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Short Note

Cis,exo-1,2,3,4,4a,13b-hexahydro-1,4-methano-5-isopropoxy-9*H*-tribenzo[*b,f*]azepine

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Abstract: The title compound—*cis,exo*-1,2,3,4,4a,13b-hexahydro-1,4-methano-5-isopropoxy-9*H*-tribenzo[*b,f*]azepine—was synthesized in 83% isolated yield by a palladium-catalyzed one-pot strategy from 1-iodo-2-isopropoxybenzene and *ortho*-bromoaniline. The azepine derivative was fully characterized (FT-IR, MS, ^{1}H and ^{13}C-NMR, elemental analysis) and all proton and carbon signals have been completely assigned by 2D NMR experiments.

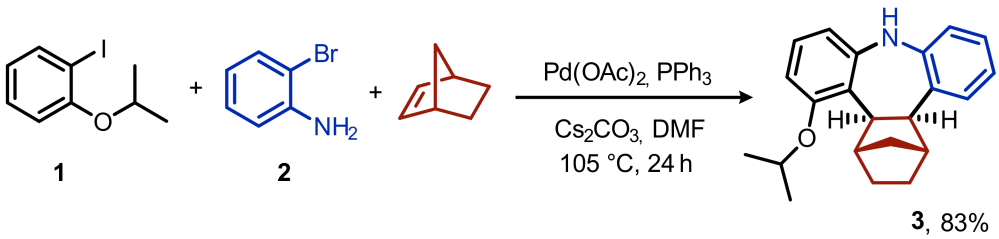
Keywords: palladium; norbornene; benzo[*b,f*]azepine; C-C and C-N couplings; multicomponent; one-pot reaction

1. Introduction

The selective activation and functionalization of inert C-H bonds is a great challenge in synthetic chemistry [1–5]. In 1997 Marta Catellani discovered an innovative strategy aimed at the derivatization of both the *ortho* and *ipso* positions of aryl halides [6]. Over the years, this palladium/norbornene-catalyzed C-H activation and functionalization reaction has been proven to be a powerful tool for the construction of complex molecules in a one-pot fashion [7,8]. In this context, we have successfully applied this methodology to the synthesis of many compounds, including natural product derivatives [9–20]. Notably, in 2011, we enriched the versatility of the Catellani reaction by the synthesis of dibenzo[*b,f*]azepines [21].

A dibenzo[*b,f*]azepine scaffold is essential for the construction of important therapeutic agents, exhibiting a variety of biological activities including anticancer, antidepressant, and antiepileptic properties [22–25].

In this Note, we report the preparation of azepine **3**—that is, *cis,exo*-1,2,3,4,4a,13b-hexahydro-1,4-methano-5-isopropoxy-9*H*-tribenzo[*b,f*]azepine—by employing the abovementioned palladium-catalyzed methodology [21] (Scheme 1). The structure of compound **3** was confirmed by NMR, MS, and FT-IR, and all data are in concordance with the assumed structure.

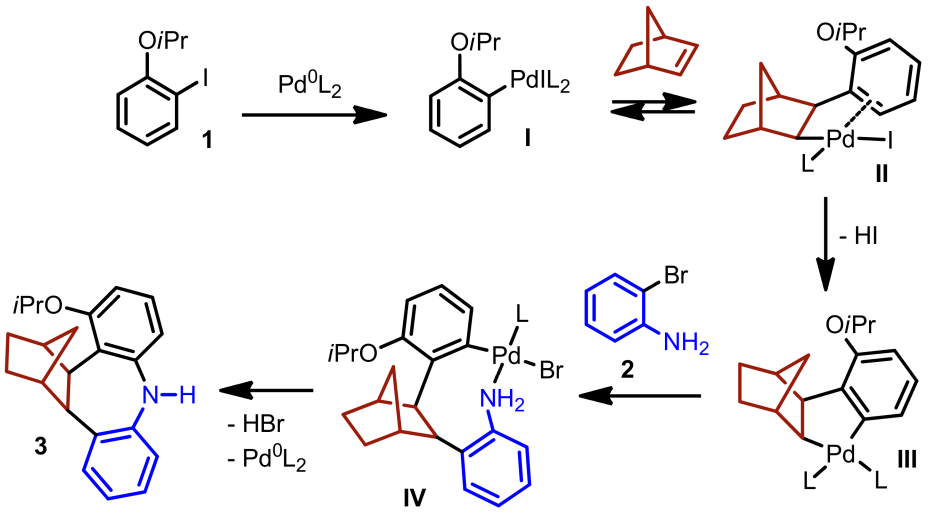


Scheme 1. Synthesis of the title compound **3**.

2. Results and Discussion

As shown in Scheme 1, *cis*,*exo*-1,2,3,4,4a,13b-hexahydro-1,4-methano-5-isopropoxy-9*H*-tribenzo [*b*,*f*]azepine (**3**) was synthesized in 83% isolated yield. The reaction was carried out using 1-iodo-2-isopropoxybenzene (**1**), *o*-bromoaniline (**2**), and norbornene, in the presence of a catalytic amount of $Pd(OAc)_2$ (5 mol %), PPh_3 (12.5 mol %), and Cs_2CO_3 as a base in DMF at 105 °C for 24 h. Notably, the isopropoxy group, which can be easily converted to a hydroxyl group [26], is well tolerated by this protocol.

A plausible reaction mechanism is shown in Scheme 2. At first, the oxidative addition of **1** to palladium(0) affords the palladium(II) complex **I**, which, after stereoselective norbornene insertion, leads to intermediate **II**. The intramolecular C-H bond activation provides the arylnorbornyl palladacycle **III**, which is able to react with 2-bromoaniline **2**, giving intermediate **IV**. Finally, an intramolecular C-N coupling affords compound **3** and palladium(0), which can start a new catalytic cycle. Contrary to many other Catellani-type reactions, norbornene is a reagent here since it is incorporated in the final product.



Scheme 2. Proposed reaction pathway.

Compound **3** was characterized by NMR (^{1}H and ^{13}C-NMR in Figures 1 and 2), FT-IR, and MS. In addition, all proton and carbon signals were assigned by 2D and ^{13}C-DEPT-NMR experiments (Figures S1–S11, Supplementary Materials) and protons on the norbornene bridge were unequivocally assigned by NOESY-2D-NMR (Figure S12, Supplementary Materials). As expected, diagnostic NOE correlations appear between H13 and H13b (green circle, Figure S12), and H1′ and H6 (blue circle, Figure S12). Furthermore, the proton marked as H14 *anti* has a strong NOE correlation with H2/H3 protons (red circle in Figure S12), while no correlation signals are present between H2/H3/H4a/H13b protons and H14 *syn*. In summary, the signal at 1.62 ppm, which accounts for H2/H3 (both *endo* and *exo*) protons, presents typical NOE correlations with H4a, H13b (orange circle in Figure S12), H4, H1 (grey circle in Figure S12), and H14 *anti* (red circle in Figure S12), as expected for the presented stereochemistry.

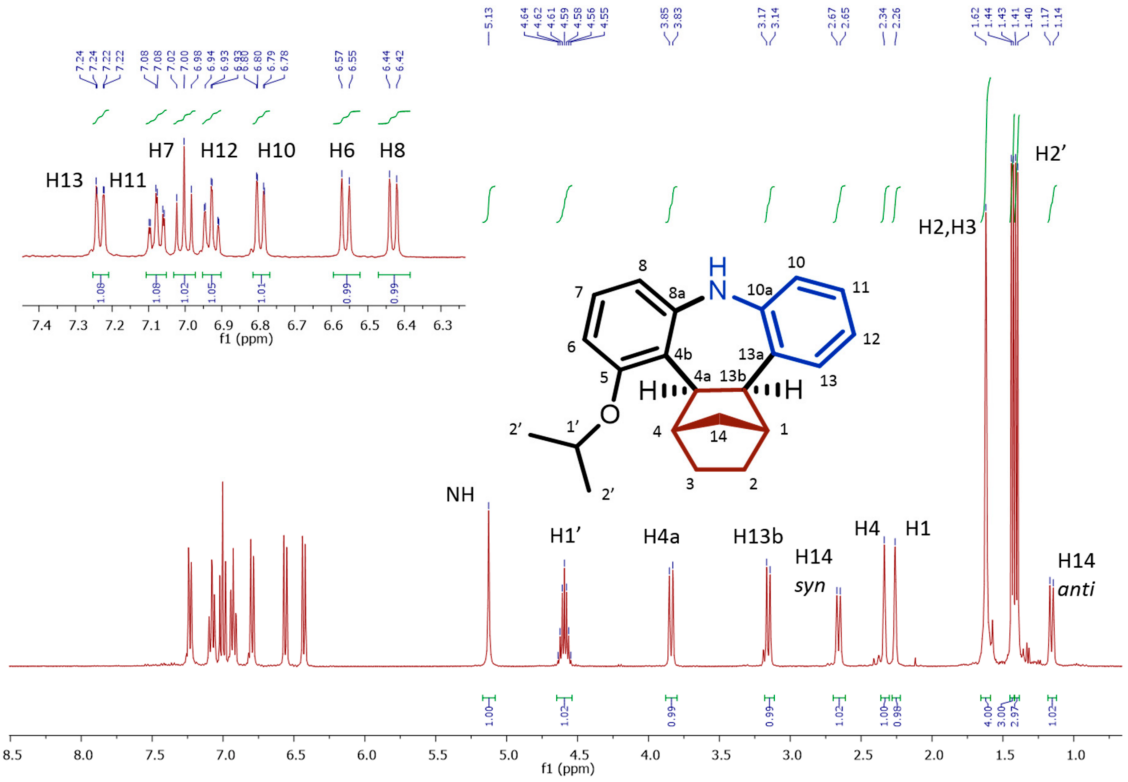


Figure 1. ^{1}H-NMR spectrum of compound **3** ($CDCl_3$, 400 MHz) and related assignment.

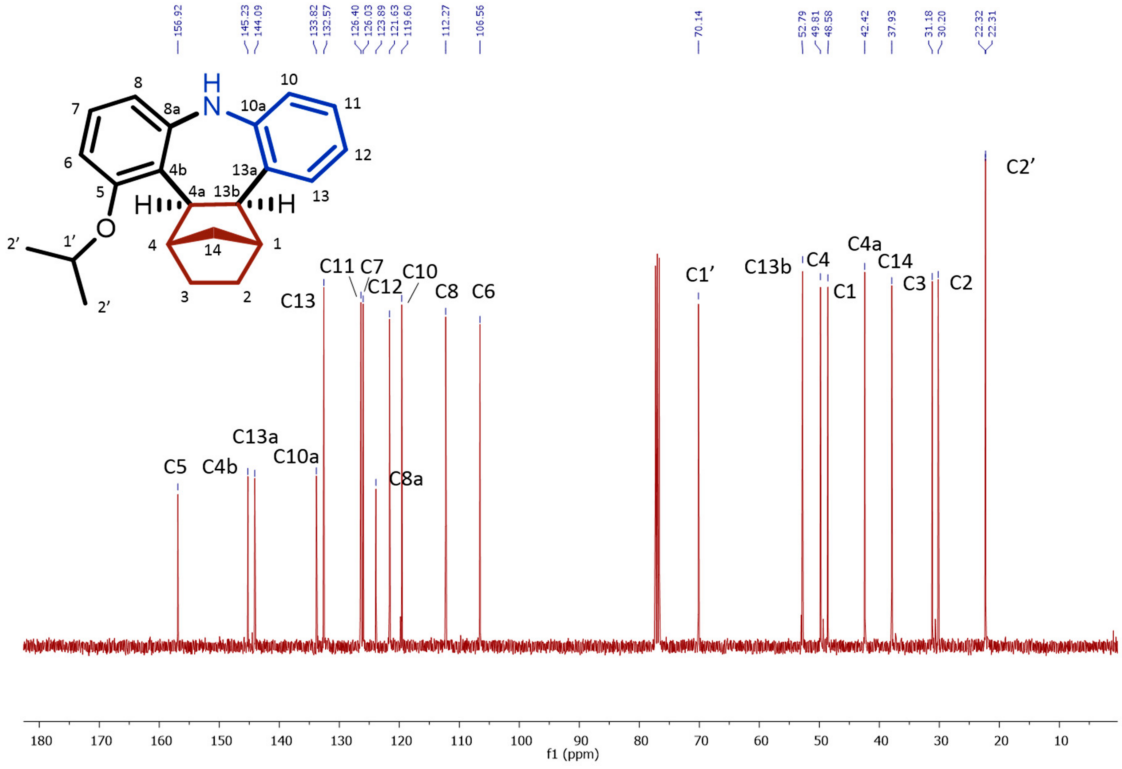


Figure 2. ^{13}C-NMR spectrum of compound **3** ($CDCl_3$, 400 MHz) and related assignment.

3. Materials and Methods

Compound **3** was synthesized according to the procedure described in the literature [21]. Other chemicals were obtained from commercial sources and were used without further purification. Gas chromatography analyses were performed with an Agilent Technology 7820A instrument (Agilent Technologies, Santa Clara, CA, USA) using a 30 m SE-30 capillary column. Column chromatography was carried out on silica gel (Merck, Darmstadt, Germany, 0.063–0.200 mm) and Thin-Layer Chromatography (TLC) on Merck 60F254 plates. Electron ionization (EI) mass spectra were obtained with an Agilent Technology instrument (Agilent Technologies, Santa Clara, CA, USA) working at 70 eV ionization energy. NMR spectra were recorded in $CDCl_3$, using the solvent residual signals as internal reference (7.26 and 77.00 ppm, respectively, for ^{1}H and ^{13}C) on a Bruker AVANCE 400 spectrometer (Bruker, Milan, Italy). Data for ^{1}H-NMR and ^{13}C-NMR are reported as follows: chemical shifts (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, hept = heptet), integration and coupling constant (Hz). IR spectrum was run on a Nicolet FT-IR 5700 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA) paired with a Diamond Smart Orbit accessory. Melting point was determined with an electrothermal apparatus. Elemental analysis was performed with a Carlo Erba EA 1108-Elemental Analyzer (Carlo Erba, Milan, Italy).

The reaction in Scheme 1 was carried out in a 20-mL Schlenk-type flask under a controlled atmosphere. The Schlenk-type flask, equipped with a magnetic stirring bar, was charged under nitrogen with Cs_2CO_3, dried at 110 °C for 2 h (326 mg, 1.0 mmol), PPh_3 (14 mg, 0.055 mmol) and $Pd(OAc)_2$ (5 mg, 0.022 mmol) in DMF (5 mL). After 10 min stirring, a DMF solution (5 mL) of 1-iodo-2-isopropoxybenzene (**1**, 126 mg, 0.48 mmol), *o*-bromoaniline (**2**, 76 mg, 0.44 mmol) and norbornene (50 mg, 0.53 mmol) was added. The resulting mixture was stirred in an oil bath at 105 °C for 24 h. After cooling to room temperature, the mixture was diluted with EtOAc (30 mL) and washed with a saturated solution of NaCl (3 × 25 mL). The organic layer was dried over anhydrous Na_2SO_4; the solvent was removed under reduced pressure and the product was isolated by flash column chromatography on silica gel using a hexane–EtOAc mixture (98:2) as eluent. Compound **3** was obtained as a white solid in 83% of yield (116 mg, 0.36 mmol). Mp 158–159 °C. IR (KBr, cm^{-1}): ν 3373, 2970, 2953, 2864, 1584, 1492, 1467, 1449, 1240, 1121, 1050, 743.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 7.7, 0.9 Hz, 1H, H13), 7.08 (td, *J* = 7.6, 1.5 Hz, 1H, H11), 7.00 (t, *J* = 8.0 Hz, 1H, H7), 6.93 (td, *J* = 7.4, 1.0 Hz, 1H, H12), 6.79 (dd, *J* = 7.7, 0.9 Hz, 1H, H10), 6.56 (d, *J* = 8.1 Hz, 1H, H6), 6.43 (d, *J* = 7.9 Hz, 1H, H8), 5.13 (s, 1H, NH), 4.59 (hept, *J* = 5.9 Hz, 1H, H1′), 3.84 (d, *J* = 9.7 Hz, 1H, H4a), 3.15 (d, *J* = 9.7 Hz, 1H, H13b), 2.66 (d, *J* = 9.6 Hz, 1H, H14 *syn*), 2.34 (s, 1H, H4), 2.26 (s, 1H, H1), 1.62 (s, 4H, H2 *endo*, H2 *exo*, H3 *endo*, H3 *exo*), 1.43 (d, *J* = 6.0 Hz, 3H, H2′), 1.40 (d, *J* = 6.0 Hz, 3H, H2′), 1.16 (d, *J* = 9.6 Hz, 1H, H14 *anti*). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 156.92 (C5), 145.23 (C4b), 144.09 (C13a), 133.82 (C10a), 132.57 (C13), 126.40 (C11), 126.03 (C7), 123.89 (C8a), 121.63 (C12), 119.60 (C10), 112.27 (C8), 106.56 (C6), 70.14 (C1′), 52.79 (C13b), 49.81 (C4), 48.58 (C1), 42.42 (C4a), 37.93(C14), 31.18 (C3), 30.20 (C2), 22.32 (C2′), 22.31 (C2′). GC-MS (EI): *m*/*z* 319 (M^+, 100), 276 (12), 252 (54), 238 (65), 210 (36), 196 (72), 180 (25), 167 (13). Anal. Calcd. for $C_{22}H_{25}NO$: C, 82.72; H, 7.89; N, 4.38. Found: C, 82.49; H, 7.78; N, 4.31.

Supplementary Materials: 1D and 2D NMR are available online, Figure from S1 to S12.

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Author Contributions: Nicola Della Ca' and Elena Motti conceived and designed the experiments; Alessandra Casnati performed the experiments; Alessandra Casnati performed and interpreted the NMR experiments; Nicola Della Ca' wrote the paper.

Conflicts of Interest: The authors declare no conflict of interest.

References and Note

1. Daugulis, O.; Do, H.-Q.; Shabashov, D. Palladium-and copper-catalyzed arylation of carbon−hydrogen bonds. *Acc. Chem. Res.* **2009**, *42*, 1074–1086. [CrossRef] [PubMed]
2. Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. Towards mild metal-catalyzed C-H bond activation. *Chem. Soc. Rev.* **2011**, *40*, 4740–4761. [CrossRef] [PubMed]
3. Neufeldt, S.R.; Sanford, M.S. Controlling site selectivity in palladium-catalyzed C-H bond functionalization. *Acc. Chem. Res.* **2012**, *45*, 936–946. [CrossRef] [PubMed]
4. Rouquet, G.; Chatani, N. Catalytic Functionalization of C(sp^2)-H and C(sp^3)-H Bonds by Using Bidentate Directing Groups. *Angew. Chem. Int. Ed.* **2013**, *52*, 11726–11743. [CrossRef] [PubMed]
5. Kim, D.S.; Park, W.I.; Jun, C.H. Metal-Organic Cooperative Catalysis in C-H and C-C Bond Activation. *Chem. Rev.* **2017**, *117*, 8977–9015. [CrossRef] [PubMed]
6. Catellani, M.; Frignani, F.; Rangoni, A. A Complex Catalytic Cycle Leading to a Regioselective Synthesis of *o*,*o*′-Disubstituted Vinylarenes. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 119–122. [CrossRef]
7. Della Ca', N.; Fontana, M.; Motti, E.; Catellani, M. Pd/Norbornene: A Winning Combination for Selective Aromatic Functionalization via C-H Bond Activation. *Acc. Chem. Res.* **2016**, *49*, 1389–1400. [CrossRef] [PubMed]
8. Ye, J.; Lautens, M. Palladium-catalysed norbornene-mediated C-H functionalization of arenes. *Nat. Chem.* **2015**, *7*, 863–870. [CrossRef] [PubMed]
9. Faccini, F.; Motti, E.; Catellani, M. A New Reaction Sequence Involving Palladium-Catalyzed Unsymmetrical Aryl Coupling. *J. Am. Chem. Soc.* **2004**, *126*, 78–79. [CrossRef] [PubMed]
10. Motti, E.; Faccini, F.; Ferrari, I.; Catellani, M.; Ferraccioli, R. Sequential Unsymmetrical Aryl Coupling of o-Substituited Aryl Iodides with o-Bromophenols and Reaction with Olefins: Palladium-Catalyzed Synthesis of 6H-Dibenzopyran Derivatives. *Org. Lett.* **2006**, *8*, 3967–3970. [CrossRef] [PubMed]
11. Della Ca', N.; Sassi, G.; Catellani, M. A Direct Palladium-Catalyzed Route to Selectively Substituted Carbazoles through Sequential C-C and C-N Bond Formation: Synthesis of Carbazomycin A. *Adv. Synth. Catal.* **2008**, *350*, 2179–2182. [CrossRef]
12. Della Ca', N.; Motti, E.; Catellani, M. Palladium-Catalyzed Synthesis of Selectively Substituted Phenanthridine Derivatives. *Adv. Synth. Catal.* **2008**, *350*, 2513–2516. [CrossRef]
13. Maestri, G.; Della Ca', N.; Catellani, M. A catalytic synthesis of selectively substituted biaryls through sequential intermolecular coupling involving arene and ketone C-H bond functionalization. *Chem. Commun.* **2009**, 4892–4894. [CrossRef] [PubMed]
14. Della Ca', N.; Maestri, G.; Catellani, M. Palladium/Norbornene-Catalyzed Synthesis of Heteroatom-Containing o-Teraryls from Aryl Iodides and Heteroarenes through Double C-H Activation in Sequence. *Chem. Eur. J.* **2009**, *15*, 7850–7853. [CrossRef] [PubMed]
15. Della Ca', N.; Motti, E.; Mega, A.; Catellani, M. One-Pot Palladium-Catalyzed Synthesis of Selectively Substituted Phenanthridines by Sequential Aryl-Aryl and Heck Couplings, Aza-Michael and Retro-Mannich Reactions. *Adv. Synth. Catal.* **2010**, *352*, 1451–1454. [CrossRef]
16. Motti, E.; Della Ca', N.; Deledda, S.; Fava, E.; Panciroli, F.; Catellani, M. Palladium-catalyzed unsymmetrical aryl couplings in sequence leading to o-teraryls: Dramatic olefin effect on selectivity. *Chem. Commun.* **2010**, *46*, 4291–4293. [CrossRef] [PubMed]
17. Motti, E.; Della Ca', N.; Xu, D.; Piersimoni, A.; Bedogni, E.; Zhou, Z.-M.; Catellani, M. A Sequential Pd/Norbornene-Catalyzed Process Generates o-Biaryl Carbaldehydes or Ketones via a Redox Reaction or 6H-Dibenzopyrans by C-O Ring Closure. *Org. Lett.* **2012**, *14*, 5792–5795. [CrossRef] [PubMed]
18. Motti, E.; Della Ca', N.; Xu, D.; Armani, S.; Aresta, B.M.; Catellani, M. Competitive pathways in Pd-catalyzed synthesis of arylphenols. *Tetrahedron* **2013**, *69*, 4421–4428. [CrossRef]
19. Xu, D.; Dai, L.; Catellani, M.; Motti, E.; Della Ca', N.; Zhou, Z. A Novel Enantioselective Synthesis of 6H-Dibenzopyran Derivatives by Combined Palladium/Norbornene and Cinchona Alkaloid Catalysis. *Org. Biomol. Chem.* **2015**, *13*, 2260–2263. [CrossRef] [PubMed]
20. Della Ca', N.; Fontana, M.; Xu, D.; Cremaschi, M.; Lucentini, R.; Zhou, Z.-M.; Catellani, M.; Motti, E. Formation of a Carbonyl Group ortho to a Biaryl Structure or a 6H-Dibenzopyran by a Palladium/Norbornene-catalyzed Ordered Reaction Sequence. *Tetrahedron* **2015**, *71*, 6389–6401. [CrossRef]

21. Della Ca', N.; Maestri, G.; Malacria, M.; Derat, E.; Catellani, M. Palladium-Catalyzed Reaction of Aryl Iodides with ortho-Bromoanilines and Norbornene/Norbornadiene: Unexpected Formation of Dibenzoazepine Derivatives. *Angew. Chem. Int. Ed.* **2011**, *50*, 12257–12261. [CrossRef] [PubMed]
22. Hirschfeld, R.M.A.; Kasper, S. A review of the evidence for carbamazepine and oxcarbazepine in the treatment of bipolar disorder. *Int. J. Neuropsychopharmacol.* **2004**, *7*, 507–522. [CrossRef] [PubMed]
23. Gomez-Arguelles, J.M.; Dorado, R.; Sepulveda, J.M.; Huet, R.; Arrojo, F.G.; Aragon, E.; Herrera, A.; Trron, C.; Anciones, B. Oxcarbazepine monotherapy in carbamazepine-unresponsive trigeminal neuralgia. *J. Clin. Neurosci.* **2008**, *15*, 516–519. [CrossRef] [PubMed]
24. Pegoraro, S.; Lang, M.; Dreker, T.; Kraus, J.; Hamm, S.; Meere, C.; Feurle, J.; Tasler, S.; Prütting, S.; Kuras, Z.; et al. Inhibitors of potassium channels $K_V1.3$ and IK-1 as immunosuppressants. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2299–2304. [CrossRef] [PubMed]
25. Nair, J.S.; Sheikh, T.; Ho, A.L.; Schwartz, G.K. PTEN Regulates Sensitivity of Melanoma Cells to RO4929097, the γ-Secretase Inhibitor. *Anticancer Res.* **2013**, *33*, 1307–1316. [PubMed]
26. The isopropoxy group can be readily converted into OH group under mild reaction conditions by various methods ($AlCl_3$, diisopropyl-carbodiimide/AlI_3, BCl_3, $TsOH{\cdot}H_2O$, $TiCl_4$, $Pd/C/H_2$). For example, isopropyl group was removed quantitatively by BCl_3 at 0 °C in 2 h (Lee, Y.-T.; Fong, Y.-T.; Chen, H.-M.; Chang, C.-Y.; Wang, C.-Y.; Chern, C.-Y.; Chen, Y.-H. Toxicity Assessments of Chalcone and Some Synthetic Chalcone Analogues in a Zebrafish Model. *Molecules* **2014**, *19*, 641–650). [CrossRef]