M) was added dropwise to adjust the pH to 2 before it was heated at reflux for 5 hours. The solution was extracted with 3 x 10 mL of DCM. The pooled organic layers were washed with 2 x 30 mL of brine, dried over anhydrous  $\text{MgSO}_4$ , filtered, and condensed via rotary evaporation. The resulting solution was purified by column chromatography (ethyl acetate/hexanes), yielding a yellow liquid (78%):  $^1\text{H}$  NMR:  $\delta$  7.44-7.40 (3H, m), 7.32-7.30 (2H, m), 7.22-7.20 (3H, m), 7.12-7.05 (2H, m), 7.03-7.00 (3H, m), 5.01 (2H, s), 3.82 (3H, s).  $^{13}\text{C}$  NMR:  $\delta$  159.47, 156.05, 146.52, 144.73, 130.00, 129.88, 129.63, 129.20, 128.21, 128.01, 127.73, 120.26, 119.10, 117.61, 113.99, 113.03, 84.38, 77.22, 55.21. IR (neat): 3073, 2917, 2860, 1652, 1595, 1576, 1484, 1445, 1380. HRMS (ESI/TOF)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd for  $\text{C}_{21}\text{H}_{19}\text{O}_3^+$  319.1329; Found 319.13427.

### Synthesis of 2-(benzyloxy)phenyl(3-methoxyphenyl)(4-methoxyphenyl)methanol (2).

Ketone **1** (1.59 g, 5 mmol) was dissolved in 10 mL of THF in a 100-mL flask charged with a stir bar, reflux condenser, drying tube, and addition funnel. Grignard reagent solution prepared from *p*-bromoanisole (5 mmol in 10 mL THF) was added dropwise to the apparatus via addition funnel. The solution was heated at reflux for 4 hours. The THF was removed by rotary evaporation before saturated  $\text{NH}_4\text{Cl}$  solution was added to the solution. The solution was extracted with 3 x 10 mL of DCM. The pooled organic layers were washed with 2 x 30 mL of brine, dried with  $\text{MgSO}_4$ , filtered, and condensed via rotary evaporation. The resulting solution was purified with column chromatography (ethyl acetate/hexane), yielding an oil (82%).  $^1\text{H}$  NMR:  $\delta$  7.27-7.16 (7H, m), 6.99 (1H, d,  $J = 8.13$ ), 6.92 (1H, s), 6.82 (6H, t,  $J = 8.61$ ), 6.75 (1H, d,  $J = 7.65$ ), 6.57 (1H, d,  $J = 7.6$ ), 5.15 (1H, s), 4.90 (2H, s), 3.80 (3H, s), 3.71 (3H, s).  $^{13}\text{C}$  NMR:  $\delta$  159.42, 158.62, 156.37, 148.80, 138.48, 136.35, 135.87, 130.22, 129.04, 128.90, 128.52, 128.39, 128.03, 127.46, 127.07, 120.65, 120.35, 113.04, 112.74, 81.63, 77.22, 70.49, 55.26, 55.14. IR (neat): 3515, 3063, 3019, 2957, 1608, 1600, 1583, 1511, 1482, 1450.

**Synthesis of (2-hydroxy(3-methoxyphenyl)(4-methoxy phenyl)methyl)phenol (3)** Alcohol **2** (500 mg, 1 equiv.) was combined with pyridine (0.5 equiv.), Pd/C (25 mg) and 15 mL of ethyl acetate in a two-neck flask charged with a stir bar. The solution was backfilled with  $\text{N}_2$  before  $\text{H}_2$  was introduced to the flask. Once the reaction was complete, the solution was filtered through Celite before it was washed with 3 x 15 mL of 0.1 HCl solution. The organic layer was dried over anhydrous  $\text{MgSO}_4$ , and condensed via rotary evaporation to obtain an oil. The solution was crystallized in ethyl acetate/hexanes to obtain a white solid (95% yield).  $^1\text{H}$  NMR:  $\delta$  8.14 (1H, bs), 7.20 (2H, m), 7.11 (2H, d,  $J = 8.27$ ), 6.81 (7H, m), 6.54 (1H, d,  $J = 7.53$ ), 3.80 (3H, s), 3.73

(3H, s), 3.67 (1H, s).  $^{13}\text{C}$  NMR:  $\delta$  159.41, 159.19, 156.04, 146.74, 137.00, 130.10, 129.95, 129.54, 129.14, 129.10, 120.20, 119.04, 117.55, 113.92, 113.47, 112.92, 84.15, 55.28, 55.21. IR (neat): 3325, 3001, 2932, 2833, 1608, 1581, 1511, 1482, 1452. HRMS (dual ESI/TOF)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd for  $\text{C}_{21}\text{H}_{19}\text{O}_4$  335.1289; Found 335.13059.

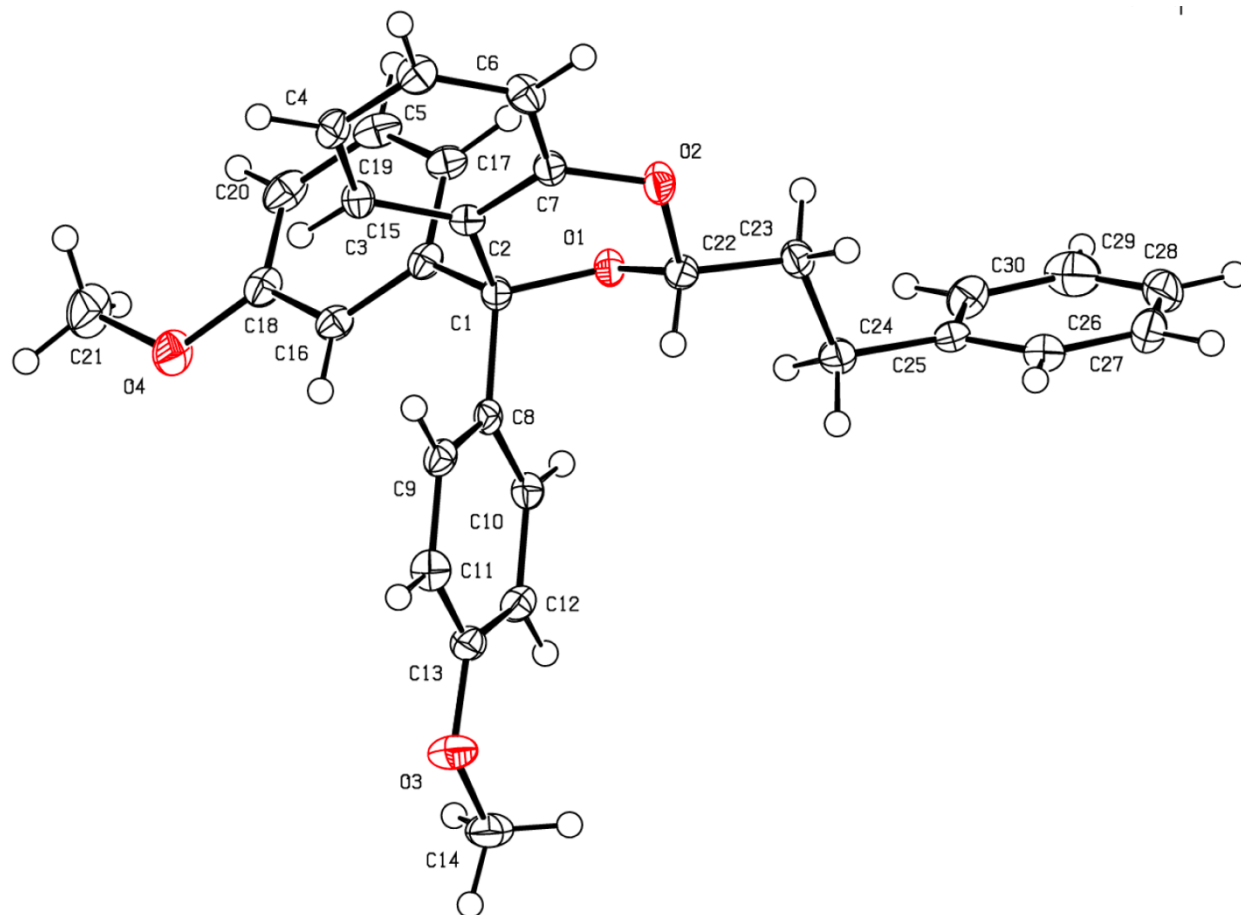
#### **Synthesis of 4-(4-methoxyphenyl)-2-phenethyl-4-(3-methoxyphenyl)-4H-**

**benzo[d][1,3]dioxine (4):** Diol **3** (336 mg, 2 mmol) was combined with 3-phenylpropanal (134 mg, 1 mmol), *p*-toluenesulfonic acid (0.01g), and 10 mL of benzene in a 25-mL flask charged with a stir bar. The solution was stirred at room temperature for 15 hours before saturated  $\text{NaHCO}_3$  solution was added to the solution. The solution was extracted with 3 x 5 mL of DCM. The pooled organic layers were dried over anhydrous  $\text{MgSO}_4$ , filtered, and condensed via rotary evaporation to obtain an oily solution. The resulting solution was crystallized in ethyl acetate/hexanes to produce a white solid (99% yield). The combined diastereomers were recrystallized using Hex/EtOAc and the first crystals isolated were determined to be the unlike racemate (R,S) and (S,R) as determined by XRD (Fig S1, section S5). The appearance of all the crystals in the batch were uniform. An NMR of a sample of the crystals showed unlike racemate and an NMR of the remaining supernatant solution was checked which had an unlike:like ratio of  $\sim 1.3:1$  consistent with that fact that the unlike racemate was isolated from the supernatant in growing crystals.  $^1\text{H}$  NMR (unlike racemate):  $\delta$  7.25-7.08 (9H, m), 6.93-6.77 (8H, m), 5.05 (1H, s), 3.84 (3H, s), 3.74 (3H, s), 2.82 (1H, m), 2.71 (1H, m), 2.16 (2H, m).  $^{13}\text{C}$  NMR (unlike racemate):  $\delta$  159.28, 159.16, 152.41, 147.98, 141.51, 136.82, 130.72, 129.53, 129.48, 128.73, 128.41, 128.32, 125.82, 125.47, 120.88, 120.19, 117.04, 114.46, 113.32, 112.40, 94.34, 83.89, 55.30, 55.19, 36.14, 29.63. IR (neat): 3063, 3028, 2959, 2927, 2888, 2836, 1608, 1581, 1509, 1484, 1455, 1395. HRMS (dual ESI/TOF)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd for  $\text{C}_{30}\text{H}_{29}\text{O}_4$  453.20604; Found 453.20712.

**Electronic structure calculations.** All ground state ( $S_0$ ) calculations were carried out by means of density functional theory (DFT) with the B3LYP hybrid functional, which includes the Becke three-parameter exchange and the Lee, Yang, and Parr correlation functionals (Becke, 1993). The standard 6-31G\* basis set was employed. Time-dependent DFT (TD-DFT) in its Tamm–Dancoff approximation (TDA)(Hirata & Head-Gordon, 1999), employing the same basis set, was used to study the excited state properties. To account for charge-transfer excitations, the CAM-B3LYP functional(Yanai et al., 2004) was used in the TD-DFT calculations. Each structure was fully optimized at the ground electronic state using the DFT/B3LYP/6-31G\* method. Then the TD-DFT/CAM-B3LYP/6-31G\* method was used to calculate the oscillator strengths and vertical excitation energies for the absorption processes to several excited states. Since the molecule's first excited states ( $S_1$ ) have significant oscillator strengths, the analysis focused on states  $S_0$  and  $S_1$ . The structure of each molecule was also optimized at the  $S_1$  excited state using the TD-DFT/CAM-B3LYP/6-31G\* method. Then the vertical (de)excitation energy was calculated for this structure with respect to the emission process back to the ground state  $S_0$ . Energies at two different structures: minima of  $S_0$  and  $S_1$ , were used to calculate the reorganization energies  $\lambda$  ( $S_1 \rightarrow S_0$ ) and  $\lambda$  ( $S_0 \rightarrow S_1$ ) at both electronic states. All calculations employed the polarized continuum model (PCM) (Miertuš et al., 1981; Miertuš & Tomasi, 1982; Tomasi et al., 2005) and conductor-like PCM (cPCM)(Cossi et al., 2003) with water as the solvent. The excited state calculations also include the optical dielectric constant of water.

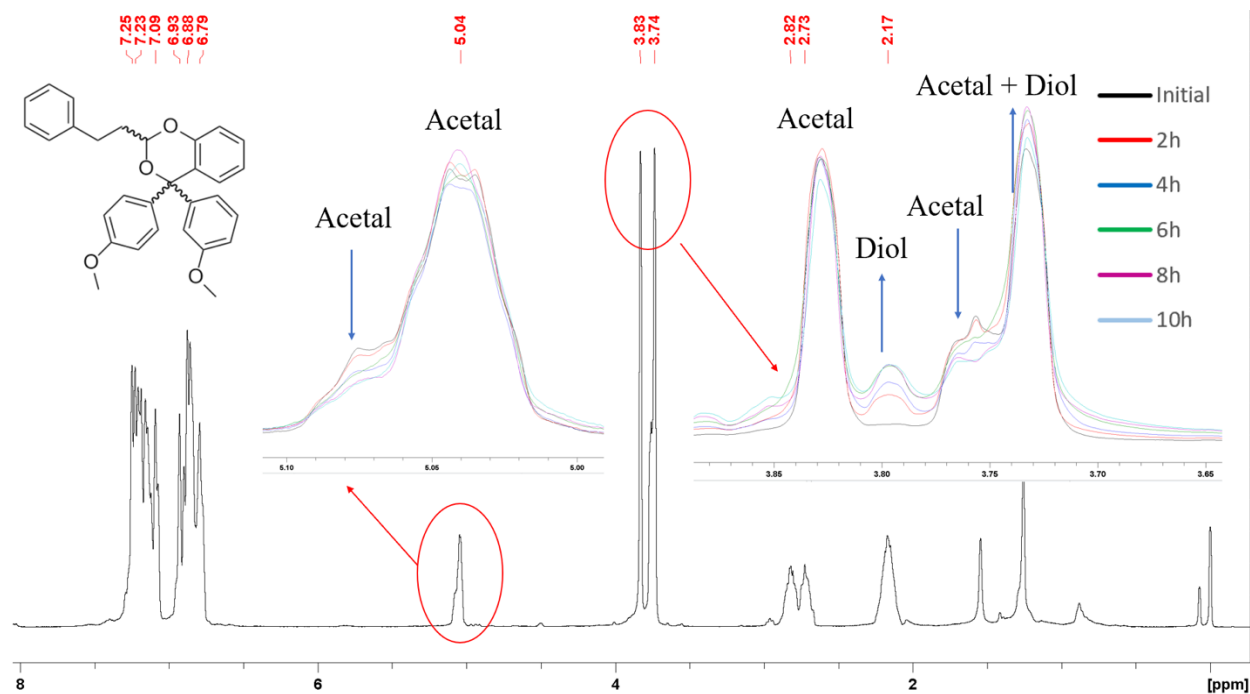
Apart from the structural differences, the like and unlike racemates can be distinguished by differences in the calculated UV/Vis absorption spectra, whereas each racemate can be distinguished from differences in the calculated electronic circular dichroism spectra. The same strategy could also be used for the experimental classification of these isomers. Other properties can be obtained from electronic structure theory calculations, that inform this mechanistic study. For example, as shown in our previous work (Yang 2019), the generalized Mulliken-Hush (GMH)(Cave & Newton, 1996, 1997) approach can be used to estimate the electronic coupling strength between the two electronic states. The nuclear force (gradient vector) at the Frank-Condon structure can be used to quantify the electronic-nuclear coupling. These properties were used to reveal the reaction mechanism.

## Section 2. Crystal structure of acetal

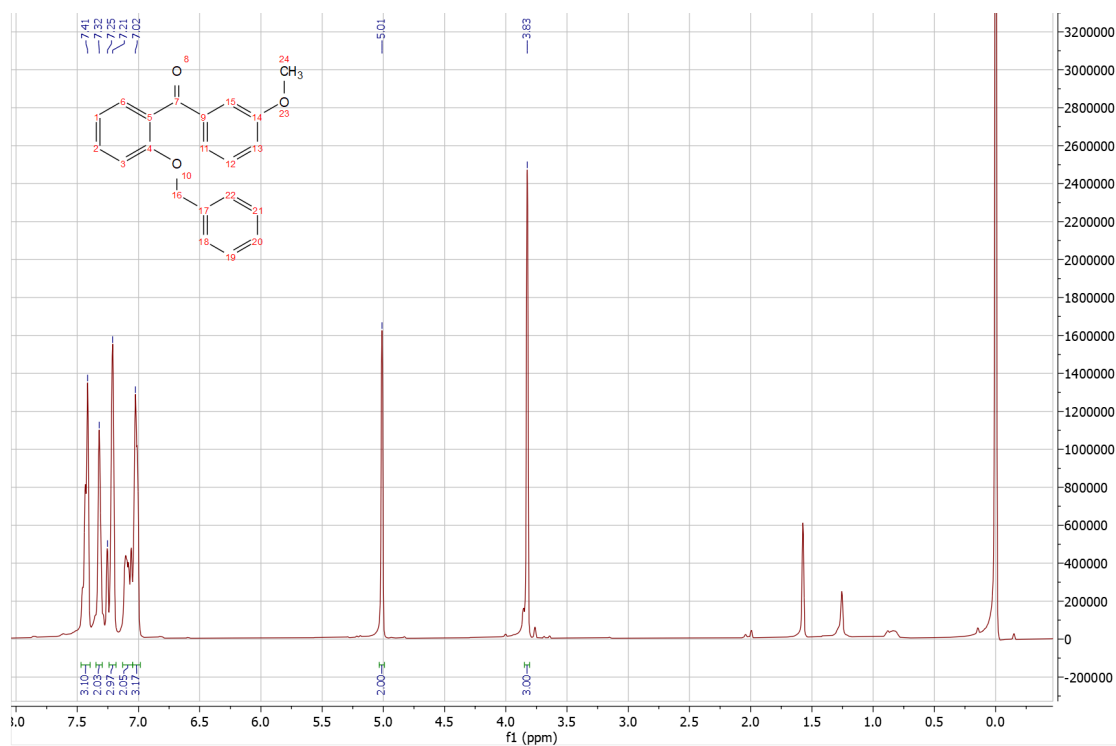


**Figure S1.** Crystal structure of (2R,4S)-4-(4-methoxyphenyl)-2-phenethyl-4-(3-methoxyphenyl)-4H-benzo[d][1,3]dioxine.

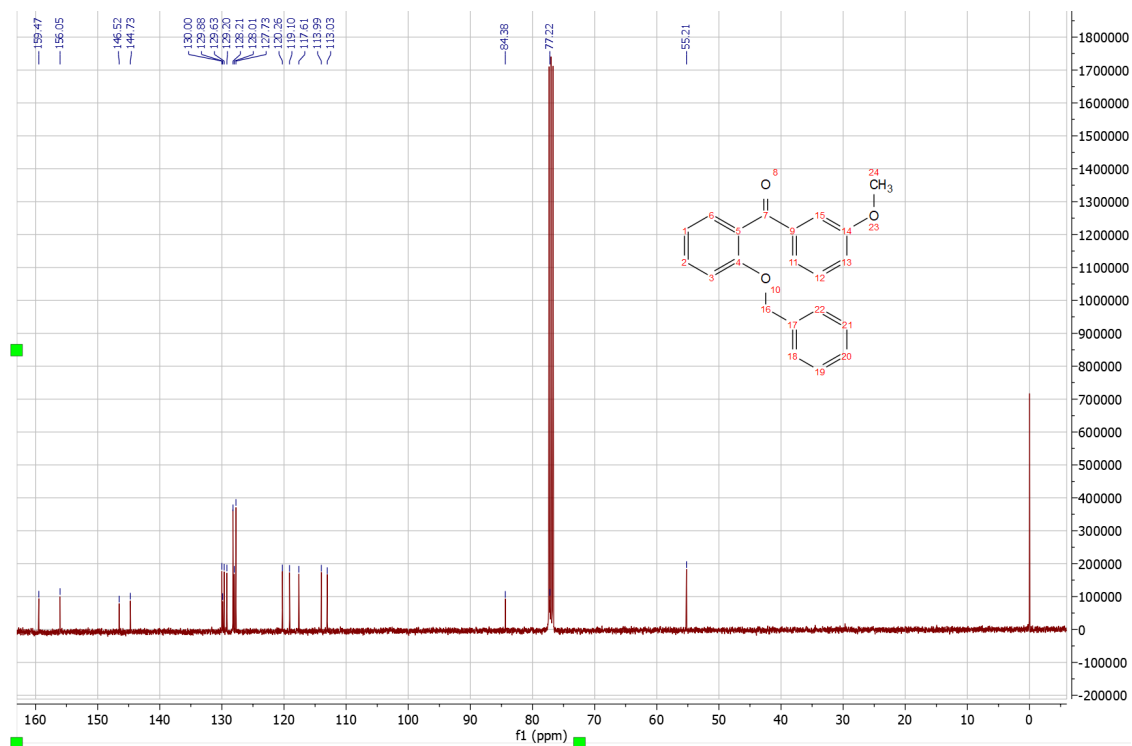
## Section 4. NMR spectra of compounds



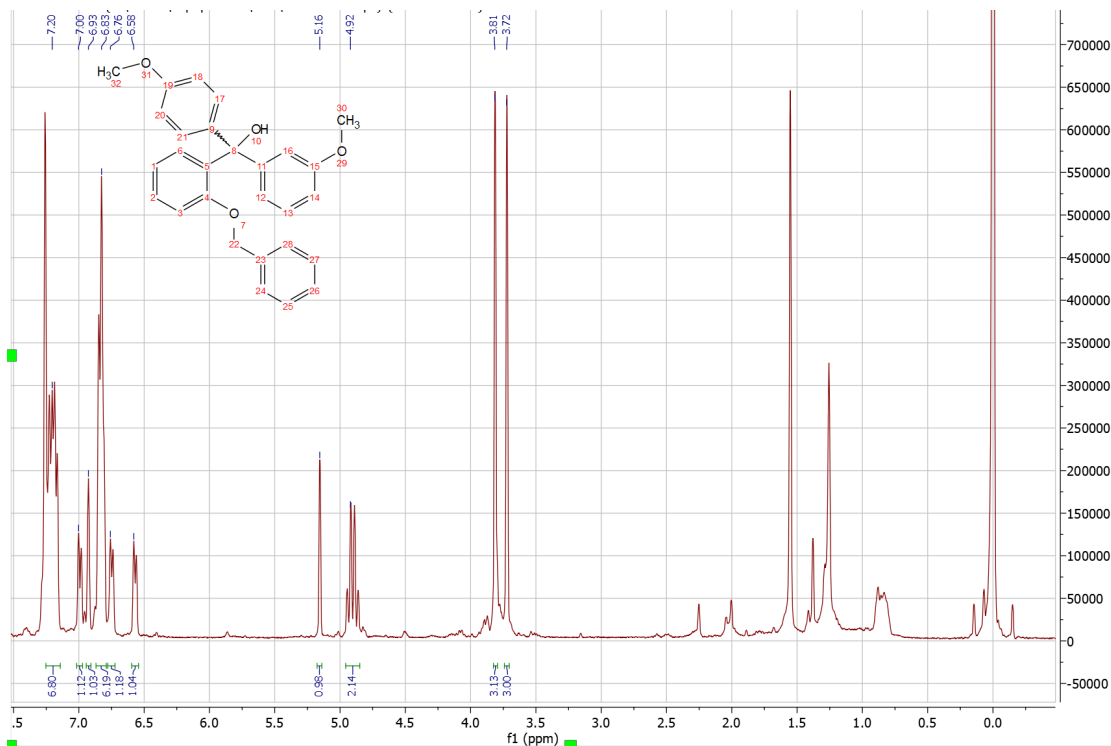
**Figure S2.**  $^1\text{H}$  NMR time series taken during 10 hour irradiation of a 76:24 (*u:l*) mixture of acetal **4** with UV.



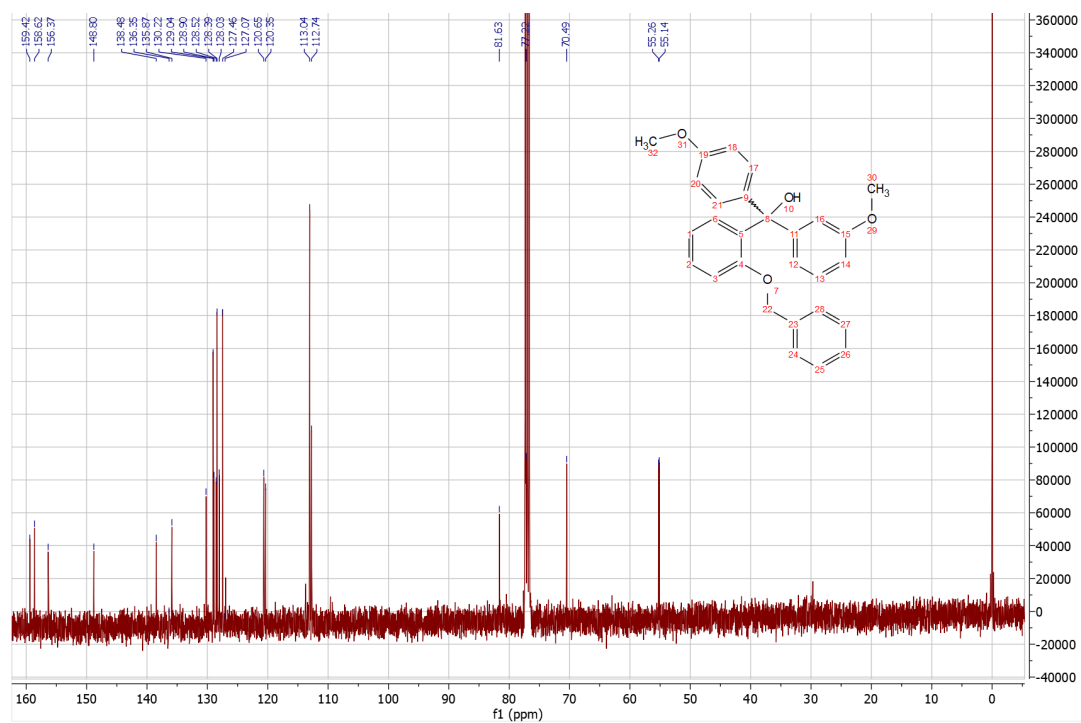
**Figure S3.**  $^1\text{H}$  NMR spectrum of (2-(benzyloxy)phenyl)(3-methoxyphenyl)methanone.



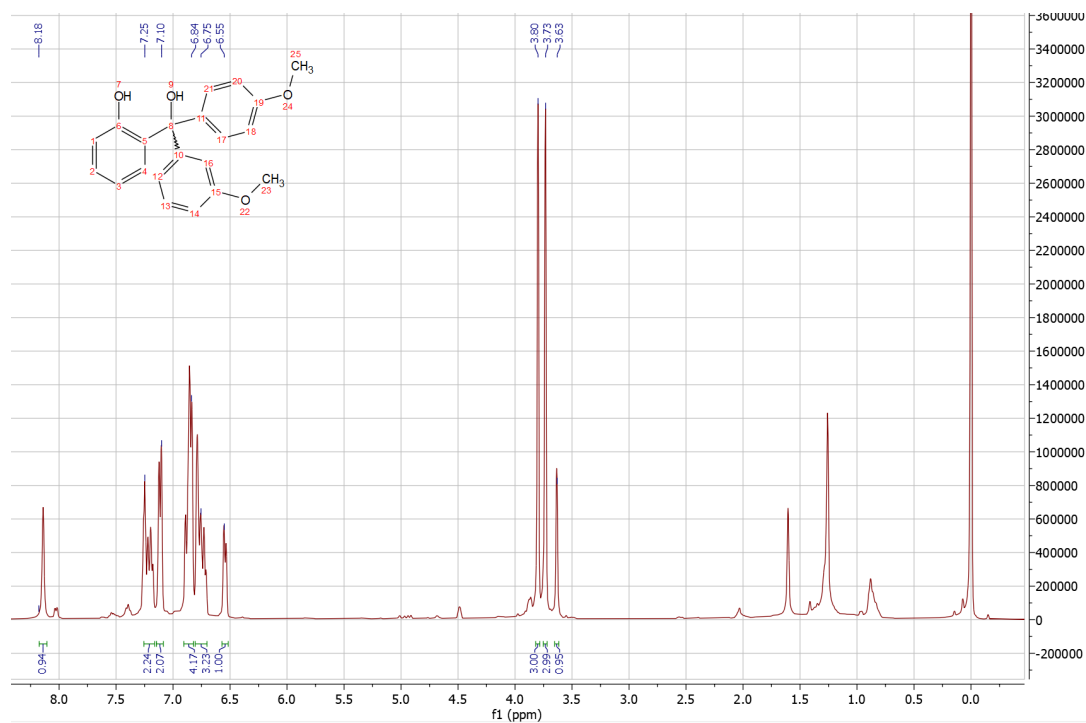
**Figure S4.**  $^{13}\text{C}$  NMR spectrum of (2-(benzyloxy)phenyl)(3-methoxyphenyl)methanone.



**Figure S5.**  $^1\text{H}$  NMR spectrum of 2-(benzyloxy)phenyl(3-methoxyphenyl)(4-methoxyphenyl)methanol.

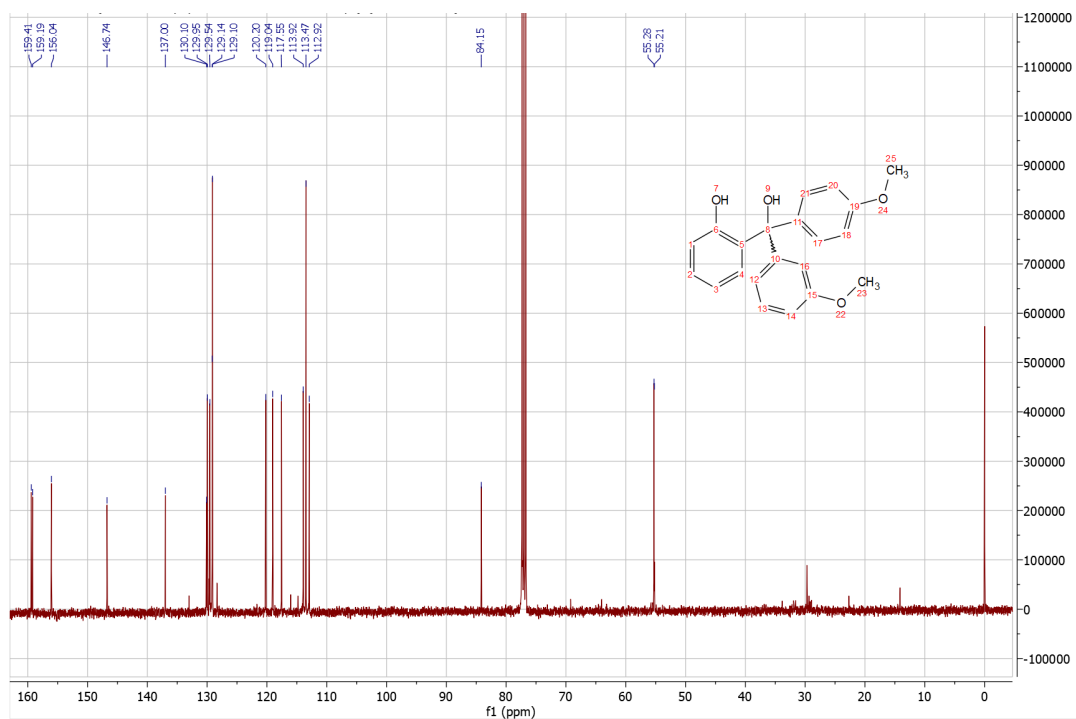


**Figure S6.**  $^{13}\text{C}$  NMR spectrum of 2-(benzyloxy)phenyl(3-methoxyphenyl)(4-methoxyphenyl)methanol

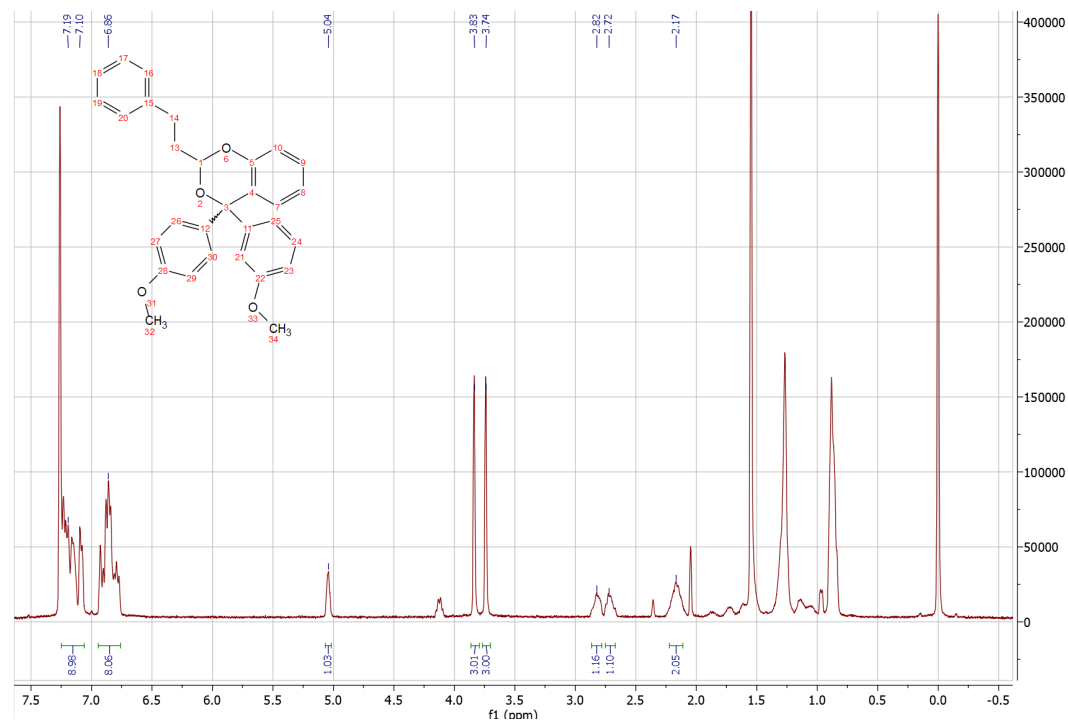


**Figure S7.**  $^1\text{H}$  NMR spectrum of (2-hydroxy(3-methoxyphenyl)(4-methoxyphenyl)methyl)phenol.

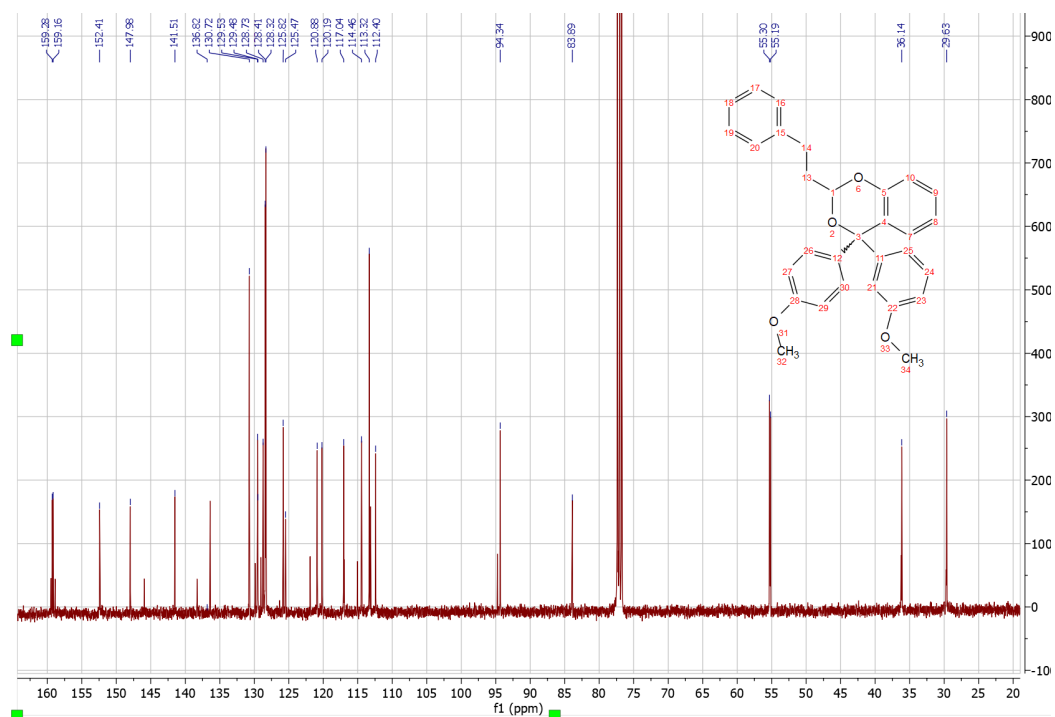




**Figure S8.** <sup>13</sup>C NMR spectrum of (2-hydroxy(3-methoxyphenyl)(4-methoxyphenyl)methyl)phenol.

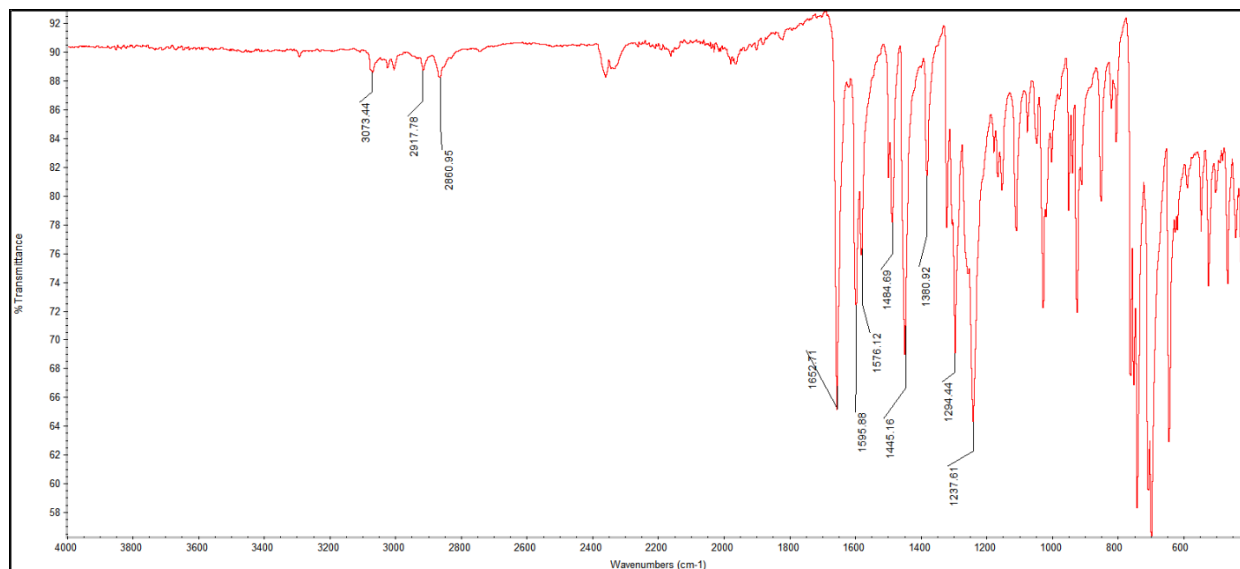


**Figure S9.** <sup>1</sup>H NMR spectrum of acetal **4**, (±)-4-(4-methoxyphenyl)-2-phenethyl-4-(3-methoxyphenyl)-4H-benzo[d][1,3]dioxine.

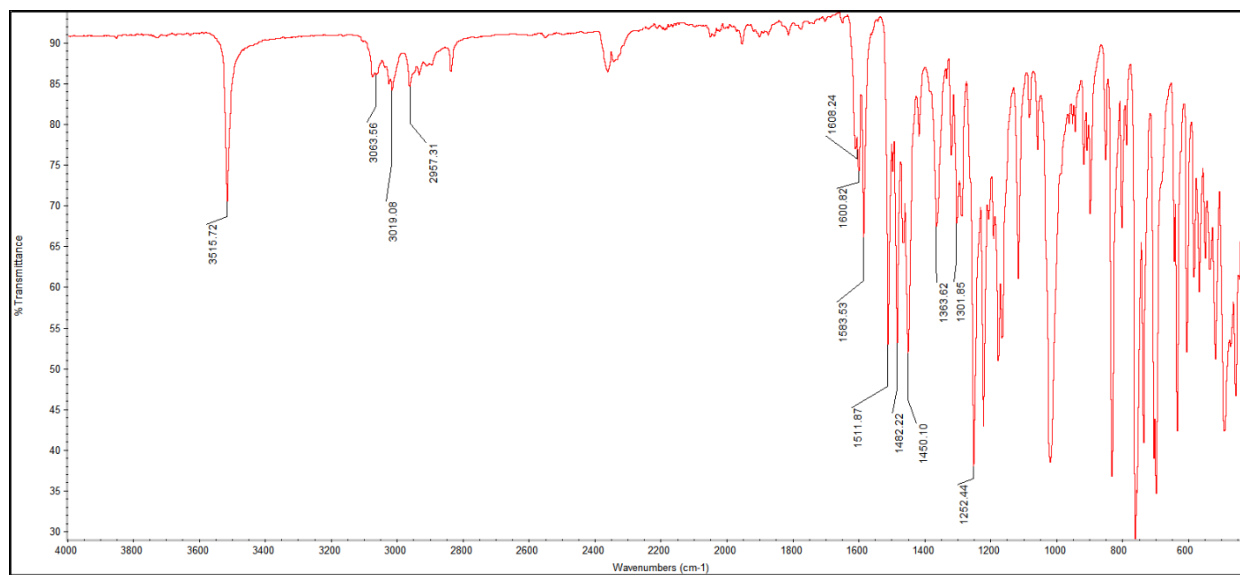


**Figure S10.**  $^{13}\text{C}$  NMR spectrum of **4**,  $(\pm)$ -4-(4-methoxyphenyl)-2-phenethyl-4-(3-methoxyphenyl)-4H-benzo[d][1,3]dioxine.

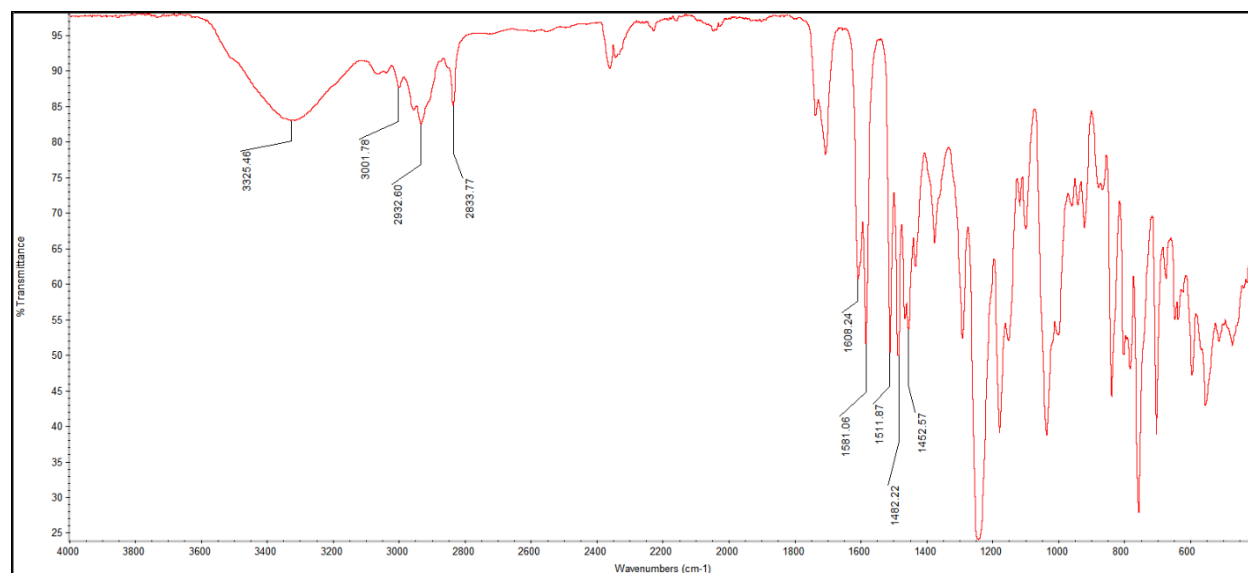
## Section 5. IR spectra of compounds



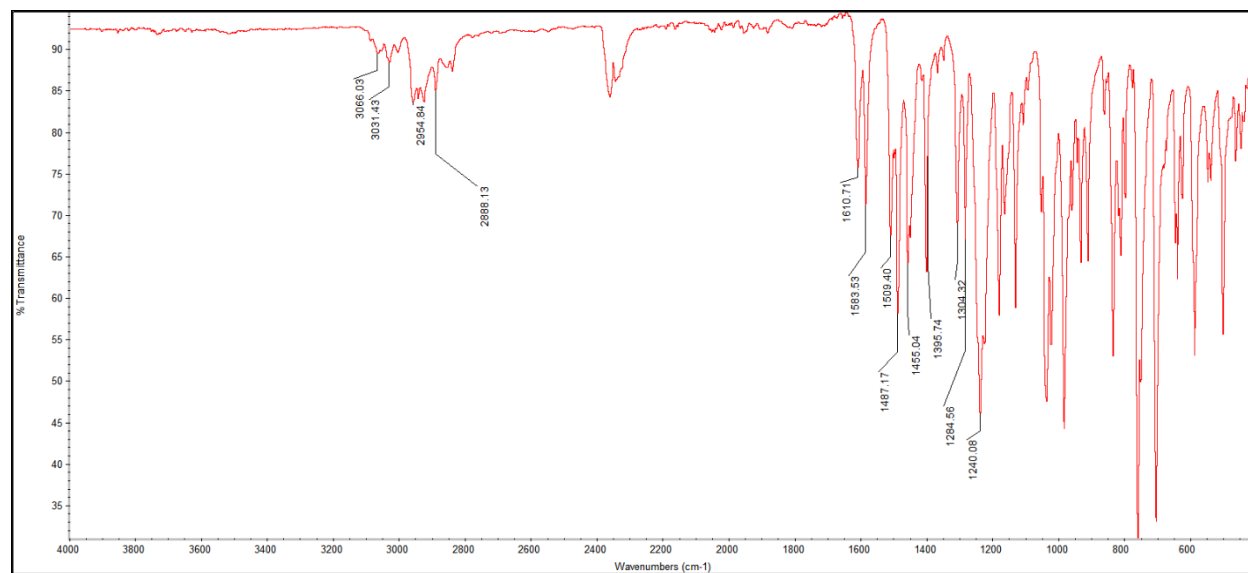
**Figure S11.** IR spectrum of (2-(benzyloxy)phenyl)(3-methoxyphenyl)methanone.



**Figure S12.** IR spectrum of 2-(benzyloxy)phenyl(3-methoxyphenyl)(4-methoxyphenyl)methanol.



**Figure S13.** IR spectrum of (2-hydroxy(3-methoxyphenyl)(4-methoxy phenyl)methyl)phenol.



**Figure S14.** IR spectrum of (±)-4-(4-methoxyphenyl)-2-phenethyl-4-(3-methoxyphenyl)-4H-benzo[d][1,3]dioxine.

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