Review

The Centennial Collection of VDR Ligands: Metabolites, Analogs, Hybrids and Non-Secosteroidal Ligands

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Abstract: Since the discovery of vitamin D a century ago, a great number of metabolites, analogs, hybrids and nonsteroidal VDR ligands have been developed. An enormous effort has been made to synthesize compounds which present beneficial properties while attaining lower calcium serum levels than calcitriol. This structural review covers VDR ligands published to date.

Keywords: metabolites; analogs; hybrids and VDR nonsecosteroidal ligands

1. Introduction

Since the chemical structure of vitamin D$_3$ (1, Figure 1 [1–36], cholecalciferol) was established in 1932, successive studies have shown it to be essential in physiological processes. Two hydroxylations of 1 are necessary before attaining its most biologically active form. The first is a 25-hydroxylation, which occurs mainly in the liver and produces the most abundant circulating metabolite, 25-hydroxyvitamin D$_3$ (11, Figure 1, 25-hydroxycholecalciferol, calcidiol, 25OHD$_3$) [12]. Subsequently, a second hydroxylation at the 1α position generates the vitamin D hormone, 1α,25-dihydroxyvitamin D$_3$ (13, Figure 1, 1α,25-dihydroxycholecalciferol, calcitriol, 1,25(OH)$_2$D$_3$) [14]. This is a pleiotropic hormone that exerts genomic actions by binding to its specific receptor (the vitamin D receptor, VDR), which is present on target cells and found in more than 200 different tissues. The biological role of 1,25(OH)$_2$D$_3$ has been related to calcium and phosphorus homeostasis. However, the effects of vitamin D are not limited to mineral homeostasis, skeletal health maintenance, or immune modulation. In addition, this hormone also has fundamental effects on cellular proliferation and differentiation, regulating genes involved in the cell cycle and apoptosis both in normal and tumor cells. These properties and its wide distribution have led to the study of its effects on various pathologies, such as osteoporosis and cancer, thus arousing interest in the field of health and the pharmaceutical industry.

Unfortunately, the therapeutic use of 1,25(OH)$_2$D$_3$ also leads to an increase in the concentration of calcium in blood (hypercalcemia), which can cause significant side effects. Therefore, numerous attempts have been made to synthesize noncalcemic analogs of 1,25(OH)$_2$D$_3$ for use in health treatment.

In recent decades, structure–function relationships (SARs) have been determined to support the chemical modifications of the secosteroid structure of 1,25(OH)$_2$D$_3$. The novel structures’ goal is to reduce their calcemic activity in comparison with calcitriol while exerting their interesting biological properties. A huge synthesis effort has been carried out, yielding interesting chemical reviews in this regard [2]. The current review updates the scientific information on the structural library of VDR ligands and incorporates nonsteroidal VDR ligands.

2. Materials and Methods

All compounds contained in this review were collected from published papers and patents. Most of the materials were freely accessible via the Internet, and paper copies
were available in other cases. After careful reading, relevant structures were drawn using CHEMDRAW software [3]. No database was generated. A structural analysis of this collection may require future elaboration of a database.

3. Results

We found 1778 VDR compounds, which are displayed chronologically in 31 figures. All of these compounds are ligands that specifically bind to their VDR receptor. This binding allows the interaction of the 1,25(OH)\(_2\)D\(_3\)-VDR complex with target genes in the cell nucleus, modulating their expression and mediating a biological response. The following color scheme was used in the figures: dark blue corresponds to marketed compounds (Figures 1, 3, 4, 8 and 9), light violet to outstanding compounds with interesting properties (Figures 2, 4–10, 12–15, 17–21 and 23–31), and dark green to non-secosteroidal VDR ligands (Figures 9, 11, 12, 15 and 20–27).

Vitamin D is closely associated with calcium and phosphorus homeostasis. No scientific rational has yet been found for the calcemic properties of a compound in comparison with calcitriol. Therefore, structure–function relationships (SARs) were carried out in order to validate the key modifications in the structure of 1,25(OH)\(_2\)D\(_3\) that may alter biological and calcemic properties. After more than 50 years of study, some hints have been obtained. For example, it is known that C-19 methylene deletion yields low calcemic analogs; it is also known that deletion/substitution of the steroidal cycles de-A ring, de-C ring, and/or de-D ring may yield low calcemic analogs. Lowering the calcemic side effects of the vitamin D analogs is important; however, we must not lose sight of other modifications that may increase the antiproliferative and prodifferentiation activity (side-chain modification with extra double and or triple bonds) as well as increase the metabolic stability (fluorine atom incorporation). In summary, the following main structural topics are covered in the current review:

- C-21 Methyl epimerization;
- C-19 Methylene deletion;
- Incorporation of fluorine atoms;
- Deletion/substitution of steroidal cycles: de-A ring, de-C ring, and/or de-D ring;
- C-2 Functionalization;
- C-3 Epimerization;
- Side-chain modification with extra double and/or triple bonds, heteroatoms, and/or branched hydrocarbons.

What is novel in this collection is the incorporation of non-secosteroidal VDR ligands (dark green). In 1999, Boehm [4] hypothesized that “non-secosteroidal VDR ligands might display different profiles of activity and metabolism than do secosteroidal 1,25(OH)\(_2\)D\(_3\), analogs, including less calcemic properties, which might render them attractive as both topical and oral pharmaceuticals for treating a variety of diseases. This hypothesis was based in part on the success that nonsteroidal androgen receptor (AR) and estrogen receptor (ER) modulators have had as drugs. Nonsteroidal compounds have been synthesized that modulate the activity of these receptors and show enhanced tissue selectivity in comparison to the steroids”.

Figure 1 (1931–1978) [1–36]. Vitamin D\(_3\) (1, cholecalciferol) [1] was discovered in 1922, but it was not chemically characterized until 1931. Dihydrotachysterol\(_2\) (8) [10] was introduced in 1934, and it is still on the market as an antitetanic agent AT-10. In 1968, the most abundant metabolite of vitamin D\(_3\) was discovered as 25-hydroxyvitamin D\(_3\) (11, 25-hydroxycholecalciferol) [18], and in 1971, 1α,25-dihydroxyvitamin D\(_3\) 13, 1α,25-dihydroxycholecalciferol, calcitriol, 1α,25(OH)\(_2\)D\(_3\) [21], the vitamin D\(_3\) hormone, was identified. Later, 1α-hydroxyvitamin D\(_3\) (21, Alfacalcidol) [25], a synthetic analog, was marketed for the treatment of secondary hyperparathyroidism (2HPT), renal failure, and osteoporosis.

Figure 2 (1978–1982) [37–52]. 25-Hydroxyvitamin D\(_2\) 26(23)-lactones (58–61) were discovered in 1980 [50–52], and they behave as antagonists of gene transcription induced by VDR. They were the first compounds discovered to have antagonist properties.
Figure 3 (1982–1987) [53–78], 26,26,26,27,27,27-Hexafluoro-1α,25-dihydroxyvitamin D₃ (70, Falcaltciclorol) [60] is used in the treatment of 2HPT and osteoporosis. 1α,25-Dihydroxy-22-oxavitamin D₃ (100, Maxacalcitrol) [76] is used in 2HPT and psoriasis.

Figure 4 (1987–1991) [78–94]. 111 (Calcipotriol, MC903) [79] is marketed as a treatment with exceptional clinical response in psoriasis. 1α,25-Dihydroxoy-22(23)-didehydrovitamin D₃ (116) [83] has shown potent antiproliferative activity. 2β-(Hydroxypropoxy)-1α,25-dihydroxyvitamin D₃ (131, ED-71) [85] is used in osteoporosis treatment.

Figure 5 (1991–1992) [95–117]. Compound 186 [107] is an important analog functionalized at C-11 that may allow the synthesis of haptons, without disturbing the VDR ligand anchoring groups (1α-OH, 3β-OH and 25-OH).

Figure 6 (1993–1994) [118–136]. Compounds 225 [93] and 208 [108] were independently developed by different research groups and are important analogs functionalized at C-18 and C-11, respectively. They may allow the synthesis of haptons without disturbing the VDR ligand anchoring groups.

Figure 7 (1994–1997) [136–148]. Compounds 308 and 309 [147] present an interesting property by exhibiting only nongenomic rapid effects at physiological concentrations. Moreover, 1α-hydroxy group addition (309) does not alter the sensitivity of nongenomic effects of 308.

Figure 8 (1997–1999) [149–158]. 1α-Hydroxyvitamin D₂ (325, Doxercalciferol) [151] is marketed as a 2HPT treatment. (22E,24E)-Diene-24,26,27-trishomo-19-nor-1α,25-dihydroxyvitamin D₃ (348, Ro 25-8584) [152] represents an outstanding compound inhibiting the proliferation in myeloid leukemia cell lines. When 2-methylene-19-nor-1α,25-dihydroxyvitamin D₃ (349, 2MD) [156] is given as oral therapy, it is at least 100 times more potent than 1α,25(OH)₂D₃ in stimulating bone mass increase. A randomized clinical trial showed that 349 increased bone turnover but not BMD (bone mass density) in postmenopausal woman with osteopenia.

Figure 9 (1999) [158–168]. 24R,25-Dihydroxyvitamin D₃ (388, Tacalcitol) [160] is prescribed for psoriasis. 24,26,27-Trishomo-1α,25-dihydroxyvitamin D₃ (406, Seocalcitol, EB 1089) [163] acts as a powerful antiproliferative used in breast, colon, or pancreas tumor models.

Figure 10 (2000–2001) [169–182]. 1α-Hydroxy-26(27)-dehydro-25-(butylcarboxylate)-vitamin D₃ (433, ZK159222) and 1α-hydroxy-26(27)-dehydro-25-(ethylpropenoate)-vitamin D₃ (434, ZK168281) [170] have been identified as VDR antagonists, though 434 is more potent than 433. Both compounds selectively stabilize an antagonist conformation of the VDR-LBD (ligand-binding domain). 1α,25-Dihydroxy-21-(3-hydroxy-3-methylbutyl)-vitamin D₃ (435, Gemini) [171] has emerged as the lead compound with superior gene transcription activity and tumor-cell-line inhibition.

Figure 11 (2001–2002) [183–196]. 1α,25-(OH)₂-16-ene-20-epi-23-yne-3-epi-D₃ (493), 1α,25(OH)₂-16-ene-23-yne-hexafluoro-3-epi-D₃ (494), and 1α,25(OH)₂-16-ene-3-epi-D₃ (495) are potent inducers of apoptosis of HL-60 cells. Their 3-natural (3β-OH) analogs have been shown to be potent modulators of HL-60 cell growth and differentiation [184]. This is the first report to demonstrate that the epimerization of the hydroxyl group at C-3 of the A-ring of 1α,25(OH)₂D₃ plays an important modulation role for HL-60 cell differentiation and apoptosis. 2,2-Difluoro-1α,25-dihydroxyvitamin D₃ (507) [185] is similar to 1,25(OH)₂D₃ in terms of in vitro antiproliferative activity, but it is different in terms of transcriptional activity. In addition, 507 is 2–3 times more transcriptionally active than calcitriol, with similar in vivo calcemic activity. 2,2-Dimethyl-1α,25-dihydroxy-19-norvitamin D₃ (509) [186] is 7.5 times less transcriptionally active than calcitriol and considerably less calcemic. Moreover, 509 strongly suppresses parathyroid hormone (PTH) secretion.

Figure 12 (2002) [197–204]. Seco-C-9,11-bisnor-17-methyl-26,26,26,27,27-hexafluoro-20-epi-1α,25-dihydroxyvitamin D₃ (533, WY1112) [197] and seco-C-9,11,21-trisnor-17-methyl-23(24)-didehydro-26,26,26,27,27,27-hexafluoro-1α,25-dihydroxyvitamin D₃ (559, CD578) [198] display high differentiation ratios between antiproliferative and calcemic effects.
26,27-Bishomo-1α-fluoro,25-hydroxy-23-en-vitamin D₃ (582, Ro-26-9228) [203] is used for treatment of osteoporosis.

Figure 13 (2003–2004) [205–218]. Dienyne 646 [215] represents the first locked side-chain analog of calcitriol with remarkable VDR transcriptional activity. Lactone 657 [217] showed one order of magnitude higher antagonist activity than lactone 66 (Figure 2).

Figure 14 (2004–2006) [218–223]. Further development in double side-chain vitamin D analogs, the Gemini series, made it possible to assess the steric VDR requirements of drug candidates. Compounds 684–695 [220] present two different side chains at C-20 that improve their toxicity profiles and pharmacokinetic drug performance.

Figure 15 (2006–2007) [224–240]. C-20 cyclopropyl vitamin D₃ analog 755 [233] showed high MLR (mixed lymphocyte reaction) activity for the suppression of interferon-γ release with no calcemic activity. Immunomodulatory activity was measured by suppression of interferon-γ release in mixed lymphocyte reaction cells. The inhibition of clonal proliferation was evaluated in the leukemia HL-60, breast cancer MCF-7, prostate PC-3, and LNCaP cell lines. Significant separation of the immunomodulatory activity from hypercalcemic effects (MTD, maximum tolerated dose) was observed. Compound 747 was 2900 times more active and 100 times less hypercalcemic than 1α,25(OH)₂D₃, while 755 was 29 times more active and 100 less hypercalcemic. In the breast cancer MCF-7 cell line, compounds 753, 754, 755, and 757 were ten thousand times more active but equally or less hypercalcemic than 1α,25(OH)₂D₃. Metabolism of 16-ene-20-cyclopropyl compounds is arrested at the 24-keto stage, which explains the increased biological activity of the 16-ene variants.

Figure 16 (2006–2008) [241–253]. Intensive research activity was carried out on the leading structures with outstanding biological properties, i.e., Gemini compounds 799–803 [246,247]. These studies focused on the structural modifications of Gemini that influenced the differentiation-inducing, antiproliferative, and transcriptional activity of the compounds in human leukemia cells. The cyclopropyl modification at the pro-R side chain decreased the activity of the compound compared to 1α,25(OH)₂D₃, and further A-ring modifications did not restore this activity. Cyclopropyl modification at the pro-S side chain of Gemini increased the VDR-induced transcriptional activity. In addition, privileged VDR antagonists lactones 804–832 and 833–864 [245,244] were studied. The antagonistic activity was markedly affected by the structure of the lactone ring, including length of the alkyl chain and the stereochemistries on the C23 and C24 positions. The VDR binding affinity of the (23S,24S)-24-alkylated vitamin D₃ lactones increased 2.3–3.7-fold as compared to the unsubstituted lactones 64–67 (Figure 2). The antagonistic activity of (23S,24S)-isomers were enhanced to be 2.2-, 3.5-, 1.8-, and 1.7-fold higher compared to the unsubstituted lactones 64–67 (Figure 2).

Figure 17 (2008–2009) [254–264]. 2-Methylene-19-nor-(20S)-1α-hydroxy-bishomopregnalciferol 942 [20(S)-2MbisP] [263] were able to suppress bone resorption, intestinal calcium, or phosphate absorption and may have potential for use in the treatment of 2HPT in chronic kidney disease.

Figure 18 (2009–2010) [265–270]. Hybrid compounds 1020 (26,27-bis-nor-25-bishomo-19-nor-25′-oxo-25′-methylcarboxamide-1α-hydroxyvitamin D₃) and 1022 (26,27-bis-nor-25-homo-19-nor-25′-(2aminophenyl)-carboxamide-1α-hydroxyvitamin D₃) [270] showed antiproliferative activity against AT84 carcinoma cells; neither of them induced hypercalcemia even at concentrations 100-fold higher than those tolerated for 1,25D. This demonstrates that it is possible to create a wide range of bifunctional molecules that possess VDR agonism and HDACi (histone deacetylases inhibitor) activity. Structural latitude is significant with a wide variety of ZBGs (zinc-binding group) amenable to incorporation into the side chain of vitamin D-like secosteroids. Importantly, several of these molecules function as antiproliferative agents against AT84 cells in vitro, while possessing minimal hypercalcemic activity in vivo.

Figure 19 (2009–2010) [271–283]. Intensive research activity was carried out on Gemini compounds 1053–1069 [273]. Calcitriol was implicated in many cellular functions including cell growth and differentiation. It was shown that Gemini compounds were active in gene
1173 were greater than those elicited by 1α,25(OH)2D3. The best hybrid, 1173 VDR ligand (4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-phenoxy)-hydroxycacetamide 1173 [295] was confirmed to significantly prevent bone loss after daily treatment without inducing hypercalcemia. These types of compound are potent inhibitors of the Hh (Hedgehog) signaling pathway. Studies show that, contrary to secoesteroidal hybrids, the optimal location for incorporating the highly hydrophilic hydroxamic acid corresponds to the portion of the molecules that serve as secoesteroidal A-ring mimetics. The best hybrid, 1173, is a full VDR agonist, as assessed by several criteria, and an efficacious antiproliferative agent against both 1,25D-sensitive (SCC25, AT84) and 1α,25(OH)2D3-resistant (SCC4) squamous carcinoma cell lines. Importantly, the activity in 1α,25(OH)2D3-resistant SCC4 cells required both the VDR agonism and HDACi activity of 1173. This study revealed the remarkable flexibility in the conversion of calcitriol analogs into fully integrated bifunctional molecules, suggesting that it may be possible to extend fully integrated bifunctionalization to other pharmacophores.

Figure 20 (2010–2012) [284–298]. 25-Diethylphosphite-1α-hydroxy-23(24)-didehydrovitamin D3 1131 [290] was tested for antiproliferative effects on several human and murine tumor cell lines: human squamous cell carcinoma HN12, human glioma T98G, and Kaposi sarcoma VSEC vGPCR cell lines. Furthermore, in human glioma T98G and human squamous cell carcinoma HN12 cell lines, the antiproliferative effects exerted by compound 1131 were greater than those elicited by 1α,25(OH)2D3. Visual observation of internal animal organs such as liver, duodenum, lungs, and kidneys showed no macroscopic morphological alterations after treatment with this compound. This compound appears to be well tolerated even at high doses. Altogether, these results suggest that compound 1131 exerts considerable antiproliferative activity at nonhypercalcemic dosages and may have therapeutic potential for the treatment of various hyperproliferative disorders. Non-secoesteroidal VDR ligand (4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-phenoxy)-hydroxycacetamide 1173 [295] was confirmed to significantly prevent bone loss after daily treatment without inducing hypercalcemia. These types of compound are potent inhibitors of the Hh (Hedgehog) signaling pathway. Studies show that, contrary to secoesteroidal hybrids, the optimal location for incorporating the highly hydrophilic hydroxamic acid corresponds to the portion of the molecules that serve as secoesteroidal A-ring mimetics. The best hybrid, 1173, is a full VDR agonist, as assessed by several criteria, and an efficacious antiproliferative agent against both 1,25D-sensitive (SCC25, AT84) and 1α,25(OH)2D3-resistant (SCC4) squamous carcinoma cell lines. Importantly, the activity in 1α,25(OH)2D3-resistant SCC4 cells required both the VDR agonism and HDACi activity of 1173. This study revealed the remarkable flexibility in the conversion of calcitriol analogs into fully integrated bifunctional molecules, suggesting that it may be possible to extend fully integrated bifunctionalization to other pharmacophores.

Figure 21 (2012–2013) [298–313]. 24S-Methyl-21-epi-2-methylene-22-oxa-1α,25-dihydroxyvitamin D3 (1191, VS-105) [306] bound to VDR is highly inductive of functional responses in vitro and effectively suppresses PTH in a dose range that does not affect serum calcium in 5/6 NX uremic rats. [6-(4-{1-Ethyl-1-[4-((E)-3-ethyl-3-hydroxy-1-pentenyl)-3-methylphenyl]propyl}-2-methylphenyl)pyridin-3-yl]acetic acid (1218) [308] showed excellent ability to prevent BMD loss in mature rats in an osteoporosis model, without severe hypercalcemia and with good PK profiling.

Figure 22 (2013–2014) [313–316]. Compounds 1247–1301 (non-secoesteroidal VDR ligands) [315] were analyzed and presented better therapeutic efficacy when compared to 1α,25(OH)2D3 in experimental models of cancer and osteoporosis with less induction of hypercalcemia, a major potential adverse effect in the clinical application of VDR ligands. Compounds 1302–1313 [316] were analyzed for their binding affinity and inhibitory activity against CYP24A1 (24-hydroxylase; this mitochondrial protein initiates the degradation of 1α,25(OH)2D3 by hydroxylation of the side chain), and the imidazole styrylbenzamides 1305–1309 were identified as potent inhibitors of CYP24A1, with similar or greater CYP27B1 (1α-hydroxylase; the protein encoded by this gene it hydroxylates 25OHD3 at the 1α-position, producing 1α,25(OH)2D3 selectivity than standard ketoconazole. Further evaluation of the 3,5-dimethoxy (1308) and 3,4,5-trimethoxy derivatives (1309) in chronic lymphocytic leukemia cells revealed that cotreatment of 1α,25-dihydroxyvitamin D3 and inhibitor upregulated GADD45α (growth arrest and DNA damage 45 gen) and CDKN1A (cyclin-dependent kinase inhibitor 1A gen).

Figure 23 (2014) [317–321]. Intensive research activity was carried out on Gemini compounds 1338–1364 [320].

Figure 24 (2014–2015) [322–336]. 1α,20S,24R-Trihydroxyvitamin D3 (1410) [332] showed a higher degree of activation, anti-inflammatory activity, and antiproliferative activity than vitamin D3 receptor.

Figure 25 (2015–2017) [337–351]. 1α,25-Dihydroxy-21-(3-hydroxy-3-methyl-1-methylene-butyl)vitamin D3 (1428, UV1) [337] presented potent antitumoral effects over a wide panel...
of tumor cell lines without inducing hypercalcemia or toxicity in vivo. The first vitamin D analog carrying an o-carborane in the side chain 1436 [340] showed that the substitution of hydroxyl group at C-25 by this apolar bulky group was possible. VDR binding was half of calcitriol’s, the transcriptional activity was similar, and the calcemic induction was significantly lower. 1436 is an outstanding B-carrier containing 10 boron atoms, which notably bind to VDR, a nuclear receptor. This suggests that 1436 may be interesting as a BNCT (boron neutron capture therapy) drug.

Figure 26 (2017–2018) [351–358]. 1,1’-(4-(3-(3-Hydroxypropoxy)-3-methylphenyl)pentan-3-yl)-1,2-phenylene[bis(oxy)]bis(3,3-dimethylbutan-2-ol) (1503) [358] displayed efficient inhibitory activity against collagen deposition and fibrotic gene expression in chronic pancreatitis. It also showed physicochemical and pharmacokinetic properties with antitumor activity, highlighting its potential therapeutic applications in cancer treatment.

Figure 27 (2018) [359–364]. (1R,3S,Z)-5-{((E)-3-[3-(6-Hydroxy-6-methylheptyl)phenyl]pent-2-en-1-ylidene)-4-methylene cyclohexane-1,3-diol (1573) [359] exhibited significant tumor growth inhibition and increased survival in SCID mouse models implanted with MDA-MB-231 breast tumor cells. Des-C-ring aromatic D-ring analog 1587 [363] showed remarkable lack of calcemic activity together with its significant antiproliferative and transcriptional activities in breast cancer cell lines, suggesting the therapeutical potential of 1587 for the treatment of breast tumors.

Figure 28 (2018–2019) [365–378]. 21-nor-17(S)-Methyl-20(22),23(24)-didehydro-26,26,26,27,27,27-hexafluoro-1α,25-dihydroxyvitamin D₃ (1600) [368] bound strongly to VDR ligand binding domain and induced VDR transcriptional activity. Hybrid 1619 [371] was found to be a potent inhibitor of Hh (Hedgehog) signaling pathway.

Figure 29 (2019–2020) [379–383]. It is known that 25(OH)D₃, down-regulates SREBP (sterol regulatory element-binding protein) independently of VDR. A screening of over 250 vitamin D congeners was carried out for their ability to inhibit the activity of an SREBP-responsive luciferase reporter. This is a VDR-responsive reporter assay. A comparison of the relative activity of the six compounds revealed 1639 [379] as the VDR-selective activator.

Figure 30 (2020–2022) [384–389]. Des-C-ring aromatic D-ring analogs 1712 and 1713 [373] showed a remarkable lack of calcemic activity together with significant antiproliferative and transcriptional properties in breast cancer cell lines, suggesting a therapeutical potential for 1712 and 1713 in breast tumor treatment.

Figure 31 (2021–2022) [390–392]. KK-052 (1746) [391], was found to be the first vitamin D-based SREBP (sterol regulatory element-binding proteins) inhibitor that mitigates hepatic lipid accumulation without calcemic action in mice. KK-052 maintained the ability of 25-hydroxyvitamin D₃ to induce the degradation of SREBP but lacked VDR-mediated activity. KK-052 serves as a valuable compound for interrogating SREBP/SCAP in vivo and may represent an unprecedented translational opportunity for synthetic vitamin D analogs.
Figure 1. (1931–1978) [1–36].
Figure 2. (1978–1982) [37–52].
Figure 3. (1982–1987) [53–78].
Figure 4. (1987–1991) [78–94].
Figure 5. (1991–1992) [95–117].
Figure 6. (1993–1994) [118–136].
Figure 7. (1994–1997) [136–148].
Figure 8. (1997–1999) [149–158].
Figure 9. (1999) [158–168].
Figure 10. (2000–2001) [169–182].
Figure 11. (2001–2002) [183–196].
Figure 12. (2002) [197–204].
Figure 13. (2003–2004) [205–218].
Figure 14. (2004–2006) [218–223].
Figure 15. (2006–2007) [224–240].
Figure 16. (2006–2008) [241–253].
Figure 17. (2008-2009) [254–264].
Figure 18. (2009–2010) [265–270].
Figure 19. (2009–2010) [271–283].

Figure 20. (2010–2012) [284–298].
Figure 20. (2010–2012) [284–298]
Figure 21. (2012–2013) [298–313].
Figure 22. (2013–2014) [313–316].
Figure 23. (2014) [317–321].
Figure 24. (2014–2015) [322–336].
Figure 25. (2015–2017) [337–351].
Figure 26. (2017–2018) [351–358].
Figure 27. (2018) [359–364].
Figure 28. (2018–2019) [365–378].
Figure 29. (2019–2020) [379–383].
Figure 30. (2020–2022) [384–389].
Figure 31. (2021–2022) [390–392].
4. Conclusions
A century has passed since vitamin D was discovered. The structural diversity achieved among vitamin D receptor ligands (1785 ligands involving metabolites, analogs, hybrids, and nonsteroidal ligands). Seeing as vitamin D plays a ubiquitous role in human physiology, VDR ligands have been found to cure or ameliorate the symptoms of various diseases. It is disheartening to note that for more than twenty years no drug based on a VDR ligand (i.e., analogues, hybrids, or nonsteroidal ligands) has been placed on the market because the structural diversity achieved in the VDR ligands might encode new therapies for other illness different than the calcium–phosphorous homeostasis.

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References
1. Askew, F.A.; Bruce, H.M.; Callow, R.K.; Philpot, L., Jr.; Webster, T.A. Crystalline vitamin D. Nature 1931, 128, 758. [CrossRef]
2. Havinga, E.; Bots, J.P.L. Studies on vitamin D I. The synthesis of vitamin D. Rec. Trav. Chim. 1954, 73, 393–400. [CrossRef]
3. Bouillon, R.; Okamura, W.H.; Norman, A.W. Structure-function relationships in vitamin D endocrine system. Endocrine Rev. 1995, 16, 200–237. [CrossRef]
4. Zhu, G.-D.; Okamura, W.H. Synthesis of vitamin D (calciferol). Chem. Rev. 1995, 95, 1877–1952. [CrossRef]
5. Saito, N.; Kittaka, A. Highly potent vitamin D receptor antagonists; design, synthesis and biological evaluation. ChemBioChem 2006, 7, 1478–1490. [CrossRef]
6. Posner, G.H.; Kahraman, M. Organic chemistry on vitamin D analogues (Deltanoids). Eur. J. Org. Chem. 2003, 2003, 3889–3895. [CrossRef]
7. PerkinElmer. CHEM DRAW v.21.0.028 Chemical Drawing Software; PerkinElmer Informatics, Inc.: Waltham, MA, USA, 2011.
8. Boehm, M.F.; Fitzgerald, P.; Zou, A.; Elgort, M.G.; Bischoff, E.D.; Mere, L.; Mais, D.E.; Bissonnette, R.P.; Heyman, R.A.; Nadzan, A.M.; et al. Novel nonsecosteroidal vitamin D mimics exert VDR-modulating activities with less calcium mobilization than 1,25-dihydroxyvitamin D. Chem. Biol. 1999, 6, 265–275. [CrossRef]
9. Windaus, A.; Linsert, O.; Lüttringhaus, A.; Weidlich, G. Über das krystallisierte vitamin D. Ann. Chem. 1932, 492, 226–241. [CrossRef]
10. Jordans, G.H.W. A.T. 10, a new drug against tetany. Ned. Tijdschr. 1934, 78, 2750–2756.
11. Albright, F.; Sulkowitch, H.W.; Bloomberg, E. A comparison of the effects of vitamin D, dihydrotachysterol (A.T. 10) and parathyroid extract on the disordered metabolism of rickets. J. Clin. Inv. 1939, 18, 165. [CrossRef]
12. Verloop, A.; Koevoet, A.L.; Havinga, E. Studies on vitamin D compounds and related compounds III. Short communication on the cis-trans isomerization of calciferol and properties of “trans”-vitamin D$_2$. Rec. Trav. Chim. 1955, 74, 1125–1130. [CrossRef]
13. Koevoet, A.L.; Verloop, A.; Havinga, E. Studies on vitamin D compounds and related compounds II. Preliminary communication on the interconversion and the possible cis-trans isomerism of previtamin D and tachysterol. Rec. Trav. Chim. 1955, 74, 788–792. [CrossRef]
14. Westerhof, P.; Keverling Buisman, J.A. Investigations on sterols. VI. The preparation of dihydrotachysterol$_2$. Rec. Trav. Chim. 1956, 75, 453–462. [CrossRef]
15. Inhoffen, H.H.; Quinkert, G.; Hess, H.-J.; Hirschkeld, H. Studien in der vitamin D-reihe, XXIV. Photo-isomerisierung der trans-vitamin D$_2$ un D$_3$ zu den vitaminen D$_2$ und D$_3$. Chem Ber. 1957, 90, 2544–2553. [CrossRef]
16. Westerhof, P.; Keverling Buisman, J.A. Investigations on sterols. IX. Dihydroderivatives of ergocalciferol. Rec. Trav. Chim. 1957, 76, 679–688. [CrossRef]
17. Inhoffen, H.H.; Irmischer, K.; Hirschkeld, H.; Stache, U.; Kreutzer, A. Partial synthesis of vitamin D$_2$ and D$_3$. J. Chem. Soc. 1959, 385–386. [CrossRef]
18. Blunt, J.W.; DeLuca, H.F.; Schnoes, H.K. 25-Hydroxycholecalciferol. A biologically active metabolite of vitamin D$_3$. Biochemistry 1960, 7, 3317–3322. [CrossRef]
19. Suda, T.; DeLuca, H.F.; Schnoes, H.K.; Tanaka, Y.; Holick, M.F. 25,26-Dihydroxycholecalciferol, a metabolite of vitamin D$_3$ with intestinal calcium transport activity. Biochemistry 1970, 9, 4776–4780. [CrossRef]
20. Redel, J.; Bell, P.; Delbarre, F.; Kodic, E. Synthese du dihydroyxy-25,26 cholecalciferol, metabolite de la vitamine D$_3$. C. R. Acad. Sc. Paris Serie D 1973, 276, 2907–2909.
21. Holick, M.F.; Schnoes, H.K.; DeLuca, H.F. Identification of 1,25-dihydroxycholecalciferol, a form of vitamin D$_3$ metabolically active in the intestine. Proc. Nat. Acad. Sci. USA 1971, 68, 803–804. [CrossRef]
22. Norman, A.W.; Myrtle, J.F.; Midgett, R.J.; Noviki, H.G.; Williams, V.; Popjak, G. 1,25-Dihydroxycholecalciferol: Identification of the proposed active form of vitamin D₃ in the intestine. *Science* **1971**, *173*, 51–54. [CrossRef] [PubMed]

23. Lawson, D.E.M.; Fraser, D.R.; Kodicek, E.; Morris, H.R.; Dudley, H.W. Calcitriol, identification of 1,25-dihydroxycholecalciferol, a new kidney controlling calcium metabolism. *Nature* **1971**, *230*, 228–230. [CrossRef] [PubMed]

24. Lam, H.-Y.; Schnoes, H.K.; DeLuca, H.F.; Chen, T.C. 24,25-Dihydroxyvitamin D₃. Synthesis and biological activity. *Biochemistry* **1973**, *12*, 4851–4855. [CrossRef] [PubMed]

25. Chalmers, T.M.; Hunter, J.O.; Davie, M.W.; Szaz, K.F.; Pelc, B.; Kodicek, E. 1-α-Hydroxycholecalciferol as a substitute for the kidney hormone 1,25-dihydroxycholecalciferol in chronic renal failure. *Lancet* **1973**, *2*, 696–699. [CrossRef]

26. Fürst, A.; Labler, L.; Meier, W.; Pfoertner, K.-H. Synthese von 1-α-hydroxycholecalciferol. *Helv. Chim. Acta* **1973**, *56*, 1708–1710. [CrossRef]

27. Barton, D.H.R.; Hesse, R.H.; Pechet, M.M.; Rizzardo, E. A convenient synthesis of 1α-hydroxyvitamin D₃. *J. Chem. Soc. Perkin I* **1974**, 2654–2657. [CrossRef]

28. Harrison, R.G.; Lythgoe, B.; Wright, P.W. Calciferol and its relatives. Part XVIII. Total synthesis of 1α,25-dihydroxyvitamin D₃. *Chem. Soc. Perkin I* **1975**, 23, 695–697. [CrossRef]

29. Harrison, R.G.; Lythgoe, B.; Wright, P.W. Calciferol and its relatives. Part XVIII. Total synthesis of 1α-hydroxy-vitamin D₃. *J. Chem. Soc. Perkin I* **1974**, 2654–2657. [CrossRef]

30. Lam, H.Y.; Schnoes, H.K.; DeLuca, H.F. 1α-Hydroxyvitamin D₃. Potent synthetic analog of vitamin D₃. *Science* **1974**, *186*, 1038–1040.

31. Ikewka, N.; Morisaki, M.; Koizumi, N.; Kato, Y.; Takeshita, T. Synthesis of active forms of vitamin D. VIII. Synthesis of [24R]- and [24S]-1α,24,25-trihydroxyvitamin D₃. *Chem. Pharm. Bull.* **1975**, 23, 3196–3198. [CrossRef]

32. Morisaki, M.; Koizumi, N.; Ikewka, N. Synthesis of active forms of vitamin D. IX. Synthesis of 1α,24-dihydroxycholecalciferol. *J. Chem. Soc. Perkin I* **1975**, 1421–1424. [CrossRef] [PubMed]

33. Lythgoe, B.; Moran, T.A.; Nambudiril, M.E.; Ruston, S.; Tideswell, J.; Wright, P.W. Allylic phosphate oxides as precursors of dienes of defined geometry: Synthesis of 3-deoxyvitamin D₃. *Tet. Lett.* **1975**, 44, 3863–3866. [CrossRef]

34. Okamura, W.H.; Hammond, M.L.; Rego, A.; Norman, A.W.; Wing, R.M. Studies on vitamin D (calciferol) and its analogues. 12. Structural and synthetic studies of 5,6-trans-vitamin D₃ and stereoisomers of 10,19-dihydrovitamin D₃ including dihydrotachysterol. *J. Org. Chem.* **1977**, 42, 2284–2291. [CrossRef] [PubMed]

35. Mouriño, A.; Blair, P.; Weckslser, W.; Johnson, R.L.; Norman, A.W.; Okamura, W.H. Studies on vitamin D (calciferol) and its analogues. 15. 24-Nor-1α,25-dihydroxyvitamin D₃ and 14-nor-25-hydroxy-5,6-trans-vitamin D₃. *J. Med. Chem.* **1978**, *21*, 1025–1029. [CrossRef] [PubMed]

36. Mouriño, A.; Okamura, W.H. Studies on vitamin D (calciferol) and its analogues. 14. On the 10,19-dihydrovitamins related to vitamin D₂ including dihydrotrachysterol. *J. Org. Chem.* **1978**, 43, 1653–1656. [CrossRef]

37. Yamada, S.; Ohmori, M.; Takayama, H. Synthesis of 24,24-difluoro-1α,25-dihydroxyvitamin D₃. *Chem. Pharm. Bull.* **1979**, *27*, 3196–3198. [CrossRef]

38. Onisko, B.L.; Schnoes, H.K.; DeLuca, H.F. 25-Aza-vitamin D₃, an inhibitor of vitamin D metabolism and action. *J. Biol. Chem.* **1979**, *254*, 3493–3496. [CrossRef]

39. Kocienski, P.J.; Lythgoe, B.; Rutson, S. Calciferol and its relatives. Part 24. A synthesis of vitamin D₄. *J. Chem. Soc. Perkin I* **1979**, 1290–1293. [CrossRef]

40. Kobayahi, Y.; Taguchi, T.; Terada, T. Synthesis of 24,24-difluoro- and 24-fluoro-25-hydroxyvitamin D₃. *Tet. Lett.* **1979**, *20*, 2023–2026. [CrossRef]

41. Yamada, S.; Ohmori, M.; Takayama, H. Synthesis of 24,24-difluoro-25-hydroxyvitamin D₃. *Tet. Lett.* **1979**, *20*, 1859–1862. [CrossRef]

42. Napoli, J.L.; Fivizzani, M.A.; Schnoes, H.K.; DeLuca, H.F. 1-Fluorovitamin D₃, a vitamin D₃ analogue more active on bone-calcium mobilization than on intestinal-calcium transport. *Biochemistry* **1979**, *18*, 1641–1646. [CrossRef] [PubMed]

43. Ishizuka, S.; Bannai, K.; Naruchi, T.; Hashimoto, Y.; Noguchi, T.; Hosoya, N. Studies on the mechanism of action of 1α,24-dihydroxyvitamin D₃. I. Synthesis of 1α,24(3)R- and 1α,24(3S)-dihydroxy-[24-3H]-vitamin D₃ and their metabolism in the rat. *J. Biochem.* **1980**, *88*, 87–95. [PubMed]

44. Holick, S.A.; Holick, M.F.; Frommer, J.E.; Henley, J.W.; Lenz, J.A. Synthesis of [3α-3H]-3-epivitamin D₃ and its metabolism in the rat. *Biochem. Bioenerg.* **1980**, *19*, 3993–3997. [CrossRef]

45. Orisko, B.L.; Schnoes, H.K., DeLuca, H.F. Inhibitors of the 25-hydroxylation of vitamin D₃ in the rat. *Bioorg. Chem.* **1980**, *9*, 187–198. [CrossRef]

46. Kobayashi, Y.; Taguchi, T.; Kanuma, N. Synthesis of 26,26,27,27,27-hexafluoro-25-hydroxyvitamin D₃. *J. Chem Soc. Chem. Comm.* **1980**, *459–460*. [CrossRef]

47. Jacobus, D.P.; Jones, H.; Yang, S.S. Cholecalciferol and Dihydrotachysterol3 Derivatives in Metabolic Blocking Drugs. Federal Republic Germany. DE2646240 A1, 28 April 1977.

48. Kocienski, P.J.; Lythgoe, B. Calciferol and its relatives. Part 27. A synthesis of 1α-hydroxyvitamin D₃ by way of 1α-hydroxytachysterol. *J. Chem. Soc. Perkin I* **1980**, 1400–1404. [CrossRef]

49. Oshida, I.-I.; Morisaki, M.; Ikewka, N. Synthesis of 25-fluoro-1α-hydroxyvitamin D₃. *Tet. Lett.* **1980**, *21*, 1755–1756. [CrossRef]

50. Ohmura, N.; Bannai, K.; Yamaguchi, H.; Hashimoto, Y.; Norman, A.W. Isolation of a new metabolite of vitamin D produced in vivo, 1α,25-dihydroxyvitamin D₃-26,23-lactone. *Arch. Biochem. Biophys.* **1980**, *204*, 387–391. [CrossRef]
51. Wichmann, J.K.; Paaren, H.E.; Fivizzani, M.A.; Schnoes, H.K.; DeLuca, H.F. Synthesis of 25-hydroxyvitamin D$_3$ 26,23-lactone. Tet. Lett. 1980, 21, 4667–4670. [CrossRef]

52. Eguchi, T.; Takatsuto, S.; Hirano, Y.; Ishiguro, M.; Ikekawa, N. Synthesis of four isomers of 25-hydroxyvitamin D$_3$ 26,23-lactone. Heterocycles 1982, 17, 359–375.

53. Paaren, H.E.; Fivizzani, M.A.; Schnoes, H.K.; DeLuca, H.F. 1α,25-Difluorovitamin D$_3$: An inert vitamin D analog. Arch. Biochem. Biophys. 1981, 209, 579–583. [CrossRef]

54. Wichmann, J.; Schnoes, H.K.; DeLuca, H.F. Isolation and identification of 24(R)-hydroxyvitamin D$_3$ from chicks given large doses of vitamin D$_3$. Biochemistry 1981, 20, 2350–2353. [CrossRef] [PubMed]

55. Wichmann, J.; Schnoes, H.K.; DeLuca, H.F. 23,24,25-Trihydroxyvitamin D$_3$, 24,25,26-trihydroxyvitamin D$_3$, 24-keto-25-hydroxyvitamin D$_3$ and 23-dehydro-25-hydroxyvitamin D$_3$. Biochemistry 1981, 20, 7385–7391. [CrossRef] [PubMed]

56. Esvelt, R.P.; Fivizzani, M.A.; Paaren, H.E.; Schnoes, H.K.; DeLuca, H.F. Synthesis of calcitroic acid, a metabolite of 1α,25-dihydroxycholecalciferol. J. Org. Chem. 1981, 46, 456–458. [CrossRef]

57. Haces, A.; Okamura, W.H. Heterocalciferols: Novel 3-thia and 3-sulfinyl analogues of 1α-hydroxyvitamin D$_3$. Tetrahedron 1981, 37, 2528–2536. [CrossRef]

58. Esvelt, R.P.; Fivizzani, M.A.; Paaren, H.E.; Schnoes, H.K.; DeLuca, H.F. Synthesis of calcitroic acid, a metabolite of 1α,25-dihydroxycholecalciferol. J. Org. Chem. 1981, 46, 456–458. [CrossRef]

59. Matoba, K.; Kondo, K.; Yamazaki, T. Syntheses of vitamin D analogs I. Arch. Biochem. Biophys. 1979, 200, 359–375.

60. Kobayashi, Y.; Taguchi, T.; Mitsihashi, S.; Eguchi, T.; Ohshima, E.; Ikekawa, N. Studies on organic fluorine compounds. XXIX. Studies on steroids. LXXIX. Synthesis of 1α,25-dihydroxyvitamin D$_3$. Chem. Pharm. Bull. 1983, 31, 2528–2536. [CrossRef]

61. Reddy, G.S.; Tserng, K.-Y. Isolation and identification of 1,24,25-trihydroxyvitamin D$_3$. Biochemistry 1981, 20, 5512–5518. [CrossRef]

62. Yamada, S.; Ohmori, M.; Takayama, H.; Takasaki, Y.; Suda, T. Isolation and identification of 1α- and 23-hydroxylated metabolites of 25-hydroxy-24-oxo-vitamin D$_3$ from in vitro incubates of chick kidney homogenates. J. Biol. Chem. 1983, 258, 457–463. [CrossRef]

63. Wovkulich, P.M.; Barcelos, B.; Batcho, A.D.; Sereno, J.F.; Baggiolini, E.G.; Hennessy, B.M.; Uskokovic, M.R. Stereospecific total synthesis of 1α,25,26-trihydroxycholecalciferol. Tetrahedron 1984, 40, 2283–2296. [CrossRef]

64. Barner, R.; Hübscher, J.; Daly, J.J.; Schönholzer, P. Zur Konfiguration des Vitamin D$_3$-Metaboliten 25,26-Dihydroxycholecalciferol: Synthese von (25,26)- und (25,26)-Dihydroxycholecalciferol. Helv. Chim. Acta 1981, 64, 915–938. [CrossRef]

65. Toh, H.T.; Okamura, W.H. Studies on a convergent route to side-chain analogues of vitamin D: 25-hydroxy-23-oxavitamin D$_3$. J. Org. Chem. 1983, 48, 1414–1417. [CrossRef]

66. Midgley, J.M.; Upton, R.M.; Watt, R.A.; Whalley, W.B.; Zhang, X.M. Unsaturated steroids. Part 11. Synthesis and differentiating action of vitamin D endoperoxides. Singlet oxygen adducts of vitamin D derivatives in human fibroblast and leukemic cell lines. Bioorg. Chem. 1983, 12, 1264–1269. [CrossRef]

67. Taguchi, T.; Mitsuhashi, S.; Yamanouchi, A.; Kabayashi, Y. Synthesis of 23,23-difluoro-25-hydroxyvitamin D$_3$. Tet. Lett. 1984, 25, 4933–4936. [CrossRef]

68. Yamada, S.; Yamamoto, K.; Naito, H.; Suzuki, T.; Ohmori, M.; Takayama, H.; Shinya, Y.; Miyaura, C.; Tanaka, H.; Abe, E.; et al. Synthesis and differentiating action of vitamin D endoperoxides. Singlet oxygen adducts of vitamin D derivatives in human myeloid leukemia cells (HL-60). J. Med. Chem. 1985, 28, 1148–1153. [CrossRef]

69. Midgley, J.M.; Upton, R.M.; Watt, R.A.; Whalley, W.B.; Zhang, X.M. Unsaturated steroids. Part 11. Synthesis of 1α-hydroxy-25-methyl vitamin D$_3$. J. Chem. Res., Synopses 1985, 11, 273.

70. Takatsuto, S.; Ikekawa, N.; Tanaka, I.; DeLuca, H.F. Highly potent inducer for differentiation of human leukemia cells HL-60. Bioorg. Chem. 1987, 15, 152–166. [CrossRef]

71. Ikekawa, N.; Eguchi, T.; Haru, N.; Takatsuto, S.; Honda, A.; Mori, Y.; Otomo, S. 26,27-Diethyl-1α,25-dihydroxyvitamin D$_3$ and 24,24-difluoro-24-homo-1α,25-dihydroxyvitamin D$_3$: Highly potent inducer for differentiation of human leukemia cells HL-60. Chem. Pharm. Bull. 1987, 35, 4362–4365. [CrossRef]
79. Calverley, M.J. Synthesis of MC 903, a biologically active vitamin D metabolite analogue. *Tetrahedron* 1987, 43, 4609–4619. [CrossRef]

80. Eguchi, T.; Sai, H.; Takatsu, S.; Hara, N.; Ikekawa, N. Synthesis of 26,27-dialkyl analogues of 1α,25-dihydroxyvitamin D₃. *Chem. Pharm. Bull.* 1988, 36, 2303–2311. [CrossRef]

81. Shiu, S.-J.; Partridge, J.J.; Uskokovic, M.R. Triply convergent synthesis of 1α,25-dihydroxy-24(R)-fluorocholecalciferol. *J. Org. Chem.* 1988, 53, 1040–1046. [CrossRef]

82. Barrack, S.A.; Gibbs, R.A.; Okamura, W.H. Potential inhibitors of vitamin D metabolism: An oxa analogue of vitamin D. *J. Org. Chem.* 1988, 53, 1790–1796. [CrossRef]

83. Baggiolini, E.G.; Hennessy, B.M.; Truitt, G.A.; Uskokovic, M.R. Dehydrocholecalciferol Derivatives. U.S. US14532882A, 20 January 1988.

84. Okano, T.; Tsugawa, N.; Masuda, S.; Takeuchi, A.; Kobayashi, T.; Takita, Y.; Nishii, Y. Regulators of cell growth and immune responses. *Biophys. Res. Commun.* 1991, 189, 1444–1449. [CrossRef]

85. Eguchi, T.; Yoshida, M.; Ikekawa, N. Synthesis and biological activities of 22-hydroxy and 22-methoxy derivatives of 1α,25-dihydroxycholecalciferol and 1α,25-dihydroxyergocalciferol. *J. Org. Chem.* 1989, 54, 655–664. [CrossRef]

86. Dauben, W.G.; Ollmann, R.R., Jr.; Corradino, R.A.; Zinsmeister, A.R.; Kumar, R. Synthesis and biological activity of novel vitamin D analogues: 24,24-difluoro-25-hydroxy-26,27-dimethylvitamin D₃ and 24,24-difluoro-1α,25-dihydroxy-26,27-dimethyl vitamin D₃. *J. Med. Chem.* 1990, 33, 480–490. [CrossRef]

87. Hara, N.; Eguchi, T.; Ikekawa, N.; Ishizuka, S.; Sato, J.-i. Synthesis and biological activity of (22R,25S)-fluorocholecalciferol. A versatile intermediate in the synthesis of 1α,25-dihydroxyvitamin D₃: Importance of side chain conformation for biological activities. *Bioorg. Chem.* 1989, 17, 294–307. [CrossRef]

88. Perlman, K.L.; DeLuca, H.F. Novel synthesis of 19-nor-vitamin compounds. *Bioorg. Chem.* 1991, 39, 3221–3224. [CrossRef]

89. Perlman, K.L.; Swenson, R.E.; Paaren, H.E.; Schnoes, H.K.; DeLuca, H.F. Synthesis and biological activity of calcium and cell differentiation activities. *Biochem. Biophys. Res. Commun.* 1988, 163, 4072–4083. [CrossRef]

90. Perlman, K.L.; DeLuca, H.F. 1α-Hydroxy-19-nor-vitamin D C-22 aldehyde. A versatile intermediate in the synthesis of side chain modified 1α,25-dihydroxy-19-nor-vitamin D₃. *Tet. Lett.* 1992, 33, 2937–2940. [CrossRef]

91. Binderup, L.; Latini, S.; Binderup, E.; Bretting, C.; Calverley, M.; Hansen, K. 20-epi-vitamin D. *Bioorg. Chem.* 1991, 29, 327–332. [CrossRef]

92. Kubodera, N.; Miyamoto, K.; Matsumoto, M.; Kawanishi, T.; Ohkawa, H.; Mori, T. Synthetic studies of vitamin D analogues. X. Synthesis and biological activity of 1α,25-dihydroxy-21-norvitamin D₃. *Chem. Pharm. Bull.* 1992, 40, 648–651. [CrossRef]

93. Baggiolini, E.G.; Hennessy, B.M.; Shiuey, S.J.; Truitt, G.A.; Uskokovic, M.R. Preparation of Dehydrocholecalciferol Derivatives for Treatment of Hyperproliferative Skin Diseases and Neoplasms and Pharmaceutical Compositions Containing Them. European Patent Organization. EP325279A1, 26 July 1989.

94. Okano, T.; Tsugawa, N.; Masuda, S.; Takeuchi, A.; Kobayashi, T.; Takita, Y.; Nishii, Y. Regulatory activities of 2β-(3-hydroxypropoxy)-1α,25-dihydroxy-vitamin D₃, a novel synthetic vitamin D₃ derivative, on calcium metabolism. *Biochem. Biophys. Res. Comm.* 1989, 163, 4072–4083. [CrossRef]

95. Eguchi, T.; Sai, H.; Takatsu, S.; Hara, N.; Ikekawa, N. Synthesis and biological activities of 22-hydroxy and 22-methoxy derivatives of 1α,25-dihydroxyvitamin D₃. *Bioorg. Chem.* 1989, 17, 294–307. [CrossRef]

96. Perlman, K.L.; DeLuca, H.F. Synthesis and biological activity of calcium and cell differentiation activities. *Biochem. Biophys. Res. Commun.* 1988, 163, 4072–4083. [CrossRef]
156. Sicinski, R.R.; Prahl, J.M.; Smith, C.M.; DeLuca, H.F. New 1α,25-dihydroxy-19-norvitamin D3 compounds of high biological activity: Synthesis and biological evaluation of 2-hydroxymethyl, 2-methyl, and 2-methylene analogues. *J. Med. Chem.* 1998, 41, 4662–4674. [CrossRef] [PubMed]

157. Posner, G.H.; Lee, J.K.; Wang, Q.; Peleg, S.; Burke, M.; Brem, H.; Dolan, P.; Kensler, T.W. Noncalcemic, antiproliferative, transcriptionally active, 24-fluorinated hybrid analogues of the hormone 1α,25-dihydroxyvitamin D3. Synthesis and preliminary biological evaluation. *J. Med. Chem.* 1998, 41, 3008–3014. [CrossRef] [PubMed]

158. Posner, G.H.; Wang, Q.; Han, G.; Lee, J.K.; Crawford, K.; Zand, S.; Brem, H.; Peleg, S.; Dolan, P.; Kensler, T.W. Conceptually new sulfone analogues of the hormone 1α,25-dihydroxyvitamin D3: Synthesis and preliminary biological evaluation. *J. Med. Chem.* 1999, 42, 3425–3435. [CrossRef]

159. Odrzywolska, M.; Chodynski, M.; Zorgdrager, J.; Van de Velde, J.-P.; Kutner, A. Diasteroselective synthesis, binding affinity for vitamin D receptor, and chiral stationary phase chromatography of hydroxy analogs of 1α,25-dihydroxycholecalciferol and 25-hydroxycholecalciferol. *Chirality* 1999, 11, 701–706. [CrossRef]

160. Kawashima, H.; Hoshina, K.; Hashimoto, Y.; Takeshita, T.; Ishimoto, S.; Noguchi, T.; Ikekawa, N.; Morisaki, M.; Orimo, H. Biological activity of 1α,24-dihydroxycholecalciferol: A new synthetic analog of the hormonal form of vitamin D. *FEBS Lett.* 1977, 76, 177–181. [CrossRef]

161. Miura, D.; Manabe, K.; Gao, Q.; Norman, A.W.; Ishizuka, S. 1α,25-Dihydroxyvitamin D3-26,23-lactone analogs antagonize differentiation of human leukemia cells (HL-60 cells) but not of human acute promyelocytic leukemia cells (NB4 cells). *FEBS Lett.* 1999, 460, 297–302. [CrossRef]

162. Fujishima, T.; Konno, K.; Nakagawa, K.; Kurobe, M.; Okano, T.; Takayama, H. Efficient synthesis and biological evaluation of all A-ring diastereomers of 1α,25-dihydroxyvitamin D3 and its 20-epimer. *Bioorg. Med. Chem. Chem.* 2000, 8, 123–134. [CrossRef]

163. El Abdaimi, K.; Dion, N.; Papavasiliou, V.; Cardinal, P.-E.; Binderup, L.; Goltzman, D.; Ste-Marie, L.-G.; Kremer, R. The vitamin D receptor S353F mutation diminishes vitamin D-dependent gene expression. *FEBS Lett.* 2000, 477, 29–32. [CrossRef]

164. Colston, K.W.; Mackay, A.G.; James, S.Y.; Binderup, L.; Chander, S.; Coombes, R.C. EB1089: A new vitamin D analog that inhibits the growth of breast cancer cells in vitro and in vivo. *Biochem. Pharmacol.* 1999, 58, 2273–2280. [CrossRef]

165. Zhou, X.; Zhu, G.-D.; Van Haver, D.; Vandewalle, M.; De Clercq, P.; Binderup, L.; Goltzman, D.; Ste-Marie, L.-G.; Kremer, R. The vitamin D analogue EB1039 prevents skeletal metastasis and prolongs survival time in nude mice transplanted with human breast cancer cells. *Cancer Res.* 2000, 60, 4412–4418.

166. Rey, M.A.; Martínez-Pérez, J.A.; Fernández-Gacío, A.; Halles, K.; Fall, Y.; Mouririño, A. New synthetic strategies to vitamin D analogues modified at the side chain and D ring. Synthesis of 1α,25-dihydroxy-16-ene-vitamin D3 and C20 analogues. *J. Org. Chem.* 1999, 64, 3196–3206. [CrossRef]

167. Perez Sestelo, J.; Mouririño, A.; Sarandesdes, L.A. Design and synthesis of a 1α,25-dihydroxyvitamin D3 dimer as a potential chemical inducer of vitamin D receptor dimerization. *Org. Lett.* 1999, 1, 1005–1007. [CrossRef] [PubMed]

168. Hishata, J.; Kuroda, T.; Kubota, T.; Hishata, Y.; Uskokovic, M.; Tomoyasu, S.; Koeffler, H.P. 5,6-trans-16-ene-Vitamin D3: A New Class of Potent Inhibitors of Proliferation of Prostate, Breast, and Myeloid Leukemic Cells. *Cancer Res.* 1999, 59, 4023–4029. [PubMed]

169. Ikeda, M.; Takahashi, K.; Dan, A.; Koyama, K.; Kubota, K.; Tanaka, T.; Hayashi, M. Synthesis and biological evaluations of A-ring isomers of 26,26,27,27,27-hexafluoro-1α,25-dihydroxyvitamin D3 analogues, diastereomeric at C17 and C20. *J. Med. Chem.* 1999, 42, 3439–3456. [CrossRef] [PubMed]

170. Herdick, M.; Steinmeyer, A.; Calberg, C. Carboxylic ester antagonist of 1α,25-dihydroxyvitamin D3 show cell-specific actions. *Chem. Biol.* 2000, 7, 885–894. [CrossRef]

171. Bonasera, T.A.; Grue-Sørensen, G.; Ortu, G.; Binderup, E.; Bergström, M.; Björkling, F.; Längström, B. The synthesis of [26,26-14C]-dihydroxyvitamin D3, a tracer for positron emission tomography (PET). *Bioorg. Med. Chem. Chem.* 2001, 9, 3123–3128. [CrossRef]

172. Gabriëls, S.; Van Haver, D.; Vandewalle, M.; De Clercq, P.; Verstuyf, A.; Bouillon, R. Development of analogues of 1α,25-dihydroxyvitamin D3 with bisected side chain orientation: Methylated des-CD-homo analogues. *Chem. Eur. J.* 2001, 7, 520–532. [CrossRef]

173. Calverley, M. Novel side chain analogs of 1α,25-dihydroxyvitamin D3: Design and synthesis of the 21,24-methano derivatives. *Steroids* 2001, 66, 249–255. [CrossRef]
179. Fujishima, T.; Zhaopeng, L.; Konno, K.; Nakagawa, K.; Okano, T.; Yamaguchi, K.; Takayama, H. Highly potent cell differentiation-inducing analogues of 1α,25-dihydroxyvitamin D3: Synthesis and biological activity of 2-methyl-1α,25-dihydroxyvitamin D3 with side-chain modifications. *Bioorg. Med. Chem.* 2001, 9, 525–533. [CrossRef]

180. Kamao, M.; Tatametsu, S.; Reddy, G.S.; Hatakeyama, S.; Sugiuira, M.; Ohashi, N.; Kubodera, N.; Okano, T. Isolation, identification and biological activity of 24,25-dihydroxy-3-epi-vitamin D3, a novel metabolite of 24R,25-dihydroxyvitamin D3 produced in rat osteosarcoma (UMR 106). *J. Nutr. Sci. Vitaminol.* 2001, 47, 108–115. [CrossRef] [PubMed]

181. Ishizuka, I.; Miura, D.; Ozono, K.; Saito, M.; Eguchi, H.; Chokkii, M.; Norman, A.W. (23S)- and (23R)-25-Dehydro-1α-hydroxyvitamin D3-26,23-lactone function as antagonist of vitamin D receptor-mediated genomic actions of 1α,25-dihydroxyvitamin D3. *Steroids* 2001, 66, 227–237. [CrossRef]

182. Steinmeyer, A.; Schwarz, K.; Haberey, M.; Langer, G.; Wiesinger, H. Synthesis and biological activities of a new series of secosteroids: Vitamin D phosphonate hybrids. *Steroids* 2001, 66, 257–266. [CrossRef]

183. White, M.C.; Burke, M.D.; Peleg, S.; Brem, H.; Posner, G.H. Conformationally restricted hybrid analogues of the hormone of 1α,25-dihydroxyvitamin D3: Design, synthesis and biological evaluation. *Bioorg. Med. Chem. Lett.* 2001, 9, 1661–1669. [CrossRef]

184. Mäenpää, P.H.; Väisänen, S.; Jääskeläinen, T.; Ryyhänens, T.; Rouvinen, J.; Duchier, C.; Mahonen, A. Vitamin D3 analogs (MD 1288, KH 1060, EB 1089, GS 1558, and CD 1093): Studies on their mechanism of action. *Steroids* 2001, 66, 223–225. [CrossRef]

185. Hatakeyama, S.; Kawase, A.; Uchiyama, Y.; Maeyama, J.; Iwabuchi, Y., Kubodera, N. Synthesis and biological characterization of 1α,24,25-trihydroxy-2β-(3-hydroxypropoxy)vitamin D3 (24-hydroxylated ED-71). *Steroids* 2001, 66, 267–276. [CrossRef]

186. Takayama, H.; Konno, K.; Fujishima, T.; Maki, S.; Liu, Z.; Miura, D.; Chokkii, M.; Ishizuka, S.; Smith, C.; DeLuca, H.F.; et al. Systematic studies on synthesis, structural elucidation and biological evaluation of A-ring diastereomers of 2-methyl-1α,25-dihydroxyvitamin D3 and 20-epi-25-methyl-1α,25-dihydroxyvitamin D3. *Steroids* 2001, 66, 277–285. [CrossRef]

187. Schuster, I.; Egger, H.; Astecker, N.; Herzig, G.; Schüsler, M.; Vorisek, G. Selective inhibitors of CYP24: Mechanistic tools to explore vitamin D metabolism in human keratinocytes. *Steroids* 2001, 66, 451–462. [CrossRef]

188. Bury, Y.; Herdick, M.; Uskokovic, M.R.; Calberg, C. Gene regulatory potential of 1α,25-dihydroxyvitamin D3 analogues with two side chains. *J. Cell Biochem.* 2001, Suppl. 36, 179–190. [CrossRef]

189. Nakagawa, K.; Sowa, Y.; Kurobe, M.; Ozono, K.; Siu-Caldera, M.-L.; Reddy, G.S.; Uskokovic, M.R.; Okano, T. Differential activities of 1α,25-dihydroxy-16-ene-vitamin D3 analogues and their 3-epimers on human promyelocytic leukemia (HL-60) cell differentiation and apoptosis. *Steroids* 2001, 66, 327–337. [CrossRef]

190. Fall, Y.; Fernández, C.; González, V.; Mourriño, A. Stereoselective synthesis of (22R)- and (22S)-25-methyl-1α,25-dihydroxyvitamin D3. *Synlett* 2001, 1567–1568. [CrossRef]

191. Hilpert, H.; Wirz, B. Novel versatile approach to an enantiopure 19-nor,des-CD vitamin D3 derivative. *Tetrahedron* 2001, 57, 681–694. [CrossRef]

192. Posner, G.H.; Woodard, B.T.; Crawford, K.R.; Peleg, S.; Brown, A.J.; Dolan, P.; Kessler, T.W. 2,2-Disubstituted analogues of the natural hormone 1α,25-dihydroxyvitamin D3: Chemistry and biology. *Bioorg. Med. Chem. Lett.* 2002, 10, 2353–2365. [CrossRef]

193. Fall, Y.; Barreiro, C.; Fernández, C.; Mourriño, A. Vitamin D heterocyclic analogues. Part 1: A stereoselective route to CD systems with pyrazole rings on their side chains. *Tet. Lett.* 2002, 43, 1433–1436. [CrossRef]

194. Fernández-Gacio, A.; Mourriño, A. Studies on the introduction of a photoreactive arylidiazirine group into the vitamin D skeleton. *Eur. J. Org. Chem.* 2002, 2529–2534. [CrossRef]

195. Pérez-Sestelo, J.; de Uña, O.; Mourriño, A.; Sarandeses, L.A. Synthesis of the first 24-amino-vitamin D3 derivatives by diastereoselective conjugate addition to a chiral methylmethoxaloxidinone in aqueous media. *Synlett* 2002, 719–722. [CrossRef]

196. Suhara, Y.; Kittaka, A.; Kishimoto, S.; Calverley, M.J.; Fujishima, T.; Saito, N.; Sugiiura, T.; Waku, K.; Takayama, H. Synthesis and testing of 2α-modified 1α,25-dihydroxyvitamin D3 analogues with a double side chain: Marked cell differentiation activity. *Bioorg. Med. Chem. Lett.* 2002, 12, 3255–3258. [CrossRef]

197. Wu, Y.; Sabbe, K.; De Clercq, P.; Vandewalle, M.; Bouillon, R.; Verstuyf, A. Vitamin D3 Synthesis of seco C-9,11,21-trisnor-17-methyl-1α,25-dihydroxyvitamin D3 analogues. *Bioorg. Med. Chem. Lett.* 2002, 12, 1629–1632. [CrossRef]

198. Wu, Y.; De Clercq, P.; Vandewalle, M.; Bouillon, R.; Verstuyf, A. Vitamin D3 Synthesis of seco C-9,11-bisnor-17-methyl-1α,25-dihydroxy vitamin D3 analogues. *Bioorg. Med. Chem. Lett.* 2002, 12, 1633–1636. [CrossRef]

199. Chodynski, M.; Wietrzyk, J.; Marcinkowska, E.; Opolski, A.; Szelejewski, W.; Kutner, A. Synthesis and antiproliferative activity of side-chain unsaturated and homologated analogs of 1α,25-dihydroxyvitamin D3 (24E)-(1S)-24-dehydro-24a-homo-1,25-dihydroxyergocalciferol and congeners. *Steroids* 2002, 67, 789–798. [CrossRef]

200. Varela, C.; Nilsson, K.; Torneiro, M.; Mourriño, A. Synthesis of tetracyclic analogues of calcitriol (1α,25-dihydroxyvitamin D3) with side-chain-locked spatial orientations at C(20). *Helv. Chim. Acta* 2002, 85, 3251–3261. [CrossRef]

201. Cornella, I.; Pérez-Sestelo, J.; Mourriño, A.; Sarandeses, L.A. Synthesis of 18-substituted analogues of calcitriol using photochemical remote functionalization. *J. Org. Chem.* 2002, 67, 4707–4714. [CrossRef]

202. Okamura, W.H.; Zhu, G.-D.; Hill, D.K.; Thomas, R.J.; Ringe, K.; Borchardt, D.B.; Norman, A.W.; Mueller, L.J. Synthesis and NMR studies of 15α-labeled vitamin D metabolites. *J. Org. Chem.* 2002, 67, 1637–1650. [CrossRef]

203. Brandl, M.; Wu, X.; Liu, Y.; Pease, J.; Holper, M.; Hooijmaaijer, E.; Lu, Y.; Wu, P. Chemical reactivity of Ro-26-9228, 1α-fluoro-25-hydroxy-10,23E-diene-26,27-bisnor-20-epi-cholecalciferol in aqueous solution. *J. Pharm. Sci.* 2003, 92, 1981–1989. [CrossRef]

204. Swann, S.L.; Bergh, J.; Farach-Carson, M.C.; Ocasio, C.A.; Koh, J.T. Structure-Based design of selective agonists for a rickets-associated mutant of the vitamin D receptor. *J. Am. Chem. Soc.* 2002, 124, 13795–13805. [CrossRef]
205. Fujishima, T.; Kojima, Y.; Azumaya, I.; Kikkawa, A.; Takayama, H. Design and synthesis of potent vitamin D receptor antagonists with A-ring modifications: Remarkable effects of 2α-methyl introduction an antagonist activity. *Bioorg. Med. Chem. 2003, 11*, 3621–3631. [CrossRef]

206. Honzawa, S.; Suhara, Y.; Nihei, K.-I.; Saito, N.; Kishimoto, S.; Fujishima, T.; Kurihara, M.; Sugiura, T.; Waku, K.; Takayama, H.; et al. Concise synthesis and biological activities of 2α-alkyl and 2α-(ω-hydroxyalkyl)-20-epi-1α,25-dihydroxyvitamin D3. *Bioorg. Med. Chem. Lett. 2003, 13*, 3903–3906. [CrossRef]

207. Verlinden, L.; Verstuyf, A.; Verboven, C.; Eelen, G.; De Ranter, C.; Gao, L.-J.; Chen, Y.-J.; Murad, I.; Choi, M.; Yamamoto, K.; et al. Precursors D3 with a trans-fused decalin CD-ring has pronounced genomic activity. *J. Biol. Chem. 2003, 278*, 35476–35482. [CrossRef] [PubMed]

208. Hanazawa, T.; Koyama, A.; Nakata, K.; Okamoto, S.; Sato, F. New convergent synthesis of 1α,25-dihydroxyvitamin D3 and its analogues by Suzuki-Miyaura coupling between A-ring and C,D-ring parts. *J. Org. Chem. 2003, 68*, 9767–9772. [CrossRef] [PubMed]

209. Blæhr, L.K.A.; Björkling, F.; Calverley, M.J.; Binderup, E.; Begtrup, M. Synthesis of novel hapten derivatives of 1α,25-dihydroxyvitamin D3 and its analogues by Suzuki-Miyaura coupling between A-ring and C,D-ring parts. *J. Org. Chem. 2003, 68*, 1367–1375. [CrossRef]

210. Ono, K.; Yoshida, A.; Saito, N.; Fujishima, T.; Honzawa, S.; Suhara, Y.; Kishimoto, S.; Sugiura, T.; Waku, K.; Takayama, H.; et al. Efficient synthesis of 2-modified 1α,25-dihydroxy-19-norvitamin D3 with Julia olefination: High potency in induction of the differentiation on HL-60 cells. *J. Org. Chem. 2003, 68*, 7407–7415. [CrossRef]

211. Kato, H.; Hashimoto, Y.; Nagasawa, K. Novel heteroatom-containing vitamin D3 analogs: Efficient synthesis of 1α,25-dihydroxyvitamin D3-26,23-lactam. *Molecules 2003, 8*, 488–499. [CrossRef]

212. Chen, Y.-J.; Gao, L.-J.; Murad, I.; Verstuyf, A.; Verlinden, L.; Verboven, C.; Bouillon, R.; Viterbo, D.; Van Haver, D.; Vandewalle, M.; et al. Synthesis, biological activity, and conformational analysis of CD-ring modified trans-decalin 1α,25-dihydroxyvitamin D3 analogs. *Org. Biomol. Chem. 2003, 1*, 257–267. [CrossRef]

213. Fujishima, T.; Kikuta, A.; Yamaoka, K.; Takeyama, K.; Kato, S.; Takayama, H. Synthesis of 2,2-dimethyl-1α,25-dihydroxyvitamin D3: A-ring structural motif that modulates interactions of vitamin D receptor with transcriptional activators. *Org. Biomol. Chem. 2003, 1*, 1863–1869. [CrossRef]

214. González-Avión, X.C.; Mourriño, A. Functionalization at C-12 of 1α,25-dihydroxyvitamin D3 strongly modulates the affinity for the vitamin D receptor (VDR). *Org. Lett. 2003*, 5, 2291–2293. [CrossRef]

215. Pérez-García, X.; Runbo, A.; Larriba, M.J.; Ordóñez, P.; Muñoz, A.; Mourriño, A. The first locked side-chain analogues of calcitriol (1α,25-dihydroxyvitamin D3) induce vitamin D receptor transcriptional activity. *Org. Lett. 2003*, 5, 4033–4036. [CrossRef] [PubMed]

216. Saito, N.; Matsunaga, T.; Fujishima, T.; Anzai, M.; Saito, H.; Takenouchi, K.; Miura, D.; Takayama, H.; Kikkawa, A. Remarkable effect of 2α-modification on the VDR antagonistic activity of 1α-hydroxyvitamin D3-26,23-lactones. *Org. Biomol. Chem. 2003, 1*, 4396–4402. [CrossRef] [PubMed]

217. Saito, N.; Suhara, Y.; Kurihara, M.; Fujishima, T.; Honzawa, S.; Suhara, Y.; Kishimoto, S.; Sugiura, T.; Waku, K.; Takayama, H.; et al. Precursors D3 with a trans-fused decalin CD-ring has pronounced genomic activity. *Bioorg. Med. Chem. Lett. 2003*, 13, 3903–3906. [CrossRef]

218. Schepens, W.; Van Haver, D.; Vandewalle, M.; De Clercq, P.; Bouillon, R.; Verstuyf, A. Synthesis and biological activity of 22-oxa-20-epimers with HL-60 cell differentiation activity. *J. Biol. Chem. 2003, 278*, 35476–35482. [CrossRef] [PubMed]

219. Kato, H.; Nakano, Y.; Sano, H.; Tanatani, A.; Kobayashi, H.; Shimazawa, R.; Koshino, H.; Hashimoto, Y.; Nagasawa, K. Synthesis of 1α,25-dihydroxyvitamin D3-26,23-lactams, a novel series of 1α,25-dihydroxyvitamin D3 antagonist. *Bioorg. Med. Chem. Lett. 2004, 14*, 2579–2583. [CrossRef] [PubMed]

220. Maehr, H.; Uskokovic, M.R. Formal desymmetrization of the diastereotopic chains in Gemini calcitriol derivatives with two different side chains at C-20. *Eur. J. Org. Chem. 2004*, 1703–1713. [CrossRef]

221. Takenouchi, K.; Sogawa, R.; Manabe, K.; Saitoh, H.; Gao, Q.; Miura, D.; Ishizuka, S. Synthesis and structure-activity relationships of TIE-9647 derivatives as vitamin D3 antagonists. *J. St. Biochem. Mol. Biol. 2004*, 89–90, 31–34. [CrossRef]

222. Schepens, W.; Van Haver, D.; Vandewalle, M.; De Clercq, P.; Bouillon, R.; Verstuyf, A. Synthesis and biological activity of 22-oxa CD-modified analogues of 1α,25-dihydroxyvitamin D3: Spiro[5,5]-undecane CF-ring analogues. *Bioorg. Med. Chem. Lett. 2004*, 14, 3889–3892. [CrossRef] [PubMed]

223. Maehr, H.; Uskokovic, M.R.; Adorini, L.; Reddy, G.S. Calcitriol derivatives with two different side chains at C20. II. Diastereoselective synthesis of the metabolically produced 24(R)-Gemini. *J. Med. Chem. 2004, 47*, 6476–6484. [CrossRef]

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

225. Saito, N.; Suhara, Y.; Kurihara, M.; Fujishima, T.; Honzawa, S.; Takayanagi, H.; Kozono, T.; Matsumoto, M.; Ohmori, M.; Miyata, N.; et al. Design and efficient synthesis of 2α-(ω-hydroxyalkyl)-1α,25-dihydroxyvitamin D3 analogues, including 2-epi-ED-71 and their 20-epimers with HL-60 cell differentiation activity. *J. Org. Chem. 2004, 69*, 7463–7471. [CrossRef] [PubMed]

226. Wu, S.-Y.; de Kecker, S.A.; Masjedizadeh, M.R. [3H] and [14C]-Ro2075646, a vitamin D analog. *Synth. Appl. Isot. Labl. Comp. 2004, 8*, 203–206. [CrossRef] [PubMed]
227. Posner, G.H.; Tony Lee, S.H.; Kim, H.J.; Peleg, S.; Dolan, P.; Kensler, T.W. Novel A-ring analogs of the hormone 1α,25-dihydroxyvitamin D₃: Synthesis and preliminary biological evaluation. *Bioorg. Med. Chem.* 2005, 13, 2959–2966. [CrossRef] [PubMed]

228. Hatcher, M.A.; Peleg, S.; Dolan, P.; Kensler, T.W.; Sarjeant, A.; Posner, G.H. A-ring hydroxymethyl 19-nor analogs of the natural hormone 1α,25-dihydroxyvitamin D₃: Synthesis and preliminary biological evaluation. *Bioorg. Med. Chem.* 2005, 13, 3964–3976. [CrossRef]

229. Gómez-Reino, C.; Vitale, C.; Maestro, M.; Mouriño, A. Pd-Catalyzed carbocyclization-Negishi cross-coupling cascade: A novel approach to 1α,25-dihydroxyvitamin D₃ and analogues. *Org. Lett.* 2005, 7, 5885–5887. [CrossRef]

230. Shimizu, M.; Miyamoto, Y.; Kobayashi, E.; Shimazaki, M.; Yamamoto, K.; Reischl, W.; Yamada, S. Synthesis and biological activities of new 1α,25-dihydroxy-19-norvitamin D₃ analogs with modifications in both A-ring and the side chain. *Bioorg. Med. Chem.* 2006, 14, 4277–4294. [CrossRef]

231. Shimizu, K.; Kawase, A.; Haneishi, T.; Kato, Y.; Kinoshita, K.; Ohmori, M.; Furuta, Y.; Emura, T.; Kato, N.; Mitsui, T.; et al. Design and evaluation of new antipsoriatic antedrug candidates having 16-en-22-oxa-vitamin D₃ structures. *Bioorg. Med. Chem. Lett.* 2006, 16, 3323–3329. [CrossRef]

232. Hatakeyama, S.; Nahashima, S.; Imai, N.; Takahashi, K.; Ishihara, J.; Sugita, A.; Nihei, T.; Saito, H.; Takahashi, F.; Kubodera, N. Synthesis and biological evaluation of a 3-position diastereomer of 1α,25-dihydroxy-2β-(3-hydroxyprooxy)vitamin D₃ (ED-71). *Bioorg. Med. Chem.* 2006, 14, 8050–8056. [CrossRef]

233. Uskokovic, M.R.; Manchand, P.; Marezak, S.; Maehr, H.; Jankowski, P.; Adorini, L.; Reddy, G.S. C-20 Cyclopropyl vitamin D analogs. *Curr. Top. Med. Chem.* 2006, 6, 1289–1296. [CrossRef]

234. Oves, D.; Fernández, S.; Verlinden, L.; Bouillon, R.; Verstuyf, A.; Ferrero, M.; Gotor, V. Novel A-ring homodimeric C-3-carbamate analogues of 1α,25-dihydroxyvitamin D₃: Synthesis and preliminary biological evaluation. *Bioorg. Med. Chem.* 2006, 14, 7512–7519. [CrossRef]

235. Hosoda, S.; Tanatani, A.; Wakabayashi, K.-i.; Makishima, M.; Imai, K.; Miyachi, H.; Nagasawa, K.; Hashimoto, Y. Ligands with a 3,3-diphenylpentane skeleton for nuclear vitamin D and androgen receptors: Dual activities and metabolic activation. *Bioorg. Med. Chem.* 2006, 14, 5489–5502. [CrossRef] [PubMed]

236. Schuster, I.; Egger, H.; Nussbaumer, P.; Kroemer, T. Inhibitors of vitamin D hydroxylases: Structure-activity relationships. *J. Cell. Biochem.* 2003, 88, 372–380. [CrossRef] [PubMed]

237. Peleg, S.; Petersen, K.S.; Suh, B.C.; Dolan, P.; Agoston, E.S.; Kensler, T.W.; Posner, G.H. Low-calcemic, antiproliferative, 1-difluoromethyl hybrid analogs of the hormone 1α,25-dihydroxyvitamin D₃: Design, synthesis and preliminary biological evaluation. *J. Med. Chem.* 2006, 49, 7513–7517. [CrossRef] [PubMed]

238. Oves, D.; Fernández, S.; Verlinden, L.; Bouillon, R.; Verstuyf, A.; De Clercq, P. Synthesis of spiro[4,5]-decane CF-ring analogues of 1α,25-dihydroxyvitamin D₃. *Org. Lett.* 2006, 8, 4247–4250. [CrossRef]

239. Ono, Y.; Watanabe, H.; Taira, I.; Takahashi, K.; Ishihara, J.; Hatakeyama, S.; Kubodera, N. Synthesis of putative metabolites of 1α,25-dihydroxyvitamin D₃ and analogues. *Steroids* 2006, 71, 529–540. [CrossRef]

240. Riveiros, R.; Rumber, A.; Sarandeses, L.A.; Mouriño, A. Synthesis and conformational analysis of 17α,21-cyclo-22-unsaturated analogues of calcitriol. *J. Org. Chem.* 2007, 72, 5477–5485. [CrossRef]

241. Yamamoto, K.; Abe, D.; Yoshimoto, N.; Choi, M.; Yamagishi, K.; Tokiwa, H.; Shimizu, M.; Makishima, M.; Yamada, S. Vitamin D receptor: Ligand recognition and allosteric network. *J. Med. Chem.* 2006, 49, 1313–1324. [CrossRef]

242. Lee, H.J.; Wislocki, A.; Goodman, C.; Ji, Y.; Ge, R.; Maehr, H.; Uskokovic, M.R.; Reiss, M.; Suh, N. A vitamin D derivative activates bone morphogenetic protein signaling in MCF10 breast epithelial cells. *Mol. Pharm.* 2006, 69, 1840–1848. [CrossRef]

243. Yoshimoto, N.; Inaba, Y.; Yamada, S.; Makishima, M.; Shimizu, M.; Yamamoto, K. 2-Methylene-19-nor-25-dehydro-1α-hydroxyvitamin D₃-26,23-lactones; synthesis, biological activities and molecular basis of passive antagonism. *Bioorg. Med. Chem.* 2006, 14, 457–473. [CrossRef]

244. Saito, N.; Matsunaga, T.; Saito, H.; Anzai, M.; Takenouchi, K.; Miura, D.; Namekawa, J.-i.; Ishizuka, S.; Kitaka, A. Further synthetic and biological studies on vitamin D hormone antagonist based on C24-alkylation and C2α-functionalization of 25-dehydro-1α-hydroxyvitamin D₃-26,23-lactones. *J. Med. Chem.* 2006, 49, 7063–7075. [CrossRef] [PubMed]

245. González-Aviñón, X.C.; Mouriño, A.; Rochel, N.; Moras, D. Novel 1α,25-dihydroxyvitamin D₃ analogs with side chain at C12. *J. Med. Chem.* 2006, 49, 1509–1516. [CrossRef] [PubMed]

246. Maeher, H.; Uskokovic, M.R.; Adorini, L.; Penna, G.; Mariani, R.; Panina, P.; Passini, N.; Bono, E.; Perego, S.; Biffi, M.; et al. Calcitriol derivatives with two different side chains at C20. III. An epimeric pair of the Gemini family with unprecedented antiproliferative effects on tumor cells and renin mRNA expression inhibition. *J. St. Biochem. Mol. Biol.* 2007, 103, 277–281. [CrossRef]

247. Garay, E.; Jankowski, P.; Lizano, P.; Marczak, S.; Maeher, H.; Adorini, L.; Uskokovic, M.R.; Studzinski, G.P. Calcitriol derivatives with two different side chains at C20. Part 4. Further side chain modifications that alter VDR-dependent monocyte differentiation potency inhuman leukemia cells. *Bioorg. Med. Chem.* 2007, 15, 4444–4455. [CrossRef] [PubMed]

248. Yamamoto, K.; Inaba, Y.; Yoshimoto, N.; Choi, M.; DeLuca, H.F.; Yamada, S. 22-Alkyl-20-epi-1α,25-dihydroxyvitamin D₃ compounds of superagonistic activity: Syntheses, biological activities and interaction with the receptor. *J. Med. Chem.* 2007, 50, 932–939. [CrossRef] [PubMed]
249. Gregorio, C.; Eduardo, S.; Rodrigues, L.C.; Regueira, M.; Fraga, R.; Riveiros, R.; Maestro, M.; Mouriño, A. Synthesis of two carboxylic haptenes for raising antibodies to 25-hydroxyvitamin D3 and 1α,25-dihydroxyvitamin D3. J. St. Biochem. Mol. Biol. 2007, 103, 227–230. [CrossRef] [PubMed]

250. Glebocka, A.; Sicinski, R.R.; Plum, L.A.; DeLuca, H.F. 2-(3′-Hydroxypropyldiene)-1α-hydroxy-19-norvitamin D compounds with truncated side chain. J. St. Biochem. Mol. Biol. 2007, 103, 310–315. [CrossRef]

251. Kobayashi, E.; Shimazaki, M.; Miyamoto, Y.; Yamamoto, K.; DeLuca, H.F.; Yamada, S.; Shimizu, M. Structure-activity relationships of 19-norvitamin D analogs having a fluoroethylene group at the C-2 position. Bioorg. Med. Chem. 2007, 15, 1475–1482. [CrossRef]

252. Inaba, Y.; Yamamoto, K.; Yoshimoto, N.; Matsunawa, M.; Uno, S.; Yamada, S.; Makishima, M. Vitamin D3 derivatives with adamantane or lactone ring side chains are cell type-selective vitamin D receptor modulators. Mol. Pharm. 2007, 71, 1298–1311. [CrossRef]

253. Chiellini, G.; Grzywack, P.; Plum, L.A.; Barycki, R.; Claggett-Dame, M.; DeLuca, H.F. Synthesis and biological properties of 2-methylene-19-nor-25-dehydro-1α-hydroxyvitamin D3,26,26-lactones-weak agonists. Bioorg. Med. Chem. 2008, 16, 8563–8573. [CrossRef]

254. Takaku, H.; Miyamoto, Y.; Asami, S.; Shimazaki, M.; Yamada, S.; Yamamoto, K.; Udagawa, N.; DeLuca, H.F.; Shimizu, M. Synthesis and structure-activity relationships of 16-ene-22-thia-1α,25-dihydroxy-26,27-dimethyl-19-norvitamin D3 analogs having side chains of different sizes. Bioorg. Med. Chem. 2008, 16, 1796–1815. [CrossRef]

255. Shimizu, M.; Miyamoto, Y.; Takaku, H.; Matsuou, M.; Nakabayashi, M.; Masuno, H.; Udagawa, N.; DeLuca, H.F.; Ikura, T.; Ito, N. 2-Substituted-16-ene-22-thia-1α,25-dihydroxy-26,27-dimethyl-19-norvitamin D3 analogs: Synthesis, biological evaluation and crystal structure. Bioorg. Med. Chem. 2008, 16, 6949–6964. [CrossRef] [PubMed]

256. Sánchez-Abella, L.; Fernández, S.; Verstuyf, A.; Verlinden, L.; Gotor, V. Synthesis and biological activity of previtamin D3 analogues with A-ring modifications. Bioorg. Med. Chem. 2008, 16, 10244–10250. [CrossRef] [PubMed]

257. Nakabayashi, M.; Yamada, S.; Yoshimoto, N.; Tanaka, T.; Igarashi, M.; Ikura, T.; Ito, N.; Makishima, M.; Tokiwa, H.; DeLuca, H.F.; et al. Crystal structures of rat vitamin D receptor bound to adamantyl vitamin D3 analogs: Structural basis for vitamin D receptor antagonism and partial agonism. J. Med. Chem. 2008, 51, 5320–5329. [CrossRef] [PubMed]

258. Hourai, S.; Rodrigues, L.C.; Antony, P.; Reina-San-Martin, B.; Ciesielski, F.; Magnier, B.C.; Schoonjans, K.; Mouriño, A.; Rochel, N.; Moras, D. Structure-based design of a superagonist ligand for the vitamin D nuclear receptor. Chem. Biol. 2008, 15, 383–392. [CrossRef] [PubMed]

259. Saito, T.; Okamoto, R.; Haritunians, T.; O’Kelly, J.; Uskokovic, M.; Maehr, H.; Marczak, S.; Jankowski, P.; Badr, R.; Koeffler, H.P. Novel Gemini vitamin D3 analogs have potent antitumor activity. J. St. Biochem. Mol. Biol. 2008, 112, 151–156. [CrossRef] [PubMed]

260. Williams, K.B.; DeLuca, H.F. 2-Methylene-19-nor-25-dehydro-1α-hydroxybispregnacalciferol [(20S)-2MbisP], an analog of vitamin D3 [1,25(OH)2D3], does not stimulate intestinal phosphate absorption at levels previously shown to suppress parathyroid hormone. Steroids 2008, 73, 1277–1284. [CrossRef]

261. Usera, A.R.; Dolan, P.; Kensler, T.W.; Posner, G.H. Novel alkyl chain sulfone 1α,25-dihydroxyvitamin D3 analogs: A comparison of in vitro antiproliferative and in vivo calcemic activities. Bioorg. Med. Chem. 2009, 17, 5627–5631. [CrossRef]

262. Plonska-Ocypa, K.; Sicinski, R.R.; Plum, L.A.; Grzywacz, P.; Frelek, J.; Claggett-Dame, M.; DeLuca, H.F. 13-Methyl-substituted des-CD analogs of (20S)-1α,25-dihydroxy-2-methylene-19-norvitamin D3 (2MD): Synthesis and biological evaluation. Bioorg. Med. Chem. 2009, 17, 1477–1483. [CrossRef]

263. Barycki, R.; Sicinski, R.R.; Plum, L.A.; Grzywacz, P.; Claggett-Dame, M.; DeLuca, H.F. Removal of the 20-methyl group from 2-methylene-19-nor-(2S)-1α-hydroxyvitamin D3 (2MD) selectively eliminates bone calcium mobilization activity. Bioorg. Med. Chem. 2009, 17, 7658–7669. [CrossRef]

264. Inaba, Y.; Yoshimoto, N.; Sakamaki, N.; Nakabayashi, T.; Ikura, T.; Tamamura, H.; Ito, N.; Shimizu, M.; Yamamoto, K. A new class of vitamin D analogues that induce structural rearrangement of the ligand-binding pocket of the receptor. J. Med. Chem. 2009, 52, 1438–1449. [CrossRef] [PubMed]

265. Laverty, G.; Penna, G.; Uskokovic, M.; Marczak, S.; Maehr, H.; Jankowski, P.; Ceailles, C.; Vouros, P.; Smith, B.; Robinson, M.; et al. Synthesis and anti-inflammatory properties of 1α,25-dihydroxy-16-ene-20-cyclopoly-24-oxovitamin D3, a hypocalcemic, stable metabolite of 1α,25-dihydroxy-16-ene-20-cyclopolyvitamin D3. J. Med. Chem. 2009, 52, 2204–2213. [CrossRef] [PubMed]

266. Sánchez-Abella, L.; Fernández, S.; Verstuyf, A.; Verlinden, L.; Gotor, V.; Ferrero, M. Synthesis, conformational analysis and biological evaluation of 19-nor-vitamin D3 analogues with A-ring modifications. J. Med. Chem. 2009, 52, 6158–6162. [CrossRef] [PubMed]

267. Minne, G.; Verlinden, L.; Verstuyf, A.; De Clercq, P.J. Synthesis of 1α,25-dihydroxyvitamin D analogues featuring a 2S2-symmetric CD-ring core. Molecules 2009, 14, 894–903. [CrossRef] [PubMed]

268. De Brysser, F.; Verlinden, L.; Verstuyf, A.; De Clercq, P.J. Synthesis of 22-oxaspiro[4.5]decane CD-ring modified analogs of 1α,25-dihydroxyvitamin D3. Tet. Lett. 2009, 50, 4174–4177. [CrossRef]

269. Gándara, Z.; Pérez, M.; Pérez-García, X.; Gómez, G.; Fall, Y. Stereoselective synthesis of (22Z)-25-hydroxyvitamin D2 and (22Z)-1α,25-dihydroxyvitamin D2. Tet. Lett. 2009, 50, 4874–4877. [CrossRef]
Gogoi, P.; Sigüeiro, R.; Eduardo, S.; Mouriño, A. An expeditious route to 1α-C-methyl analogue of 25-hydroxyvitamin D3: Interaction with the mutant vitamin D receptor Arg274Leu. *Tetrahedron* 2009, 65, 7135–7147. [CrossRef]

Ben Shabat, S.; Sintov, A. Substituted Cyclohexylidene-Ethyldiene-Octahydro-Indene Compounds. World Patent Organization. WO2009153782 A1, 23 December 2009.

Maehr, H.; Lee, H.J.; Perry, B.; Suh, N.; Uskokovic, M.R. Calcitriol derivatives with two different side chain at C-20. V. Potent inhibitors of mammary carcinogenesis and inducers of leukemia differentiation. *J. Med. Chem.* 2009, 52, 5505–5519. [CrossRef]

Gogoi, P.; Sigüeiro, R.; Eduardo, S.; Mouriño, A. An expeditious route to 1α,25-dihydroxyvitamin D3 and its analogues by an aqueous tandem palladium-catalyzed A-ring closure and Suzuki coupling to the C/D unit. *Chem. Eur. J.* 2010, 16, 1432–1435. [CrossRef]

Sakamaki, Y.; Inaba, Y.; Yoshimoto, N.; Yamamoto, K. Potent antagonist for the vitamin D receptor: Vitamin D analogues with simple side chain structure. *J. Med. Chem.* 2010, 53, 5813–5826. [CrossRef]

Yoshino, M.; Eto, K.; Takahashi, K.; Ishihara, J.; Hatakeyama, S.; Ono, Y.; Saito, H.; Kubodera, N. Synthesis of 20-epi-eldecalcitol [20-epi-1α,25-dihydroxy-2β-(3-hydroxypropoxy)vitamin D3: 20-epi-ED-71]. *Heterocycles* 2010, 81, 381–394. [CrossRef]

Grzywacz, P.; Chiellini, G.; Plum, L.A.; Clagett-Dame, M.; DeLuca, H.F. Removal of the 26-methyl group from 2-methylene-19-nor-1α,25-dihydroxyvitamin D3 markedly reduces in vivo calcemic activity without altering in vitro VDR binding. *HL-60 cell differentiation, and transcription*. *J. Med. Chem.* 2010, 53, 8642–8649. [CrossRef] [PubMed]

Antony, P.; Sigüeiro, R.; Huet, T.; Sato, Y.; Ramalanjaona, N.; Rodrigues, L.C.; Mourriño, A.; Rochel, N.; Moras, D. Structure-function relationships and crystal structures of the vitamin D receptor bound 2α-methyl-(20S,23R)- and 2α-methyl-(20S,23S)-epoxyethano-1α,25-dihydroxyvitamin D3. *J. Med. Chem.* 2010, 53, 1159–1171. [CrossRef] [PubMed]

Sawada, D.; Tsukuda, Y.; Saito, H.; Takagi, K.-i.; Ochiai, E.; Ishizuka, S.; Takenouchi, K.; Kittaka, A. Synthesis of 2β-substituted-14-epi-previtamin D3 and testing its genomic activity. *J. St. Biochem. Mol. Biol.* 2010, 121, 20–24. [CrossRef]

Sokolowska, K.; Mourriño, A.; Sicinski, R.R.; Sigüeiro, R.; Plum, L.A.; DeLuca, H.F. Synthesis and biological evaluation of 6-methyl analog of 1α,25-dihydroxyvitamin D3. *J. St. Biochem. Mol. Biol.* 2010, 121, 29–33. [CrossRef]

Glebocka, A.; Sicinski, R.R.; Plum, L.A.; DeLuca, H.F. New 1α,25-dihydroxy-19-nor-vitamin D3 analogs with frozen A-ring conformation. *J. St. Biochem. Mol. Biol.* 2010, 121, 46–50. [CrossRef]

Sibilska, I.; Barycka, K.M.; Sicinski, R.R.; Plum, L.A.; DeLuca, H.F. 1-Desoxy analog of 2MD: (20S)-25-hydroxy-2-methylene-19-nor-vitamin D3. *J. St. Biochem. Mol. Biol.* 2010, 121, 51–55. [CrossRef]

Sawada, D.; Katayama, T.; Tsukuda, Y.; Yamashita, A.; Saito, N.; Saito, H.; Takagi, K.-i.; Ochiai, E.; Ishizuka, S.; Takenouchi, K.; et al. Synthesis of 2α-nd β-2-substituted-14-epi-previtamin D3 and their genomic activity. *Tetrahedron* 2010, 66, 5407–5423. [CrossRef]

Glebocka, A.; Sicinski, R.R.; Plum, L.A.; DeLuca, H.F. Synthesis and biological activity of 2-3′(3-hydroxypropyldien)-1α-hydroxy-19-norvitamin D analogs with alkyl side chains. *J. Med. Chem.* 2011, 54, 6832–6842. [CrossRef]

Kashiwagi, H.; Ono, Y.; Shimizu, K.; Haneishi, T.; Ito, T.; Iijima, S.; Kobayashi, T.; Ichikawa, T.; Harada, S.; Sato, H.; et al. Novel nonsecosteroidal vitamin D3 carboxylic acid analogs for osteoporosis and SAR analysis. *Bioorg. Med. Chem.* 2011, 19, 4721–4729. [CrossRef]

Fujii, S.; Masuno, H.; Taoda, Y.; Kano, A.; Wongmayura, A.; Nakabayashi, M.; Ito, N.; Shimizu, M.; Kawachi, E.; Hirano, T.; et al. Boron cluster-based development of potent nonsecosteroidal vitamin D receptor ligands: Direct observation of hydrophobic interaction between protein surface and carborane. *J. Am. Chem. Soc.* 2011, 133, 20933–20941. [CrossRef] [PubMed]

Verlinden, L.; Verstuyf, A.; Eelen, G.; Bouillon, R.; Ordóñez-Morán, P.; Larriba, M.J.; Muñoz, A.; Rochel, N.; Sato, Y.; Moras, D.; et al. Synthesis, structure, and biological activity of des-side chain analogues of 1α,25-dihydroxyvitamin D3 with substituents at C18. *ChemMedChem* 2011, 6, 788–793. [CrossRef] [PubMed]

Sawada, D.; Tsukuda, Y.; Saito, H.; Takimoto-Kamimura, M.; Ochiai, E.; Ishizuka, S.; Takenouchi, K.; Kittaka, A. Development of 14-α-19-nortachysterol and its unprecedented binding configuration for the human vitamin D receptor. *J. Am. Chem. Soc.* 2011, 133, 7215–7221. [CrossRef] [PubMed]

Regueira, M.A.; Samanta, S.; Malloy, P.J.; Ordóñez-Morán, P.; Resende, D.; Sussman, F.; Muñoz, A.; Mourriño, A.; Feldman, D.; Torneiro, M. *Synthesis and biological evaluation of 1α,25-dihydroxyvitamin D3 analogues hydroxymethylated at C26. J. Med. Chem.* 2011, 54, 3950–3962. [CrossRef] [PubMed]

Salomón, D.G.; Grioli, S.M.; Buschiazzo, M.; Mascaro, E.; Vitale, C.; Radivoy, G.; Perez, M.; Fall, Y.; Mesri, E.A.; Curino, A.C.; et al. Novel alkynylphospate analogue of calcitriol with potent antiproliferative effects in cancer cells and lack of calcemic activity. *ACS Med. Chem. Lett.* 2011, 2, 503–508. [CrossRef] [PubMed]

Saito, H.; Chida, T.; Takagi, K.; Horie, K.; Sawai, Y.; Nakamura, Y.; Harada, Y.; Takenouchi, K.; Kittaka, A. Synthesis of C-2 substituted vitamin D derivatives having ringed side chains and their biological evaluation, especially biological effect on bone by modification at the C-2 position. *Org. Biomol. Chem.* 2011, 9, 3954–3964. [CrossRef]

Shindo, K.; Kumagai, G.; Takano, M.; Sawada, D.; Saito, N.; Saito, H.; Kakuda, S.; Takagi, K.-i.; Ochiai, E.; Horie, K.; et al. New C15-substituted active vitamin D3. *Org. Lett.* 2011, 13, 2852–2855. [CrossRef]
293. Molnár, F.; Siqueiro, R.; Sato, Y.; Araujo, C.; Schuster, I.; Antony, P.; Peluso, J.; Muller, C.; Mourino, A.; Moras, D.; et al. 1α,25-(OH)2-3-epi-vitamin D3, a natural metabolite of vitamin D3: Its synthesis, biological activity and crystal structure with its receptor. *PLoS ONE* 2011, 6, e19124. [CrossRef]

294. Wongmayura, A.; Fujii, S.; Ito, S.; Kano, A.; Taoda, Y.; Kawachi, E.; Kagechika, H.; Tanatani, A. Novel vitamin D receptor ligands bearing a spherical hydrophobic core structure-comparison of bicyclic hydrocarbon derivatives with boron cluster derivatives. *Bioorg. Med. Chem. Lett.* 2012, 22, 1756–1760. [CrossRef]

295. Fischer, J.; Wang, T.-T.; Kaldre, D.; Rochel, N.; Moras, D.; White, J.H.; Gleason, J.L. Synthetically accessible non-seco steroidal hybrid molecules combining vitamin D receptor agonism and histone deacetylase inhibition. *Chem. Biol.* 2012, 19, 963–971. [CrossRef]

296. Fraga, R.; Zacconi, F.; Sussman, F.; Ordóñez-Morán, P.; Muñoz, A.; Huet, T.; Molnar, F.; Moras, D.; Rochel, N.; Maestro, M.; et al. Design, synthesis, evaluation, and structure of vitamin D analogues with furan side chains. *Chem. Eur. J.* 2012, 18, 603–612. [CrossRef]

297. Sawada, D.; Tsukuda, Y.; Yasuda, K.; Sakaki, T.; Saito, H.; Takagi, K.-i.; Takenouchi, K.; Chen, T.C.; Reddy, G.S.; et al. A series of 1α,25-dihydroxy-22-methyl-2-methylene-19-norvitamin D analogues prepared from cyclohexadienyl sulfone. *Chem. Pharm. Bull.* 2012, 60, 1343–1346. [CrossRef] [PubMed]

298. Sikervar, V.; Fleet, J.C.; Fuchs, P.L. A general approach to the synthesis of enantiopure 19-nor-vitamin D3 and its C-2 phosphate analogs prepared from cyclohexadienyl sulfone. *Chem. Comm.* 2012, 48, 9077–9079. [CrossRef] [PubMed]

299. Carballa, D.M.; Rumbo, A.; Torneiro, M.; Maestro, M.; Mourino, A. Synthesis of (1α,25)-dihydroxyvitamin D3 with a β-positioned seven-carbon side chain at C12. *Heli. Chem. Acta* 2012, 95, 1842–1850. [CrossRef]

300. Flores, A.; Sicsinski, R.K.; Grzywacz, P.; Thoden, J.B.; Plum, L.A.; Clagett-Dame, M.; DeLuca, H.F. A 20S Combined with 22R configuration markedly increases both in vivo and in vitro biological activity of 1α,25-dihydroxy-22-methyl-2-methylene-19-norvitamin D3. *J. Med. Chem.* 2012, 55, 4352–4366. [CrossRef]

301. Carballa, D.M.; Seoane, S.; Zacconi, F.; Pérez, X.; Rumbo, A.; Álvarez-Díaz, S.; Larriba, M.J.; Pérez-Fernández, R.; Muñoz, A.; Maestro, M.; et al. Synthesis and biological evaluation of 1α,25-dihydroxyvitamin D3 analogues with a long side chain at C12 and short C17 side chains. *J. Med. Chem.* 2012, 55, 8642–8656. [CrossRef]

302. Lu, Y.; Chen, J.; Janjetovic, Z.; Michaels, P.; Tang, E.K.Y.; Wang, J.; Tuckey, R.; Slominski, A.T.; Li, W.; Miller, D.D. Design, synthesis, and biological activity of (20R)-hydroxysteroid D3. *J. Med. Chem.* 2012, 55, 3573–3577. [CrossRef]

303. Yoshimoto, N.; Sakamaki, Y.; Haeta, M.; Kato, A.; Inaba, Y.; Itoh, T.; Nakabayashi, M.; Itoh, N.; Yamamoto, K. Butyl pocket formation in the vitamin D3 receptor strongly affects the agonistic or antagonistic behavior of ligands. *J. Med. Chem.* 2012, 55, 4373–4381. [CrossRef]

304. Sikervar, V.; Fleet, J.C.; Fuchs, P.L. Fluoride-mediated elimination of allyl sulfones: Application to the synthesis of a 2,4-dimethyl-A-ring vitamin D3 analogue. *J. Org. Chem.* 2012, 77, 5132–5138. [CrossRef]

305. Ciesielski, F.; Sato, Y.; Chebaro, Y.; Moras, D.; Dejaegere, A.; Rochel, N. Structural basis for the accommodation of bis- and tris-aromatic derivatives in vitamin D nuclear receptor. *J. Med. Chem.* 2012, 55, 8440–8449. [CrossRef]

306. Chen, B.; Kawai, M.; Wu-Wong, R. Synthesis of VS-105: A novel and potent vitamin receptor agonist with reduced hypercalcemic effects. *Bioorg. Med. Chem. Lett.* 2012, 23, 5949–5952. [CrossRef] [PubMed]

307. Milczarek, M.; Chodynski, M.; Filip-Purska, B.; Martowicz, A.; Krup, M.; Krajewski, K.; Kutter, A.; Wietrzyk, J. Synthesis and biological activity of diastereomeric and geometric analogs of calcipotriol, PRI-2202 and PRI-2205, against human HL-60 leukemia and MCF-7 breast cancer cells. *Cancers* 2013, 5, 1355–1378. [CrossRef] [PubMed]

308. Kashiwagi, H.; Ono, Y.; Ohta, M.; Itoh, S.; Ichikawa, F.; Harada, S.; Takeda, S.; Sekiguchi, N.; Ishigai, M.; Takahashi, T. A series of nonseco steroidal vitamin D receptor agonists for osteoporosis therapy. *Bioorg. Med. Chem. 2013, 21, 1823–1833. [CrossRef] [PubMed]

309. Kashiwagi, H.; Ohta, M.; Ono, Y.; Morikami, K.; Itoh, S.; Sato, H.; Takahashi, T. Effects of fluorines on nonseco steroidal vitamin D receptor agonists. *Bioorg. Med. Chem. 2013, 21, 712–716. [CrossRef]

310. Sibilska, I.S.; Szybinski, M.; Sicinski, R.R.; Plum, L.A.; DeLuca, H.F. Highly potent 2-methylene analogs of 1α,25-dihydroxyvitamin D3: Synthesis and biological evaluation. *J. St. Biochem. Mol. Biol.* 2013, 36, 9–13. [CrossRef]

311. Sibilska, I.S.; Sicinski, R.R.; Plum, L.A.; DeLuca, H.F. Synthesis and biological activity of 25-hydroxy-2-methylene-vitamin D3 compounds. *J. St. Biochem. Mol. Biol.* 2013, 136, 17–22. [CrossRef]

312. Kulezka, U.; Mourino, A.; Plum, L.A.; DeLuca, H.F.; Sicinski, R.R. Synthesis of 19-norvitamin D3 analogs with unnatural triene system. *J. St. Biochem. Mol. Biol.* 2013, 136, 23–26. [CrossRef]

313. Sokolowska, K.; Sicinski, R.R.; Plum, L.A.; DeLuca, H.F.; Mourino, A. Synthesis and biological evaluation of novel 6-substituted analogs of 1α,25-dihydroxy-19-norvitamin D3. *J. St. Biochem. Mol. Biol.* 2013, 136, 30–33. [CrossRef]

314. Glebocka, A.; Sicinski, R.R.; Plum, L.A.; DeLuca, H.F. Ring-A-seco analogs of 1α,25-dihydroxy-19-norvitamin D3. *J. St. Biochem. Mol. Biol.* 2013, 136, 39–43. [CrossRef]

315. Yamada, S.; Makishima, M. Structure-activity relationship of nonseco steroidal vitamin D receptor modulators. *Trends Phar. Sci.* 2014, 35, 324–337. [CrossRef]

316. Ferla, S.; Aboraia, A.S.; Brancale, A.; Pepper, C.J.; Zhu, J.; Ochalek, J.T.; DeLuca, H.F.; Simons, C. Small-molecule inhibitors of 25-hydroxyvitamin D-24-hydroxylase (CYP24A1): Synthesis and biological evaluation. *J. Med. Chem.* 2014, 57, 7702–7715. [CrossRef] [PubMed]
340. Otero, R.; Seoane, S.; Sigüeiro, R.; Belorussova, A.Y.; Maestro, M.A.; Pérez-Fernández, R.; Rochel, N.; Mourriño, A. Carborane-based design of a potent vitamin D receptor agonist. Chem. Sci. 2016, 7, 1033–1037. [CrossRef] [PubMed]

341. Nijenhuis, T.; van der Eerden, B.; Zügel, U.; Steinmeyer, A.; Weins, H.; Hoenderop, J.G.J.; van Leeuwen, J.P.T.M.; Bindels, R.J.M. The novel vitamin D analog ZK191784 as an intestine-specific vitamin D antagonist. FEBS J. 2016, 20, 2171–2173. [CrossRef]

342. Lin, Z.; Marepally, S.R.; Ma, D.; Kim, T.-K.; Oak, A.S.W.; Myers, L.; Tuckey, R.C.; Slominski, A.T.; Miller, D.D.; Li, W. Synthesis and biological evaluation of vitamin D3 metabolite 20,23-dihydroxyvitamin D3 and its 23R epimer. J. Med. Chem. 2016, 59, 5102–5108. [CrossRef] [PubMed]

343. Vinhas, S.; Vinhas, C.; Rodríguez-Docampo, Z.; Zacconi, F.; Maestro, M.A.; Mourriño, A. Stereoselective synthesis of 1β,25-dihydroxyvitamin D3 and its 26,27-hexa-derated derivative. J. St. Biochem. Mol. Biol. 2016, 164, 56–58. [CrossRef]

344. Ahmad, M.I.; Raghuvanshi, D.S.; Singh, S.; John, A.A.; Prakash, R.; Nainwat, K.S.; Singh, D.; Tripathi, S.; Sharma, A.; Gupta, A. Design and synthesis of 3-arylbenzopyran based non-steroidal vitamin D3 mimics as osteogenic agents. Med. Chem. Commun. 2016, 7, 2381–2394. [CrossRef]

345. Ahmad, M.I.; Raghuvanshi, D.S.; Singh, S.; John, A.A.; Prakash, R.; Nainwat, K.S.; Singh, D.; Tripathi, S.; Sharma, A.; Gupta, A. Design and synthesis of 3-arylbenzopyran based non-steroidal vitamin D3 mimics as osteogenic agents. Med. Chem. Commun. 2016, 7, 2381–2394. [CrossRef]

346. Sawada, D.; Kakuda, S.; Kamimura-Takimoto, M.; Takeuchi, A.; Matsumoto, Y.; Kittaka, A. Revisiting the 7,8-cis-vitamin D3 derivatives: Synthesis, evaluating the biological activity, and study of the binding configuration. Tetrahedron 2016, 72, 2838–2848. [CrossRef]

347. Kattner, L.; Bernardi, D. An efficient synthesis of 1α,25-dihydroxyvitamin D3 and its 26,27-hexa-derated derivative. J. St. Biochem. Mol. Biol. 2016, 164, 56–58. [CrossRef]

348. Ahmad, M.I.; Raghuvanshi, D.S.; Singh, S.; John, A.A.; Prakash, R.; Nainwat, K.S.; Singh, D.; Tripathi, S.; Sharma, A.; Gupta, A. Design and synthesis of 3-arylbenzopyran based non-steroidal vitamin D3 mimics as osteogenic agents. Med. Chem. Commun. 2016, 7, 2381–2394. [CrossRef]

349. Ahmad, M.I.; Raghuvanshi, D.S.; Singh, S.; John, A.A.; Prakash, R.; Nainwat, K.S.; Singh, D.; Tripathi, S.; Sharma, A.; Gupta, A. Design and synthesis of 3-arylbenzopyran based non-steroidal vitamin D3 mimics as osteogenic agents. Med. Chem. Commun. 2016, 7, 2381–2394. [CrossRef]

350. Hernández-Martín, A.; Fernández, S.; Verstuyf, A.; Verlinden, L.; Ferrero, M. A-Ring-modified 2-hydroxyethylidine previtamin D3 analogues: Synthesis and biological evaluation. Eur. J. Org. Chem. 2017, 2017, 504–513. [CrossRef]

351. Chiellini, G.; Rapposelli, S.; Nesi, G.; Sestito, S.; Sabatini, M.; Zhu, J.; Massarelli, I.; Plum, L.A.; Clagett-Dame, M.; DeLuca, H.F. Synthesis and biological evaluation of cycloprenylamine vitamin D-like CYP24A1 inhibitors. ChemistrySelect 2017, 2, 8346–8353. [CrossRef]

352. Szybinski, M.; Brzemincki, P.; Fabisiak, A.; Berkowska, K.; Marcinkowska, E.; Sicinski, R.R. Seco-B-ring steroidal dienynes with aromatic D ring: Design, synthesis and biological evaluation. Int. J. Mol. Sci. 2017, 18, 2162–2176. [CrossRef]

353. Kato, A.; Yamao, M.; Hashihara, Y.; Ishida, H.; Toh, T.; Yamamoto, K. Vitamin D analogues with a p-hydroxyphenyl group at C25 position: Crystal structure of vitamin D receptor ligand-binding domain complexed with the ligand explains the mechanism underlying full antagonistic action. J. Med. Chem. 2017, 60, 8394–8406. [CrossRef]

354. Szybinski, M.; Sokolowska, K.; Sicinski, R.R.; Plum, L.A.; DeLuca, H.F. D-seco-Vitamin D analogs having reversed configurations at C-13 and C-14: Synthesis, dockings studies and biological evaluation. J. St. Biochem. Mol. Biol. 2017, 173, 57–63. [CrossRef]

355. Szybinski, M.; Sektas, K.; Sicinski, R.R.; Plum, L.A.; Frelek, J.; DeLuca, H.F. Design, synthesis and biological properties of seco-D-ring modified 1α,25-dihydroxyvitamin D3 analogues. J. St. Biochem. Mol. Biol. 2017, 171, 144–154. [CrossRef]

356. Kattner, L.; Bernardi, D. An efficient synthesis of 1α,25-dihydroxyvitamin D3 LC-biotin. J. St. Biochem. Mol. Biol. 2017, 173, 89–92. [CrossRef] [PubMed]

357. Vinhas, S.; Vázquez, S.; Rodríguez-Borges, J.E.; Sigüeiro, R. A convergent approach to the side-chain homologated of 1α,25-dihydroxyergocalciferol. J. St. Biochem. Mol. Biol. 2017, 173, 83–85. [CrossRef] [PubMed]

358. Kang, Z.-S.; Wang, C.; Han, X.-L.; Du, J.-J.; Li, Y.-Y.; Zhang, C. Design, synthesis and biological evaluation of non-secosteroidal vitamin D receptor ligand bearing double side chain for the treatment of chronic pancreatitis. Eur. J. Med. Chem. 2018, 146, 541–553. [CrossRef]

359. Kang, Z.-S.; Wang, C.; Han, X.-L.; Wang, B.; Yuan, H.-L.; Hao, M.; Hou, S.-Y.; Hao, M.-X.; Du, J.-J.; Li, Y.-Y.; et al. Sulfonyl-containing phenyl-pyrryl pentane analogues: Novel non-secosteroidal vitamin D receptor modulators with favorable physicochemical properties, pharmacokinetic properties and anti-tumor activity. Eur. J. Med. Chem. 2018, 157, 1174–1191. [CrossRef] [PubMed]

360. Hao, M.; Hou, S.; Xue, L.; Yuan, H.; Zhu, L.; Wang, C.; Wang, B.; Tang, C.; Zhang, C. Further developments of the phenyl-pyrryl pentane series of nonsteroidal vitamin D receptor modulators as anticancer agents. J. Med. Chem. 2018, 61, 3059–3075. [CrossRef] [PubMed]

361. Carballa, D.; Sigüeiro, R.; Rodríguez-Docampo, Z.; Zacconi, F.; Maestro, M.A.; Mourriño, A. Stereoselective palladium-catalyzed approach to vitamin D3 derivatives in protic medium. Chem. Eur. J. 2018, 24, 3314–3320. [CrossRef] [PubMed]

362. Yoshizawa, M.; Itoh, T.; Hori, T.; Kato, A.; Anami, Y.; Yoshimoto, N.; Yamamoto, K. Identification of the histidine residue in vitamin D receptor that covalently binds to electrphilic ligands. J. Med. Chem. 2018, 61, 6339–6349. [CrossRef] [PubMed]

363. Gogoi, P.; Seoane, S.; Sigüeiro, R.; Guiberteau, T.; Maestro, M.A.; Pérez-Fernández, R.; Rochel, N.; Mourriño, A. Aromatic-based design of highly active and non calcemic vitamin D receptor agonists. J. Med. Chem. 2018, 61, 4928–4937. [CrossRef]
364. Otero, R.; Ishizawa, M.; Numoto, N.; Ikura, T.; Ito, N.; Tokiwa, H.; Mourão, A.; Makishima, M.; Yamada, S. 25S-Adamantyl-23-
yne-26,27-dinor-1α,25-dihydroxyvitamin D3: Synthesis, tissue selective biological activities, and X-ray crystal structural analysis of its vitamin D complex. J. Med. Chem. 2016, 61, 6658–6673. [CrossRef]

365. Brzeminski, P.; Fabisiak, A.; Sekta, K.; Berkowska, K.; Marcinkowska, E.; Sicinski, R.R. Synthesis of 19-norcaltioriolog analogs with elongated side chain. J. St. Biochem. Mol. Biol. 2018, 177, 231–234. [CrossRef]

366. Fabisiak, A.; Brzeminski, P.; Berkowska, K.; Marcinkowska, E.; Sicinski, R.R. Synthesis of 19-norcaltioriolog analogs with alkylidene moieties at C-2 based on succinic acid and L-methionine. J. St. Biochem. Mol. Biol. 2018, 177, 235–239. [CrossRef][PubMed]

367. Sawada, D.; Kakuda, S.; Takeuchi, A.; Kawagoe, F.; Takimoto-Kamimura, M.; Kitakata, A. Effects of 2-substitution on 14-epi-19-
nortachysterol-mediated biological events; based on synthesis and X-ray co-crystographic analysis with the human vitamin D receptor. Org. Biomol. Chem. 2018, 16, 2448–2455. [CrossRef][PubMed]

368. Sigüeiro, R.; Maestro, M.A.; Mourão, A. Synthesis of side-chain locked analogs of 1α,25-dihydroxyvitamin D3 bearing a C17 methyl group. Org. Lett. 2018, 20, 2641–2644. [CrossRef][PubMed]

369. Lin, Z.; Marepally, S.R.; Goh, E.S.Y.; Chen, C.Y.S.; Janjetovic, Z.; Kim, T.-k.; Miller, D.D.; Postlehwaite, A.E.; Slominski, A.T.; Tuckey, R.C.; et al. Investigation of 20S-hydroxyvitamin D3 analogs and their 1α-OH derivatives as potent vitamin D receptor agonists with anti-inflammatory activities. Sci. Rep. 2018, 8, 1478–1489. [CrossRef][PubMed]

370. Kawagoe, F.; Yasuda, K.; Mototani, S.; Sugiyama, T.; Uesugi, M.; Sakaki, T.; Kittaka, A. Synthesis and CYP24A1-dependent metabolism of 23-fluorinated vitamin D3 analogues. ACS Omega 2019, 4, 11332–11337. [CrossRef][PubMed]

371. Maschinot, C.A.; Chau, L.Q.; Wechsler-Reya, R.J.; Hadden, M.K. Synthesis and evaluating of third generation vitamin D analogs as inhibitors of Hedgehog signaling. J. St. Biochem. Mol. Biol. 2019, 162, 495–506. [CrossRef][PubMed]

372. Sigüeiro, R.; Loureiro, J.; González-Berduñas, P.; Mourão, A.; Maestro, M.A. Synthesis of 28,28,28-trideutero-25-hydroxydihydr-
ortacholesterol. J. St. Biochem. Mol. Biol. 2019, 185, 248–250. [CrossRef][PubMed]

373. Ferronato, M.J.; Obio, D.J.; Alonso, E.N.; Guevara, J.A.; Grioli, S.M.; Mascaró, M.; Rivadulla, M.L.; Martínez, A.; Gómez, G.; Fall, Y.; et al. Synthesis of a novel analog of calcitriol and its biological evaluation as antitumor agent. J. St. Biochem. Mol. Biol. 2019, 185, 118–136. [CrossRef][PubMed]

374. Wang, W.; Zhao, G.-D.; Cui, J.-i.; Li, M.-Q.; Liu, Z.-P. Synthesis of 1α,25-dihydroxyvitamin D3 Analogues with α,α-
difluorocycloketone at the CD-ring side chains and their biological properties in ovariectomized rats. J. St. Biochem. Mol. Biol. 2019, 186, 66–73. [CrossRef][PubMed]

375. Kawagoe, F.; Sugiyama, T.; Yasuda, K.; Uesugi, M.; Sakaki, T.; Kittaka, A. Concise synthesis of 23-hydroxylated vitamin D3 metabolites. J. St. Biochem. Mol. Biol. 2019, 186, 161–168. [CrossRef][PubMed]

376. Fujishima, T.; Suena, T.; Kawahata, M.; Yamaguchi, K. Synthesis and characterization of 20-hydroxyvitamin D3 with the A-ring modification. J. St. Biochem. Mol. Biol. 2019, 187, 27–33. [CrossRef][PubMed]

377. Kawagoe, F.; Mototani, S.; Yasuda, K.; Nagasawa, K.; Uesugi, M.; Sakaki, T.; Kittaka, A. Introduction of fluorne atoms to vitamin D3 side-chain and synthesis of 24,24-difluoro-25-hydroxyvitamin D3. J. St. Biochem. Mol. Biol. 2019, 195, 105477. [CrossRef][PubMed]

378. Fabisiak, A.; Brzeminski, P.; Berkowska, K.; Marcinkowska, E.; Sicinski, R.R. Synthesis of 19-norcaltioriolog with pegylated alkylidene chains at C-2. J. St. Biochem. Mol. Biol. 2019, 185, 251–255. [CrossRef][PubMed]

379. Nagata, A.; Akagi, Y.; Asano, L.; Kotake, K.; Kawagoe, F.; Mendoza, A.; Masoud, S.S.; Usuda, K.; Takemoto, Y.; Kittaka, A.; et al. Synthetic chemical probes that dissect vitamin D activities. ACS Chem. Biol. 2019, 14, 2851–2858. [CrossRef][CrossRef]

380. Ibe, K.; Yamada, T.; Okamoto, S. Synthesis and vitamin D receptor affinity of 16-oxavitamin D3 analogues. Org. Biomol. Chem. 2019, 17, 10188–10200. [CrossRef][CrossRef]

381. Fujishima, T.; Komatsu, T.; Takao, Y.; Yonamine, W.; Suena, T.; Isono, H.; Morikawa, M.; Takaguchi, K. Design and concise synthesis of novel vitamin D analogues bearing a functionalized aromatic ring on the side chain. Tetrahelectron 2019, 75, 1098–1106. [CrossRef][CrossRef]

382. Sibilska-Kaminski, I.K.; Sicinski, R.R.; Plum, L.A.; DeLuca, H.F. Synthesis and biological activity of 2,22-dimethylene analogues of 19-norcaltioriolog and related compounds. J. Med. Chem. 2020, 63, 7355–7368. [CrossRef][CrossRef]

383. Katner, L.; Rauch, E. Efficient synthesis of 3-TBDMS-11α,25-dihydroxyvitamin D1 and D2 ethers. J. St. Biochem. Mol. Biol. 2020, 200, 105638. [CrossRef][CrossRef]

384. Brzeminski, P.; Fabisiak, A.; Berkowska, K.; Rárova, L.; Marcinkowska, E.; Sicinski, R.R. Synthesis of Gemini analogs of 19-norcaltioriolog and their platinum(II) complexes. Bioorg. Chem. 2020, 100, 103883. [CrossRef][CrossRef]

385. Fabisiak, A.; Brzeminski, P.; Berkowska, K.; Rárova, L.; Marcinkowska, E.; Sicinski, R.R. Design, synthesis and biological evaluation of novel 2-alkylidene 19-norcaltioriolog analogs. Bioorg. Chem. 2020, 100, 104013. [CrossRef][CrossRef]

386. Sibilska-Kaminski, I.K.; Fabisiak, A.; Brzeminski, P.; Plum, L.A.; Sicinski, R.R.; DeLuca, H.F. Novel superagonist analogs of 2-methylene calcirotiol: Design, molecular docking, synthesis and biological evaluation. Bioorg. Chem. 2022, 118, 105416. [CrossRef][PubMed]

387. Obelleiro, A.; Gómez-Bouzó, U.; Gómez, G.; Fall, Y.; Santalla, H. Design and efficient synthesis of novel vitamin D analogues bearing an anline moiety in their side chains. Tet. Lett. 2020, 61, 152493. [CrossRef][CrossRef]

388. Fraga, R.; Len, K.; Lutting, R.; Laverny, G.; Loureiro, J.; Maestro, M.A.; Rochel, N.; Rodriguez-Borges, E.; Mourião, A. Design, synthesis, evaluation and structure of allenic 1α,25-dihydroxyvitamin D3 analogs with locked mobility at C17. Chem. Eur. J. 2021, 27, 13384–13389. [CrossRef][PubMed]
389. Seoane, S.; Gogoi, P.; Zárate-Ruiz, A.; Peluso-Iltis, C.; Peters, S.; Guiberteau, T.; Maestro, M.A.; Pérez-Fernández, R.; Rochel, N.; Mouriño, A. Design, synthesis, biological activity and structural analysis of novel des-C—Ring aromatic-D-ring analogues of 1α,25-dihydroxyvitamin D₃. *J. Med. Chem.* **2022**, *65*, 13112–13124. [CrossRef] [PubMed]

390. Ibe, K.; Nakada, H.; Ohgami, M.; Yamada, T.; Okamoto, S. Design, synthesis, and properties of des-D-ring interphenylene derivatives of 1α,25-dihydroxyvitamin D₃. *Eur. J. Med. Chem.* **2022**, *243*, 114795. [CrossRef]

391. Kawagoe, F.; Mendoza, A.; Hayata, Y.; Asano, L.; Kotake, K.; Mototani, S.; Kawamura, S.; Kurosaki, S.; Akagi, Y.; Takemoto, Y.; et al. Discovery of a vitamin D receptor-silent vitamin D derivative that impairs regulatory element-binding protein in vivo. *J. Med. Chem.* **2021**, *64*, 5689–5709. [CrossRef]

392. Saito, H.; Horie, K.; Suga, A.; Kaibara, Y.; Mashiko, T. Vitamin D Derivative Having Cyclic Amine in Side Chain. World Patent Organization. WO2022059684A1, 24 March 2022.