European Journal of Medicinal Chemistry 107 (2016) 48–62

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Research paper

Novel nonsecosteroidal VDR ligands with phenyl-pyrrolyl pentane skeleton for cancer therapy

Zhixin Ge, Meixi Hao, Meng Xu, Zhigui Su, Zisheng Kang, Lingjing Xue**, Can Zhang*

State Key Laboratory of Nature Medicines and Jiangsu Key Laboratory of Drug Discovery for Metabolic Disease, Center of Drug Discovery, China Pharmaceutical University, 24 Tong Jia Xiang, Nanjing, 210009, China

ARTICLE INFO

Article history:
Received 16 March 2015
Received in revised form
21 October 2015
Accepted 25 October 2015
Available online 3 November 2015

Keywords:
VDR
Nonsecosteroid
Phenyl-pyrrolyl pentane skeleton
Cancer therapy
Hypercalcemia
Anti-proliferation
Vitamin D_3-agonistic activity

ABSTRACT

A series of nonsecosteroidal vitamin D_3 receptor (VDR) ligands with phenyl-pyrrolyl pentane skeleton were synthesized for cancer therapy. In contrast to 1α,25-dihydroxyvitamin D_3 (Calcitriol), these VDR ligands exhibited anti-proliferative activity without inducing hypercalcemia. These compounds were evaluated for vitamin D_3-agonistic ability and anti-proliferative activity *in vitro*. Among them, compounds **5k** and **5i** exhibited equivalent vitamin D_3-agonistic activity compared with Calcitriol. Meanwhile, compound **5k** displayed promising inhibiting profile against MCF-7, HepG-2 and Caco-2 with IC_{50} values of 0.00586 μM, 0.176 μM, and 1.01 μM (Calcitriol: 5.58 μM, 80.83 μM and 4.46 μM) respectively. Compound **5i** inhibited proliferation of PC-3 with IC_{50} value of 0.00798 μM (Calcitriol: 17.25 μM). Additionally, neither of these compounds significantly elevated serum calcium in rats.

1. Introduction

1α,25-dihydroxyvitamin D_3 (1α,25$(OH)_2D_3$, Fig. 1), one of biologically active forms of vitamin D_3, regulates calcium and phosphate metabolism and is essential for bone [1,2]. The biological effects of 1α,25$(OH)_2D_3$ are mediated by the vitamin D_3 receptor (VDR) which belongs to the nuclear receptor superfamily. When 1α,25$(OH)_2D_3$ binds to VDR, they form a heterodimer with the retinoid X receptor (RXR). Then, the ligand-bound VDR-RXR complex associates with vitamin D_3 responsive element (VDRE) in the promoters of the target gene, resulting in the transcriptional regulation of gene expression [3–5]. 1α,25$(OH)_2D_3$ have been proved to play an important role in many signal pathways including differentiation, anti-proliferation and apoptosis [6–8]. Therefore, it has the potential to affect cancer development and growth.

However, the high potency of 1α,25 $(OH)_2D_3$ to increase serum calcium precludes its wide use in most cases. In order to obtain potent VDR agonists retaining greater selectivity with less toxic (hypercalcemic) side effects, more than 3000 secosteroid analogs have been synthesized by chemical structure modification [9,10]. Although some of them have been successfully used in treatments of psoriasis and osteoporosis, the potential risk of *adverse effect limits their application for long-term therapy* such as cancer and autoimmune diseases. Therefore, there is an urgent clinical need for novel VDR agonists without risks of increasing serum calcium. In 1999, a series of bis-phenyl nonsecosteroidal derivatives including LG190155 (Fig. 1) were reported. They mimic various activities of 1α,25$(OH)_2D_3$ but exhibited no calcemic potential *in vivo* [11]. In 2013, tris-aromatic derivatives have been shown as potent VDR agonists. So far, a lot of nonsecosteroidal derivatives have been synthesized and investigated to study their structure–activity relationship [12,13].

Recently, demonstrations of signaling pathway of 1α,25$(OH)_2D_3$ in cancer make nonsecosteroidal VDR derivatives suitable for anticancer therapeutics [14–16]. Here we have designed and synthesized phenyl-pyrrolyl pentane skeleton nonsecosteroidal VDR derivatives. Among them, the compound sw-22 (Fig. 1) inhibited the proliferation of MCF-7 with the IC_{50} value of 0.32 μM [17]. In order to improve the anti-proliferative activity, the pyrrolyl side chains were further modified (Fig. 1). First, hydrophilic moieties were introduced to skeleton structure, which could form -hydrogen binding interaction with amino acid residues of VDR

* Corresponding author.
** Corresponding author.
E-mail addresses: xuelingjing65@163.com (L. Xue), zhangcan@cpu.edu.cn (C. Zhang).

http://dx.doi.org/10.1016/j.ejmech.2015.10.042
0223-5234/

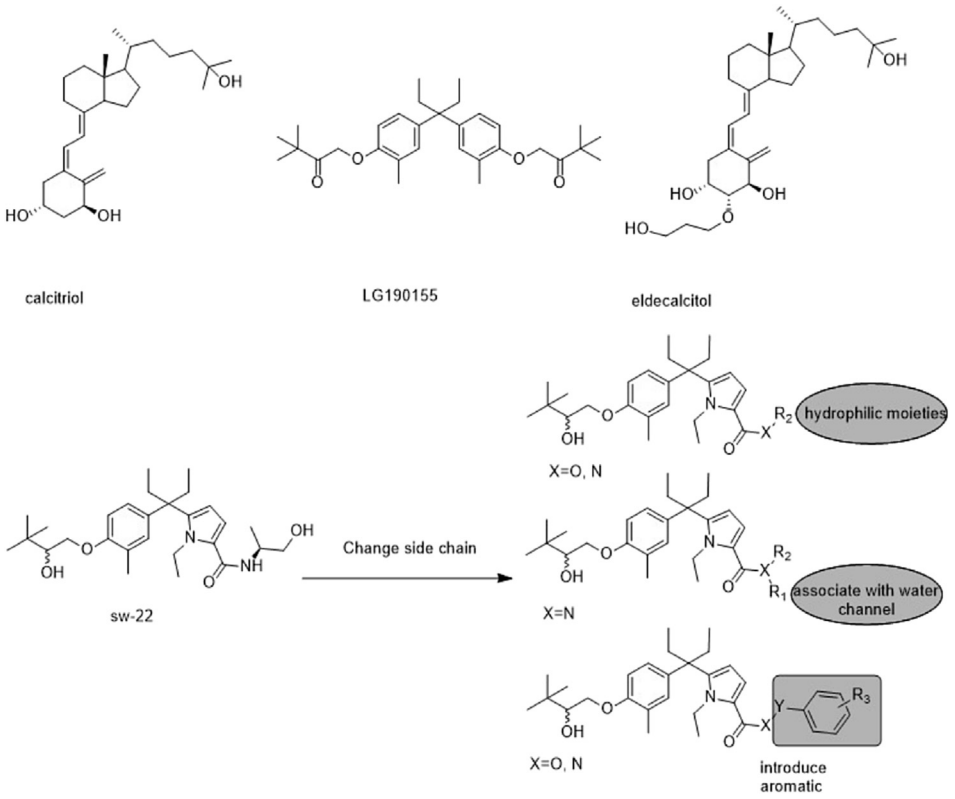


Fig. 1. The designed VDR ligands.

through miming the roles of the 1α-hydroxyl and 25- hydroxyl groups of 1α,25(OH)$_2$D$_3$. Secondly, a short chain was added to amide bond in order to associate with water channel, which is supported by the structure activity relationship of Eldecalcitol (Fig. 1). At last, a series of tris-aromatic analogues were synthesized through introducing aromatic ring according the design of compound CD4849 which has been proved to maintain similar hydrogen binding network and hydrophobic interactions as the natural ligand [18]. The vitamin D$_3$-agonistic activity of compounds was estimated by HL-60 cell differentiation. The results showed that compounds **5i**, **5k**, **6a** and **7a** demonstrated excellent VDR agonistic ability. Especially, compound **7a** showed better agonistic activity compared with Calcitriol. Compound **5k** exhibited promising anti-proliferative activity on MCF-7, Caco-2 and HepG-2 cells and compound **5i** was the most potent compound for the inhibition of PC-3 cell. Meanwhile, **5i** and **5k** showed no potential on rising serum calcium. Furthermore, we have also performed docking study to understand the structure–activity relationship.

2. Results and discussion

2.1. Chemistry

The synthesis of VDR ligands was depicted in Scheme 1. The key compound **3** was prepared by previously reported approach by our group [17]. Compounds **4a**–**4r**, **8a**–**8e** and **10a**–**10b** were prepared in a single step by the treatment of compound **3** with different amines or esters. All of them were reduced to obtain compounds **5a**–**5r**, **9a**–**9e** and **11a**–**11b** by sodium borohydride in methanol. Hydrolyzed by lithium hydroxide, compounds **6a** and **6b** were synthesized, where the R$_2$ is carboxylic acid ester and X is a nitrogen atom. Compounds **7a** and **7b** were obtained through reduction reaction in the same way.

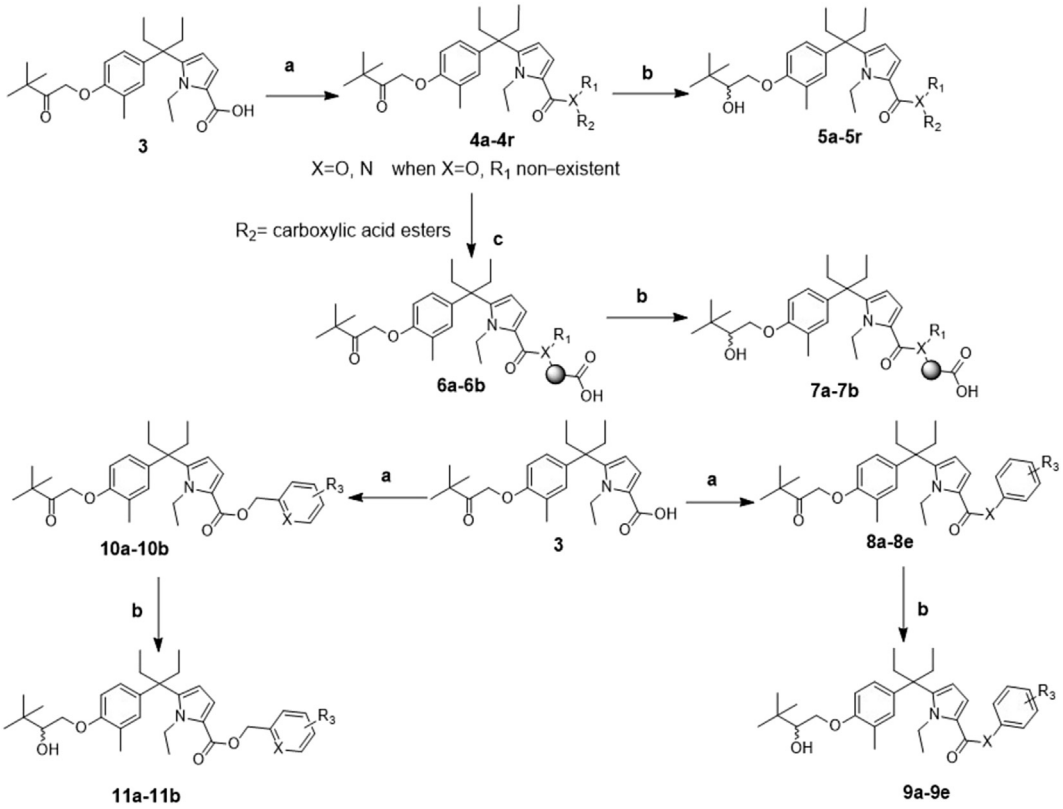
2.2. Biological activities

2.2.1. In vitro VDR-binding ability assay

To determine if the phenyl-pyrrolyl pentane derivatives bound directly to VDR *in vitro*, the competitive binding experiment was performed using PolarScreen VDR Competitor Assay Red. Many of the selected compounds demonstrated nice VDR binding ability compared with Calcitriol, as shown in Fig. 2. Compounds **5f, 5i, 5k,** and **7a** displayed better VDR binding ability than **4f, 4i, 4k**, and **6a,** which indicated that hydroxyl group could raise binding ability obviously. Compound **5e, 5i, 5k**, also showed significantly VDR binding ability because of the introduction of amino or substituted amino groups. This observation could prove the novel compounds we designed belong to VDR ligands.

2.2.2. Vitamin D$_3$-agonistic activity (estimated by HL-60 cell differentiation induction)

It is proved that vitamin D$_3$-agonistic activity is associated with HL-60 cell differentiation induction [19,20]. Therefore, the vitamin D$_3$-agonistic ability can be estimated as the potential to differentiate human promyelocytic leukemia cell line (HL-60) into macrophages. All synthesized compounds were tested for HL-60 cell differentiation using Calcitriol as the positive control, as shown in Table 1. Compounds **5a**–**5r** demonstrated better vitamin D$_3$-agonistic activity than compounds **4a**–**4r**, which indicated that it is necessary to introduce hydroxyl group into the chain beside phenyl ring. Compounds **5a**, **5d**, **5i**, **5k 6a**, and **7a** displayed excellent vitamin D$_3$-agonistic ability because of the hydrophilic moieties being introduced into pyrrolyl side chain, especially, compound **7a** showed better vitamin D$_3$-agonistic activity compared with Calcitriol. The compounds with tris-aromatic exhibited poor vitamin D$_3$-agonistic activity compared to other VDR agonists. When a hydrophilic chain was added to amide bond compounds **4o** and **5o**



Scheme 1. Reagents and reaction conditions: (a) Amino acid methyl ester hydrochloride, EDCI, HOBT, Et_3N, DMF, 25 °C, overnight/p-nitrobenzenesulfonyl chloride, DMAP, CH_3CN, 70 °C, overnight/EDCI, DMAP, CH_3Cl, 70 °C, overnight; (b) $NaBH_4$, CH_3OH, 0 °C–25 °C, 2 h–6 h; (c) $LiOH{\cdot}H_2O$, THF, H_2O, 25 °C, overnight.

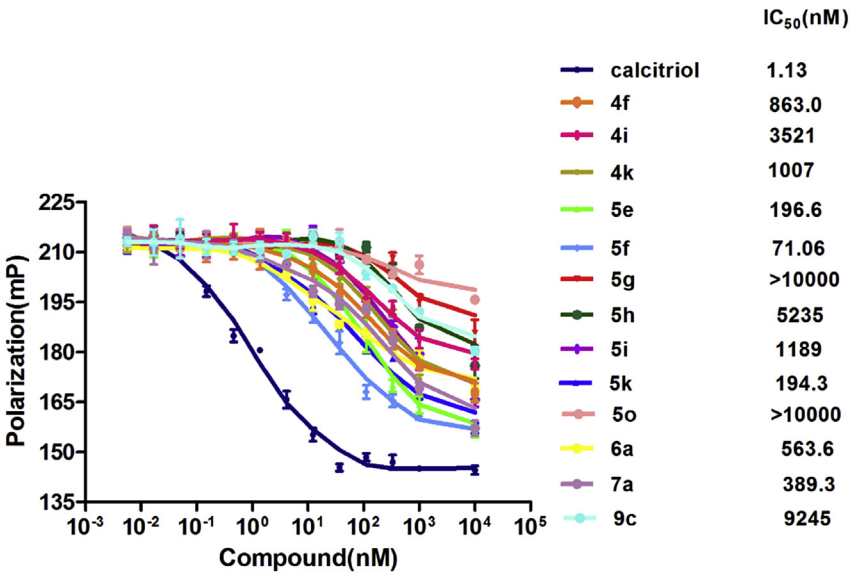


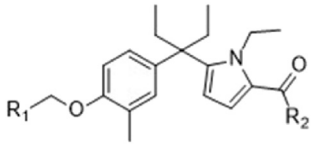
Fig. 2. Competitive binding assay of selected phenyl-pyrrolyl pentane derivatives.

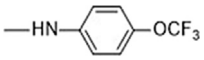
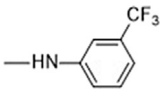
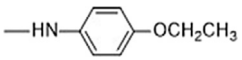
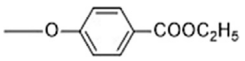
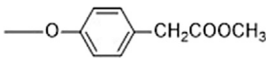
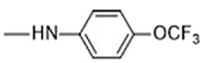
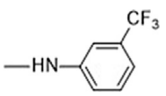
showed moderate vitamin D_3-agonistic activity.

2.2.3. *In vitro* anti-proliferation activity assay

In vitro anti-proliferation activity of phenyl-pyrrolyl pentane derivatives was evaluated against cancer cells MCF-7, Caco-2, HepG-2, PC-3 and normal cell L02 (human normal liver cell line) by MTT assay, using Calcitriol as the positive control. As shown in Table 2, most of designed compounds showed better inhibition activity against PC-3 cell compared with other cancer cells. Especially, compound **5i** displayed the best anti-proliferative activity with IC_{50} value of 0.00797 μM against PC-3 cell, and compound **5k** exhibited significantly inhibition activity with the values of 0.00587, 1.01 and 0.176 μM against MCF-7, Caco-2 and HepG-2 cells, respectively. Both compounds **5i** and **5k** demonstrated better promising anti-proliferative activity compared with positive compound Calcitriol. The result of L02 cell showed VDR ligands had

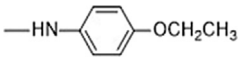
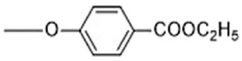
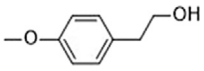
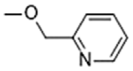
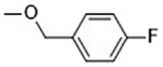
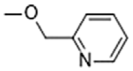
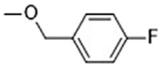
Table 1
The structures and vitamin D_3-agonistic activity of phenyl-pyrrolyl pentane derivatives.



Compd	R_1	R_2	HL-60 cell differentiation inducing activity[a] EC_{50}[b] (μM)
4a	$-COC(CH_3)_3$	(L)-$NHCH[CH(CH_3)C_2H_5]COOCH_3$	0.59 ± 0.17
4b	$-COC(CH_3)_3$	$-N(CH_3)CH_2COOC_2H_5$	>50
4c	$-COC(CH_3)_3$	$-NHCH_2CH_2N(CH_2CH_3)_2$	0.091 ± 0.022
4d	$-COC(CH_3)_3$	$-NHCH_2CH_2N(CH_3)_2$	0.077 ± 0.015
4e	$-COC(CH_3)_3$	$-NHCH_2CH_2CH_2N(CH_3)_2$	0.096 ± 0.031
4f	$-COC(CH_3)_3$	$-NHCH_2CH_2CH_2N(CH_2CH_3)_2$	0.022 ± 0.008
4g	$-COC(CH_3)_3$	$-NHCH_2C{\equiv}CH$	2.2 ± 0.5
4h	$-COC(CH_3)_3$	$-NHCH_2CH(OCH_3)_2$	0.13 ± 0.04
4i	$-COC(CH_3)_3$	$-NHCH_2CH_2CH_2N(CH_2CH_2)_2O$	0.24 ± 0.07
4j	$-COC(CH_3)_3$	$-NHCH_2CH_2Br$	1.9 ± 0.7
4k	$-COC(CH_3)_3$	$-NHCH_2CH_2NH_2$	0.12 ± 0.02
4l	$-COC(CH_3)_3$	$-N(CH_3)CH_2CH_2CN$	9.8 ± 2.8
4m	$-COC(CH_3)_3$	$-N(CH_3)CH_2C{=}CH_2$	21.6 ± 2.1
4n	$-COC(CH_3)_3$	$-N(CH_3)C_6H_5$	18.5 ± 1.8
4o	$-COC(CH_3)_3$	$-N(CH_2CH_2CN)CH_2CH_2CN$	0.87 ± 0.18
4p	$-COC(CH_3)_3$	$-OCH(CH_3)C{\equiv}CH$	0.21 ± 0.03
4q	$-COC(CH_3)_3$	$-OCH_2CH_2C{\equiv}CH$	28.8 ± 1.7
4r	$-COC(CH_3)_3$	$-OCH(CH_3)CH_2COOC_2H_5$	>50
5a	$-CH(OH)C(CH_3)_3$	(L)-$NHCH[CH(CH_3)C_2H_5]COOCH_3$	0.026 ± 0.008
5b	$-CH(OH)C(CH_3)_3$	$-N(CH_3)CH_2COOC_2H_5$	0.21 ± 0.03
5c	$-CH(OH)C(CH_3)_3$	$-NHCH_2CH_2N(CH_2CH_3)_2$	0.11 ± 0.02
5d	$-CH(OH)C(CH_3)_3$	$-NHCH_2CH_2N(CH_3)_2$	0.014 ± 0.002
5e	$-CH(OH)C(CH_3)_3$	$-NHCH_2CH_2CH_2N(CH_3)_2$	0.037 ± 0.005
5f	$-CH(OH)C(CH_3)_3$	$-NHCH_2CH_2CH_2N(CH_2CH_3)_2$	0.066 ± 0.012
5g	$-CH(OH)C(CH_3)_3$	$-NHCH_2C{\equiv}CH$	0.24 ± 0.01
5h	$-CH(OH)C(CH_3)_3$	$-NHCH_2CH(OCH_3)_2$	0.15 ± 0.02
5i	$-CH(OH)C(CH_3)_3$	$-NHCH_2CH_2CH_2N(CH_2CH_2)_2O$	0.018 ± 0.001
5j	$-CH(OH)C(CH_3)_3$	$-NHCH_2CH_2Br$	0.13 ± 0.03
5k	$-CH(OH)C(CH_3)_3$	$-NHCH_2CH_2NH_2$	0.01 ± 0.0017
5l	$-CH(OH)C(CH_3)_3$	$-N(CH_3)CH_2CH_2CN$	1.96 ± 0.18
5m	$-CH(OH)C(CH_3)_3$	$-N(CH_3)CH_2C{=}CH_2$	3.95 ± 0.33
5n	$-CH(OH)C(CH_3)_3$	$-N(CH_3)C_6H_5$	6.4 ± 0.38
5o	$-CH(OH)C(CH_3)_3$	$-N(CH_2CH_2CN)CH_2CH_2CN$	0.097 ± 0.011
5p	$-CH(OH)C(CH_3)_3$	$-OCH(CH_3)C{\equiv}CH$	0.2 ± 0.008
5q	$-CH(OH)C(CH_3)_3$	$-OCH_2CH_2C{\equiv}CH$	1.03 ± 0.28
5r	$-CH(OH)C(CH_3)_3$	$-OCH(CH_3)CH_2CH_2OH$	0.38 ± 0.005
6a	$-COC(CH_3)_3$	(L)-$NHCH[CH(CH_3)C_2H_5]COOH$	0.01 ± 0.003
6b	$-COC(CH_3)_3$	$-N(CH_3)CH_2COOH$	1.39 ± 0.21
7a	$-CH(OH)C(CH_3)_3$	(L)-$NHCH[CH(CH_3)C_2H_5]COOH$	0.0023 ± 0.001
7b	$-CH(OH)C(CH_3)_3$	$-N(CH_3)CH_2COOH$	0.74 ± 0.18
8a	$-COC(CH_3)_3$		>50
8b	$-COC(CH_3)_3$		>50
8c	$-COC(CH_3)_3$		>50
8d	$-COC(CH_3)_3$		45.6 ± 5.18
8e	$-COC(CH_3)_3$		2.32 ± 0.18
9a	$-CH(OH)C(CH_3)_3$		>50
9b	$-CH(OH)C(CH_3)_3$		>50

(*continued on next page*)

Table 1 (*continued*)

Compd	R_1	R_2	HL-60 cell differentiation inducing activity[a] EC_{50}[b] (μM)
9c	$-CH(OH)C(CH_3)_3$		0.63 ± 0.21
9d	$-CH(OH)C(CH_3)_3$		>50
9e	$-CH(OH)C(CH_3)_3$		5.1 ± 1.1
10a	$-COC(CH_3)_3$		>50
10b	$-COC(CH_3)_3$		9.5 ± 0.88
11a	$-CH(OH)C(CH_3)_3$		>50
11b	$-CH(OH)C(CH_3)_3$		>50
LG190155			0.59 ± 0.18
Calcitriol			0.009 ± 0.0012
sw-22			0.0085 ± 0.0012

[a] Vitamin D_3-agonistic activity was estimated as HL-60 differentiation inducing ability.
[b] Data represent mean ± SD, n = 3, *P < 0.05.

Table 2
Cellular anti-proliferative activities of the novel phenyl-pyrrolyl pentane derivatives.

Compd	Cell inhibition IC_{50}[a] (μM)				L02[c]
	PC-3[b]	MCF-7	Caco-2	HepG-2	
4c	0.03 ± 0.007	0.69 ± 0.11	1.6 ± 0.2	0.62 ± 0.01	2.5 ± 1.3
4d	2.3 ± 0.31	0.52 ± 0.08	1.6 ± 0.3	2.3 ± 0.45	2.5 ± 0.32
4e	1.6 ± 0.25	0.34 ± 0.01	1.4 ± 0.05	0.96 ± 0.23	0.67 ± 0.02
4f	1.8 ± 0.21	0.53 ± 0.07	1.0 ± 0.01	0.18 ± 0.01	2.3 ± 0.3
4i	0.011 ± 0.03	5.2 ± 0.67	3.6 ± 0.33	1.6 ± 0.31	0.31 ± 0.7
4k	0.48 ± 0.01	0.075 ± 0.01	1.9 ± 0.41	0.18 ± 0.03	2.5 ± 0.6
5b	25.5 ± 2.3	9.2 ± 2.9	12.2 ± 0.01	>50	10.1 ± 1.3
5c	0.22 ± 0.02	0.69 ± 0.26	2.31 ± 0.11	0.49 ± 0.01	2.5 ± 0.8
5d	1.63 ± 0.03	0.66 ± 0.03	1.3 ± 0.05	0.87 ± 0.01	2.6 ± 0.3
5e	3.1 ± 0.34	0.49 ± 0.01	1.9 ± 0.91	0.36 ± 0.04	0.47 ± 0.01
5f	2.5 ± 0.61	0.19 ± 0.015	1.8 ± 0.67	1.1 ± 0.3	2.5 ± 1.2
5g	16.2 ± 2.8	>50	39.1 ± 7.8	>50	4.4 ± 1.5
5h	14.6 ± 1.8	>50	>50	23.2 ± 5.3	22.2 ± 3.6
5i	0.0079 ± 0.0023	2.07 ± 0.28	5.9 ± 1.1	1.29	0.81 ± 0.07
5k	0.94 ± 0.37	0.0059 ± 0.0021	1.0 ± 0.2	0.176	2.4 ± 0.3
5l	1.7 ± 0.4	>50	>50	>50	14.9 ± 2.3
5m	25.9 ± 3.6	>50	>50	>50	6.3 ± 1.6
5o	7.8 ± 1.7	0.48 ± 0.08	7.1 ± 1.8	41.95	1.7 ± 0.3
5p	38.2 ± 2.1	>50	>50	>50	23.7 ± 3.7
6a	1.6 ± 0.3	0.16 ± 0.01	4.5 ± 0.8	0.247	1.5 ± 0.2
6b	18.4 ± 4.2	28.6 ± 2.9	35.9 ± 5.2	25.23	8.7 ± 1.8
7a	1.9 ± 0.2	2.0 ± 0.7	3.4 ± 0.2	0.127	1.4 ± 0.7
7b	23.9 ± 4.2	25.4 ± 3.2	31.9 ± 2.7	17.05	32.6 ± 5.8
9e	6.3 ± 1.7	>50	>50	>50	22.7 ± 3.4
11b	>50	>50	>50	>50	14.9 ± 2.8
LG190155	>50	7.8 ± 2.8	16.9 ± 2.5	>50	5.1 ± 1.8
Calcitriol	17.2 ± 3.8	5.6 ± 1.7	4.4 ± 0.8	>50	0.67 ± 0.05
sw-22	17.5 ± 2.6	2.8 ± 0.5	>50	47.55	17.3 ± 1.7

[a] b Data represent mean ± SD, n = 3, *P < 0.05.
[b] PC-3 is a cells human prostate cancer cell lines which over-expresses VDR.
[c] L02 is a human normal liver cell line.

moderate selective antitumor property.

It could be found that compounds **5a**–**5r** exhibited better anti-proliferative activity than compounds **4a**–**4r**, indicating that introduction of hydroxyl group into side chains of phenyl ring can significantly improve activity than carbonyl group. When amino or substituted amino groups were added to pyrrolyl side chains,

compound **5c**–**5f** and **5i** displayed stronger anti-proliferative activity. It suggested that replacement of the amino group with morpholine ring also demonstrated promising inhibition activity by the result of compound **5k**. Compound **6a**–**6b** with the amino acids structure exhibited moderate antitumor activity. In addition, it is worthy to note that compound **5o** with the structure of nitrile group introduced into amide bond showed good vitamin D_3-agonistic activity and remarkable anti-proliferation ability compared with **5l**–**5n**. It was disappointing that the inhibition activities of tris-aromatic analogs, phenyl amines or hydroxy benzene directly conjugating to pyrrolyl side, were almost lost.

2.2.4. *In vivo* calcemic activity assay

The level of serum calcium was measured to evaluate the safety profile of these compounds [21]. Compounds **5i** and **5k** were chosen for calcemic activity assay *in vivo*, using Calcitriol as the positive control and normal saline as blank, as shown in Fig. 3.

A remarkable increasing in serum calcium (13.11 mg/dl, compared with 7.25 mg/dl in blank control, $P < 0.01$) was noted after given Calcitriol (0.5 μg/kg/day) for 7 days. However, there was no significant change on serum calcium in rats when treated with compounds **5i**, and **5k** (0.5 mg/kg/day, 10 mg/kg/day and 30 mg/kg/day, respectively). Compared with Calcitriol, sw-22 and LG190155 (given 30 mg/kg/day each, $P < 0.05$ for sw-22, $P < 0.05$ for LG190155) as well as **5i** and **5k** ($P < 0.05$ for **5i**, $P < 0.01$ for **5k**) dramatically decreased serum calcium level.

2.3. Molecular docking study

Docking study was carried out using Schrödinger Glide version 7.3 and MOE 2009. Compounds **5i** and **5k** were docked into VDR ligand binding domain (VDR LBD, PDB ID: 2ZFX). The resulting structures of the active site were shown in Fig. 4. Also, the structures of VDR LBD-**5i** and VDR LBD-**5k** complexes overlapped with the VDR LBD-1α,25$(OH)_2D_3$ complex were demonstrated in Fig. 5.

Hydroxyl group beside phenyl ring of compound **5k** was able to form hydrogen binding interactions with the His 393 and His 301 of VDR LBD. On the other side of structure the groups of amine and carbonyl formed hydrogen binding with Arg 270 and Ser 274, respectively. Hydroxyl of compound **5i** formed same hydrogen binding interaction with His 393 and His 301 and the morpholine ring was able to form hydrogen binding interaction with Arg 270. It is interesting that carbonyl of compound **5i** formed hydrogen binding with Ser 233 but not Ser 274 because of the morpholine ring, which resulted from the structure of spatial configuration reversal. In addition, it is worth noting that compounds **5i** and **5k** exhibited similar hydrogen binding interaction to compound R301 which 2′-hydroxy forms hydrogen bonds with His 301 and His 393 and 2-hydroxy does with Ser 233, and Arg 270 [22].

The docking study revealed that the compounds **5i** and **5k** mimicked the roles of the 1α-hydroxyl and 25-hydroxyl groups of 1α,25$(OH)_2D_3$ without direct structural relationship to 1α,25$(OH)_2D_3$. Compared with 1α,25$(OH)_2D_3$, compounds **5i** and **5k** formed hydrogen binding interaction with Ser 233, Arg 270, His 301 and His 393 as discussed above, which were embed in the same position of the binding pocket. Apart from this, compounds **5i** and **5k** were also able to form hydrogen bonds with Ser 233 and Ser 274, respectively. All of the above suggested that compounds **5i** and **5k** worked similarly as 1α,25$(OH)_2D_3$.

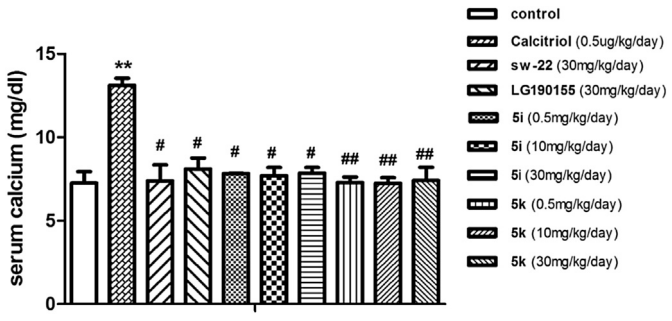


Fig. 3. *In vivo* calcemic activity of Calcitriol, LG190155, sw-22, compounds **5i** and **5k**.

3. Conclusions

In summary, a series of novel phenyl-pyrrolyl pentane derivatives were synthesized and systematically tested for cancer therapy. The VDR binding ability was tested using PolarScreen VDR Competitor Assay Red and Vitamin D_3-agonistic activity was estimated via inducing differentiation ability on HL-60 cells *in vitro*. The result indicated that introducing hydroxyl group into one side, beside phenyl ring and adding hydrophilic moieties to pyrrolyl ring, were able to improve vitamin D_3-agonistic activity significantly. *In vitro* cell cytotoxicity was evaluated against PC-3, MCF-7, Caco-2 and HepG-2 cells by MTT assay. Among all, compound **5i** exhibited best selective activity against PC-3 cell with IC_{50} value of 0.00797 μM. Meanwhile, compound **5k** demonstrated excellent inhibition against MCF-7, Caco-2 and HepG-2 cells with IC_{50} value of 0.00587, 1.01 and 0.176 μM, respectively. Therefore, the most promising compounds **5i** and **5k** were chosen to evaluate safety *in vivo*, and neither of them showed potential on raising serum calcium level. Docking study proved that the spatial structures of compounds **5i** and **5k** were similar to 1.25$(OH)_2D_3$. These findings indicated that the compounds with phenyl-pyrrolyl pentane skeleton are potentially applicable for cancer therapy as non-secosteroidal VDR ligands.

4. Experimental sections

4.1. Chemistry experiment

4.1.1. Materials and instruments

All reagents and reactants were purchased from commercial suppliers unless additional informed. ^1H NMR and ^{13}C NMR were recorded employing Bruker AV-300 or AV-500 instruments using $CDCl_3$. Chemical shifts are reported in d (ppm) units relative to the internal standard tetramethylsilane (TMS). The reactions were monitored by thin layer chromatography (TLC). Column chromatography separations were progressed on silica gel (200–300 mesh).

4.1.2. Purity analysis

The purity of the synthesized compounds were measured by high performance liquid chromatography (HPLC, Shimadzu LC-2010 system, Kyoto, Japan) equipped with a Diamonsil C18 column (5 μm particle size, 250 mm × 4.6 mm). The mobile phase consisted of acetonitrile and water with a flow rate of 1.0 mL/min. The detection wavelength was 540 nm and sample injected volume was 20 μL. All compounds evaluated for VDR agonistic potency had a purity of ≥95%.

4.1.3. General procedure for the synthesis of phenyl-pyrrolyl pentane derivatives (**4a**–**4r**, **5a**–**5r**, **6a**–**6b**, **7a**–**7b**)

*4.1.3.1. Methyl (5-(3-(4-(3,3-dimethyl-2-oxobutoxy)-3-methylphenyl)pentan-3-yl)-1-ethyl-1H-pyrrole-2-carbonyl)-L-alloisoleucinate (**4a**).* To a solution of compound 3 (0.50 g, 1.2 mmol) in $CHCl_3$ (10 mL) was added EDCI (0.25 g, 1.3 mmol) and HOBT (0.18 g, 1.3 mmol). After stirring at 25 °C for 2.0 h, L-isoleucine (0.24 g,

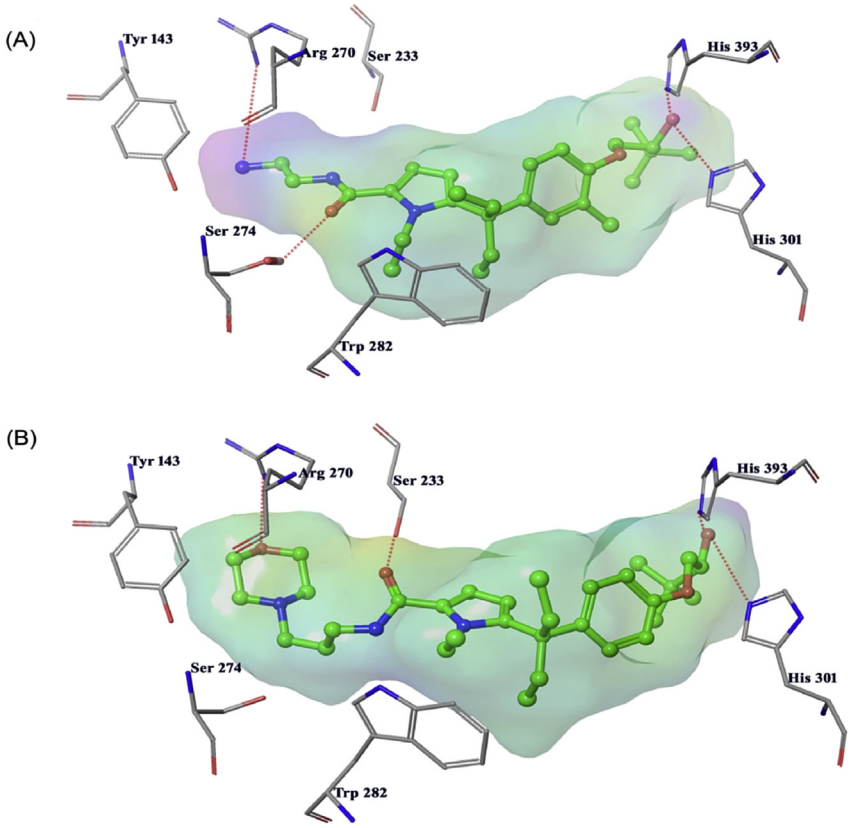


Fig. 4. Binding models of compounds **5k** and **5i** docked into VDR ligand binding domain (VDR LBD).

1.3 mmol) and Et_3N (0.61 g, 6.0 mmol) were added, the reaction mixture was stirred at room temperature overnight and poured into H_2O. The solution was extracted with ethyl acetate (3 × 15 mL) and the organic layer was washed with brine, then dried over $MgSO_4$ and filtered. The ethyl acetate extracts were concentrated. The oil was purified by column chromatography with petroleum-ether/ethyl acetate (4/1, v/v) to give compound 4a as white oil (0.73 g, 73% yield). HRMS, ESI^+, *m/z*: calcd for $C_{32}H_{48}N_2O_5$ $(M+H)^+$ 541.3636 found 541.3639. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.02 (1H, s), 6.98 (1H, d, *J* = 8.4 Hz), 6.54 (1H, d, *J* = 1.8 Hz), 6.50 (1H, d, *J* = 8.4 Hz), 6.27 (1H, d, *J* = 1.8 Hz), 4.84 (2H, s), 4.63 (1H, m), 4.28 (2H, q, *J* = 7.2 Hz), 3.73 (3H, s), 2.26 (3H, s), 1.93 (6H, m), 1.48 (1H, m), 1.34 (3H, t, *J* = 7.2 Hz), 1.12 (9H, s), 0.91 (6H, m), 0.65 (6H, t, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 210.02, 172.92, 161.59, 154.11, 140.67, 131.15, 130.47, 125.84, 125.03, 123.73, 111.57, 110.20, 69.23, 56.16, 51.98, 44.95, 43.71, 38.19, 30.36, 26.53, 25.41, 17.18, 16.66, 15.48, 11.56, 8.54.

*4.1.3.2. Ethyl N-(5-(3-(4-(3,3-dimethyl-2-oxobutoxy)-3-methylphenyl)pentan-3-yl)-1-ethyl-1H-pyrrole-2-carbonyl)-N-methylglycinate (**4b**).* To a solution of compound 3 (0.50 g, 1.2 mmol) in CH_3CN (10 mL) was added 4-dimethylaminopyridine (0.59 g, 4.8 mmol) and 4-nitrobenzenesulfonyl chloride (0.28 g, 1.3 mmol). After stirring at 70 °C for 2.0 h, ethyl sarcosinate hydrochloride (0.20 g, 1.3 mmol) was added. The reaction mixture was stirred overnight and poured into H_2O. The solution was extracted with ethyl acetate (3 × 10 mL) and the organic layer was washed with brine, then dried over $MgSO_4$ and filtered. The ethyl acetate extracts were concentrated. The oil was purified by column chromatography with petroleumether/ethyl acetate (5/1, v/v) to give compound **4b** as white oil (0.51 g, 81% yield). HRMS, ESI^+, *m/z*: calcd for $C_{30}H_{44}N_2O_5$ $(M+H)^+$ 513.3323, found 513.3329. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.01 (1H, s), 6.95 (1H, d, *J* = 7.3 Hz), 6.50 (1H, d, 1.8 Hz), 6.47 (1H, d, *J* = 7.3 Hz), 6.05 (1H, d, *J* = 1.8 Hz), 4.82 (2H, s), 4.15 (6H, m), 3.14 (3H, s), 2.24 (3H, s), 1.88 (4H, q, *J* = 7.5 Hz), 1.31 (3H, t, *J* = 7.2 Hz), 1.12 (9H, s), 0.64 (6H, t, *J* = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 190.32, 169.54, 162.35, 154.83, 140.67, 130.57, 130.41, 125.89, 125.79, 123.03, 110.12, 69.64, 61.15, 45.10, 43.04, 30.82, 26.35, 17.11, 16.61, 14.13, 8.64.

*4.1.3.3. N-(2-(diethylamino)ethyl)-5-(3-(4-(3,3-dimethyl-2-oxobutoxy)-3-methylphenyl)pentan-3-yl)-1-ethyl-1H-pyrrole-2-carboxamide (**4c**).* In the same method as **4a**, **4c** was prepared from 3 and N, N-diethylethylenediamine. White oil, 0.53 g, 85% yield. HRMS, ESI^+, *m/z*: calcd for $C_{31}H_{49}N_3O_3(M+H)^+$ 512.3847 found 512.3853. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.02 (1H,s), 6.98 (1H, d, *J* = 8.6 Hz), 6.70 (1H, d, *J* = 1.5 Hz), 6.51 (1H, d, *J* = 8.6 Hz), 6.46 (1H, d, *J* = 1.5 Hz), 4.84 (2H,s), 4.30 (2H, q, *J* = 7.2 Hz), 3.75 (2H, q, *J* = 6.0 Hz), 3.11 (6H, m), 2.25 (3H,s), 1.94 (4H, q, *J* = 7.2 Hz), 1.34 (9H, m), 1.26 (9H,s), 0.65 (6H, t, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 210.32, 162.12, 154.42, 140.34, 130.88, 130.37, 125.94, 125.40, 124.38, 124.32, 111.36, 110.15, 69.32, 51.84, 46.98, 44.97, 43.59, 36.78, 33.60, 30.53, 26.07, 17.25, 16.61, 11.80, 8.58.

*4.1.3.4. 5-(3-(4-(3,3-Dimethyl-2-oxobutoxy)-3-methylphenyl)pentan-3-yl)-N-(2-(dimethlamino)ethyl)-1-ethyl-1H-pyrrole-2-carboxamide (**4d**).* In the same method as **4a**, **4d** was prepared from 3 and 2-aminoethyldime-thylamine. White oil, 0.47 g, 81% yield. HRMS, ESI^+, *m/z*: calcd for $C_{29}H_{45}N_3O_3$ $(M+H)^+$ 484.3534 found 484.3539. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.98 (1H, s), 6.94 (1H, d, *J* = 8.4 Hz), 6.94 (1H, d, *J* = 1.8 Hz), 6.56 (1H, d, *J* = 8.4 Hz), 6.45 (1H, d, *J* = 1.8 Hz), 5.06 (2H, s), 4.27 (2H, d, *J* = 6.9 Hz), 3.28 (2H, q,

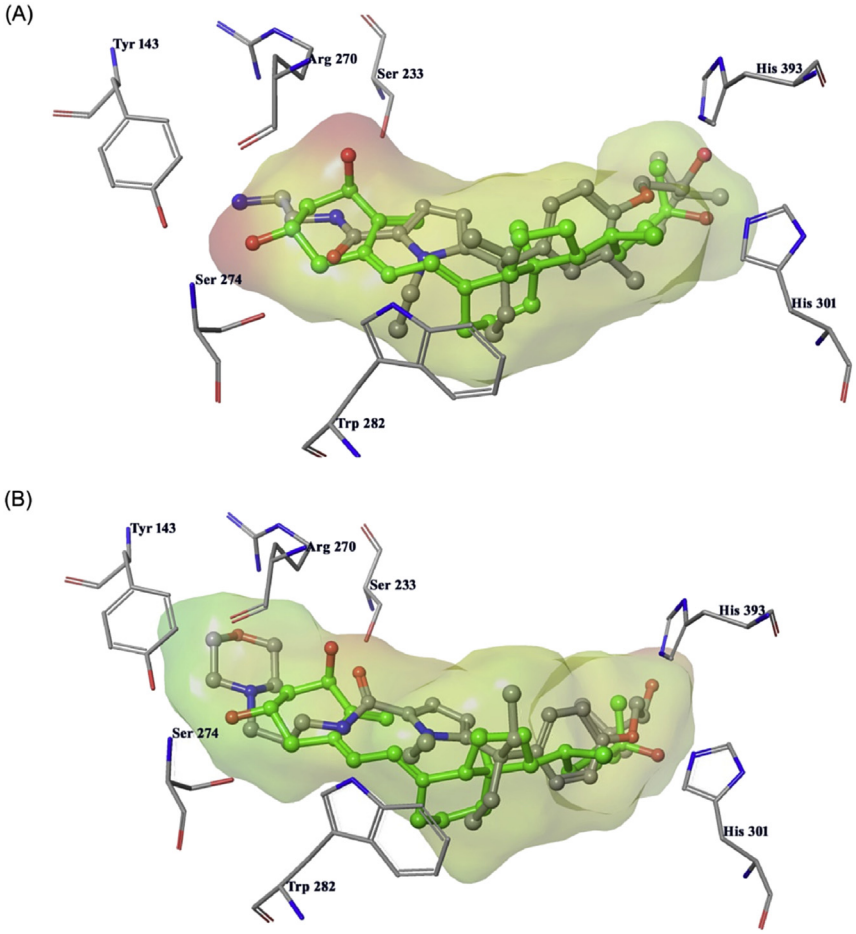


Fig. 5. Structures of VDR LBD-**5k** and VDR LBD-**5i** complexes overlapped with the VDR LBD-1α,25(OH)$_2$D$_3$ complex.

J = 6.3 Hz), 2.63 (2H, t, J = 6.3 Hz), 2.38 (6H, s), 2.15 (3H, s), 1.89 (4H, q, J = 6.9 Hz), 1.23 (3H, q, J = 6.9 Hz). 1.11 (9H, s), 0.65 (6H, q, J = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 210.34, 162.45, 153.94, 140.77, 131.35, 130.43, 124.93, 123.15, 118.69, 110.73, 110.13, 69.47, 58.04, 45.82, 44.81, 43.74, 34.68, 30.21, 26.36, 17.23, 16.64, 8.54.

*4.1.3.5. 5-(3-(4-(3,3-Dimethyl-2-oxobutoxy)-3-methylphenyl)pentan-3-yl)-N-(3-(dimethylamino)propyl)-1-ethyl-1H-pyrrole-2-carboxamide (**4e**).* In the same method as **4a**, **4e** was prepared from 3 and 1-amino-3-dimethylaminopropane. White oil, 0.48 g, 86% yield. HRMS, ESI$^+$, m/z: calcd for $C_{30}H_{47}N_3O_3$ $(M+H)^+$ 498.3691 found 498.3694. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.03 (1H, s), 6.97 (1H, d, J = 7.8 Hz), 6.53 (1H, d, J = 1.8 Hz), 6.49 (1H, d, J = 8.7 Hz), 6.26 (1H, d, J = 1.8 Hz), 4.85 (2H, s), 4.31 (2H, q, J = 6.9 Hz), 3.45 (2H, m), 2.68 (2H, t, J = 6.6 Hz), 2.41 (6H, s), 2.26 (3H, s), 1.91 (6H.m), 1.37 (3H, t, J = 6.9 Hz), 1.12 (9H, s), 0.66 (6H, t, J = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 210.29, 162.30, 153.99, 140.77, 131.17, 130.46, 125.79, 124.85, 123.62, 69.54, 58.24, 44.86, 43.69, 35.58, 30.27, 26.66, 17.25, 8.66.

*4.1.3.6. N-(3-(Diethylamino)propyl)-5-(3-(4-(3,3-dimethyl-2-oxobutoxy)-3-methylphenyl)pentan-3-yl)-1-ethyl-1H-pyrrole-2-carboxamide (**4f**).* In the same method as **4a**, **4f** was prepared from 3 and 3-diethylaminopropylamine. Yellow oil, 0.52 g, 83% yield. HRMS, ESI$^+$, m/z: calcd for $C_{32}H_{51}N_3O_3$ $(M+H)^+$ 526.4003 found 526.4014. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.99 (1H, s), 6.97 (1H, d, J = 8.7), 6.50 (1H, d, J = 1.8 Hz), 6.47 (1H, d, J = 8.7 Hz), 6.27 (1H, d, J = 1.8 Hz), 4.82 (2H, s), 4.31 (2H, q, J = 8.1 Hz), 3.34 (2H, m), 2.72 (6H, m), 2.26 (3H, s), 1.86 (6H, m), 1.32 (3H, t, J = 8.1 Hz), 1.24 (9H, s), 1.09 (6H, t, J = 7.2 Hz), 0.64 (6H, t, J = 7.2 Hz). ^{13}C NMR 75 MHz, $CDCl_3$) δ: 210.17, 162.37, 153.98, 140.84, 131.15, 125.97, 124.38, 112.07, 110.10, 69.53, 51.03, 46.57, 45.85, 44.86, 43.61, 37.95, 26.65, 24.53, 17.23, 9.77, 8.53.

*4.1.3.7. 5-(3-(4-(3,3-Dimethyl-2-oxobutoxy)-3-methylphenyl)pentan-3-yl)-1-ethyl-N-(prop-2-yn-1-yl)-1H-pyrrole-2-carboxamide (**4g**).* In the same method as **4a**, **4g** was prepared from 3 and 2-propynylamine. White oil, 0.38 g, 71% yield. HRMS, ESI$^+$, m/z: calcd for $C_{28}H_{38}N_2O_3$ $(M+H)^+$ 451.2955 found 451.2957. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.02 (1H, s), 6.98 (1H, d, J = 6.6 Hz), 6.60 (1H, d, J = 1.8 Hz), 6.52 (1H, d, J = 6.6 Hz), 6.21 (1H, d, J = 1.8 Hz), 5.92 (1H, bs), 4.86 (1H. s), 4.34 (2H, q, J = 6.9 Hz), 4.13 (1H, m), 2.25 (3H, s), 1.95 (4H, q, J = 6.3 Hz), 1.40 (3H, J = 6.9 Hz), 1.27 (9H, s), 0.67 (6H, t, J = 6.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 210.10, 161.42, 154.09, 149.65, 131.30, 130.48, 125.93, 123.39, 111.90, 110.08, 80.04, 71.30, 69.52, 44.94, 43.76, 30.27, 26.36, 17.21, 8.52.

*4.1.3.8. N-(2,2-Dimethoxyethyl)-5-(3-(4-(3,3-dimethyl-2-oxobutoxy)-3-methylphenyl)pentan-3-yl)-1-ethyl-1H-pyrrole-2-carboxamide (**4h**).* In the same method as **4a**, **4h** was prepared from 3 and 2,2-dimethoxyethylamine. White oil, 0.49 g, 84% yield. HRMS, ESI$^+$, m/zm/z: calcd for $C_{29}H_{44}N_2O_4$ $(M+H)^+$ 501.3323 found 501.3325. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.01 (1H, s), 6.96 (1H, d, J = 10.5 Hz), 6.55 (1H, d, J = 16 Hz), 6.51 (1H, d, J = 10.5 Hz), 6.19 (1H, d, J = 16 Hz), 4.84 (2H, s), 4.42 (1H, t, J = 5.4 Hz), 4.33 (2H, q, J = 8.2 Hz), 3.47 (2H, t, J = 5.4 Hz), 3.41 (6H, s), 2.24 (3H, s), 1.90 (4H,

q, J = 7.2 Hz), 1.36 (3H, t, J = 8.2 Hz), 1.26 (9H, s), 0.64 (6H, t, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 210.17, 161.23, 140.69, 130.48, 125.92, 125.81, 124.72, 111.52, 110.14, 103.00, 69.60, 54.43, 44.95, 43.69, 40.69, 54.43, 44.95, 43.69, 40.69, 30.36, 26.35, 26.05, 17.22, 16.66, 8.54.

*4.1.3.9. 5-(3-(4-(3,3-Dimethyl-2-oxobutoxy)-3-methylphenyl)pentan-3-yl)-1-ethyl-N-(3-morpholinopropyl)-1H-pyrrole-2-carboxamide (**4i**).* In the same method as **4a**, **4i** was prepared from 3 and 3-morpholinopropan-1-amine. Light yellow oil, 0.53 g, 82% yield. HRMS, ESI$^+$, m/z: calcd for $C_{32}H_{49}N_3O_4$ $(M+H)^+$ 540.3796 found 540.3802. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.02 (1H, s), 6.99 (1H, d, J = 8.4 Hz), 6.58 (1H, d, J = 1.8 Hz), 6.51 (1H, d, J = 8.4 Hz), 6.21 (1H, d, J = 1.8 Hz), 4.85 (2H, s), 4.34 (2H, q, J = 7.2 Hz), 3.68 (4H, m), 3.45 (2H, m), 2.56 (6H, m), 2.21 (3H, s), 1.95 (4H, q, J = 7.2 Hz), 1.35 (3H, t, J = 7.2 Hz), 0.65 (6H, t, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 210.13, 162.13, 154.06, 140.82, 131.22, 130.39, 125.89, 124.44, 111.33, 110.17, 69.52, 66.23, 58.33, 53.61, 45.80, 44.87, 43.63, 39.11, 30.08, 26.36, 24.45, 17.27, 8.49.

*4.1.3.10. N-(2-Bromoethyl)-5-(3-(4-(3,3-dimethyl-2-oxobutoxy)-3-methylphenyl)pentan-3-yl)-1-ethyl-1H-pyrrole-2-carboxamide (**4j**).* In the same method as **4a**, **4j** was prepared from 3 and 2-bromoethylamine hydrobromide. Light yellow oil, 0.45 g, 73% yield. HRMS, ESI$^+$, m/z: calcd for $C_{29}H_{39}BrN_2O_3$ $(M\text{-}Br+H)^+$ 439.2955 found 439.2960. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.01 (1H, s), 6.96 (1H, d, J = 8.1 Hz), 6.54 (1H, d, J = 1.8 Hz), 6.51 (1H,d, J = 8.1 Hz), 6.47 (1H, d, J = 1.8 Hz), 4.82 (2H, s), 4.32 (2H, q, J = 7.2 Hz), 4.23 (2H, t, J = 8.7 Hz), 3.99 (2H, t, J = 8.7 Hz), 2.24 (3H, s), 1.92 (4H, q, J = 7.5 Hz), 1.34 (3H, t, J = 7.2 Hz), 1.25 (9H,s), 0.67 (6H, t, J = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 209.35, 154.03, 140.85, 131.65, 130.46, 125.78, 124.44, 114.72, 110.21, 69.72, 65.90, 55.18, 44.94, 43.48, 30.42, 26.36, 16.79, 16.65, 8.58.

*4.1.3.11. N-(2-Aminoethyl)-5-(3-(4-(3,3-dimethyl-2-oxobutoxy)-3-methylphenyl)pentan-3-yl)-1-ethyl-1H-pyrrole-2-carboxamide (**4k**).* In the same method as **4a**, **4k** was prepared from 3 and ethylenediamine. White oil, 0.44 g, 80% yield. HRMS, ESI$^+$, m/z: calcd for $C_{29}H_{41}N_3O_3$ $(M+H)^+$ 456.3221 found 456.3225. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.10 (1H, s), 6.94 (1H, d, J = 8.1 Hz), 6.56 (1H, d, J = 1.6 Hz), 6.48 (1H, d, J = 8.1 Hz), 6.43 (1H, d, J = 1.6 Hz), 5.04 (2H, s), 4.21 (2H, q, J = 6.5 Hz), 3.50 (2H, bs), 3.05 (2H, bs), 2.18 (3H,s), 1.89 (4H, q, J = 6.9 Hz), 1.25 (3H, t, J = 6.6 Hz), 1.21 (9H,s), 0.60 (6H, q, J = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 210.17, 160.23, 153.89, 140.86, 131.25, 130.42, 125.84, 125.12, 113.38, 69.51, 44.86, 43.75, 30.22, 26.34, 17.20, 16.61, 8.55.

*4.1.3.12. N-(2-Cyanoethyl)-5-(3-(4-(3,3-dimethyl-2-oxobutoxy)-3-methylphenyl)pentan-3-yl)-1-ethyl-N-methyl-1H-pyrrole-2-carboxamide (**4l**).* In the same method as **4b**, **4l** was prepared from 3 and 3-methylaminopropionitrile. White oil, 0.43 g, 75% yield. HRMS, ESI$^+$, m/z: calcd for $C_{29}H_{41}N_3O_3$ $(M+H)^+$ 480.3221 found 480.3216. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.03 (1H, s), 6.98 (1H, d, J = 8.7 Hz), 6.56 (1H, d, J = 1.8 Hz), 6.51 (1H, d, J = 8.7 Hz), 6.08 (1H, d, J = 1.8 Hz), 4.86 (2H, s), 4.13 (2H, q, J = 7.2 Hz), 3.71 (2H, t, J = 6.6 Hz), 3.25 (3H, s), 2.72 (2H, t, J = 6.6 Hz), 2.21 (3H, s), 1.92 (4H, q, J = 7.5 Hz), 1.36 (3H, t, J = 7.2 Hz), 1.26 (9H, s), 0.67 (6H, t, J = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 210.11, 164.61, 154.06, 140.56, 130.65, 130.52, 125.87, 123.36, 122.78, 113.72, 110.10, 69.55, 45.14, 45.07, 43.12, 30.70, 26.36, 17.20. 16.66, 16.27, 8.63.

*4.1.3.13. N-Allyl-5-(3-(4-(3,3-dimethyl-2-oxobutoxy)-3-methylphenyl)pentan-3-yl)-1-ethyl-N-methyl-1H-pyrrole-2-carboxamide (**4m**).* In the same method as **4b**, **4m** was prepared from 3 and N-allylmethylamine. White oil, 0.41 g, 73% yield. HRMS, ESI$^+$, m/z: calcd for $C_{29}H_{42}N_2O_3$ $(M+H)^+$ 467.3268 found 467.3259. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.02 (1H, s), 6.98 (1H, d, J = 8.4 Hz), 6.49 (1H,d, J = 1.8 Hz), 6.48 (1H, d, J = 8.4 Hz), 6.07 (1H, d, J = 1.8 Hz), 5.81 (1H, m), 5.18 (1H, m), 4.83 (2H, s), 4.08 (4H, m), 3.02 (3H, s), 2.25 (3H, s), 1.90 (4H, q, J = 7.5 Hz), 1.34 (3H, t, J = 7.2 Hz), 1.25 (9H, s), 0.65 (6H, t, J = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.32, 152.42, 140.75, 133.35, 130.60, 130.22, 125.87, 125.77, 122.67, 117.11, 112.71, 110.09, 69.64, 45.10, 42.94, 30.83, 26.35, 17.23, 16.62, 8.65.

*4.1.3.14. 5-(3-(4-(3,3-Dimethyl-2-oxobutoxy)-3-methylphenyl)pentan-3-yl)-1-ethyl-N-methyl-N-phenyl-1H-pyrrole-2-carboxamide (**4n**).* In the same method as **4b**, **4n** was prepared from 3 and monomethylaniline. Yellow oil, 0.41 g, 68% yield. HRMS, ESI$^+$, m/z: calcd for $C_{32}H_{42}N_2O_3$ $(M+H)^+$ 503.3268 found 503.3258. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.26 (3H, m), 7.15 (1H, d, J = 7.2 Hz), 7.05 (1H, s), 7.03 (1H, s), 6.81 (1H, d, J = 8.7 Hz), 6.73 (1H, d, J = 1.8 Hz), 6.41 (1H, d, J = 8.7 Hz), 6.38 (1H, d, J = 1.8 Hz), 4.82 (2H, s), 4.23 (2H, q, J = 7.2 Hz), 3.40 (3H, s), 2.21 (3H, s), 1.68 (4H, m), 1.42 (3H, t, J = 7.2 Hz), 1.26 (9H, s), 0.43 (6H, t, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 210.05, 163.78, 153.91, 146.01, 140.67, 130.29, 128.93, 126.68, 126.19, 125.68, 122.80, 116.50, 109.98, 69.67, 44.76, 43.30, 37.80, 30.50, 26.37, 17.40, 16.65, 8.47.

*4.1.3.15. N,N-Bis(2-Cyanoethyl)-5-(3-(4-(3,3-dimethyl-2-oxobutoxy)-3-methylphenyl)-pentan-3-yl)-1-ethyl-1H-pyrrole-2-carboxamide (**4o**).* In the same method as **4b**, **4o** was prepared from 3 and 3.3'-iminodipropionitrile. White oil, 0.45 g, 72% yield. HRMS, ESI$^+$, m/z: calcd for $C_{31}H_{42}N_4O_3$ $(M+H)^+$ 519.3330 found 519.3329. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.01 (1H, s), 6.96 (1H, d, J = 8.4 Hz), 6.59 (1H, d, J = 1.8 Hz), 6.51 (1H, d, J = 8.4 Hz), 6.00 (1H, d, J = 1.8 Hz), 4.85 (2H, s), 4.06 (2H, q, J = 7.2 Hz), 3.80 (2H, t, J = 6.6 Hz), 2.64 (2H, d, J = 6.6 Hz), 2.20 (3H, s), 1.91 (4H, q, J = 6.9 Hz), 1.35 (3H, t, J = 7.2 Hz), 1.23 (9H, s), 0.65 (6H, t, J = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 217.12, 165.32, 154.13, 140.37, 131.46, 130.33, 125.85, 123.65, 122.34, 117.56, 112.39, 110.31, 69.51, 45.07, 44.89, 43.06, 30.52, 26.64, 26.34, 17.20, 17.08, 16.65, 8.61.

*4.1.3.16. But-3-yn-2-yl 5-(3-(4-(3,3-dimethyl-2-oxobutoxy)-3-methylphenyl)pentan-3-yl)-1-ethyl-1H-pyrrole-2-carboxylate (**4p**).* To a solution of compound 3 (0.50 g, 1.2 mmol) in CH_3Cl (10 mL) was added 4-dimethylaminopyridine (0.03 g, 0.24 mmol). After stirring at 0 °C for 0.5 h, EDCl (0.25 g, 1.3 mmol) and but-3-yn-2-ol (0.09 g, 1.3 mmol) were added. The reaction mixture was stirred at 60 °C overnight and poured into H_2O. The solution was extracted with ethyl acetate (3 × 10 mL) and the organic layer was washed with brine, then dried over $MgSO_4$ and filtered. The ethyl acetate extracts were concentrated. The oil was purified by column chromatography with petroleumether/ethyl acetate (25/1, v/v) to give compound 4p as white oil (0.46 g, 83% yield). HRMS, ESI$^+$, m/z: calcd for $C_{29}H_{39}NO_4$ $(M+H)^+$ 466.2952 found 466.2955. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.01 (1H, s), 6.98 (1H, d, J = 8.4 Hz), 6.76 (1H, d, J = 2.1 Hz), 6.59 (1H, d, J = 2.1 Hz), 6.53 (1H, d, J = 8.4 Hz), 5.57 (1H, m), 4.86 (2H, s), 4.29 (2H, q, J = 7.2 Hz), 3.72 (1H, m), 2.28 (3H, s), 1.95 (4H, q, J = 6.9 Hz), 1.59 (3H, d, J = 6.9 Hz), 1.37 (3H, t, J = 7.2 Hz), 1.25 (9H, s), 0.66 (6H, t, J = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 210.06, 159.85, 154.10, 140.53, 131.90, 130.43, 127.11, 125.96, 125.77, 119.99, 118.03, 110.21, 82.78, 72.57, 69.62, 59.16, 44.88, 44.02, 30.36, 26.36, 26.07, 21.42, 17.04, 16.68, 8.53.

*4.1.3.17. But-3-yn-1-yl 5-(3-(4-(3,3-dimethyl-2-oxobutoxy)-3-methylphenyl)pentan-3-yl)-1-ethyl-1H-pyrrole-2-carboxylate (**4q**).* In the same method as **4p**, **4q** was prepared from 3 and 3-butyn-1-ol. White oil, 0.36 g, 78% yield. HRMS, ESI$^+$, m/z: calcd for $C_{29}H_{39}NO_4$ $(M+H)^+$ 466.2952 found 466.2953. ^{1}H NMR (300 MHz,

$CDCl_3$) δ: 7.02 (1H, s), 6.98 (1H, d, J = 7.8 Hz), 6.73 (1H, d, J = 1.8 Hz), 6.58 (1H, d, J = 1.8 Hz), 6.51 (1H, d, J = 7.8 Hz), 4.84 (2H, s), 4.30 (4H, m), 3.76 (1H, s), 2.60 (2H, m), 2.26 (3H, s). 1.94 (4H, q, J = 7.2 Hz), 1.36 (3H, t, J = 7.2 Hz) 1.25 (9H, s), 0.65 (6H, t, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 210.31, 162.32, 154.09, 140.49, 131.85, 130.44, 126.57, 125.95, 125.76, 117.88, 117.49, 110.17, 80.29, 69.85, 69.60, 61.44, 50.80, 44.90, 44.01, 30.42, 26.67, 26.36, 26.21, 19.18, 17.07, 16.68, 14.45, 8.55.

*4.1.3.18. 4-Ethoxy-4-oxobutan-2-yl 5-(3-(4-(3,3-dimethyl-2-oxobutoxy)-3-methylphenyl)pentan-3-yl)-1-ethyl-1H-pyrrole-2-carboxylate (**4r**).* In the same method as **4p**, **4r** was prepared from 3 and Ethyl 3-hydroxybutyrate. White oil, 0.43 g, 81% yield. HRMS, ESI^+, m/z: calcd for $C_{31}H_{45}NO_6$ $(M+H)^+$ 528.3320 found 528.3321. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.01 (1H, s), 6.96 (1H, d, J = 8.4 Hz), 6.64 (1H, d, J = 1.8 Hz), 6.55 (1H, d, J = 1.8 Hz), 6.50 (1H, d, J = 8.4 Hz), 5.37 (1H, q, J = 6.6 Hz), 4.84 (2H, s), 4.26 (2H, q, J = 7.2 Hz), 4.10 (2H, q, J = 7.2 Hz), 2.65 (2H, m), 2.25 (3H, s), 1.92 (4H. q, J = 7.3 Hz), 1.32 (6H, m), 1.25 (9H, s), 1.19 (3H, t, J = 7.2 Hz), 0.64 (6H, t, J = 7.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 210.05, 170.50, 160.31, 154.07, 140.56, 231.64, 130.44, 126.66, 125.91, 125.76, 120.60, 117.52, 110.14, 64.24, 60.53, 42.73.41.23, 30.38, 26.36, 26.06, 20.15, 17.06, 16.66, 14.12, 8.52.

*4.1.3.19. Methyl (1-ethyl-5-(3-(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)pentan-3-yl)-1H-pyrrole-2-carbonyl)-L-alloisoleucinate (**5a**).* To a solution of compound **4a** (0.15 g, 0.28 mmol) in CH_3OH (10 mL) was added $NaBH_4$ (0.05 g, 1.40 mmol). The reaction mixture was stirred at room temperature for 2.0 h, then H_2O (10 mL) was added slowly. The solution was extracted with ethyl acetate (3 × 10 mL) and the organic layer was washed with brine, then dried over $MgSO_4$ and filtered. The ethyl acetate extracts were concentrated. The oil was purified by column chromatography with dichloromethane/methanol (16/1, v/v) to give compound 5a as white oil (0.14 g, 92% yield). HRMS, ESI^+, m/z: calcd for $C_{32}H_{50}N_2O_5$ $(M+H)^+$ 543.3792 found 543.3794. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.03 (1H, d, J = 9.0 Hz), 7.02 (1H, s), 6.73 (1H, d, J = 9.0 Hz), 6.55 (1H, d, J = 1.5 Hz), 6.28 (1H, d, J = 1.5 Hz), 4.63 (1H, m), 4.28 (2H, q, J = 7.2 Hz), 4.08 (1H, m), 3.85 (1H, m), 3.78 (1H, m), 3.73 (3H, s), 2.26 (3H, s), 1.93 (6H, m), 1.48 (1H, m), 1.34 (3H, t, J = 7.2 Hz), 1.12 (9H, s), 0.91 (6H, m), 0.65 (6H, t, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.33, 161.58, 154.43, 140.34, 131.18, 125.95, 125.47, 125.02, 111.53, 110.16, 69.23, 52.02, 44.94, 43.73, 38.23, 33.57, 30.36, 26.07, 25.41, 17.20, 15.48, 11.58, 8.55.

*4.1.3.20. Ethyl N-(1-ethyl-5-(3-(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)pentan-3-yl)-1H-pyrrole-2-carbonyl)-N-methylglycinate (**5b**).* In the same method as **5a**, **5b** was prepared from **4b**. White oil, 0.14 g, 93% yield. HRMS, ESI^+, m/z: calcd for $C_{30}H_{46}N_2O_5$ $(M+H)^+$ 515.3323 found 515.3332. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.02 (1H, d, J = 9.0 Hz), 7.01 (1H, s), 6.69 (1H, d, J = 9.0 Hz), 6.51 (1H, d, J = 1.8 Hz), 6.06 (1H, d, J = 1.8 Hz), 4.11 (5H, m), 3.85 (1H, m), 3.69 (3H, m), 3.15 (3H, s), 2.10 (3H, s), 1.92 (4H, q, J = 9.0 Hz), 1.23 (6H, m), 1.01 (9H, s), 0.65 (6H, t, J = 9.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.03, 154.68, 140.34, 130.46, 125.98, 125.32, 123.08, 110.08, 69.25, 52.06, 43.08, 30.81, 26.06, 17.09, 16.58, 8.63.

*4.1.3.21. N-(2-(Diethylamino)ethyl)-1-ethyl-5-(3-(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)pentan-3-yl)-1H-pyrrole-2-carboxamide (**5c**).* In the same method as **5a**, **5c** was prepared from 4c.White oil, 0.13 g, 87% yield. HRMS, ESI^+, m/z: calcd for $C_{31}H_{51}N_3O_3$ $(M+H)^+$ 514.4003 found 514.4004 ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.91 (1H, s), 6.85 (1H, d, J = 7.2 Hz), 6.42 (1H, d, J = 1.8 Hz), 6.38 (1H, d, J = 7.2 Hz), 6.21 (1H, d, J = 1.8 Hz), 4.27 (2H, q, J = 6.9 Hz), 4.00 (1H, m), 3.75 (1H, m), 3.63 (1H, m), 3.31 (2H, m), 2.34 (6H, m), 2.10 (3H, s), 1.82 (4H, q, J = 7.3 Hz), 1.57 (2H, m), 1.18 (2H, t, J = 6.9 Hz), 1.10 (6H, m), 0.93 (9H, s), 0.57 (6H, t, J = 7.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.72, 152.32, 142.45, 130.37, 125.92, 123.82, 111.38, 110.12, 69.27, 53.09, 46.82, 43.58, 40.17, 30.29, 26.05, 25.07, 17.28, 16.60, 11.44, 8.53.

*4.1.3.22. N-(2-(Dimethylamino)ethyl)-1-ethyl-5-(3-(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)pentan-3-yl)-1H-pyrrole-2-carboxamide (**5d**).* In the same method as **5a**, **5d** was prepared from **4d**. White oil, 0.14 g, 93% yield. HRMS, ESI^+, m/z: calcd for $C_{29}H_{47}N_3O_3$ $(M+H)^+$ 486.3690 found 486.3689. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.24 (1H, d, J = 8.7 Hz), 7.23 (1H, s), 6.73 (1H, d, J = 8.6 Hz), 6.54 (1H s), 6.27 (1H, s), 4.33 (2H, q, J = 6.9 Hz), 4.10 (1H,m), 3.98 (1H, m), 3.86 (1H, s), 3.45 (2H, t, J = 5.1 Hz), 2.51 (1H, t, J = 5.1 Hz), 2.28 (6H, s), 2.21 (3H, s), 1.93 (4H, q, J = 6.9 Hz), 1.37 (3H, t, J = 6.9 Hz), 1.02 (9H, s), 0.66 (6H, t, J = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.21, 154.37, 140.33, 131.04, 130.34, 125.90, 125.37, 124.51, 124.05, 111.82, 110.13, 69.30, 52.01, 47.19, 44.92, 43.61, 36.27, 33.58, 30.46, 26.06, 17.25, 16.61, 8.56.

*4.1.3.23. N-(3-(Dimethylamino)propyl)-1-ethyl-5-(3-(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)pentan-3-yl)-1H-pyrrole-2-carboxamide (**5e**).* In the same method as **5a**, **5e** was prepared from 4e. White solid, 0.13 g, 88% yield. HRMS, ESI^+, m/z: calcd for $C_{30}H_{49}N_3O_3$ $(M+H)^+$ 500.3847 found 500.3851. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.05 (1H, d, J = 8.1 Hz), 7.04 (1H, s), 6.72 (1H, d, J = 8.1 Hz), 6.53 (1H, d, J = 1.8 Hz), 6.11 (1H, d, J = 1.8 Hz), 4.35 (2H, q, J = 6.9 Hz), 4.10 (1H, m), 3.86 (1H, m), 3.71 (1H, m), 3.41 (2H, t, J = 6.3 Hz), 2.42 (2H, t, J = 6.3 Hz), 2.16 (9H, m), 1.93 (4H, q, J = 7.2 Hz), 1.72 (2H, m), 1.38 (3H, t, J = 6.9 Hz), 1.02 (9H, s), 0.67 (6H, t, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.05, 154.38, 140.46, 130.92, 130.38, 125.94, 125.37, 123.95, 111.29, 110.13, 69.28, 58.86, 44.93, 43.59, 39.25, 33.58, 26.41, 25.79, 17.30, 16.65, 1.02.

*4.1.3.24. N-(3-(Diethylamino)propyl)-1-ethyl-5-(3-(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)pentan-3-yl)-1H-pyrrole-2-carboxamide (**5f**).* In the same method as **5a**, **5f** was prepared from 4f. White oil, 0.13 g, 85% yield. HRMS, ESI^+, m/z: calcd for $C_{32}H_{53}N_3O_3$ $(M + H)^+$ 528.4160 found 528.4163. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.02 (1H, d, J = 8.7 Hz), 7.01 (1H, s), 6.69 (1H, d, J = 8.7 Hz), 6.57 (1H, d, J = 2.1 Hz), 6.50 (1H, d, J = 2.1 Hz), 4.31 (2H, q, J = 6.9 Hz), 4.08 (1H, m), 3.85 (1H, m), 3.69 (1H, m), 3.46 (2H, t, J = 6.9 Hz), 2.72 (6H, m), 2.21 (3H, s), 1.91 (4H, q, J = 7.2 Hz), 1.57 (2H, m), 1.35 (3H, t, J = 6.9 Hz), 1.01 (9H, s), 0.85 (6H, t, J = 6.6 Hz), 0.64 (6H, t, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.19, 154.36, 140.33, 131.03, 130.34, 125.89, 125.36, 124.50, 124.05, 111.77, 110.09, 69.24, 51.96, 47.14, 44.91, 43.63, 36.31, 33.58, 30.44, 26.07, 17.27, 16.64, 11.07, 8.57.

*4.1.3.25. 1-Ethyl-5-(3-(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)pentan-3-yl)-N-(prop-2-yn-1-yl)-1H-pyrrole-2-carboxamide (**5g**).* In the same method as **5a**, **5g** was prepared from 4**g**. White oil, 0.14 g, 93% yield. HRMS, ESI^+, m/z: calcd for $C_{28}H_{40}N_2O_3$ $(M + H)^+$ 453.3112 found 453.3119. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.02 (1H, d, J = 8.4 Hz), 7.01 (1H, s), 6.72 (1H, d, J = 8.4 Hz), 6.59 (1H, d, J = 1.8 Hz), 6.20 (1H, d, J = 1.8 Hz), 4.32 (2H, q, J = 6.9 Hz), 4.11 (3H, m), 3.88 (1H, m), 3.71 (1H, m), 2.50 (1H, s), 2.21 (3H, s), 1.92 (2H, q, J = 7.2 Hz), 1.37 (3H, t, J = 6.9 Hz), 1.01 (9H, s), 0.65 (6H, t, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.73, 154.44, 131.36, 130.35, 125.92, 125.48, 124.99, 123.40, 111.82, 110.11, 80.02, 77.30, 77.04, 76.62, 71.36, 69.23, 44.94, 43.78, 33.58, 30.26, 28.84, 26.07, 17.22, 16.67, 8.52.

4.1.3.26. N-(2,2-Dimethoxyethyl)-1-ethyl-5-(3-(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)pentan-3-yl)-1H-pyrrole-2-

*carboxamide (**5h**).* In the same method as **5a**, **5h** was prepared from **4h**. White oil, 0.12 g, 83% yield. HRMS, ESI$^+$, *m/z*: calcd for $C_{29}H_{46}N_2O_5$ (M+H)$^+$ 503.3479 found 503.3485. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.04 (1H, d, J = 8.1 Hz), 7.01 (1H, s), 6.72 (1H, d, J = 8.1 Hz), 6.56 (1H, d, J = 1.8 Hz), 6.19 (1H, d, J = 1.8 Hz), 4.93 (1H, t, J = 5.7 Hz), 4.32 (2H, q, J = 7.2 Hz), 4.10 (1H, m), 3.86 (1H, m), 3.70 (1H, m), 3.47 (2H, d, J = 5.7 Hz), 3.41 (6H, s), 2.17 (3H, s), 1.93 (4H, q, J = 7.5 Hz), 1.34 (3H, t, J = 7.2 Hz), 1.01 (9H, s), 0.62 (6H, t, J = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.02, 154.43, 141.92, 133.38, 131.13, 125.92, 125.46, 124.72, 123.93, 111.48, 110.15, 85.19, 54.44, 44.94, 43.70, 40.69, 30.32, 26.05, 17.22, 16.63, 8.53.

*4.1.3.27. 1-Ethyl-5-(3-(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)pentan-3-yl)-N-(3-morpholinopropyl)-1H-pyrrole-2-carboxamide (**5i**).* In the same method as **5a**, **5i** was prepared from **4i**. White oil, 0.13 g, 87% yield. HRMS, ESI$^+$, *m/z*: calcd for $C_{32}H_{51}N_3O_4$ (M+H)$^+$ 542.3952 found 542.3955. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.04 (1H, d, J = 8.4 Hz), 7.03 (1H, s), 6.72 (1H, d, J = 8.4 Hz), 6.60 (1H, d, J = 1.5 Hz), 6.12 (1H, d, J = 1.5 Hz), 4.35 (2H, q, J = 7.2 Hz), 4.12 (1H, m), 3.87 (1H, m), 3.70 (1H, m), 3.51 (6H, m), 2.46 (6H, m), 2.20 (3H, s), 1.93 (4H, q, J = 7.2 Hz), 1.71 (2H, m), 1.16 (9H, s), 0.66 (6H, t, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.07, 154.47, 140.44, 131.33, 130.28, 125.75, 125.44, 124.68, 124.07, 111.07, 110.03, 69.25, 66.23, 58.88, 53.83, 44.84, 43.62, 39.72, 33.61, 29.98, 26.07, 24.43, 17.27, 16.66, 8.46.

*4.1.3.28. N-(2-Bromoethyl)-1-ethyl-5-(3-(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)pentan-3-yl)-1H-pyrrole-2-carboxamide (**5j**).* In the same method as **5a**, **5j** was prepared from **4j**. White oil, 0.13 g, 91% yield. HRMS, ESI$^+$, *m/z*: calcd for $C_{27}H_{41}BrN_2O_3$ (M-Br+H)$^+$ 441.3112 found 441.3109. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.03 (1H, d, J = 6.4 Hz), 7.02 (1H, s), 6.72 (1H, d, J = 6.4 Hz), 6.54 (1H, d, J = 2.4 Hz), 6.47 (1H, d, J = 2.4 Hz), 4.31 (2H, d, J = 7.2 Hz), 4.23(2H, d, J = 8.7 Hz), 4.10 (1H, m), 3.88 (2H, d, J = 8.7 Hz), 3.85 (1H, m), 2.17 (3H, s), 1.91(4H, q, J = 7.2 Hz), 1.35 (3H, t, J = 7.2 Hz), 1.01 (9H, s), 0.63 (6H, t, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.32, 130.35, 125.91, 124.38, 114.69, 65.88, 55.21, 43.46, 30.41, 26.05, 16.77, 8.57.

*4.1.3.29. N-(2-Aminoethyl)-1-ethyl-5-(3-(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)pentan-3-yl)-1H-pyrrole-2-carboxamide (**5k**).* In the same method as **5a**, **5k** was prepared from **4k**.White oil, 0.14 g, 92% yield. HRMS, ESI$^+$, *m/z*: calcd for $C_{27}H_{43}N_3O_3$ (M+H)$^+$ 458.3377 found 458.3389. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.03 (1H, d, J = 7.5 Hz), 7.02 (1H, s), 6.78 (1H, d, J = 7.5 Hz), 6.56 (1H, d, J = 1.8 Hz), 6.22 (1H, d, J = 1.8 Hz), 4.32 (2H, q, J = 7.2 Hz), 4.11 (1H, m), 3.86 (1H, m), 3.68 (1H, m), 3.36 (2H, t, J = 5.7 Hz), 2.85 (2H, t, J = 5.7 Hz), 2.16 (3H, s), 1.92 (4H, q, J = 7.2 Hz), 1.36 (3H, t, J = 7.2 Hz), 1.00 (9H, s), 0.64 (6H, t, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.40, 154.42, 140.42, 131.17, 130.34, 125.92, 125.43, 124.58, 111.44, 110.12, 69.29, 44.91, 43.71, 41.48, 33.61, 30.24, 26.07, 17.25, 16.65, 8.53.

*4.1.3.30. N-(2-Cyanoethyl)-1-ethyl-5-(3-(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)pentan-3-yl)-N-methyl-1H-pyrrole-2-carboxamide (**5l**).* In the same method as **5a**, **5l** was prepared from **4l**. White oil, 0.13 g, 87% yield. HRMS, ESI$^+$, *m/z*: calcd for $C_{29}H_{43}N_3O_3$ (M+H)$^+$ 482.3377 found 482.3368. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.02 (1H, d, J = 9.0 Hz), 7.01 (1H, s), 6.63 (1H, d, J = 9.0 Hz), 6.46 (1H, d, J = 1.8 Hz), 5.99 (1H, d, J = 1.8 Hz), 4.04 (3H, m), 3.78 (1H, m), 3.63 (3H, m), 3.17 (3H, s), 2.63 (2H, t, J = 6.6 Hz), 2.11 (3H, s), 1.84 (2H, q, J = 7.5 Hz), 1.27 (3H, t, J = 7.2 Hz), 0.96 (9H, s), 0.58 (6H, t, J = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.02, 140.21, 130.68, 130.41, 125.97, 125.36, 123.37, 113.69, 110.05, 69.20, 45.07, 43.14, 33.57, 30.73, 26.07, 17.21, 16.64, 16.28, 8.63.

*4.1.3.31. N-Allyl-1-ethyl-5-(3-(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)pentan-3-yl)-N-methyl-1H-pyrrole-2-carboxamide (**5m**).* In the same method as **5a**, **5m** was prepared from **4m**. White oil, 0.14 g, 94% yield. HRMS, ESI$^+$, *m/z*: calcd for $C_{29}H_{44}N_2O_3$ (M+H)$^+$ 469.3425 found 469.3415. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.03 (1H, d, J = 8.7 Hz), 7.02 (1H, s), 6.69 (1H, d, J = 8.7 Hz), 6.49 (1H, d, J = 1.5 Hz), 5.78 (1H, m), 5.18 (2H, m), 4.10 (5H, m), 3.85 (1H, m), 3.70 (1H, m), 3.02 (3H, s), 2.24 (3H, s), 1.90 (4H, q, J = 7.5 Hz), 1.33 (3H, t, J = 7.2 Hz), 1.01 (9H, s), 0.65 (6H, t, J = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.31, 154.32, 140.39, 133.33, 130.48, 130.23, 125.97, 125.28, 122.70, 117.14, 112.74, 110.01, 69.20, 45.07, 42.96, 33.57, 30.84, 26.07, 17.26, 16.62, 8.66.

*4.1.3.32. 1-Ethyl-5-(3-(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)pentan-3-yl)-N-methyl-N-phenyl-1H-pyrrole-2-carboxamide (**5n**).* In the same method as **5a**, **5n** was prepared from **4n**. White oil, 0.13 g, 88% yield. HRMS, ESI$^+$, *m/z*: calcd for $C_{34}H_{44}N_2O_3$ (M+H)$^+$ 505.3425 found 505.3415. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.25 (3H, m), 7.05(2H, m), 6.82 (2H, m), 6.62 (1H, d, J = 8.4 Hz), 6.36 (1H, d, J = 1.8 Hz), 4.25 (2H, q, J = 7.2 Hz), 4.09 (1H, m), 3.85 (1H, m), 3.71 (1H, m), 3.42 (3H, s), 2.16 (3H, s), 1.66 (4H, q, J = 7.2 Hz), 1.41 (3H, t, J = 7.2 Hz), 1.03 (9H, s), 0.46 (6H, t, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.79, 154.21, 146.04, 140.34, 130.16, 130.04, 128.93, 126.68, 126.15, 125.80, 125.16, 123.85, 122.79, 116.48, 110.00, 69.25, 44.75, 43.30, 37.82, 33.58, 30.51, 26.07, 17.14, 16.61, 8.48.

*4.1.3.33. N,N-bis(2-Cyanoethyl)-1-ethyl-5-(3-(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)pentan-3-yl)-1H-pyrrole-2-carboxamide (**5o**).* In the same method as **5a**, **5o** was prepared from **4o**. White oil, 0.13 g, 88% yield. HRMS, ESI$^+$, *m/z*: calcd for $C_{31}H_{44}N_4O_3$ (M+H)$^+$ 521.3486 found 521.3484. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.94 (1H, d, J = 9.0 Hz), 6.93 (1H, s), 6.64 (2H, d, J = 9.0 Hz), 6.52 (1H, d, J = 1.5 Hz), 5.95 (1H, d, J = 1.5 Hz), 4.00 (3H, m), 3.78 (5H, m), 3.62 (1H, m), 2.58 (4H, t, J = 6.9 Hz), 2.12 (3H, s), 1.85 (4H, q, J = 7.5 Hz), 1.27 (3H, t, J = 7.2 Hz), 0.93 (9H, s), 0.59 (6H, t, J = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.07, 154.52, 139.95, 131.53, 130.24, 125.90, 125.50, 123.73, 123.23, 122.30, 117.52, 112.38, 110.22, 69.32, 45.07, 43.08, 33.60, 30.57, 26.07, 17.24, 8.62.

*4.1.3.34. But-3-yn-2-yl 1-ethyl-5-(3-(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)pentan-3-yl)-1H-pyrrole-2-carboxylate (**5p**).* In the same method as **5a**, **5p** was prepared from **4p**. White oil, 0.14 g, 95% yield. HRMS, ESI$^+$, *m/z*: calcd for $C_{29}H_{41}NO_4$ (M+H)$^+$ 468.3108 found 468.3108. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.04 (1H, d, J = 8.4 Hz), 7.03 (1H, s), 6.77 (1H, d, J = 2.4 Hz), 6.74 (1H, d, J = 9.0 Hz), 6.50 (1H, d, J = 2.1 Hz), 6.57 (1H, m), 4.23 (2H, q, J = 7.2 Hz), 4.13 (1H, m), 3.92 (1H, m), 3.75 (1H, m), 2.46 (1H, m), 2.22 (2H, s), 1.97 (4H, q, J = 7.5 Hz), 1.59 (3H, d, J = 6.6 Hz), 1.16 (9H,s), 0.67 (6H, t, J = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.13, 154.23, 140.21, 131.94, 130.30, 127.06, 125.90, 125.48, 118.01, 110.17, 82.78, 69.24, 59.16, 44.89, 44.04, 33.57, 26.07, 21.42, 17.05, 16.65, 8.53.

*4.1.3.35. But-3-yn-1-yl 1-ethyl-5-(3-(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)pentan-3-yl)-1H-pyrrole-2-carboxylate (**5q**).* In the same method as **5a**, **5q** was prepared from **4q**. White oil, 0.13 g, 87% yield. HRMS, ESI$^+$, *m/z*: calcd for $C_{29}H_{41}NO_4$ (M+H)$^+$ 468.3108 found 468.3110. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.03 (1H, d, J = 7.5 Hz), 7.02 (1H, s), 6.74 (1H, d, J = 1.8 Hz), 6.70 (1H, d, J = 7.5 Hz), 6.58 (1H, d, J = 1.8 Hz), 4.24 (4H, m), 4.11 (1H, m), 3.87 (1H, m), 3.71 (1H, m), 2.61 (2H, m), 2.20 (3H, s), 2.03 (1H, m), 1.95 (4H, q, J = 7.2 Hz), 1.36 (3H, t, J = 6.9 Hz), 1.01 (9H, s), 0.66 (6H, t, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.69, 154.42, 140.17, 131.89, 130.31, 126.86, 125.89, 125.47, 120.21, 117.86, 110.16,

80.30, 69.85, 69.24, 61.45, 44.90, 44.02, 33.57, 30.43, 26.07, 19.18, 17.08, 16.65, 8.55.

*4.1.3.36. 4-Hydroxybutan-2-yl 1-ethyl-5-(3-(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)pentan-3-yl)-1H-pyrrole-2-carboxylate (**5r**).* In the same method as **5a**, **5r** was prepared from **4r**. White oil, 0.14 g, 95% yield. HRMS, ESI$^+$, *m/z*: calcd for $C_{29}H_{45}NO_5$ $(M+H)^+$ 488.3371 found 488.3379. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.03 (1H, d, $J = 8.4$ Hz), 7.02 (1H, s), 6.77 (1H, d, $J = 8.4$ Hz), 6.67 (1H, d, $J = 1.8$ Hz), 6.57 (1H, d, $J = 1.8$ Hz), 5.38 (1H, m), 4.27 (2H, q, $J = 6.9$ Hz), 4.11 (2H, d, $J = 6.6$ Hz), 3.87 (1H, m), 3.72 (1H, m), 3.36 (1H, m), 2.19 (3H. s), 1.96 (4H, q, $J = 7.5$ Hz), 1.37 (3H, t, $J = 6.9$ Hz), 1.30 (3H, d, $J = 7.2$ Hz), 1.19 (2H, m), 1.02 (9H, m), 0.66 (6H, t, $J = 7.5$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.31, 154.44, 140.22, 131.68, 130.30, 126.61, 125.91, 125.46, 117.55, 110.23, 69.32, 66.75, 60.51, 51.64, 44.92, 43.94, 41.23, 33.59, 30.45, 26.06, 17.04, 14.41, 8.54.

*4.1.3.37. (5-(3-(4-(3,3-dimethyl-2-oxobutoxy)-3-methylphenyl)pentan-3-yl)-1-ethyl-1H-pyrrole-2-carbonyl)-L-alloisoleucine (**6a**).*
To a solution of compound **4a** (0.36 g, 0.68 mmol) in THF (10 mL) and H_2O (1.0 ml), LiOH. H_2O (0.14 g, 3.40 mmol) was added. The reaction mixture was stirred at room temperature overnight, then H_2O (10 mL) was added slowly and the pH value was adjusted to about 3–4. The solution was extracted with ethyl acetate (3 × 10 mL) and the organic layer was washed with brine, then dried over $MgSO_4$ and filtered. The ethyl acetate extracts were concentrated. The oil was purified by column chromatography with dichloromethane/methanol (25/1, v/v) to give compound 6a as white oil (0.28 g, 82% yield). HRMS, ESI$^+$, *m/z*: calcd for $C_{31}H_{46}N_2O_5$ $(M + H)^+$ 527.3479 found 527.3486. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.00 (1H, s), 6.96 (1H, d, $J = 8.7$ Hz), 6.69 (1H, d, $J = 8.7$ Hz), 6.49 (1H, d, $J = 1.8$ Hz), 6.34 (1H, d, $J = 1.8$ Hz), 4.82 (2H, s), 4.08 (3H, m), 2.23 (3H, s), 1.89 (6H, m), 1.44 (1H, m), 1.28 (12H, m), 0.82 (6H, m), 0.62 (6H, t, $J = 6.3$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 210.3, 174.7, 162.4, 155.4, 140.67, 131.07, 125.90, 124.87, 123.91, 111.78, 110.29, 59.4, 44.91, 43.60, 37.24, 26.08, 25.23, 16.61, 11.44, 8.56.

*4.1.3.38. N-(5-(3-(4-(3,3-Dimethyl-2-oxobutoxy)-3-methylphenyl) pentan-3-yl)-1-ethyl-1H-pyrrole-2-carbonyl)-N-methylglycine (**6b**).*
In the same method as **6a**, **6b** was prepared from **4b**. White oil, 0.28 g, 85% yield. HRMS, ESI$^+$, *m/z*: calcd for $C_{28}H_{44}N_2O_5$ $(M+H)^+$ 485.3010 found 485.3010. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.93 (1H, s), 6.86 (1H, d, $J = 6.9$ Hz), 6.58 (1H, d, $J = 6.9$ Hz), 6.41 (1H, s), 6.08 (1H, s), 4.80 (2H, s), 3.83 (4H, m), 3.43 (3H, s), 2.21 (3H, s), 1.85 (4H, q, $J = 6.9$ Hz), 1.24 (12H, m), 0.60 (6H, t, $J = 6.9$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 210.32, 173.13, 162.31, 153.99, 143.36, 130.50, 125.73, 110.13, 106.47, 69.58, 50.52, 45.03, 39.56, 30.78, 26.34, 17.08, 8.64.

*4.1.3.39. (1-Ethyl-5-(3-(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)pentan-3-yl)-1H-pyrrole-2-carbonyl)-L-alloisoleucine (**7a**).* To a solution of compound **6a** (0.15 g, 0.29 mmol) in CH_3OH (10 mL) was added $NaBH_4$ (0.05 g, 1.45 mmol). The reaction mixture was stirred at room temperature for 2.0 h, then H_2O (10 mL) was added slowly. The solution was extracted with ethyl acetate (3 × 10 mL) and the organic layer was washed with brine, then dried over $MgSO_4$ and filtered. The ethyl acetate extracts were concentrated. The oil was purified by column chromatography with dichloromethane/methanol (20/1, v/v) to give compound 7a as white oil (0.14 g, 92% yield). HRMS, ESI$^+$, *m/z*: calcd for $C_{31}H_{48}N_2O_5$ $(M + H)^+$ 529.3636 found 529.3641. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.00 (1H, s), 6.97 (1H, d, $J = 8.7$ Hz), 6.49 (1H, d, $J = 8.7$ Hz), 6.41 (1H, s), 6.35 (1H, s), 4.82 (2H, s), 3.95 (3H, m), 2.23 (3H, s), 1.95 (6H, m), 1.44 (1H, m), 1.23 (12H, m), 0.83 (6H, m), 0.61 (6H, t, $J = 6.6$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.71, 162.44, 153.37, 140.67, 131.07, 125.90, 124.87, 123.91, 111.78, 110.23, 69.64, 59.43, 44.36, 43.60, 37.24, 30.45, 26.08, 25.23, 16.61, 15.80, 11.41, 8.56.

*4.1.3.40. N-(1-Ethyl-5-(3-(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)pentan-3-yl)-1H-pyrrole-2-carbonyl)-N-methylglycine (**7b**).* In the same method as **7a**, **7b** was prepared from **6b**. White oil, 0.13 g, 87% yield. HRMS, ESI$^+$, *m/z*: calcd for $C_{28}H_{42}N_2O_5$ $(M+H)^+$ 487.3166 found 487.3175. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.02 (1H, d, $J = 8.7$ Hz), 6.99 (1H, s), 6.66 (1H, d, $J = 8.7$ Hz), 6.37 (1H, s), 6.03 (1H, s), 4.04 (1H, m), 3.91 (1H, m), 3.86 (4H, m), 3.72 (1H, m), 3.04 (3H, s), 2.21 (3H, s), 1.87 (4H, q, $J = 6.9$ Hz), 1.74 (3H, t, $J = 7.3$ Hz), 0.98 (9H, s), 0.61 (6H, t, $J = 6.9$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.12, 163.23, 154.39, 140.30, 130.36, 125.33, 123.35, 45.08, 33.60, 30.74, 26.07, 16.95, 8.64.

*4.1.4. General procedure for the synthesize of phenyl-pyrrolyl pentane derivatives (**8a**–**8e**, **9a**–**9e**, **10a**–**10b**, **11a**–**11b**)*

*4.1.4.1. 5-(3-(4-(3,3-dimethyl-2-oxobutoxy)-3-methylphenyl)pentan-3-yl)-1-ethyl-N-(4-(trifluoromethoxy)phenyl)-1H-pyrrole-2-carboxamide (**8a**).* In the same method as **4a**, **8a** was prepared from 3 and 4-(trifluoromethyl)aniline. White oil, 0.50 g, 75% yield. HRMS, ESI$^+$, *m/z*: calcd for $C_{32}H_{39}F_3N_2O_4$ $(M+H)^+$ 573.2935 found 573.2935. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.60 (1H, s), 7.57 (1H, s), 7.18 (1H, s), 7.15 (1H, s), 7.02 (1H, s), 7.01 (1H, d, $J = 8.4$ Hz), 6.71 (1H, d, $J = 1.8$ Hz), 6.52 (1H, d, $J = 8.4$ Hz), 6.38 (1H, d, $J = 1.8$ Hz), 4.88 (2H, s), 4.38 (2H, q, $J = 7.2$ Hz), 2.26 (3H, s), 1.94 (4H, q, $J = 7.2$ Hz), 1.37 (3H, t, $J = 7.2$ Hz), 1.27 (9H, s), 0.68 (6H, t, $J = 7.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 210.17, 159.77, 154.16, 144.81, 137.03, 131.64, 130.52, 125.95, 123.76, 121.62, 121.02, 112.47, 110.06, 69.41, 45.00, 43.99, 43.12, 30.24, 26.35, 17.21, 16.66, 8.51.

*4.1.4.2. 5-(3-(4-(3,3-Dimethyl-2-oxobutoxy)-3-methylphenyl)pentan-3-yl)-1-ethyl-N-(3-(trifluoromethyl)phenyl)-1H-pyrrole-2-carboxamide (**8b**).* In the same method as **4a**, **8b** was prepared from 3 and 3-aminobenzotrifluoride. White oil, 0.40 g, 72% yield. HRMS, ESI$^+$, *m/z*: calcd for $C_{32}H_{39}F_3N_2O_3$ $(M+H)^+$ 557.2986 found 557.2993. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.78 (2H, s), 7.42 (1H, m), 7.32 (1H, m), 7.04 (1H, s), 7.01 (1H, d, $J = 8.4$ Hz), 6.70 (1H, d, $J = 1.8$ Hz), 6.52 (1H, d, $J = 8.4$ Hz), 6.39 (1H, d, $J = 1.8$ Hz), 4.88 (2H, s), 4.38 (2H, q, $J = 7.2$ Hz), 2.26 (3H, s), 1.98 (4H, q, $J = 7.2$ Hz), 1.45 (3H, t, $J = 7.2$ Hz), 1.27 (9H, s), 0.68 (6H, t, $J = 7.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 210.17, 159.74, 154.17, 140.48, 138.92, 131.73, 130.52, 129.36, 126.04, 123.64, 122.82, 116.52, 112.63, 110.07, 69.42, 45.01, 43.99, 30.24, 26.35, 17.20, 8.51.

*4.1.4.3. 5-(3-(4-(3,3-Dimethyl-2-oxobutoxy)-3-methylphenyl)pentan-3-yl)-N-(4-ethoxyphenyl)-1-ethyl-1H-pyrrole-2-carboxamide (**8c**).* In the same method as **4a**, **8c** was prepared from 3 and phenetidine. White oil, 0.48 g, 78% yield. HRMS, ESI$^+$, *m/z*: calcd for $C_{33}H_{44}N_2O_4$ $(M+H)^+$ 533.3374 found 533.3381. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.44 (2H, m), 7.05 (1H, s), 7.01 (1H, d, $J = 8.4$ Hz), 6.88 (2H, m), 6.64 (1H, d, $J = 1.8$ Hz), 6.53 (1H, d, $J = 8.4$ Hz), 6.31(1H, d, $J = 1.8$ Hz), 4.87 (2H, s), 4.37 (2H, q, $J = 6.9$ Hz), 4.02 (2H, q, $J = 7.2$ Hz), 2.18 (3H, s), 1.96 (4H, q, $J = 7.2$ Hz), 1.42 (6H, m), 1.27 (9H, s), 0.68 (6H, t, $J = 7.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 210.3, 159.85, 154.49, 140.35, 131.11, 130.36, 125.95, 125.31, 121.86, 114.80, 111.70, 110.18, 69.27, 63.70, 46.21, 44.99, 36.47, 30.28, 26.01, 17.26, 14.83, 11.60, 8.54.

*4.1.4.4. 4-(Ethoxycarbonyl)phenyl 5-(3-(4-(3,3-dimethyl-2-oxobutoxy)-3-methylphenyl)pentan-3-yl)-1-ethyl-1H-pyrrole-2-carboxylate (**8d**).* In the same method as **4a**, **8d** was prepared from 3 and 4-hydroxybenzoic acid ethyl ester. White oil, 0.44 g, 68% yield. HRMS, ESI$^+$, *m/z*: calcd for $C_{34}H_{43}NO_6$ $(M+H)^+$ 562.3163 found 562.3176. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.02 (1H, s), 7.99 (1H,

s), 7.27 (1H, m), 7.10 (1H, s), 6.97 (1H, s), 6.93 (1H, d, $J = 8.4$ Hz), 6.86 (1H, d, $J = 1.8$ Hz), 6.63 (1H, d, $J = 1.8$ Hz), 6.45 (1H, d, $J = 8.4$ Hz), 4.78 (2H, s), 4.29 (4H, m), 2.20 (3H, s), 1.90 (4H, q, $J = 5.4$ Hz), 1.31 (6H, m), 1.18 (9H, s), 0.58 (6H, t, $J = 5.4$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 210.04, 158.60, 154.49, 140.29, 132.53, 130.99, 130.40, 128.26, 127.52, 126.07,125.74, 121.88, 119.14, 110.22, 69.56, 60.99, 44.94, 44.14, 30.38, 26.37, 16.97, 14.33, 8.55.

*4.1.4.5. 4-(2-Methoxy-2-oxoethyl)phenyl 5-(3-(4-(3,3-dimethyl-2-oxobutoxy)-3-methylphenyl)pentan-3-yl)-1-ethyl-1H-pyrrole-2-carboxylate (**8e**).* In the same method as **4a**, **8e** was prepared from 3 and p-hydroxybenzoate ethyl ester. White oil, 0.44 g, 68% yield. HRMS, ESI$^+$, *m/z*: calcd for $C_{34}H_{43}NO_6$ $(M+H)^+$ 562.3163 found 562.3173. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46 (2H, m), 7.28 (2H, m), 7.19 (1H, s), 7.13 (1H, d, $J = 8.4$ Hz), 7.06 (1H, d, $J = 2.1$ Hz), 6.81 (1H, d, $J = 2.1$ Hz), 6.67 (1H, d, $J = 8.4$ Hz), 4.99 (2H, s), 4.44 (2H, q, $J = 7.2$ Hz),3.87 (3H, s), 3.76 (2H, s), 2.42 (3H, s), 2.11 (4H, q, $J = 7.2$ Hz), 1.51 (3H, t, $J = 7.2$ Hz), 1.40 (9H, s), 0.82 (6H, t, $J = 7.1$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 210. 33, 173.54, 154.18, 140.38, 132.33, 130.42, 127.87, 126.06, 122.10, 118.80, 110.28, 69.62, 52.05, 44.13, 40.63, 30.43, 26.36, 16.98, 8.56.

*4.1.4.6. 1-Ethyl-5-(3-(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)pentan-3-yl)-N-(4-(trifluoromethoxy)phenyl)-1H-pyrrole-2-carboxamide (**9a**).* In the same method as 5a, **9a** was prepared from **8a**. White oil, 0.14 g, 92% yield. HRMS, ESI$^+$, *m/z*: calcd for $C_{32}H_{41}F_3N_2O_4$ $(M+H)^+$ 575.3091 found 575.3096. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.72 (2H, m), 7.41 (1H, m), 7.32 (1H, m), 7.05 (1H, d, $J = 8.1$ Hz), 7.04 (1H, s), 6.75 (1H, d, $J = 8.1$ Hz), 6.59 (1H, d, $J = 1.8$ Hz), 6.40 (1H, d, $J = 1.8$ Hz), 4.33 (2H, q, $J = 7.2$ Hz), 4.12 (1H, m), 3.88 (1H, m), 3.71 (1H, m), 2.25 (3H, s), 1.99 (4H, q, $J = 7.2$ Hz), 1.42 (3H, t, $J = 7.2$ Hz), 1.02 (9H, s), 0.63 (6H, t, $J = 7.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.73, 154.56, 140.20, 138.86, 131.82, 130.34, 129.40, 126.14, 122.85, 120.17, 116.51, 112.51, 110.21, 69.29, 59.62, 45.00, 44.01, 33.59, 30.42, 26.06, 17.06, 14.44, 8.52.

*4.1.4.7. 1-Ethyl-5-(3-(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)pentan-3-yl)-N-(3-(trifluoromethyl)phenyl)-1H-pyrrole-2-carboxamide (**9b**).* In the same method as **5a**, **9b** was prepared from **8b**. White oil, 0.13 g, 88% yield. HRMS, ESI$^+$, *m/z*: calcd for $C_{32}H_{41}F_3N_2O_3$ $(M+H)^+$ 559.3142 found 559.3149. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.66 (1H, s), 7.56 (1H, m), 7.28 (2H, m), 7.07 (1H, d, $J = 8.4$ Hz), 6.75 (1H, d, $J = 8.4$ Hz), 6.69 (1H, d, $J = 1.8$ Hz), 6.40 (1H, d, $J = 1.8$ Hz), 4.37 (2H, q, $J = 7.2$ Hz), 4.11 (1H, m), 3.88 (1H, m), 3.73 (1H, m), 2.29 (3H, s), 1.97 (4H, q, $J = 7.2$ Hz), 1.42 (3H, t, $J = 7.2$ Hz), 1.02 (9H, s), 0.69 (6H, t, $J = 7.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.76, 154.57, 144.88, 140.23, 131.74, 130.34, 125.94, 123.78, 112.56, 110.21, 59.62, 45.00, 44.01, 33.60, 30.43, 26.06, 17.06, 14.43, 8.52.

*4.1.4.8. N-(4-Ethoxyphenyl)-1-ethyl-5-(3-(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)pentan-3-yl)-1H-pyrrole-2-carboxamide (**9c**).* In the same method as **5a**, **9c** was prepared from **8c**. White oil, 0.13 g, 87% yield. HRMS, ESI$^+$, *m/z*: calcd for $C_{33}H_{46}N_2O_4$ $(M+H)^+$ 535.3530 found 535.3531. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41 (2H, m), 7.05 (1H, d, $J = 8.1$ Hz), 7.03 (1H, s), 6.84 (2H, m), 6.73 (1H, d, $J = 8.1$ Hz), 6.63 (1H, d, $J = 1.8$ Hz), 6.30 (1H, d, $J = 1.8$ Hz), 4.36 (2H, q, $J = 7.2$ Hz), 4.23 (1H, m), 4.01 (2H, q, $J = 6.9$ Hz), 3.86 (1H, m), 3.70 (1H, m), 2.21 (3H, s), 1.95 (4H, q, $J = 7.2$ Hz), 1.38 (6H, m), 1.15 (9H, s), 0.67 (6H, t, $J = 7.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.85, 154.49, 140.34, 131.42, 130.36, 125.95, 124.27, 114.80, 111.70, 110.18, 69.27, 63.70, 57.53, 44.99, 43.87, 36.47, 33.58, 26.06, 17.26.14.83, 8.54.

*4.1.4.9. 4-(Ethoxycarbonyl)phenyl 1-ethyl-5-(3-(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)pentan-3-yl)-1H-pyrrole-2-carboxylate (**9d**).* In the same method as **5a**, **9d** was prepared from **8d**. White oil, 0.12 g, 88% yield. HRMS, ESI$^+$, *m/z*: calcd for $C_{34}H_{45}NO_6$ $(M+H)^+$ 564.3321 found 564.3325. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.09 (1H, m), 7.18 (2H, m), 6.98 (2H, d, $J = 8.4$ Hz), 6.99 (1H, s), 6.87 (1H, d, $J = 1.8$ Hz), 6.68 (1H, d, $J = 8.4$ Hz), 6.61 (1H, d, $J = 1.8$ Hz), 4.26 (4H, m), 4.03 (1H, m), 3.81 (1H, m), 3.64 (1H, m), 2.14 (3H, s), 1.90 (4H, q, $J = 7.5$ Hz), 1.29 (6H, m), 1.18 (9H, s),0.61 (6H, t, $J = 7.5$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.31, 158.61, 154.51, 139.97, 132.59, 130.99, 130.26, 128.19, 127.53, 125.88, 121.87, 119.12, 110.21, 69.25, 61.00, 44.94, 44.16, 35.58, 30.38, 26.07, 16.97, 14.34, 8.55.

*4.1.4.10. 4-(2-Hydroxyethyl)phenyl 1-ethyl-5-(3-(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)pentan-3-yl)-1H-pyrrole-2-carboxylate (**9e**).* In the same method as **5a**, **9e** was prepared from **8e**. White oil, 0.12 g, 86% yield. HRMS, ESI$^+$, *m/z*: calcd for $C_{33}H_{45}NO_5$ $(M+H)^+$ 536.3371 found 536.3377. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.30 (2H, m), 7.14 (2H, m), 7.11 (1H, s), 6.95 (1H, m), 6.78 (2H, m), 6.71 (1H, m), 4.33 (2H, q, $J = 5.7$ Hz), 4.13 (1H, m), 3.88 (2H, m), 3.83 (1H, m), 3.75 (2H, m), 3.64 (1H, m), 2.24 (3H, s), 1.97 (4H, q, $J = 6.9$ Hz), 1.38 (3H, t, $J = 5.7$ Hz), 1.03 (9H, s), 0.70 (6H, t, $J = 6.9$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.34, 156.45, 140.07, 132.42, 130.41, 129.93, 127.85, 126.58, 125.89, 125.57, 122.12, 118.80, 117.54, 110.22, 69.21, 63.65, 50.87, 44.92, 38.59, 33.59, 30.38, 26.08, 17.01, 8.56.

*4.1.4.11. Pyridin-2-ylmethyl 5-(3-(4-(3,3-dimethyl-2-oxobutoxy)-3-methylphenyl)pentan-3-yl)-1-ethyl-1H-pyrrole-2-carboxylate (**10a**).* In the same method as **4a**, **10a** was prepared from 3 and 2-pyridinemethanol. White oil, 0.45 g, 77% yield. HRMS, ESI$^+$, *m/z*: calcd for $C_{31}H_{40}N_2O_4$ $(M+Na)^+$ 527.2880 found 527.2886. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.57 (1H, m), 7.70 (1H, m). 7.37 (1H, m), 7.22 (1H, m), 5.53 (2H, s), 4.86 (2H, s), 4.29 (2H, q, $J = 7.2$ Hz), 2.29 (3H, s), 1.93 (4H, q, $J = 7.2$ Hz), 1.35 (3H, t, $J = 7.2$ Hz), 1.24 (9H, s), 0.65 (6H, t, $J = 7.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 210.03, 160.32, 154.11, 149.24, 136.78, 130.44, 127.08, 125.77, 122.62, 121.61, 117.93, 110.23, 69.63, 65.93, 43.97, 30.44, 26.35, 17.03, 8.54.

*4.1.4.12. 4-Fluorobenzyl 5-(3-(4-(3,3-dimethyl-2-oxobutoxy)-3-methylphenyl)pentan-3-yl)-1-ethyl-1H-pyrrole-2-carboxylate (**10b**).* In the same method as **4a**, **10b** was prepared from 3 and 4-fluorobenzyl alcohol. White oil, 0.44 g, 73% yield. HRMS, ESI$^+$, *m/z*: calcd for $C_{32}H_{40}FNO_4$ $(M+Na)^+$ 544.2834 found 544.2824. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33 (1H, m), 7.16 (2H, m), 7.01 (3H, m), 6.76 (1H, d, $J = 2.1$ Hz), 6.60 (1H, d, $J = 2.1$ Hz), 6.52 (1H, d, $J = 8.4$ Hz), 5.23 (2H, s), 4.84 (2H, s), 4.31 (2H, q, $J = 7.2$ Hz), 2.17 (3H, s), 1.93 (2H, q, $J = 7.5$ Hz), 1.25 (9H, s), 0.65 (6H, t, $J = 7.5$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 210.03, 160.37, 154.13, 140.47, 131.94, 130.07, 127.06, 125.77, 123.44, 117.85, 114.97, 110.22, 69.63, 64.45, 44.93, 43.97, 30.45, 26.35, 17.03, 16.66, 8.54.

*4.1.4.13. Pyridin-2-ylmethyl 1-ethyl-5-(3-(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)pentan-3-yl)-1H-pyrrole-2-carboxylate (**11a**).* In the same method as **5a**, **11a** was prepared from **10a**. White oil, 0.14 g, 94% yield. HRMS, ESI$^+$, *m/z*: calcd for $C_{31}H_{42}N_2O_4$ $(M+H)^+$ 507.3217 found 507.3205. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.51 (1H, m), 7.63 (1H, m), 7.34 (1H, m), 7.14 (1H, m), 6.96 (1H, d, $J = 7.8$ Hz), 6.95 (1H, s), 6.63 (2H, s), 6.54 (1H, d, $J = 1.8$ Hz), 5.28 (2H, s), 4.23 (2H, q, $J = 7.2$ Hz), 4.03 (1H, m), 3.79 (1H, m), 3.62 (1H, m), 2.13 (3H, s), 1.88 (2H, q, $J = 7.2$ Hz), 1.29 (3H, t, $J = 7.2$ Hz), 0.94 (9H, s), 0.59 (6H, t, $J = 7.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.47, 154.45, 149.27, 140.15, 136.74, 131.95, 130.29, 127.03,126.51, 125.89, 122.62, 121.62, 117.38, 110.22, 69.28, 65.95, 50.78, 44.93, 43.98, 33.58, 30.44, 26.06, 17.04, 8.54.

*4.1.4.14. 4-Fluorobenzyl 1-ethyl-5-(3-(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)pentan-3-yl)-1H-pyrrole-2-carboxylate (**11b**).* In the same method as **5a**, **11b** was prepared from **10b**. White oil, 0.14 g, 92% yield. HRMS, ESI$^+$, *m/z*: calcd for $C_{32}H_{42}FNO_4$ $(M+H)^+$ 526.3171 found 526.3162. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32 (1H, m), 7.15 (1H, m), 7.02 (3H, m), 6.72 (2H, m), 6.60 (1H, d, $J = 2.1$ Hz), 5.22 (2H, s), 4.29 (2H, q, $J = 7.2$ Hz), 4.10 (1H, m), 3.87 (1H, m), 3.73 (1H, m), 2.20 (3H, s), 1.95 (4H, q, $J = 7.5$ Hz), 1.36 (3H, t, $J = 7.2$ Hz), 1.02 (9H, s), 0.67 (6H, t, $J = 7.6$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.8, 154.44, 140.14, 131.98, 130.07, 127.02, 125.90, 125.49, 123.44, 117.83, 117.49, 114.97, 110.19, 69.25, 64.46, 50.80, 43.99, 33.57, 30.43, 26.06, 17.04, 8.54.

4.2. Biological experiment and methods

4.2.1. In vitro VDR binding ability assay

PolarScreen VDR Competitor Assay Red was provided by Life Technologies. The test compounds and calcitriol were dissolved in DMSO and diluted with NR Buffer with 1% DMSO to different concentrations. Varying amounts of tested compounds were incubated for 4 h at room temperature in the presence of 1 nM Fluormone™ VDR Red and 0.7 nM VDR. The fluorescence polarization value (mP) of each well was measured on a fluorescence polarization plate reader. The compound IC_{50} values were calculated using GraphPad Prism 5.0.

4.2.2. Differetiation induction of HL-60 cells assay

The human promyelocytic leukemia cell line (HL-60) was provided by Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences. HL-60 cells were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS), and Penicillin 100 U/mL and Streptomycin 100 U/mL were added. Cell cultures were maintained in a humidified atmosphere of 5% CO_2 at 37 °C. The cell concentration at seeding was adjusted to 1×10^4 cells/mL in 96-well plates in a volume of 100 μL per well. The test compounds and positive control were dissolved in DMSO and diluted with culture medium to different concentrations (the final concentration of DMSO was 0.1%). 20 μL of the test compound solution was added in duplicates, and incubation continued for 96 h in a humidified atmosphere of 5% CO_2 at 37 °C. After incubation, The HL-60 cells were collected by centrifugation, washed with phosphate-buffered saline (PBS), and re-suspended in the medium. To the cell suspension was added NBT (Sigma) and 12-O-tetradecanoylphorbol- 13-acetate (TPA, Sigma). Final concentrations of NBT and TPA were 0.1% and 100 ng/mL, respectively. The mixture was incubated at 37 °C for 3 h, and cells were collected by centrifugation and re-suspended in PBS. Smear was prepared and Wright stain. The ratio of NBT-positive cells was counted under a microscope. The compound EC_{50} values were calculated using GraphPad Prism 5.0.

4.2.3. In vitro anti-proliferation activity assay

Human prostate cancer cell line (PC-3), human breast cancer cell line (MCF-7), human colorectal adenocarcinoma cell (Caco-2), Human hepatoma cell line (HepG-2) and human liver cell line (L02) were provided by Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences. PC-3 cell was cultured in DMEM/F-12 medium supplemented with 10% FBS, and Penicillin 100 U/mL and Streptomycin 100 U/mL were added. Cell cultures were maintained in a humidified atmosphere of 5% CO_2 at 37 °C. Cells were seeded at respective density (1×10^5 cells/ml) in 96-well plates in a volume of 200 μL per well. After seeding 24 h, the medium was removed. The test compounds were dissolved in DMSO and diluted with culture medium to different concentrations (the final concentration of DMSO was 0.1%). 200 μL of the test compound solution was added in duplicates, and incubation continued for 48 h in a humidified atmosphere of 5% CO_2 at 37 °C. Remove the medium, and cells were fixed with Methylthiazolyldiphenyl-tetrazolium bromide (MTT) 20 μL. The mixture was incubated at 37 °C for 4.0 h. Remove the medium carefully. 150 μL of DMSO was added to each well, and the absorbance was measured at 570 nm using a microplate reader. The compound IC_{50} values were calculated using GraphPad Prism 5.0. Anti-proliferation activity assay of MCF-7 cell, Caco-2 cell, HepG-2 cell and L02 cell were the same as PC-3 cell except culture condition.

4.2.4. In vivo calcemic activity assay

ICR mice (18–22 g) were obtained from the Shanghai Silaike Laboratory Animal Ltd., were housed on standard laboratory diet at an ambient temperature and humidity in air-conditioned chambers and were used for the present studies. All the animals were pathogen free and allowed to access food and water freely. All animal experiments were conducted in full compliance with local, national, ethical and regulatory principles with the approval of the Institutional Animal Care and Use Committee at China Pharmaceutical University. Six week old ICR mice were weighed and randomly divided into three groups including control group, positive group and test group respectively. All the mice were fed with a vitamin D-replete diet (0.2% calcium, 1% phosphate, and 2000 units vitamin) for a week. The hypercalcemic effect of the analogues was tested by daily subcutaneous injections of serial dilutions of $1.25(OH)_2D_3$ or analogues for 7 consecutive days. All compounds dissolved in the mixed solution of ethanol/propanediol (1:4). And the control group was given mixed solution 100 μL/day, the positive group was given Calcitriol (0.5 μg/kg/day), sw-22 and LG190155 (30 mg/kg/day each), the test group was given compounds **5i**, and **5k** (0.5 mg/kg/day, 10 mg/kg/day and 30 mg/kg/day, respectively). Serum calcium were measured as calcemic parameters using a calcium assay kit (Nanjing Jiangcheng Bioengineering institute).

Acknowledgments

This work was supported by the National Natural Science Foundation of China (81273468, 81473153), National Basic Research Program of China (2015CB755500), and 111 Project from the Ministry of Education of China and the State Administration of Foreign Expert Affairs of China (No. 111-2-07). We greatly appreciated Professor Yisheng Lai and Ms. Jianhu Xiao at China Pharmaceutical University for docking study.

References

[1] Q.M. Song, I.N. Sergeev, High vitamin D and calcium intakes increase bone mineral (Ca and P) content in high-fat diet-induced obese mice, Nutr. Res. 35 (2015) 146–154.
[2] L.L. Ooi, Y. Zheng, H. Zhou, Vitamin D deficiency promotes growth of MCF-7 human breast cancer in a rodent model of osteosclerotic bone metastasis, Bone 47 (2010) 795–803.
[3] M.R. Haussler, G.K. Whitfield, I. Kaneko, C.A. Hasussler, D. Hsieh, J.C. Hsieh, P.W. Jurutka, Molecular mechanisms of vitamin D action, Calcif. Tissue Int. 92 (2013) 77–98.
[4] S. Yamada, M. Shimizu, K. Yamamoto, Relationships of vitamin D including ligand recognition by the vitamin D receptor, Med. Res. Rev. 23 (2003) 89–115.
[5] R. Bouillon, G. Eelen, L. Verlinden, C. Mathieu, G. Carmeliet, A. Verstuyf, Vitamin D and cancer, J. Steroid Biochem. 102 (2006) 156–162.
[6] J.C. Fleet, Molecular actions of vitamin D contributing to cancer prevention, Mol. Asp. Med. 29 (2008) 388–396.
[7] M.F. Holick, Vitamin D: its role in cancer prevention and treatment, Prog. Biophys. Mol. Biol. 92 (2006) 49–59.
[8] D. Feldman, A.V. Krishnan, S. Swami, E. Giovannucci, B.J. Feldman, The role of vitamin D in reducing cancer risk and progression, Nat. Rev. Cancer 14 (2014) 342–357.
[9] Y. Anami, T. Itoh, D. Egawa, N. Yoshimoto, K. Yamamoto, A mixed population of antagonist and agonist binding conformers in a single crystal explains

partial agonism against vitamin D receptor: active vitamin D analogues with 22R-Alkyl group, J. Med. Chem. 57 (2014) 4351–4367.
[10] H. Maehr, N. Rochel, H.J. Hong, N. Suh, M.R. Uskokovic, Diastereotopic and deuterium effects in Gemini, J. Med. Chem. 56 (2013) 3878–3888.
[11] M.F. Boehm, P. Fitzgerald, A. Zou, M.G. Elgort, E.D. Bischoff, L. Mere, D.E. Mais, R.P. Bissonnette, R.A. Heyman, A.M. Nadzan, M. Reichman, E.A. Allegretto, Novel nonsecosteroidal vitamin D mimics exert VDR-modulating activities with less calcium mobilization than 1,25-dihydroxyvitamin D_3, Chem. Biol. 6 (1999) 265–275.
[12] H. Kashiwagi, Y. Ono, M. Ohta, S. Itoh, F. Ichikawa, S. Harada, S. Takeda, N. Sekiquchi, M. Ishiqaim, T. Takahashi, A series of nonsecosteroidal vitamin D receptor agonists for osteoporosis therapy, Bioorg. Med. Chem. 21 (2013) 1823–1833.
[13] S. Yamada, M. Makishima, Structure–activity relationship of nonsecosteroidal vitamin D receptor modulators, Trends Pharmacol. Sci. 35 (2014) 324–337.
[14] L.A. Plum, H.F. Deluca, Vitamin D, disease and therapeutic opportunities, Nat. Rev. Drug Discov. 9 (2010) 941–955.
[15] E.S. Yang, K.L. Burnstein, Vitamin D inhibits G_1 to S progression in LNCaP prostate cancer cells through $p27^{Kip1}$ stabilization and Cdk2 mislocalization to the cytoplasm, J. Biol. Chem. 278 (2003) 46862–46868.
[16] K.K. Deeb, D.L. Trump, C.S. Johnson, Vitamin D signalling pathways in cancer: potential for anticancer therapeutics, Nat. Rev. Cancer 7 (2007) 684–700.
[17] W. Shen, J.W. Xue, Z.K. zhao, C. Zhang, Novel nonsecosteroidal VDR agonists with phenyl-pyrrolyl pentane skeleton, Eur. J. Med. Chem. 69 (2013) 768–778.
[18] F. Ciesielski, Y. Sato, Y. Chebaro, D. Moras, A. Dejacegere, N. Rochel, Structural basis for the accommodation of bis- and tris-aromatic serivatives in vitamin D nuclear receptor, J. Med. Chem. 55 (2012) 8440–8449.
[19] S. Hosoda, A. Tanatani, K.I. Wakabayashi, Y. Nakano, H. Miyachi, K. Nagasawa, Y. Hashimoto, Ligands with dual vitamin D_3-agonistic and androgen-antagonistic activities, Bioorg. Med. Chem. Lett. 15 (2005) 4327–4331.
[20] E. Thomas, J.D. Brion, J.F. Peyrat, Synthesis and preliminary biological evaluation of new antiproliferative aromatic analogues of 1α,25-dihydroxyvitamin D3, Eur. J. Med. Chem. 36 (2014) 381–393.
[21] L. Verlinden, A. Verstuyf, M. Van Camp, S. Marcelis, K. Sabbe, X.Y. Zhao, P. De Clercq, M. Vandewalle, R. Bouillon, Two novel 14-Epi-analogues of 1,25-dihydroxyvitamin D3 inhibit the growth of human breast cancer cells in vitro and in vivo, Cancer Res. 60 (2000) 2673–2679.
[22] S. Kakuda, K. Okada, H. Eguchi, K. Takemouchi, W. Hakamata, M. Kurihara, M.T. Kamimura, Structure of the ligand-binding domain of rat VDR in complex with the nonsecosteroidal vitamin D_3 analogue YR301, Acta Cryst. 64 (2008) 970–973.