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Rational design 2-hydroxypropylphosphonium salts as cancer cell mitochondria-targeted vectors: Synthesis, structure, and biological properties

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Abstract

It has been shown for a wide range of epoxy compounds that their interaction with triphenylphosphonium triflate occurs with a high chemoselectivity and leads to the formation of (2-hydroxypropyl)triphenylphosphonium triflates 3 substituted in the 3-position with an alkoxy, alkylcarboxyl group, or halogen, which were isolated in a high yield. Using the methodology for the disclosure of epichlorohydrin with alcohols in the presence of boron trifluoride ether-ate, followed by the substitution of iodine for chlorine and treatment with triphenylphosphine, 2-hydroxypropyltriphenylphosphonium iodides 4 were also obtained. The molecular and supramolec-ular structure of the obtained phosphonium salts was established, and their high antitumor activity was revealed in relation to duodenal adenocarcinoma. The formation of liposomal systems based on phosphonium salt 3 and L-α-phosphatidylcholine (PC) was employed for improving the bioavailabil-ity and reducing the toxicity. They were produced by the thin film rehydration method and exhibited cytotoxic properties. This rational design of phosphonium salts 3 and 4 has promising potential of new vectors for targeted delivery into mitochondria of tumor cells.

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Keywords

Addition reaction, Glycidyl ether, Nucleophilic substitution, Oxirane, Phosphonium salt, P–C bond formation, Triphenylphosphine

References

[1] Moura, I.M.R.; Tranquilino, A.; Sátiro, B.G.; Silva, R.O.; de Oliveira-Silva, D.; Oliveirsa, R.A.; Menezes, P.H. Unusual application for phosphonium salts and phosphoranes: Synthesis of chalcogenides. J. Org. Chem. 2021, 86, 5954–5964. [CrossRef]

[2] Fink, J. Hydraulic Fracturing Chemicals and Fluids Technology, 2nd ed.; Elsevier: Amsterdam, The Netherlands, 2020.

[3] Wakelyn, P.J. Environmentally friendly flame resistant textiles. In Advances in Fire Retardant Materials, 1st ed.; Horrocks, A.R., Price, D., Eds.; Woodhead Publishing Limited: Sawston, UK; CRC Press: Boca Raton, FL, USA, 2008; pp. 188–212.

[4] Corbridge, D.E.C. Phosphorus: An Outline of Its Chemistry, Biochemistry, and Technology, 5th ed.; Elsevier: Amsterdam, The Netherlands, 1995; p. 1220.

[5] Li, H.; Liu, H.; Guo, H. Recent Advances in Phosphonium Salt Catalysis. Adv. Synth. Catal. 2021, 363, 2023–2036. [CrossRef]

[6] Jean, S.R.; Ahmed, M.; Lei, E.K.; Wisnovsky, S.P.; Kelley, S.O. Peptide-mediated delivery of chemical probes and therapeutics to mitochondria. Acc. Chem. Res. 2016, 49, 1893–1902. [CrossRef] [PubMed]

[7] Smith, R.A.J.; Hartley, R.C.; Murphy, M.P. Mitochondria-targeted small molecule therapeutics and probes. Antioxid. Redox Signal. 2011, 15, 30231–33038. [CrossRef]

[8] Murphy, M. Targeting lipophilic cations to mitochondria. Biochim. Biophys. Acta Bioenerg. 2008, 1777, 1028–1031. [CrossRef] [PubMed]

[9] Murphy, M.P.; Smith, R.A. Targeting antioxidants to mitochondria by conjugation to lipophilic cations. Annu. Rev. Pharmacol. Toxicol. 2007, 47, 629–656. [CrossRef]

[10] Ross, M.F.; Prime, T.A.; Abakumova, I.; James, A.M.; Porteous, C.M.; Smith, R.A.; Murphy, M.P. Rapid and extensive uptake and activation of hydrophobic triphenylphosphonium cations within cells. Biochem. J. 2008, 411, 633–645. [CrossRef]

[11] Zielonka, J.; Joseph, J.; Sikora, A.; Hardy, M.; Ouari, O.; Vasquez-Vivar, J.; Cheng, G.; Lopez, M.; Kalyanaraman, B. Mitochondria-targeted triphenylphosphonium-based compounds: Syntheses, mechanisms of action, and therapeutic and diagnostic applications. Chem. Rev. 2017, 117, 10043–10120. [CrossRef]

[12] Pourahmad, J.; Salimi, A.; Seydi, E. Mitochondrial targeting for drug development. In Toxicology Studies—Cells, Drugs and Environment, 1st ed.; Andreazza, A.C., Scola, G., Eds.; InTech: Rijeka, Croatia, 2015; pp. 61–82.

[13] Apostolova, N.; Victor, V.M. Molecular strategies for targeting antioxidants to mitochondria: Therapeutic implications. Antioxid. Redox Signal. 2015, 22, 686–729. [CrossRef]

[14] Kelso, G.F.; Porteous, C.M.; Coulter, C.V.; Hughes, G.; Porteous, W.K.; Ledgerwood, E.C.; Smith, R.A.; Murphy, M.P. Selective targeting of a redox-active ubiquinone to mitochondria within cells: Antioxidant and antiapoptotic properties. J. Biol. Chem. 2001, 276, 4588–4596. [CrossRef]

[15] Asin-Cayuela, J.; Manas, A.R.; James, A.M.; Smith, R.A.; Murphy, M.P. Fine-tuning the hydrophobicity of a mitochondria-targeted antioxidant. FEBS Lett. 2004, 571, 9–16. [CrossRef]

[16] Smith, R.A.; Porteous, C.M.; Coulter, C.M.; Murphy, M.P. Selective targeting of an antioxidant to mitochondria. Eur. J. Biochem. 1999, 263, 709–716. [CrossRef]

[17] Filipovska, A.; Kelso, G.F.; Brown, S.E.; Beer, S.M.; Smith, R.A.; Murphy, M.P. Synthesis and characterization of a triphenylphosphonium-conjugated peroxidase mimetic: Insights into the interaction of ebselen with mitochondria. J. Biol. Chem. 2005, 280, 24113–24126. [CrossRef]

[18] Finichiu, P.G.; Larsen, D.S.; Evans, C.; Larsen, L.; Bright, T.P.; Robb, E.L.; Trnka, J.; Prime, T.A.; James, A.M.; Smith, R.A.; et al. A mitochondria-targeted derivative of ascorbate: MitoC. Free Radic. Biol. Med. 2015, 89, 668–678. [CrossRef]

[19] Langley, M.; Ghosh, A.; Charli, A.; Sarkar, S.; Ay, M.; Luo, J.; Zielonka, J.; Brenza, T.; Bennett, B.; Jin, H.; et al. Mito-apocynin prevents mitochondrial dysfunction, microglial activation, oxidative damage, and progressive neurodegeneration in mitopark transgenic mice. Antioxid. Redox Signal. 2017, 27, 1048–1066. [CrossRef] [PubMed]

[20] Trnka, J.; Blaikie, F.H.; Smith, R.A.; Murphy, M.P. A mitochondria-targeted nitroxide is reduced to its hydroxylamine by ubiquinol in mitochondria. Free Radic. Biol. Med. 2008, 44, 1406–1419. [CrossRef] [PubMed]

[21] Pavlova, J.A.; Khairullina, Z.Z.; Tereshchenkov, A.G.; Nazarov, P.A.; Lukianov, D.A.; Volynkina, I.A.; Skvortsov, D.A.; Makarov, G.I.; Abad, E.; Murayama, S.Y.; et al. Triphenilphosphonium analogs of chloramphenicol as dual-acting antimicrobial and antiproliferating agents. Antibiotics 2021, 10, 489. [CrossRef]

[22] Millard, M.; Gallagher, J.D.; Olenyuk, B.Z.; Neamati, N. A selective mitochondrial-targeted chlorambucil with remarkable cytotoxicity in breast and pancreatic cancers. J. Med. Chem. 2013, 56, 9170–9179. [CrossRef] [PubMed]

[23] Zhou, J.; Zhao, W.Y.; Ma, X.; Ju, R.J.; Li, X.Y.; Li, N.; Sun, M.G.; Shi, J.F.; Zhang, C.X.; Lu, W.L. The anticancer efficacy of paclitaxel liposomes modified with mitochondrial targeting conjugate in resistant lung cancer. Biomaterials 2013, 34, 3626–3638. [CrossRef]

[24] Liu, H.N.; Guo, N.N.; Wang, T.T.; Guo, W.W.; Lin, M.T.; Huang-Fu, M.Y.; Vakili, M.R.; Xu, W.H.; Chen, J.J.; Wei, Q.C.; et al. Mitochondrial Targeted Doxorubicin-Triphenylphosphonium Delivered by Hyaluronic Acid Modified and pH Responsive Nanocarriers to Breast Tumor: In Vitro and in Vivo Studies. Mol. Pharm. 2018, 15, 882–891. [CrossRef] [PubMed]

[25] Cheng, G.; Zielonka, J.; Ouari, O.; Lopez, M.; McAllister, D.; Boyle, K.; Barrios, C.S.; Weber, J.J.; Johnson, B.D.; Hardy, M.; et al. Mitochondria-targeted analogues of metformin exhibit enhanced antiproliferative and radiosensitizing effects in pancreatic cancer cells. Cancer Res. 2016, 76, 3904–3915. [CrossRef]

[26] Kang, S.; Sunwoo, K.; Jung, Y.; Hur, J.K.; Park, K.H.; Kim, J.S.; Kim, D. Membrane-targeting triphenylphosphonium functionalized ciprofloxacin for methicillin-resistant Staphylococcus aureus (MRSA). Antibiotics 2020, 9, 758. [CrossRef]

[27] Sunwoo, K.; Won, M.; Ko, K.P.; Choi, M.; Arambula, J.F.; Chi, S.G.; Sessler, J.L.; Verwilst, P.; Kim, J.S. Mitochondrial relocation of a common synthetic antibiotic: A non-genotoxic approach to cancer therapy. Chemistry 2020, 6, 1408–1419. [CrossRef]

[28] Cochrane, E.J.; Hulit, J.; Lagasse, F.P.; Lechertier, T.; Stevenson, B.; Tudor, C.; Trebicka, D.; Sparey, T.; Ratcliffe, A.J. Impact of Mitochondrial Targeting Antibiotics on Mitochondrial Function and Proliferation of Cancer Cells. ACS Med. Chem. Lett. 2021, 12, 579–584. [CrossRef]

[29] Ózsvári, B.; Magalhães, L.G.; Latimer, J.; Kangasmetsa, J.; Sotgia, F.; Lisanti, M.P. A myristoyl amide derivative of doxycycline potently targets cancer stem cells (CSCs) and prevents spontaneous metastasis, without retaining antibiotic activity. Front. Oncol. 2020, 10, 1528. [CrossRef] [PubMed]

[30] Kulkarni, C.A.; Fink, B.D.; Gibbs, B.E.; Chheda, P.R.; Wu, M.; Sivitz, W.I.; Kerns, R.J. A novel triphenylphosphonium carrier to target mitochondria without uncoupling oxidative phosphorylation. J. Med. Chem. 2021, 64, 662–676. [CrossRef] [PubMed]

[31] Millard, M.; Pathania, D.; Shabaik, Y.; Taheri, L.; Deng, J.; Neamati, N. From broad-spectrum biocides to quorum sensing disruptors and mussel repellents: Antifouling profile of alkyl triphenylphosphonium salts. PLoS ONE 2010, 5, e0123652.

[32] Reily, C.; Mitchell, T.; Chacko, B.K.; Benavides, G.; Murphy, M.P.; Darley-Usmar, V. Mitochondrially targeted compounds and their impact on cellular bioenergetics. Redox Biol. 2013, 1, 86–93. [CrossRef]

[33] Trnka, J.; Elkalaf, M.; Anděl, M. Lipophilic triphenylphosphonium cations inhibit mitochondrial electron transport chain and induce mitochondrial proton leak. PLoS ONE 2015, 10, e0121837. [CrossRef]

[34] Elkalaf, M.; Tuma, P.; Weiszenstein, M.; Polák, J.; Trnka, J. Mitochondrial probe methyltriphenylphosphonium (TPMP) inhibits the krebs cycle enzyme 2-Oxoglutarate dehydrogenase. PLoS ONE 2016, 11, e0161413. [CrossRef]

[35] Filipczaka, N.; Pana, J.; Yalamartya, S.S.K.; Torchilin, V.P. Recent advancements in liposome technology. Adv. Drug Deliv. Rev. 2020, 156, 4–22. [CrossRef] [PubMed]

[36] Wang, H.; Shi, W.; Zeng, D.; Huang, Q.; Xie, J.; Wen, H.; Li, J.; Yu, X.; Qin, L.; Zhou, Y. pH-activated, mitochondria-targeted, and redox-responsive delivery of paclitaxel nanomicelles to overcome drug resistance and suppress metastasis in lung cancer. J. Nanobiotech. 2021, 19, 152. [CrossRef]

[37] Lee, Y.H.; Park, H.I.; Chang, W.S.; Choi, J.S. Triphenylphosphonium-conjugated glycol chitosan microspheres for mitochondria-targeted drug delivery. Int. J. Biol. Macromol. 2021, 167, 35–45. [CrossRef]

[38] Oladimeji, O.; Akinyelu, J.; Daniels, A.; Singh, M. Modified gold nanoparticles for efficient delivery of betulinic acid to cancer cell mitochondria. Int. J. Mol. Sci. 2021, 22, 5072. [CrossRef]

[39] Denney, D.B.; Smith, L.C. Preparation and Reactions of Some Phosphobetaines. J. Org. Chem. 1962, 27, 3404–3408. [CrossRef]

[40] Wei-Li, D.; Bi, J.; Sheng-Lian, L.; Xu-Biao, L.; Xin-Man, T.; Chak-Tong, A. Functionalized phosphonium-based ionic liquids as efficient catalysts for the synthesis of cyclic carbonate from epoxides and carbon dioxide. Appl. Catal. A Gen. 2014, 470, 183–188. [CrossRef]

[41] Hudson, R.F.; Chopard, P.A. Structure et réactions du composé d'addition: Triphénylphosphine–anhydride maléique. Helv. Chim. Acta 1963, 46, 2178–2185. [CrossRef]

[42] Findlay, J.A.; Kwan, D. Metabolites from a Scytalidium Species. Can. J. Chem. 1973, 51, 3299–3301. [CrossRef]

[43] Hayashi, M.; Wakatsuka, H.; Kori, S. Trans-Δ2-Prostaglandins. U.S. Patent 3931296, 6 January 1976.

[44] Bundy, G.L. Phenyl-Substituted Prostaglandin-f Type Analogs. U.S. Patent 3987087, 19 October 1976.

[45] Narayanan, K.S.; Berlin, K.D. Novel synthesis of.omega.-(diphenylphosphinyl)alkylcarboxylic acids from triphenyl-.omega.-carboxyalkylphosphonium salts. J. Org. Chem. 1980, 45, 2240–2243. [CrossRef]

[46] Hann, M.M.; Sammes, P.G.; Kennewell, P.D.; Taylor, J.B. On the double bond isostere of the peptide bond: Preparation of an enkephalin analogue. J. Chem. Soc. Perkin Trans. 1 1982, 1, 307–314. [CrossRef]

[47] Maryanoff, B.E.; Reitz, A.B.; Duhl-Emswiler, B.A. Stereochemistry of the Wittig reaction. Effect of nucleophilic groups in the phosphonium ylide. J. Am. Chem. Soc. 1985, 107, 217–226. [CrossRef]

[48] Carr, G.; Whittaker, D. Lactone formation in superacidic media. J. Chem. Soc. Perkin Trans. II 1987, 12, 1877–1880. [CrossRef]

[49] Cheskis, B.A.; Shpiro, N.A.; Moiseenkov, A.M. Effective synthesis of femrrulactone II based on the use of 2-carhoxyethyltrip-henylphosphonium bromide. Russ. Chem. Bull. 1993, 42, 760–763. [CrossRef]

[50] Wakita, H.; Yoshiwara, H.; Nishiyama, H.; Nagase, H. Total Synthesis of Optically Active m-Phenyline PGI2 Derivative: Beraprost. Heterocycles 2000, 53, 1085–1110.

[51] Wiech, N.L.; Lan-Hargest, H.-Y. Histone Deacetylase Inhibitors. U.S. Patent 2006160902, 20 July 2006.

[52] Ahmed, R.; Altieri, A.; D'Souza, D.M.; Leigh, D.A.; Mullen, K.M.; Papmeyer, M.; Slawin, A.M.Z.; Wong, J.K.Y.; Woollins, J.D. Phosphorus-Based Functional Groups as Hydrogen Bonding Templates for Rotaxane Formation. J. Am. Chem. Soc. 2011, 133, 12304–12310. [CrossRef]

[53] Bakhtiyarova, Y.V.; Aksunova, A.F.; Galkina, I.V.; Galkin, V.I.; Lodochnikova, O.A.; Kataeva, O.N. Crystal structure of new carboxylate phosphabetaines and phosphonium salts conjugated with them. Russ. Chem. Bull. 2016, 65, 1313–1318. [CrossRef]

[54] Xu, J.; Zeng, F.; Wu, H.; Wu, S. A Mitochondria-targeted and NO-based Anticancer Nanosystem with Enhanced Photo-controllability and Low Dark-toxicity. J. Mater. Chem. B 2015, 3, 4904–4912. [CrossRef]

[55] Sodano, F.; Rolando, B.; Spyrakis, F.; Failla, M.; Lazzarato, L.; Gazzano, E.; Riganti, C.; Fruttero, R.; Gasco, A.; Sortino, S. Tuning the Hydrophobicity of a Mitochondria-Targeted NO Photodonor. ChemMedChem 2018, 13, 1238–1245. [CrossRef]

[56] Brooks, A.F.; Ichiishi, N.; Jackson, I.M.; Lee, S.J.; Sanford, M.S.; Scott, P.J.H.; Thompson, S. Synthesis of [F]---fluoro-α,β-unsaturated esters and ketones via vinylogousF-fluorination of α-diazoacetates with [F]AgF. Synthesis 2019, 51, 4401–4407.

[57] Drikermann, D.; Mößel, R.S.; Al-Jammal, W.K.; Vilotijevic, I. Synthesis of Allylboranes via Cu(I)-catalyzed B-H Insertion of Vinyldiazoacetates into Phosphine-Borane Adducts. Org. Lett. 2020, 22, 1091–1095. [CrossRef]

[58] Testai, L.; Sestito, S.; Martelli, A.; Gorica, E.; Flori, L.; Calderone, V.; Rapposelli, S. Synthesis and pharmacological characterization of mitochondrial KATP channel openers with enhanced mitochondriotropic effects. Bioorg. Chem. 2021, 107, 104572. [CrossRef] [PubMed]

[59] Chen, Y.; Wang, Y.; Wang, S.; Ma, Y.-Y.; Zhao, D.-G.; Zhan, R.; Huang, H. Asymmetric Construction of Cyclobutanes via Direct Vinylogous Michael Addition/Cyclization of β,γ-Unsaturated Amides. Org. Lett. 2020, 22, 7135–7140. [CrossRef]

[60] Schweizer, E.E.; Wehmann, A.T. Reactions of phosphorus compounds. Part XXII. A reinvestigation of the reactions of activated alkynes with triphenylphosphine hydrobromide. An investigation of the reactions with bases of the vinylphosphonium salts prepared. J. Chem. Soc. C 1970, 1901–1905. [CrossRef]

[61] Bundy, G.L.; Nelson, N.A. Cis-4,5-didehydro-15 or 16-Alkylated 11-Deoxy-PGE1 Analogs. U.S. Patent 3987072, 19 October 1976.

[62] Kato, K.; Ohkawa, S.; Terao, S.; Terashita, Z.; Nishikawa, K. Thromboxane synthetase inhibitors (TXSI). Design, synthesis, and evaluation of a novel series of.omega.-pyridylalkenoic acids. J. Med. Chem. 1985, 28, 287–294. [CrossRef]

[63] Caldwell, C.; Chapman, K.T.; Hale, J.; Kim, D.; Lynch, C.; Maccoss, M.; Mills, S.G.; Rosauer, K.; Willoughby, C.; Berk, S. Pyrrolidine Modulators of Chemokine Receptor Activity. U.S. Patent 6265434, 24 July 2001.

[64] Mukku, V.J.R.V.; Maskey, R.P.; Monecke, P.; Grün-Wollny, I.; Laatsch, H. 5-(2-Methylphenyl)-4-pentenoic Acid from a Terrestrial Streptomycete. Z. Naturforsch. B 2002, 57, 335–337. [CrossRef]

[65] Wube, A.A.; Hüfner, A.; Thomaschitz, C.; Blunder, M.; Kollroser, M.; Bauer, R.; Bucar, F. Design, synthesis and antimycobacterial activities of 1-methyl-2-alkenyl-4(1H)-quinolones. Bioorg. Med. Chem. 2011, 19, 567–579. [CrossRef]

[66] Luo, D.; Sharma, H.; Yedlapudi, D.; Antonio, T.; Reith, M.E.A.; Dutta, A.K. Novel multifunctional dopamine D2/D3 receptors agonists with potential neuroprotection and anti-alpha synuclein protein aggregation properties. Bioorg. Med. Chem. 2016, 24, 5088–5102. [CrossRef]

[67] Chevalier, A.; Zhang, Y.; Khdour, O.M.; Hecht, S.M. Selective Functionalization of Antimycin A Through an N-Transacylation Reaction. Org. Lett. 2016, 18, 2395–2398. [CrossRef]

[68] Yalla, R.; Raghavan, S. Synthesis of solandelactone F, constanolactone A and an advanced intermediate towards solandelactone E from a common synthetic intermediate. Org. Biomol. Chem. 2019, 17, 4572–4592. [CrossRef]

[69] Wang, Y.; Wei, G.; Yang, G.; Zhang, X.; Zhao, J.; Zhou, S. Stepwise dual targeting and dual responsive polymer micelles for mitochondrion therapy. J. Control. Release 2020, 322, 157–169.

[70] Deng, H.; Discordia, R.; Feng, X.; Jin, Z.; Leigh, C.; Moshos, K.; Sun, G. Cannabinoids and Uses Thereof. W.O. Patent 2021113669, 10 June 2021.

[71] Plattner, J.J.; Bhalerao, U.T.; Rapoport, H. Synthesis of dl-Sirenin. J. Am. Chem. Soc. 1969, 91, 4933–4934. [CrossRef]

[72] Uijttewaal, A.P.; Jonkers, F.L.; Van der Gen, A. Reactions of esters with phosphorus ylides. 3. Direct conversion into branched olefins. J. Org. Chem. 1979, 44, 3157–3168. [CrossRef]

[73] Bergman, N.A.; Jansson, M.; Chiang, Y.; Kresge, A.J.; Yin, Y. Synthesis and kinetic studies of a simple prostacyclin model. J. Org. Chem. 1987, 52, 4449–4453. [CrossRef]

[74] Misra, R.N.; Hüfner Sher, P.M.; Stein, P.D.; Hall, S.E.; Floyd, D.; Barrish, J.C. 7-Oxabicycloheptyl Substituted Heterocyclic Amide or Ester Prostaglandin Analogs Useful in the Treatment of Thrombotic and Vasospastic Disease. U.S. Patent 5100889, 31 March 1992.

[75] Provent, C.; Chautemps, P.; Gellon, G.; Pierre, J.-L. Double Wittig reactions with 4-carboxybutylidene triphenylphosphorane as the key step in the synthesis of benzene derivatives metadisubstituted with ωω'-difunctionalized six-carbon chains. Tetrahedron Lett. 1996, 37, 1393–1396. [CrossRef]

[76] Rey, M.D.L.A.; Martinez-Perez, J.A.; Fernandez-Gacio, A.; Halkes, K.; Fall, Y.; Granja, J.; Mourino, A. New Synthetic Strategies to Vitamin D Analogues Modified at the Side Chain and D Ring. Synthesis of 1alpha,25-Dihydroxy-16-ene-vitamin D(3) and C-20 Analogues(1). J. Org. Chem. 1999, 64, 3196–3206.

[77] Henry-Riyad, H.; Tidwell, T.T. Cyclization of 5-hexenyl radicals from nitroxyl radical additions to 4-pentenylketenes and from the acyloin reaction. Canad. J. Chem. 2003, 81, 697–704. [CrossRef]

[78] Aotsuka, T.; Kumazawa, K.; Wagatsuma, N.; Ishitani, K. Novel 1,8-Naphthyridin-2(1H)-one Derivatives. U.S. Patent 2003036651, 4 December 2003.

[79] Henschke, J.P.; Liu, Y.; Huang, X.; Chen, Y.; Meng, D.; Xia, L.; Wei, X.; Xie, A.; Li, D.; Huang, Q.; et al. The Manufacture of a Homochiral 4-Silyloxycyclopentenone Intermediate for the Synthesis of Prostaglandin Analogues. Org. Proc. Res. Dev. 2012, 16, 1905–1916. [CrossRef]

[80] Wang, K. Preparation Method of Optically Pure Dextro Cloprostenol Sodium. Patent CN 104513186, 5 October 2016.

[81] Ye, Y.; Zhang, T.; Yuan, H.; Li, D.; Lou, H.; Fan, P. Mitochondria-Targeted Lupane Triterpenoid Derivatives and Their Selective Apoptosis-Inducing Anticancer Mechanisms. J. Med. Chem. 2017, 60, 6353–6363.

[82] Cui, D.; Yue, C.; Yang, Y. Mitochondrion-Targeting Nano-Drug Delivery System and Preparation Method and Application Thereof. Patent CN 105833289, 9 April 2019.

[83] Hamri, S.; Jouha, J.; Oumessaoud, A.; Pujol, M.D.; Khouili, M.; Guillaumet, G. Convenient approach for the synthesis of ONO-LB-457, a potent leukotriene B receptor antagonist. Tetrahedron 2021, 77, 131740. [CrossRef]

[84] Bogdanov, A.A.; Chen, C.-W.; Khairullina, Z.Z.; Konevega, A.L.; Lukianov, D.A.; Makarov, G.I.; Osterman, I.A.; Paleskava, A.; Pavlova, J.A.; Polikanov, Y.S.; et al. Binding and Action of Triphenylphosphonium Analog of Chloramphenicol upon the Bacterial Ribosome. Antibiotics 2021, 10, 390.

[85] Castellanos, L.; Gateau-Olesker, A.; Panne-Jacolot, F.; Cleophax, J.; Gero, S.D. Synthèse d'analogues de derives dioxaprostanoïques à partir du D et DU L-xylose. Tetrahedron 1981, 37, 1691–1696. [CrossRef]

[86] Dobner, B.; Nuhn, P.; Burkhardt, U. Synthese mittelständig methylverzweigter Fettsäuren. Z. Chem. 1987, 27, 63–64. [CrossRef]

[87] Carballeira, N.M.; Cruz, H.; Hill, C.A.; De Voss, J.J.; Garson, M. Identification and Total Synthesis of Novel Fatty Acids from the Siphonarid Limpet Siphonaria denticulate. J. Nat. Prod. 2001, 64, 1426–1429. [CrossRef] [PubMed]

[88] Momán, E.; Nicoletti, D.; Mouriño, A. Synthesis of novel analogues of 1α,25-dihydroxyvitamin D3 with side chains at C-18. J. Org. Chem. 2004, 69, 4615–4625. [CrossRef] [PubMed]

[89] Ramon-Azcon, J.; Galve, R.; Sanchez-Baeza, F.; Marco, M.-P. Development of An Enzyme-Linked Immunosorbent Assay (ELISA) for the Determination of the Linear Alkylbenzene Sulfonates (LAS) and long chain Sulfophenhyl Carboxylates (SPCs) using Antibodies Generated by pseudo-Heterologous Immunization. Anal. Chem. 2006, 78, 71–81. [CrossRef] [PubMed]

[90] Hardouin, C.; Kelso, M.J.; Romero, F.A.; Rayl, T.J.; Leung, D.; Hwang, I.; Cravatt, B.F.; Boger, D.L. Structure–Activity Relationships of α-Keto Oxazole Inhibitors of Fatty Acid Amide Hydrolase. J. Med. Chem. 2007, 50, 3359–3368. [CrossRef] [PubMed]

[91] Boger, D.L. Tricyclic Inhibitors of Fatty Acid Amide Hydrolase. Patent WO 2008150492, 11 December 2008.

[92] Zhao, G.; Yang, C.; Li, B.; Xia, W. A new phenylethyl alkyl amide from the Ambrostoma quadriimpressum Motschulsky. Beilstein J. Org. Chem. 2011, 7, 1342–1346. [CrossRef] [PubMed]

[93] Kristiansen, K.; Mainkar, P.S. PPAR Modulators. U.S. Patent 2011178112, 21 July 2011.

[94] Wang, Y.; Wang, B.; Liao, H.; Song, X.; Wu, H.; Wang, H.; Shen, H.; Ma, X.; Tan, M. Liposomal nanohybrid cerasomes for mitochondria-targeted drug delivery. J. Mater. Chem. B 2015, 3, 7291–7299. [CrossRef]

[95] Guo, R.; Huang, J.; Huang, H.; Zhao, X. Organoselenium-Catalyzed Synthesis of Oxygen-and Nitrogen-Containing Heterocycles. Org. Lett. 2016, 18, 504–507. [CrossRef]

[96] Kalathil, A.A.; Kumar, A.; Banik, B.; Ruiter, T.A.; Pathak, R.K.; Dhar, S. New formulation of old aspirin for better delivery. Chem. Comm. 2016, 52, 140–143. [CrossRef] [PubMed]

[97] Chang, Y.-T.; Alamudi, S.H.; Satapathy, R.; Su, D. Background-Free Fluorescent Probes for Live Cell Imaging. Patent WO 201778623, 30 March 2011.

[98] Cheng, J. Method for Preparing 6-Bromotriphenylphosphonio-n-Caproic Acid. Patent CN 106632474, 7 September 2018.

[99] Kalathil, A.A.; Banik, B.; Kumar, A.; Dhar, S. Modification of Drugs for Incorporation into Nanoparticles. U.S. Patent 2017087167, 30 March 2017.

[100] Dhar, S.; Pathak, R. Precise Delivery of Therapeutic Agents to Cell Mitochondria for Anti-Cancer Therapy. U.S. Patent 10004809, 26 June 2018.

[101] Pantelia, A.; Daskalaki, I.; Cuquerella, M.C.; Rotas, G.; Miranda, M.A.; Vougioukalakis, G.C. Synthesis and Chemiluminescent Properties of Amino-Acylated luminol Derivatives Bearing Phosphonium Cations. Molecules 2019, 24, 3957. [CrossRef] [PubMed]

[102] Chen, Z.; Zhang, Z.; Chen, M.; Xie, S.; Wang, T.; Li, X. Synergistic antitumor efficacy of hybrid micelles with mitochondrial targeting and stimuli-responsive drug release. J. Mater. Chem. B 2019, 7, 1415–1426. [CrossRef]

[103] Bundy, G.L. 9-Deoxy-PGF Analogs. U.S. Patent 4033989, 5 July 1977.

[104] Bundy, G.L.; Nelson, N.A. 2a,2b-Dihomo-11-deoxy-17(substituted phenyl)-18,19,20-trinor-PGE Compounds and Their Corre-sponding Esters. U.S. Patent 4029693, 14 July 1977.

[105] Youngdale, G.A. 2a,2b-Dihomo-16,16-dimethyl-PGF Analogs. U.S. Patent 4067891, 10 January 1978.

[106] Smith, H.W. 13,14-Didehydro-PGA Compounds. U.S. Patent 4086258, 25 April 1978.

[107] Nelson, N.A. 15-Epi-15-methyl-16-phenoxy-PGE Compounds. U.S. Patent 4154950, 15 May 1979.

[108] Allais, A.; Clemence, F.; Meier, J.; Deraedt, R. Novel Carboxylic Acids, Benzoyl Phenyl Alkanoic Acids and Use Thereof. U.S. Patent 4337353, 29 June 1982.

[109] Johnson, A.T.; Jiao, G.-S. Hydroxamic Acid Derivatives of 3-Phenyl Propionic Acids Useful as Therapeutic Agents for Treating Anthrax Poisoning. U.S. Patent 2008188566, 5 October 2010.

[110] Kim, S.; Jiao, G.-S.; Moayeri, M.; Crown, D.; Cregar-Hernandez, L.; McKasson, L.; Margosiak, S.A.; Leppla, S.H.; Johnson, A.T. Antidotes to anthrax lethal factor intoxication. Part 2: Structural modifications leading to improved in vivo efficacy. Bioorg. Med. Chem. Lett. 2011, 21, 2030–2033. [CrossRef] [PubMed]

[111] Migglautsch, A.K.; Willim, M.; Schweda, B.; Glieder, A.; Breinbauer, R.; Winkler, M. Aliphatic hydroxylation and epoxidation of capsaicin by cytochrome P450 CYP505X. Tetrahedron 2018, 74, 6199–6204. [CrossRef]

[112] Li, S.; Quan, X.; Xu, J.; Li, J.; Xie, J. Preparation and Application of Quaternary Phosphonium Salt Modified Dendriform Molecule. Patent CN 104844650, 29 December 2017.

[113] Suzuki, Y.; Takahashi, Y. Cationic Lipid. Patent EP 3476832, 1 May 2019.

[114] Chun, J.; Cincilla, G.; Del Valle, C.R.; Devesa, I.; Ferrer-Montiel, A.V.; González-Gil, I.; Hernández-Torres, G.; Khiar-Fernández, N.; Kihara, Y.; López-Rodríguez, M.L.; et al. A novel agonist of the type 1 lysophosphatidic acid receptor (LPA1), UCM-05194, shows efficacy in neuropathic pain amelioration. J. Med. Chem. 2019, 63, 2372–2390.

[115] Dawson, M.I.; Vasser, M. Synthesis of prostaglandin synthetase substrate analogs. 1. (Z)-14-Hydroxy-12-13-methano-8-nonadecenoic acid. J. Org. Chem. 1977, 42, 2783–2785. [CrossRef]

[116] Guthrie, R.W.; Kierstead, R.W. Pyridine Compounds Which Are Useful in Treating a Disease State Characterized by an Excess of Platelet Activating Factors. U.S. Patent 4927838, 22 May 1990.

[117] Nanda, S.; Yadav, J.S. Asymmetric synthesis of unnatural (Z, Z, E)-octadecatrienoid and eicosatrienoid by lipoxygenase-catalyzed oxygenation. Tetrahedron Asymm. 2003, 14, 1799–1806. [CrossRef]

[118] Mor, M.; Lodola, A.; Rivara, S.; Vacondio, F.; Duranti, A.; Tontini, A.; Sanchini, S.; Piersanti, G.F.; Clapper, J.R.; King, A.R.; et al. Synthesis and Quantitative Structure−Activity Relationship of Fatty Acid Amide Hydrolase Inhibitors: Modulation at the N-Portion of Biphenyl-3-yl Alkylcarbamates. J. Med. Chem. 2008, 51, 3487–3498. [CrossRef]

[119] Sparey, T.; Ratcliffe, A.; Cochrane, E.; Stevenson, B.; Hallett, D.; Lagasse, F.; Lassalle, G.; Froidbise, A. Azithromycin Derivatives Containing a Phosphonium Ion as Anticancer Agents. Patent WO 2018193113, 25 October 2018.

[120] Linnebank, P.R.; Ferreira, S.F.; Kluwer, A.M.; Reek, J.N.H. Regioselective Hydroformylation of Internal and Terminal Alkenes via Remote Supramolecular Control. Chem. Eur. J. 2020, 26, 8214–8219. [CrossRef]

[121] Sparey, T.; Ratcliffe, A.; Cochrane, E.; Stevenson, B.; Hallett, D.; Lagasse, F.; Lassalle, G.; Froidbise, A. Phosphonium-Ion Tethered Tetracycline Drugs for Treatment of Cancer. U.S. Patent 2020123182, 23 April 2020.

[122] Lou, H.; Wang, X.; Liu, J. Triazole Compounds, Preparation Method and Application of Triazole Compounds in Antifungal Drugs. Patent CN 111647019, 11 September 2020.

[123] Rao, A.V.R.; Reddy, E.R.; Purandare, A.V.; Varaprasad, C.V.N.S. Stereoselective synthesis of unsaturated C-18 hydroxy fatty acids the self defensive substances. Tetrahedron 1987, 43, 4385–4394. [CrossRef]

[124] Buchanan, G.W.; Smits, R.; Munteanu, E. Synthesis andF NMR study of R-oleic acid-F. J. Fluor. Chem. 2003, 123, 255–259. [CrossRef]

[125] Duffy, P.E.; Quinn, S.M.; Roche, H.M.; Evans, P. Synthesis of trans-vaccenic acid and cis-9-trans-11-conjugated linoleic acid. Tetrahedron 2006, 62, 4838–4843. [CrossRef]

[126] Thurnhofer, S.; Saskia, W. Synthesis of (S)-(+)-enantiomers of food-relevant (n-5)-monoenoic and saturated anteiso-fatty acids by a Wittig reaction. Tetrahedron 2007, 63, 1140–1145. [CrossRef]

[127] Andjelkovic, M.; Ceccarelli, S.M.; Chomienne, O.; Kaplan, G.L.; Mattei, P.; Tilley, J.W. 4-Dimethylaminobutyric Acid Derivatives. U.S. Patent 2009270505, 29 October 2009.

[128] Kumari, A.; Gholap, S.P.; Fernandes, R.A. Tandem IBX-Promoted Primary Alcohol Oxidation/Opening of Intermediate β, γ-Diolcarbonate Aldehydes to (E)-γ-Hydroxy-α, β-enals. Chem. Asian J. 2019, 14, 2278–2290. [CrossRef] [PubMed]

[129] Wood, M.; Whiteman, M.; Perry, A. Hydrogen Sulfide Releasing Compounds and Their Use. Patent WO 201345951, 4 April 2013.

[130] Le Trionnaire, S.; Perry, A.; Szczesny, B.; Szabo, C.; Winyard, P.G.; Whatmore, J.L.; Wood, M.E.; Whiteman, M. The synthesis and functional evaluation of a mitochondria-targeted hydrogen sulfide donor,(10-oxo-10-(--(3-thioxo-3 H-1,2-dithiol-5-yl) phenoxy) decyl) triphenylphosphonium bromide (AP39). MedChemComm 2014, 5, 728–736. [CrossRef]

[131] Sparey, T.; Ratcliffe, A.; Hallett, D.; Cochrane, E.; Lassalle, G.; Froidbise, A.; Stevenson, B. Triphenylphosphonium-Tethered Tetracyclines for Use in Treating Cancer. Patent WO 2018193114, 25 October 2018.

[132] Baran, J.S.; Lowrie, H.S. Metabolites of Pentanedioic Acid Derivatives. U.S. Patent 5055613, 8 October 1991.

[133] Müller, S.; Schmidt, R.R. Synthesis of Unique Ceramides and Cerebrosides Occurring in Human Epidermis. Helv. Chim. Acta 1993, 76, 616–630. [CrossRef]

[134] Skulachev, M.V.; Skulachev, V.P.; Zamyatin, A.A.; Efremov, E.S.; Tashlitsky, V.N.; Yaguzhinsky, L.S.; Korshunova, G.A.; Sumbatyan, N.V.; Antonenko, Y.N.; Severina, I.I.; et al. Pharmaceutical Substances on the Basis of Mitochondria-Addressed Antioxidants. U.S. Patent 2012259110, 12 January 2016.

[135] Martín-Rodríguez, A.J.; Babarro, J.M.F.; Lahoz, F.; Sansón, M.; Martín, V.S.; Norte, M.; Fernández, J.J. From broad-spectrum biocides to quorum sensing disruptors and mussel repellents: Antifouling profile of alkyl triphenylphosphonium salts. PLoS ONE 2015, 10, e0123652. [CrossRef] [PubMed]

[136] Opálka, L.; Kováčik, A.; Sochorová, M.; Roh, J.; Kuneš, J.; Lenčo, J.; Vávrová, K. Scalable Synthesis of Human Ultralong Chain Ceramides. Org. Lett. 2015, 17, 5456–5459. [CrossRef]

[137] Kluba, C.A.; Bauman, A.; Valverde, I.E.; Vomstein, S.; Mindt, T.L. Dual-targeting conjugates designed to improve the efficacy of radiolabeled peptides. Org. Biomol. Chem. 2012, 10, 7594–7602. [CrossRef]

[138] Leavens, W.J.; Lane, S.J.; Carr, R.M.; Lockie, A.M.; Waterhouse, I. Derivatization for liquid chromatography/electrospray mass spectrometry: Synthesis of tris(trimethoxyphenyl)phosphonium compounds and their derivatives of amine and carboxylic acids. Rapid Commun. Mass Spectr. 2002, 16, 433–441. [CrossRef] [PubMed]

[139] Hoffmann, H. Zur Reaktion von Triphenylphosphin mit Olefinen. Chem. Ber. 1961, 94, 1331–1336. [CrossRef]

[140] Romanov, S.; Aksunova, A.; Bakhtiyarova, Y.; Shulaeva, M.; Pozdeev, O.; Egorova, S.; Galkina, I.; Galkin, V. Tertiary phosphines in reactions with substituted cinnamic acids. J. Organomet. Chem. 2020, 910, 121130. [CrossRef]

[141] Bestmann, H.J.; Mott, L.; Lienert, J. Reaktionen mit Triphenylphosphin sowie dessen Hydrobromid und Dibromid, III. Äther und Esterspaltungen mit Triphenylphosphinhydrobromid. Justus Liebigs Ann. Chem. 1967, 709, 105–112. [CrossRef]

[142] Kiuchi, F.; Nakamura, N.; Saito, M.; Komagome, K.; Hiramatsu, H.; Takimoto, N.; Akao, N.; Kondo, K.; Tsuda, Y. Synthesis and Nematocidal Activity of Aralkyl-and Aralkenylamides Related to Piperamide on Second-Stage Larvae of Toxocara canis. Chem. Pharm. Bull. 1997, 45, 685–696. [CrossRef]

[143] Sancéau, J.-Y.; Maltais, R.; Poirier, D.; Marette, A. Total Synthesis of the Antidiabetic (Type 2) Lipid Mediator Protectin DX/PDX. J. Org. Chem. 2019, 84, 495–505. [CrossRef]

[144] Virieux, D.; Volle, J.-N.; Pirat, J.-L. Product class 12: Alkylphosphonium salts. Sci. Synth. 2009, 42, 503–594.

[145] Büttner, H.; Steinbauer, J.; Werner, T. Synthesis of Cyclic Carbonates from Epoxides and Carbon Dioxide by Using Bifunctional One-Component Phosphorus-Based Organocatalysts. ChemSusChem 2015, 8, 2655–2669. [CrossRef]

[146] Wang, Y.; Jiang, M.; Liu, J.-T. Copper-Catalyzed Diastereoselective Synthesis of Trifluoromethylated Tetrahydrofurans. Adv. Synth. Cat. 2016, 358, 1322–1327. [CrossRef]

[147] Atkinson, J.; Stuart, J.; Kagan, V.E.; Stoyanovsky, D.A.; Epperly, M.W.; Greenberger, J.S.; Bayir, H. Mitochondria-Targeted Inhibitors of Cytochrome C Peroxidase for Protection from Apoptosis. U.S. Patent 9365597, 14 June 2016.

[148] Lei, H.; Atkinson, J. Synthesis of phytyl-and chroman-derivatized photoaffinity labels based on α-tocopherol. J. Org. Chem. 2000, 65, 2560–2567. [CrossRef] [PubMed]

[149] Horiike, M.; Tanouchi, M.; Hirano, C. Synthesis of insect sex pheromones and their homologues;(Z)-6-Alkenyl acetates from the Wittig reaction. Agric. Biol. Chem. 1978, 42, 1963–1965.

[150] Cripe, T.A.; Connor, D.S.; Vinson, P.K.; Burckett-St, L.J.C.; Willman, K.W. Polyoxyalkylene Surfactants. U.S. Patent 6093856, 25 July 2000.

[151] Culcasi, M.; Casano, G.; Lucchesi, C.; Mercier, A.; Clement, J.-L.; Pique, V.; Michelet, L.; Krieger-Liszkay, A.; Robin, M.; Pietri, S. Synthesis and biological characterization of new aminophosphonates for mitochondrial pH determination byP NMR spectroscopy. J. Med. Chem. 2013, 56, 2487–2499. [CrossRef] [PubMed]

[152] Muratore, A.; Plessis, C.; Chanot, J.-J. Novel Cycloalkane Aldehydes, Method for Preparing Same, and Use Thereof in the Perfume Industry. U.S. Patent 9051531, 9 June 2015.

[153] He, J.; Baldwin, J.E.; Lee, V. Studies towards the Synthesis of the Antibiotic Tetrodecamycin. Synlett 2018, 29, 1117–1121.

[154] Xue, J.; Zhao, X.; Huang, Y. Double-Targeted Phthalocyanine Anti-Cancer Photosensitizer and Preparation Method Thereof. Patent CN 109081852, 25 December 2018.

[155] Horiike, M.; Hirano, C. A Facile Synthesis of the Sex Pheromones (Z)-7-Dodecen-1-yl Acetate and Its Homologues. Agric. Biol. Chem. 1980, 44, 2229–2230. [CrossRef]

[156] Horiike, M.; Tanouchi, M.; Hirano, C. A convenient method for synthesizing (Z)-alkenols and their acetates. Agric. Biol. Chem. 1980, 44, 257–261. [CrossRef]

[157] Jara, J.A.; Castro-Castillo, V.; Saavedra-Olavarría, J.; Peredo, L.; Pavanni, M.; Jana, F.; Letelier, M.E.; Parra, E.; Becker, M.I.; Morello, A.; et al. Antiproliferative and uncoupling effects of delocalized, lipophilic, cationic gallic acid derivatives on cancer cell lines. Validation in vivo in singenic mice. J. Med. Chem. 2014, 57, 2440–2454. [CrossRef]

[158] Bruns, H.; Thiel, V.; Voget, S.; Patzelt, D.; Daniel, R.; Wagner-Doebler, I.; Schulz, S. N-acylated alanine methyl esters (NAMEs) from Roseovarius tolerans, structural analogs of quorum-sensing autoinducers, N-acylhomoserine lactones. Chem. Biodiver. 2013, 10, 1559–1573. [CrossRef]

[159] Bruns, H.; Herrmann, J.; Müller, R.; Wang, H.; Wagner-Döbler, I.; Schulz, S. Oxygenated N-acyl alanine methyl esters (NAMEs) from the marine bacterium Roseovarius tolerans EL-164//Journal of natural products. J. Nat. Prod. 2018, 81, 131–139. [CrossRef] [PubMed]

[160] Zhong, J.; Sun, X.; Yuan, C.; Ma, S.; Zhou, Y.; Bian, Q.; Wang, M. Method for Synthesizing Grassland Spodoptera Litura Sex Pheromone Active Ingredients. Patent CN 111269114, 12 June 2020.

[161] Baker, S.R.; Ross, W.J. Sulfur Containing Alkenylenyl Substituted Benzoic Acids and Phenyl Tetrazoles and Their Use as Anti-allergic Agents. U.S. Patent 4675335, 23 June 1987.

[162] Lermer, L.; Neeland, E.G.; Ounsworth, J.P.; Sims, R.J.; Tischler, S.A.; Weiler, L. The synthesis of β-keto lactones via cyclization of β-keto ester dianions or the cyclization of Meldrum's acid derivatives. Can. J. Chem. 1992, 70, 1427–1445. [CrossRef]

[163] Okuda, K.; Hasui, K.; Abe, M.; Matsumoto, K.; Shindo, M. Molecular design, synthesis, and evaluation of novel potent apoptosis inhibitors inspired from bongkrekic acid. Chem. Res. Toxicol. 2012, 25, 2253–2260. [CrossRef] [PubMed]

[164] Liang, B.; Shao, W.; Zhu, C.; Wen, G.; Yue, X.; Wang, R.; Quan, J.; Du, J.; Bu, X. Mitochondria-targeted approach: Remarkably enhanced cellular bioactivities of TPP2a as selective inhibitor and probe toward TrxR. ACS Chem. Biol. 2016, 11, 425–434. [CrossRef] [PubMed]

[165] Catalán, M.; Castro-Castillo, V.; Gajardo-de la Fuente, J.; Aguilera, J.; Ferreira, J.; Ramires-Fernandez, R.; Olmedo, I.; Molina-Berríos, A.; Palominos, C.; Valencia, M.; et al. Continuous flow synthesis of lipophilic cations derived from benzoic acid as new cytotoxic chemical entities in human head and neck carcinoma cell lines. RSC Med. Chem. 2020, 11, 1210–1225. [CrossRef] [PubMed]

[166] Liu, F.; Zhang, Z.; Kong, X.; Zhang, S. Micromelalopha Troglodyta Sex Pheromone Attractant Composition, Lure and Preparation Method and Application Thereof. Patent CN 110959613, 17 April 2020.

[167] Alunda, J.M.; Cueto-Díaz, E.J.; Dardonville, C.; Gamarro, F.; Herraiz, T.; Manzano, J.I.; Olías-Molero, A.I.; Perea, A.; Torrado, J.J. Discovery and pharmacological studies of 4-hydroxyphenyl-derived phosphonium salts active in a mouse model of visceral leishmaniasis. J. Med. Chem. 2019, 62, 10664–10675.

[168] Mannu, A.; Di Pietro, M.E.; Priola, E.; Baldino, S.; Sacchetti, A.; Mele, A. Unconventional reactivity of epichlorohydrin in the presence of triphenylphosphine: Isolation of ((1,4-dioxane-2,5-diyl)-bis-(methylne))-bis-(triphenylphosphonium) chloride. Res. Chem. Intermed. 2021, 47, 1663–1674. [CrossRef]

[169] Wada, M.; Tsuboi, A. Reactions of tris(2,6-dimethoxyphenyl)phosphine with epoxides. J. Chem. Soc. Perkin Trans. 1 1987, 151–154. [CrossRef]

[170] Yamamoto, S.; Okuma, K.; Ohta, H. General synthesis of 2-, 3-, and 4-hydroxyalkylphosphonium salts by the reaction of triphenylphosphine with cyclic ethers in the presence of strong acids. Bull. Chem. Soc. Jpn. 1988, 61, 4476–4478. [CrossRef]

[171] Yamamoto, S.-I.; Takeuchi, H.; Tanaka, Y.; Okuma, K.; Ohta, H. Synthesis and reaction of optically active 2-and 3-hydroxyalkylphosphonium salts. Chem. Lett. 1991, 20, 113–116. [CrossRef]

[172] Plénat, F.; Grelet, D.; Ozon, V.; Cristau, H.-J. Synthesis of new functionalized hydroxyalkyl phosphonium salts. Synlett 1994, 4, 269–270. [CrossRef]

[173] Mironov, V.F.; Karaseva, A.N.; Nizamov, I.S.; Kedrov, I.S.; Konovalov, A.I. Triphenylphosphonium Trifluoromethanesulfonate in Reactions with Epoxy Derivatives. Russ. J. Org. Chem. 2004, 40, 910–911. [CrossRef]

[174] Christol, H.; Grelet, D.; Darvich, M.R.; Fallouh, F.; Plenat, F.; Cristau, H.-J. Réaction des oxiranes avec la triphénylphosphine en milieu phénolique. Bull. Soc. Chim. Fr. 1989, 477–483.

[175] Tolstikova, L.L.; Bel'skikh, A.V.; Shainyan, B.A. Protonation and alkylation of organophosphorus compounds with trifluo-romethanesulfonic acid derivatives. Russ. J. Gen. Chem. 2011, 81, 474–480. [CrossRef]

[176] Parker, R.E.; Isaacs, N.S. Mechanisms of epoxide reactions. Chem. Rev. 1959, 59, 737–799. [CrossRef]

[177] Rosowsky, A. Ethylene Oxides. In Heterocyclic Compounds with Three-and Four-Membered Rings; Weissberger, A., Ed.; Interscie: New York, NY, USA; London, UK; Sydney, Australia, 1964; Part I, pp. 1–523.

[178] Wohl, R.A. Mechanism of acid-catalyzed ring-opening of epoxides-reinterpretative review. Chimia 1974, 28, 1–5.

[179] Gray, G.A. Carbon-13 nuclear magnetic resonance of organophosphorus compounds. VIII. Triphenylphosphoranes and triph-enylphosphonium salts. J. Am. Chem. Soc. 1973, 95, 7736–7742. [CrossRef]

[180] Flores-Gallardo, H.; Pollard, C.B. Epoxy ethers and ether amino alcohols. J. Org. Chem. 1947, 12, 831–833. [CrossRef]

[181] Giodini, L.; Lo Re, F.; Campagnol, D.; Marangon, E.; Posocco, B.; Dreussi, E.; Toffoli, G. Nanocarriers in cancer clinical practice: A pharmacokinetic issue. Nanomed. Nanotechnol. Biol. Med. 2017, 13, 583–599. [CrossRef] [PubMed]

[182] Allen, T.M.; Cullis, P.R. Liposomal drug delivery systems: From concept to clinical applications. Adv. Drug Deliv. Rev. 2013, 65, 36–48. [CrossRef] [PubMed]

[183] Barenholz, Y. Doxil®—The first FDA-approved nano-drug: Lessons learned. J. Control. Release 2012, 160, 117–134. [CrossRef] [PubMed]

[184] Forssen, E.A. The design and development of DaunoXome® for solid tumor targeting in vivo. Adv. Drug Deliv. Rev. 1997, 24, 133–150. [CrossRef]

[185] Leonard, R.C.F.; Williams, S.; Tulpule, A.; Levine, A.M.; Oliveros, S. The design and development of DaunoXome® for solid tumor targeting in vivo. Breast 2009, 18, 218–224. [CrossRef]

[186] Bourquin, J.; Milosevic, A.; Hauser, D.; Lehner, R.; Blank, F.; Petri-Fink, A.; Rothen-Rutishauser, B. Biodistribution, clearance, and long-term fate of clinically relevant nanomaterials. Adv. Mater. 2018, 30, 1704307. [CrossRef]

[187] Tomsen-Melero, J.; Passemard, S.; Garcia-Aranda, N.; Diaz-Riascos, Z.V.; Gonzalez-Rioja, R.; Pedersen, J.N.; Lyngsø, J.; Merlo-Mas, J.; Cristobal-Lecina, E.; Corchero, J.L.; et al. Impact of chemical composition on the nanostructure and biological activity of α-galactosidase-loaded nanovesicles for fabry disease treatment. ACS Appl. Mater. Interfaces 2021, 13, 7825–7838. [CrossRef]

[188] Pashirova, T.N.; Sapunova, A.S.; Lukashenko, S.S.; Burilova, E.A.; Lubina, A.P.; Shaihutdinova, Z.M.; Gerasimova, T.P.; Kovalenko, V.I.; Voloshina, A.D.; Souto, E.B.; et al. Synthesis, structure-activity relationship and biological evaluation of tetracationic gemini Dabco-surfactants for transdermal liposomal formulations. Int. J. Pharm. 2020, 575, 118953. [CrossRef]

[189] Sęk, A.; Perczyk, P.; Wydro, P.; Gruszecki, W.I.; Szczes, A. Effect of trace amounts of ionic surfactants on the zeta potential of DPPC liposomes. Chem. Phys. Lipids 2021, 235, 105059. [CrossRef]

[190] Pashirova, T.N.; Burilova, E.A.; Tagasheva, R.G.; Zueva, I.V.; Gibadullina, E.M.; Nizameev, I.R.; Sudakov, I.A.; Vyshtakalyuk, A.B.; Voloshina, A.D.; Kadirov, M.K.; et al. Delivery nanosystems based on sterically hindered phenol derivatives containing a quaternary ammonium moiety: Synthesis, cholinesterase inhibition and antioxidant activity. Chem. Biol. Interact. 2019, 310, 108753. [CrossRef] [PubMed]

[191] Sheldrick, G.; SADABS. Program for Empirical X-ray Absorption Correction; Bruker-Nonius: Gottingen, Germany, 2004.

[192] APEX2 (Version 2.1), SAINTPlus. Data Reduction and Correction Program (Version 7.31A); BrukerAXS Inc.: Madison, WI, USA, 2006.

[193] Sheldrick, G.M. SHELXT—Integrated space-group and crystal-structure determination. Acta Crystallogr. Sect. A 2015, 71, 3–8. [CrossRef] [PubMed]

[194] Sheldrick, G.M. Crystal structure refinement with SHELXL. Acta Crystallogr. Sect. C 2015, 71, 3–8. [CrossRef] [PubMed]

[195] Straver, L.H.; Schierbeek, A.J. MOLEN. Structure Determination System. Program Description; Nonius, B.V.: Delft, The Netherlands, 1994; Volume 1, p. 180.

[196] Farrugia, L. WinGX and ORTEP for Windows: An update. J. Appl. Crystallogr. 2012, 45, 849–854. [CrossRef]

[197] Spek, A.L. Structure validation in chemical crystallography. Acta Crystallogr. Sect. D 2009, 65, 148–155. [CrossRef] [PubMed]

[198] Macrae, C.F.; Edgington, P.R.; McCabe, P.; Pidcock, E.; Shields, G.P.; Taylor, R.; Towler, M.; van de Streek, J. Mercury: Visualization and analysis of crystal structures. J. Appl. Crystallogr. 2006, 39, 453–459. [CrossRef]

[199] Al-Lal, A.M.; Garcна-González, J.E.; Llamas, A.; Monjas, A.; Canoira, L.L. A new route to synthesize tert-butyl ethers of bioglycerol. Fuel 2012, 93, 632–637. [CrossRef]

[200] Solov'ev, D.V.; Kolomenskaya, L.V.; Rodin, A.A.; Zenkevich, I.G.; Lavrent'ev, A.N. Fluorine-containing 2, 3-epoxypropyl ethers. synthesis and spectral characteristics. J. Gen. Chem. USSR 1991, 61, 611–615.

[201] Il'in, A.A.; Il'in, A.N.; Bakhmutov, Y.L.; Furin, G.G.; Pokrovskii, L.M. Promising prospects for using partially fluorinated alcohols as O-nucleophilic reagents in organofluoric synthesis. Russ. J. Appl. Chem. 2007, 80, 405–418. [CrossRef]

[202] Pfeiffer, P.; Bauer, K. Synthese des Bis-ß-chromanons. Chem. Ber. 1947, 80, 7–19. [CrossRef]

[203] Reyhanoglu, Y.; Sahmetlioglu, E.; Gokturk, E. Alternative approach for synthesizing polyglycolic acid copolymers from C1 feedstocks and fatty ester epoxides. ACS Sustain. Chem. Eng. 2019, 7, 5103–5110. [CrossRef]