

A Convenient Four-Step Synthesis of 1- β -[3-(4-Methoxy-phenyl)Propoxy]-4-Methoxyphenethyl-1H-Imidazole Hydrochloride as a Probing Tool for SOCE Assays

Camille Déliko Evelyne Dago, Estelle Messé, Olivier D Mignen, Christophe D

Brigaudeau, Yves-Alain Békro, Jean-Pierre Bazureau

▶ To cite this version:

Camille Déliko Evelyne Dago, Estelle Messé, Olivier D
 Mignen, Christophe D Brigaudeau, Yves-Alain Békro, et al.. A Convenient Four-Step Synthesis of 1-
 β -[3-(4-Methoxy-phenyl)Propoxy]-4-Methoxy
phenethyl-1H-Imidazole Hydrochloride as a Probing Tool for SOCE Assays. Molbank, 2016, 2016 (4), pp.M909. 10.3390/M909 . hal-01451699

HAL Id: hal-01451699 https://hal.science/hal-01451699

Submitted on 1 Feb 2017

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Communication



A Convenient Four-Step Synthesis of 1-{β-[3-(4-Methoxy-phenyl)Propoxy]-4-Methoxyphenethyl}-1*H*-Imidazole Hydrochloride as a Probing Tool for SOCE Assays

Camille D. Dago ^{1,2}, Estelle Messé ¹, Olivier Mignen ^{3,4}, Christophe Brigaudeau ^{3,4}, Yves-Alain Békro ² and Jean-Pierre Bazureau ^{1,5,*}

- Institut des Sciences Chimiques de Rennes (ISCR), UMR CNRS 6226, groupe CORINT, Université de Rennes 1, Campus de Beaulieu, Bât. 10A, 263 Avenue du Général Leclerc, CS 74205, 35042 Rennes Cedex, France; deliko.dago@univ-rennes1.fr (C.D.D.), estellem1994@gmail.com (E.M.)
- ² Laboratoire de Chimie Bio Organique et de Substances Naturelles (LCBOSN), Université Nangui Abrogoua (UNA), BP 802, Abidjan, Cote d'Ivoire; bekro2001@yahoo.fr
- ³ Laboratoire Canalopathies & Signalisation Calcique, Inserm U1078, Université de Bretagne Occidentale, 22 Avenue Camille Desmoulins, 29200 Brest Cedex, France; olivier.mignen@univ-brest.fr (O.M.), christophe.brigaudeau@univ-brest.fr (C.B.)
- ⁴ CalciScreen platform, Université de Bretagne Occidentale,
 22 Avenue Camille Desmoulins, 29200 Brest Cedex, France
- ⁵ S2 Wave platform SFS ScanMAT, Université de Rennes 1, Campus de Beaulieu, Bât. 10A, 263 Avenue du Général Leclerc, CS 74205, 35042 Rennes Cedex, France
- * Correspondence: jean-pierre.bazureau@univ-rennes1.fr; Tel.: +33-0223-236-603

Academic Editor: Norbert Haider

Received: 17 August 2016; Accepted: 19 September 2016; Published: 22 September 2016

Abstract: 1-{ β -[3-(4-Methoxy-phenyl)propoxy]-4-methoxyphenethyl}-1*H*-imidazole hydrochloride 7, or SKF-96365, was synthesized in four steps with an overall yield of 9%. The structure of 7 was confirmed by ¹H-, ¹³C-NMR, HRMS, and elemental analysis. The intermediates **3** and **4** were also isolated and characterized by ¹H-, ¹³C-NMR, and HRMS.

Keywords: SKF-96365; imidazole; modulator; SOCE

1. Introduction

Variations in cytoplasmic Ca²⁺ concentration ([Ca²⁺]_i) play an important role in mediating fundamental biological activities for cell proliferation, differentiation, apoptotosis, and gene expression. Calcium influx through store-operated Ca²⁺ entry (SOCE) triggered by the depletion of endoplasmic reticulum (ER) Ca²⁺ stores largely contributes to changes in ([Ca²⁺]_i) and regulates a large variety of cellular functions [1–3]. The first identified inhibitor of the CRAC (Ca²⁺ release-activated Ca²⁺ channel) channel, the archetypal SOCE channel, was the 1-{ β -[3-(4-methoxy-phenyl)propoxy]-4-methoxyphenethyl}-1*H*-imidazole hydrochloride, also known as SKF-96365 [4], and this imidazole derivative inhibited thapsigargin-induced SOCE in Jurkat cells with an IC₅₀ of 12 μ M in a dose-dependant manner [5]. Although this inhibitor, in a mouse model of breast cancer, prevented the development of tumor metathesis [6]. In the imidazole group, econazole and miconazole have been also identified as inhibitors of CRAC channels, but some studies mentioned that these imidazole coumpounds showed non-specific effects by inhibiting the cytochrome P450 activity [7] or other Ca²⁺ channels [8]. However, SKF-96365 is still used as a tool for the probing of receptor-mediated Ca²⁺ entry processes, particularly in non-excitable cells [9–11]. To our surprise, the synthesis of SKF-96365 was not patented or not detailed in academic literature, but it is interesting to note

that the enantiomers has been subjected to a chiral high pressure liquid chromatography (HPLC) study [12]. In this context and due to the recent interest of SKF-96365 for their anticancer effect in a mouse xenograph model [13], we developed efforts on a complete and detailed preparation of $1-\{\beta-[3-(4-methoxy-phenyl)propoxy]-4-methoxyphenethyl\}-1H-imidazole hydrochloride.$

2. Results

The synthetic route for the preparation of the title compound 7 was achieved in four steps, as presented in Scheme 1. In the first step, reaction of commercial imidazole 1 with 2-bromo-4'-methoxyacetophenone 2 produced mainly the corresponding 2-(1*H*-imidazol-1-yl)-1-[4-methoxyphenyl)ethanone 3 in a 51% yield. This *N*-alkylation was conducted in DMF at 5 °C and after a reaction time of two hours; the crude reaction mixture was treated with deionized water in order to eliminate the undesired *N*-protoned derivative 3.



Scheme 1. Synthesis of $1-\{\beta-[3-(4-methoxy-phenyl)propoxy]-4-methoxyphenethyl}-1H-imidazole hydrochloride (7).$

For the second step, the acetophenone derivative **3** in a dry methanol solution was converted into its corresponding alcohol **4** [14] in a 63% yield by the addition of sodium borohydride (2 equiv.). In the third step, treatment of alcohol **3** with 4-methoxyphenylpropylbromide **5** in a basic (KOH, 5 equiv.) solution of dimethylsulfoxide led to the desired *O*-alkyl compound **6** together with the *N*-alkyl derivative of **6** as a by-product. Compound **6** was purified by preparative chromatography on silica gel using a step-wise gradient of $CH_2Cl_2/MeOH (0-1\%)$. Finally, from a solution of 1M HCl in diethyl ether, pure *O*-alkyl imidazole intermediate **6** was transformed into imidazolium chloride **7**. It is interesting to note that the crystallization was achieved after one day at 25 °C in a 29% yield. Compound **7** was prepared with an overall yield of 9%. The structure of **7** was confirmed by ¹H-NMR, and the data were in agreement with those previously described in literature [12]. ¹³C-NMR, HRMS, and elemental analysis of **7** completed the data and are in accordance with this structure.

3. Experimental Section

3.1. General Information

Preparative chromatography was realized on a Combi Flash R_f 200 psi UV ref. 208K20284 (Serlabo Technologies, Entraigues-sur-la-Sorgue, France) using pre-packed column of alumina gel 60 F 254 Merck equipped with a DAD UV/Vis 200–360-nm detector . Thin-layer chromatography (TLC) was accomplished on 0.2-mm precoated plates of neutral alumina gel 60 F-254 (Merck) with appropriate eluent. Visualization was made with ultraviolet light (254 and 365 nm) or with a fluorescence indicator. Solvents were evaporated with a BUCHI rotary evaporator. All reagents and solvents were purchased from Acros Fisher, Sigma-Aldrich Chimie, and Fluka France and were used without further purification. ¹H-NMR spectra were recorded on a BRUKER AC 300 P (300 MHz) spectrometer, and ¹³C-NMR spectra on BRUKER AC 300 P (75 MHz) spectrometer (Bruker France Scientifique, Voisins-le-Bretonneux, France). Chemical shifts are expressed in parts per million downfield. Data are given in the following order: δ value, multiplicity (s: singlet; d: doublet; t: triplet; q: quartet; quint: quintuplet: m: multiplet;

br: broad), number of protons, coupling constants *J* is given in Hertz. The high-resolution mass spectra (HRMS) were recorded in positive mode using direct electrospray infusion, respectively on Waters Q-Tof 2 or on Thermo Fisher Scientific Q-Exactive spectrometers, and the purity of the final compound 1-{ β -[3-(4-methoxy-phenyl)propoxy]-4-methoxyphenethyl}-1*H*-imidazole hydrochloride 7 was performed on a microanalyzer Flash EA1112 CHNS/O Thermo Electron (Thermo Electron, Villebon-sur-Yvette, France). The obtained results were within \pm 0.4% of the theorical values at the "Centre Régional de Mesures Physiques de l'Ouest" SFS ScanMAT (CRMPO SFS ScanMAT, Rennes, France). Melting points were determined on a Kofler melting point apparatus and were uncorrected.

3.2. Synthesis of 2-(1H-Imidazol-1-Yl)-1-[4-Methoxyphenyl]Ethanone (3)

In a 50-mL round-bottomed flask provided with a magnetic stirrer and condenser containing a suspension of commercial imidazole (1, 3.09 g, 45.4 mmol, 5.2 equiv.) in DMF (2.16 mL) cooled at 5 °C (with an ice bath), small portions of 2-bromo-4'-methoxyacetophenone (2, 2 g, 8.73 mmol, 1 equiv.) were added over a period of 15 min. The resulting suspension was stirred vigorously (500 rpm) for 2 h at a temperature below 15 °C. The reaction mixture was monitored by thin-layer chromatography on 0.2-mm pre-coated plates of silica gel 60F-254 (Merck) using a mixture of $CH_2Cl_2/MeOH$ (9:1 v/v) as eluent. Deionized water (60 mL) was added to the heterogeneous mixture, and the flask was manually swirled twice for 5 min to homogenize; then, the resulting mixture was maintained at 5 °C (refrigerator) without stirring for 12 h to improve precipitation and decantation. The resulting precipitate in the reaction mixture was collected by filtration on a Büchner funnel (porosity N°4) and solubilized in methylene chloride (44 mL). The organic phase was filtered on filter paper and transferred into a separating funnel. The organic phase was washed with saturated sodium bicarbonate (4 \times 44 mL) and dried over magnesium sulfate. The filtrate was concentrated in a rotary evaporator under reduced pressure and finally dried in a high vacuum (10^{-2} Torr) at 25 °C for 2 h. The desired compound **3** was obtained in a 51% yield as a beige powder and was further used without purification. Mp = 135-137 °C. ¹H-NMR (300 MHz, DMSO-*d*₆) δ 3.87 (s, 3H, OCH₃), 5.66 (s, 2H, CH₂, H-2), 6.91 (t, 1H, *J* = 1.1 Hz, H-5', Ar), 7.10 (t, 1H, J = 1.2 Hz, H-4', Ar), 7.11 (d, 2H, J = 8.9 Hz, H-3'', H-5''), 7.57 (t, 1H, J = 1.1 Hz, H-2', Ar), 8.02 (d, 2H, J = 8.9 Hz, H-2", H-6", Ar). ¹³C-NMR (75 MHz, DMSO- d_6) δ 52.2 (OCH₃), 55.7 (C-2), 114.2 (C-3", C-5"), 121.0 (C-5'), 127.3 (C-1"), 127.8 (C-4'), 130.4 (C-2", C-6"), 138.4 (C-2'), 163.7 (C-4"), 191.9 (C-1). ES⁺ HRMS, m/z = 216.0790 found (calculated for C₁₂H₁₂N₂O₂Na [M + Na]⁺ requires 216.0971).

3.3. Synthesis of 2-(1H-Imidazol-1-Yl)-1-[4-Methoxyphenyl]Ethanol (4)

In a 100-mL round-bottomed flask provided with a magnetic stirrer and condenser, 2-(1H-imidazol-1-yl)-1-[4-methoxyphenyl]ethanone (3, 1.046 g, 4.84 mmol, 1 equiv.) was solubilized in methanol for HPLC (41.8 mL) at 0 °C (in ice bath) under vigorous magnetic stirring (550 rpm). Commercial sodium borohydride (366 mg, 9.67 mmol, 2 equiv.) was added to this homogeneous solution in small portions over a period of 10 min. The resulting mixture was stirred at room temperature for 2 h and monitored by thin-layer chromatography on 0.2 mm pre-coated plates of silica gel 60F-254 (Merck) using a mixture of $CH_2Cl_2/MeOH$ (95:5 v/v) as eluent. Then, the reaction mixture was concentrated in a rotary evaporator under reduced pressure, and the crude residue was dissolved in deionized water (43.5 mL). This solution was transferred into a separating funnel and extracted with methylene chloride (3 \times 43.5 mL). The combined organic phases were dried over magnesium sulphate and filtered on filter paper, and the solvent of the filtrate was eliminated in vacuo. The desired compound 4 was obtained in a 63% yield as a white powder and further used without purification. Mp = $167-169 \circ C.^{1}$ H-NMR (300 MHz, DMSO- d_{6}) δ 3.74 (s, 3H, OCH₃), 4.00 (dd, 1H, J = 7.6, 13.8 Hz, CH, H-2), 4.08 (dd, 1H, J = 4.4, 13.8 Hz, CH, H-2), 4.66–4.80 (dt, 1H, J = 4.4, 8.4 Hz, CH, H-1), 5.56 (br d, 1H, J = 4.5 Hz, OH), 6.81 (t, 1H, J = 1.0 Hz, H-5', Ar), 6.84–6.92 (d, 2H, J = 1.1 Hz, H-3", H-5", Ar), 7.09 (t, 1H, J = 1.2 Hz, H-4', Ar), 7.20–7.27 (m, 2H, H-2", H-6", Ar), 7.47 (t, 1H, J = 1.1 Hz, H-2', Ar). ¹³C-NMR (75 MHz, DMSO-*d*₆) δ 53.6 (C-2), 55.0 (OCH₃), 71.6 (C-1), 113.4 (C-3", C-5"), 120.0 (C-5'),

127.2 (C-2", C-6"), 127.7 (C-4'), 134.6 (C-1"), 137.6 (C-2'), 158.5 (C-4"). ES⁺ HRMS, m/z = 249.0949 found (calculated for C₁₂H₁₄N₂O₂Na [M + Na]⁺ requires 241.0948).

3.4. Synthesis of 1-{ β -[3-(4-Methoxy-Phenyl)Propoxy]-4-Methoxyphenethyl}-1H-Imidazole Hydrochloride (7)

A portion of 2-(1*H*-imidazol-1-yl)-1-[4-methoxyphenyl]ethanol (4, 790 mg, 3.62 mmol, 1 equiv.), pellets of potassium hydroxide (1.015 g, 18.1 mmol, 5 equiv.), and dry dimethylsulfoxide (13.7 mL) were placed successively in a 10-mL two-necked round-bottomed flask (provided with a magnetic stirrer and condenser) under a stream of argon. This mixture was stirred (500 rpm) at room temperature for 1 h, and one portion of 1-(3-bromoproyl)-4-methoxy benzene (5, 0.63 mL, 3.62 mmol, 1 equiv.) was added. The reaction mixture was heated at 60 °C for 48 h under vigorous magnetic stirring (700 rpm) under an argon atmosphere and monitored by thin-layer chromatography on 0.2-mm pre-coated plates of silica gel 60F-254 (Merck) using a mixture of $CH_2Cl_2/MeOH$ (9:1 v/v) as eluent. After cooling down to room temperature, saturated brine (79 mL) was poured into the reaction mixture. The resulting solution was transferred into a separating funnel and extracted twice with diethyl ether (39.5 mL). After decantation, the organic phase was washed three times with water (79 mL), dried over magnesium sulphate, and filtered through filter paper. The solvent of the filtrate was eliminated in a rotary evaporator. The oily residue (crude $1-\{\beta-[3-(4-methoxy-phenyl)propoxy]-4-methoxyphenethyl\}-1H-imidazole 6)$ was submitted to purification by preparative chromatography (Combi Flash $R_f 200$ psi apparatus with a DAD 200/360 nm detector) on a pre-packed column of silica gel 60F 254 (Merck) using a stepwise gradient of methylene chloride/methanol (0-1%). Pooling (flow rate: 18 mL/min during 60 min, retention time: 45 min) and the elimination of the solvent in vacuo gave the pure desired intermediate $1-\{\beta-[3-(4-methoxy-phenyl)propoxy]-4-methoxyphenethyl\}-1H-imidazole (6, 470 mg, 1.28 mmol) as a$ mobile pale orange oil.

The oily compound 6 was dissolved in dry ether (6.6 mL) under a stream of argon with magnetic stirring (200 rpm). A solution of 1M HCl in ether (1.28 mL, 1.28 mmol) was poured into the homogeneous solution. During mixing at 25 °C, the initial pale orange solution began to crystallize progressively on the circumference of the round flask after 15 min, and mixing was pursued until the complete precipitation of the 1- $\{\beta$ -[3-(4-methoxy-phenyl)propoxy]-4-methoxyphenethyl}-1H-imidazole hydrochloride 7 (after 12 h at 25 °C). The resulting precipitate was carefully triturated in the flask with ether to obtain a divided powder, and this slurry was mixed vigorously (600 rpm) for 12 h. The insoluble salt was finally collected in a Büchner funnel (porosity N°4), was washed with dry ether $(3 \times 10 \text{ mL})$, and was dried under a high vacuum (10^{-2} Torr) at 25 °C for 8 h. ¹H, ¹³C-NMR, HRMS, and centesimal analysis characterized the hydrochloride salt 7 obtained in a 29% yield as a white powder. Mp = 117.5–119.5 °C. ¹H-NMR (300 MHz, MeOH-d₄) δ 1.77 (tt, *J* = 6.2, 7.5 Hz, 2H, CH₂, H-2a), 2.51 (dd, J = 6.6, 8.4 Hz, 2H, CH₂, H-3a), 3.22 (dt, J = 6.1, 9.4 Hz, 1H, CH, H-1a), 3.36 (dt, J = 6.2, 9.4 Hz, 1H, CH, H-1a), 3.74 (s, 3H, OCH₃), 3.80 (s, 3H, OCH₃), 4.40–4.48 (m, 2H, CH₂, H-2), 4.64 (dd, *J* = 5.2, 6.6 Hz, 1H, CH, H-1), 6.78 (d, J = 8.6 Hz, 2H, H-2b, H-6b, Ar), 6.90–7.04 (m, 4H, H-3", H-5", H-3b, H-5b, Ar), 7.25 (d, J = 8.7 Hz, 2H, H-2", H-6", Ar), 7.56 (t, J = 1.7 Hz, 1H, H-5', Ar), 7.62 (t, J = 1.7 Hz, 1H, H-4', Ar), 8.84 (t, J = 1.7 Hz, 1H, H-2', Ar).¹³C-NMR (75 MHz, MeOH-d₄) δ 32.3 (C-2a), 32.6 (C-3a), 55.7 (OCH₃), 55.8 (OCH₃), 56.0 (C-2), 69.1 (C-1a), 80.6 (C-1), 114.8 (C-2b, C-6b), 115.3 (C-3b, C-5b), 120.6 (C-5'), 124.3 (C-4'), 129.1 (C-2", C-6"), 130.3 (C-3", C-5"), 130.6 (C-1b), 134.9 (C-1"), 137.3 (C-2'Z), 159.4 (C-4b), 161.6 (C-4"). ES⁺ HRMS, m/z = 367.2015 found (calculated for $C_{22}H_{27}N_2O_3$ [M + H]⁺ requires 367.2016 and 389.1829 found (calculated for $C_{22}H_{26}N_2O_3Na$ [M + Na]⁺ requires 389.1836). Anal. calcd. for C₂₂H₂₇ClN₂O₃ (402.91): C, 65.58; H, 6.75; N, 6.95. Found: C, 65.48; H, 6.56; N, 6.75.

Supplementary Materials: Copies of the ¹H-, ¹³C-NMR for compounds **3**, **4**, and **7**, and MS spectra of **7**, as well as the molfile for **7**, can be found at http://www.mdpi.com/1422-8599/2016/4/M909/s1.

Acknowledgments: One of us (C.D.D.) wishes to thank the "Fondation Benianh International" and the "Ministère de l'Enseignement Supérieur et de la Recherche Scientifique de Côte d'Ivoire" for grants. Financial support of this program carried out under the French National Cancer Institute "Cancéropôle Grand Ouest" by contract "Ion Channel-Network CGO 2012", is gratefully acknowledged. The authors are grateful to the assistance

of the staff of the CRMPO analytical chemistry core facility for HRMS and centesimal analysis (CRMPO platform SFS ScanMAT, Université de Rennes 1, Bât. 11A, Campus de Beaulieu, Rennes, France).

Author Contributions: J-P.B. designed the experiments and wrote the manuscript; C.D.D. and E.M. performed the synthetic experiments; C.D.D. wrote the experimental section of the manuscript; Y-A.B. and O.M. contributed to the manuscript; C.B. evaluated compound 7 within the *CalciScreen* platform (Ca²⁺ flux measurements). All authors read and approved the final manuscript.

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

References

- 1. Tian, C.; Du, L.; Zhou, Y.; Li, M. Store-operated CRAC channel inhibitors: opportunities and challenges. *Future Med. Chem.* **2016**, *8*, 817–832. [CrossRef] [PubMed]
- 2. Jairaman, A.; Prakriya, M. Molecular pharmacology of store-operated CRAC channels. *Channels* **2013**, *7*, 402–414. [CrossRef] [PubMed]
- 3. Pevarello, P.; Silvia Cainarca, S.; Liberati, C.; Tarroni, P.; Piscitelli, F.; Severi, E. Ca²⁺ release-activated Ca²⁺ channel inhibitors. *Pharm. Pat. Anal.* **2014**, *3*, 171–182. [CrossRef] [PubMed]
- 4. Merritt, J.E.; Amstrong, W.P.; Benham, C.D.; Hallam, T.J.; Jacob, R.; Jaxa-Chamiec, A.; Leigh, B.K.; Mc Carthy, S.A.; Moores, K.E.; Rink, T.J. SK&F 96365, a novel inhibitor of receptor-mediated calcium entry. *Biochem. J.* **1990**, *271*, 515–522. [PubMed]
- Sage, S.O.; Reast, R.; Rink, T.J. ADP evokes biphasic Ca²⁺ influx in fura-2-loaded human platelets. *Biochem. J.* 1990, 265, 675–680. [CrossRef] [PubMed]
- 6. Clare Chung, S.; Mc Donald, T.V.; Gardner, P. Inhibition by SK&F 96365 of Ca²⁺ current, IL-2 production and activation of T lymphocytes. *Br. J. Pharmacol.* **1994**, *113*, 861–868.
- Franzius, D.; Hoth, M.; Penner, R. Non-specific effects of calcium entry antagonists in mast cells. *Pflügers Arch.* 1994, 428, 433–438. [CrossRef] [PubMed]
- 8. Sweeney, Z.K.; Minatti, A.; Button, D.C.; Patrick, S. Small-Molecule Inhibitors of Store-Operated Calcium Entry. *ChemMedChem* **2009**, *4*, 706–718. [CrossRef] [PubMed]
- Yonetoku, Y.; Kubota, H.; Okamoto, Y.; Toyoshima, A.; Funatsu, M.; Ishikawa, J.; Takeuchi, M.; Ohta, M.; Tsukamoto, S. Novel potent and selective calcium-release-activated calcium (CRAC) channel inhibitors. Part 1: Synthesis and inhibitory activity of 5-(1-methyl-3-trifluoromethyl-1*H*-pyrazol-5-yl)-2thiophenecarboxamides. *Bioorg. Med. Chem.* 2006, 14, 4750–4760. [CrossRef] [PubMed]
- Yonetoku, Y.; Kubota, H.; Okamoto, Y.; Toyoshima, A.; Funatsu, M.; Ishikawa, J.; Takeuchi, M.; Ohta, M.; Tsukamoto, S. Novel potent and selective calcium-release-activated calcium (CRAC) channel inhibitors. Part 2: Synthesis and inhibitory activity of aryl-3-trifluoromethylpyrazoles. *Bioorg. Med. Chem.* 2006, 14, 5370–5383. [CrossRef] [PubMed]
- Yonetoku, Y.; Kubota, H.; Miyazaki, Y.; Okamoto, Y.; Funatsu, M.; Yoshimura-Ishikawa, N.; Ishikawa, J.; Yoshino, T.; Takeuchi, M.; Ohta, M. Novel potent and selective Ca²⁺ release-activated Ca²⁺ (CRAC) channel inhibitors. Part 3: Synthesis and CRAC channel inhibitory activity of 4'-[(trifluoromethyl)pyrazol-1yl]carboxanilides. *Bioorg. Med. Chem.* 2008, *16*, 9457–9466. [CrossRef] [PubMed]
- 12. Reid, D.G.; Mc Lachlan, L.K.; Robinson, S.P.; Camilleri, P.; Dyke, C.A.; Thorpe, C.J. Calmodulin Discriminates Between the Two Enantiomers of the Receptor-OperatedCalcium Channel Blocker SK&F 96365: A Study Using 'H-NMR and Chiral HPLC. *Chirality* **1990**, *2*, 229–232. [PubMed]
- Jing, Z.; Sui, X.; Yao, J.; Xie, J.; Jiang, L.; Zhou, Y.; Pan, H.; Han, W. SKF-96365 activates cytoprotective autophagy to delay apoptosis in colorectal cancer cells through inhibition of the calcium/CaMKIIγ/ AKT-mediated pathway. *Cancer Lett.* 2016, 372, 226–238. [CrossRef] [PubMed]
- 14. Godefroi, E.F.; Heeres, J.; Cutsem, J.V.; Janssen, P.A. Preparation and antimycotic properties of derivatives of 1-phenethylimidazole. *J. Med. Chem.* **1969**, *12*, 784–791. [CrossRef] [PubMed]



© 2016 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC-BY) license (http://creativecommons.org/licenses/by/4.0/).