Design, synthesis and biological evaluation of curcumin analogues as novel LSD1 inhibitors

Jiming Wang, Xiangyu Zhang, Jiangkun Yan, Wei Li, Qinwen Jiang, Xinran Wang, Dongmei Zhao, Maosheng Cheng

PII: S0960-894X(19)30633-X

DOI: https://doi.org/10.1016/j.bmcl.2019.126683

Reference: BMCL 126683

To appear in:

Received date: 9 May 2019

Revised date: 10 September 2019

Accepted date: 12 September 2019

Please cite this article as: J. Wang, X. Zhang, J. Yan, et al., Design, synthesis and biological evaluation of curcumin analogues as novel LSD1 inhibitors, (2019), https://doi.org/10.1016/j.bmcl.2019.126683

Design, synthesis and biological evaluation of curcumin analogues as novel LSD1 inhibitors

Jiming Wang[a], Xiangyu Zhang[a], Jiangkun Yan[a], Wei Li[a], Qinwen Jiang[a], Xinran Wang[a], Dongmei Zhao[a,]*, Maosheng Cheng[a]

[a]Key Laboratory of Structure-Based Drug Design & Discovery, Ministry of Education, Shenyang Pharmaceutical University, Shenyang 110016, Liaoning, P. R. China.

*Corresponding author. Prof. Zhao: E-mail address: medchemzhao@163.com;

Abstract:

Histone lysine-specific demethylase 1 (LSD1) was the first discovered histone demethylase. Inactivating LSD1 or downregulating its expression inhibits cancer-cell development, and thus, it is an attractive molecular target for the development of novel cancer therapeutics. In this study, we worked on the structural optimization of natural products and identified 30 novel LSD1 inhibitors. Utilizing a structure-based drug design strategy, we designed and synthesized a series of curcumin analogues that were shown to be potent LSD1 inhibitors in the enzyme assay. Compound **WB07** displayed the most potent LSD1 inhibitory activity, with an IC_{50} value of 0.8 μM. Moreover, **WA20** showed an anticlonogenic effect on A549 cells with an IC_{50} value of 4.4 μM. Molecular docking simulations were also carried out, and the results indicated that the inhibitors bound to the protein active site located around the key residues of Asp555 and Asp556. These findings suggested that compounds **WA20** and **WB07** are the first curcumin analogue-based LSD1 inhibitors with remarkable A549 suppressive activity, providing a novel scaffold for the development of LSD1 inhibitors.

Keywords: Natural Product; LSD1 inhibitors; Curcumin Analogues; Molecular Docking; Cellular Activity

Several studies have shown that epigenetic modifications play important roles in regulating carcinogenesis[1]. Epigenetic regulation includes DNA methylation modification and histone acetylation, phosphorylation, methylation and other modifications. So far, acetylation and phosphorylation of histones have been studied for a long time. However, histone methylation has only been extensively studied in the past 10 years. Before 2004, histone methylation was considered to be an irreversible reaction until the discovery of histone lysine-specific demethylase 1 (LSD1), which officially marked the confirmation of a histone methylation reversibility process[2]. The revolutionary discovery provided new research ideas for the development of histone modifications in epigenetics. In the past 10 years, it has become a research hotspot.

LSD1 belongs to the family of monoamine oxidases and uses FAD (flavin adenine dinucleotide) as a cofactor to specifically remove mono- or dimethylated histones H3 lysine 4 (H3K4) and H3 lysine 9 (H3K9)[3]. LSD1 has been reported to be overexpressed in numerous types of cancer, including lung and bladder cancers[4], neuroblastoma[5], retinoblastoma[6] and breast cancer[7-8]. LSD1 is involved in promoting cell proliferation, migration, invasion, and metastasis by epithelial mesenchymal transition (EMT) induction.

Numerous LSD1 inhibitors have been synthesized and evaluated in preclinical and clinical studies. Currently in the clinical stage are three representative irreversible tranylcypromine derivatives, ORY-1001[9], GSK-2879552[10-11], and IMG-7289[12-13]. These three inhibitors can be used alone or in combination with other therapeutic

agents. With the deepening of research into LSD1 inhibitors, a large number of LSD1 inhibitors have been reported[14-15]. However, in the continuous development of histone demethylase inhibitor research, promising drug candidates are rare, and novel potent LSD1 inhibitors still need further exploration.

Natural products have made significant contributions to cancer chemotherapy over the past decades[16]. Even with the advances of alternative drug discovery technologies, such as rational drug design, high throughput screening, and combinatorial chemistry, natural products remain an essential element in drug discovery. As an indispensable source for lead generation and drug discovery, natural products have provided molecular diversity and structural novelty inaccessible by other means.

Curcumin is the main active ingredient of turmeric (*Curcuma longa*) and is one of the most popular natural multitarget molecule[17]. Curcumin has a simple molecular structure, low toxicity, and various pharmacological activities. It has antibacterial[18], anti-inflammatory[19-20], anti-oxidant[21], and anti-cancer effects[22]. Recent studies have found that curcumin has a certain inhibitory effect on LSD1[23]. This report aroused our interest in structural optimization of natural products to obtain new LSD1 inhibitor skeleton structures. Combined with the docking results of computer molecules, we synthesized a series of curcumin derivatives to increase their LSD1 inhibitory potency. The new compounds clearly demonstrated the relevant substituents for inhibitory activity and their interaction with the key residues of the active site.

Abdulla A et al. reported that curcumin is a potent inhibitor of LSD1, but further studies have not been disclosed. We consider that curcumin may provide a new skeleton for developing LSD1 inhibitors, so we tested its inhibitory activity against to LSD1 and found IC_{50} = 9.6 μM. The activity results confirmed our confidence in the optimization of curcumin as the lead. To understand the inhibitory activities of curcumin against LSD1, we subjected them to molecular docking analysis using maestro 9.6 and predicted their binding affinity with LSD1 (PDB code: 5lhi). As shown in Figure 1, co-crystallization of 5lhi (white) approaches the FAD co-factor (yellow) and is located around Asp555 and Asp556, which are located below the thienopyrrole plane. The modeling of curcumin 1 (Figure 1) is similar to moiety 1 in a binding pocket, and the phenolic hydroxyl group H-bonds to Trp552 in a narrow catalytic binding groove. Meanwhile, the dicarbonyl structure of curcumin is apt to be tautomerized and transformed into an enol structure, which is the main reason for the instability of the curcumin structure and its low bioavailability[24-26]. Therefore, we transformed the structure of the dicarbonyl into a monocarbonyl, thus destroying its conjugate system, increasing its stability and fundamentally changing its pharmacokinetic characteristics, and we introduced a positively charged piperidine tail to form H-bonds with the key residues of Asp555 and Asp556 (Scheme 1). We therefore have reasonably designed a set of curcumin analogues to produce a series of new LSD1 inhibitors.

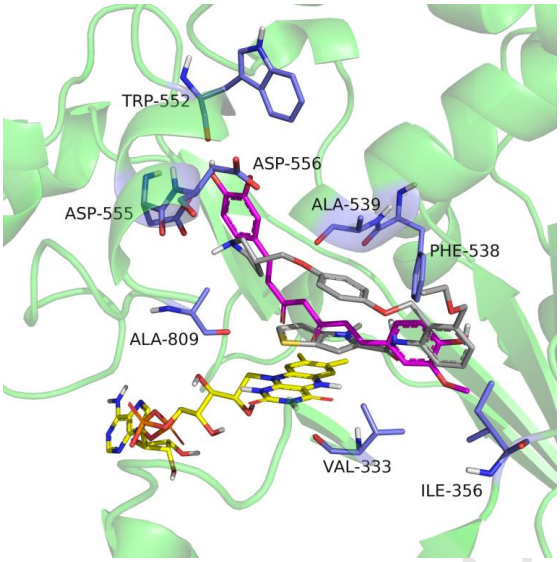
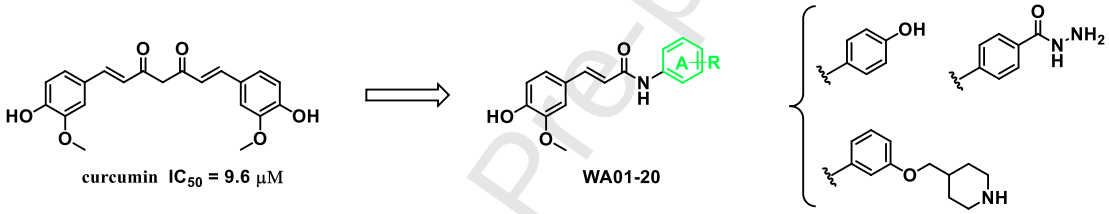
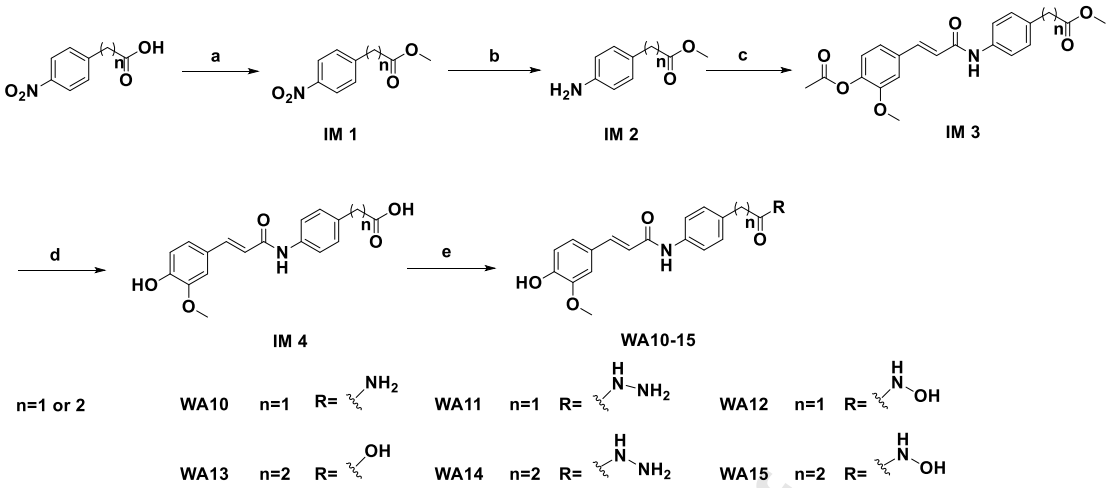


Figure 1. The predicted binding modes between curcumin (magenta) and LSD1 (PDB code: 5LHI). The ligand of LSD1 was highlighted in grey, and key residues of LSD1 was showed in light blue. The FAD of LSD1 was represented as yellow sticks.



Scheme 1. Structures of curcumin and target compounds WA**01-20**

We changed the substituent on the part A to study the effect of the electrical, spatial position and volume of the substituent on its pharmacological activity. As shown in Scheme 2, a different substituted nitrobenzene was esterified via methanol to give the intermediate **IM1**, and its nitro groups were transformed into anilines **IM2** and through an amide condensation reaction with 3-(4-acetoxy-3-methoxyphenyl) acrylic acid generated **IM3** that was further hydrolyzed to **IM4**. The final compounds **WA10-15** were obtained by treatment with hydrazine hydrate or hydroxylamine hydrochloride.

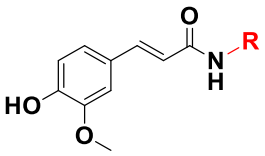


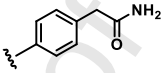
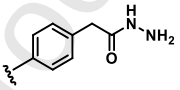
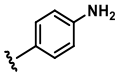
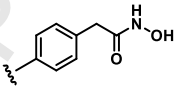
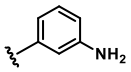
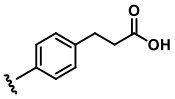
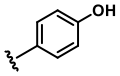
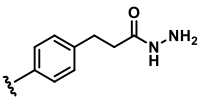
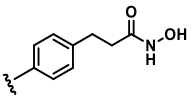
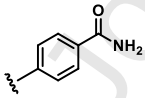
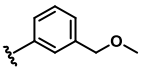
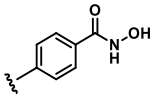
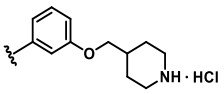
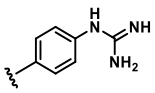
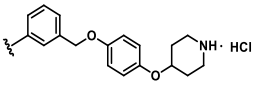
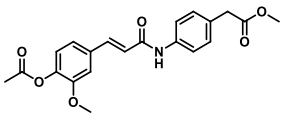
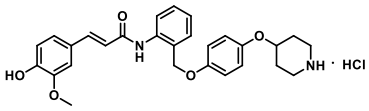
Scheme 2. Synthesis of compounds WA10-15. Reagents and conditions: (a) $SOCl_2$, MeOH, r.t., 92.8%-93.5%; (b) H_2, Pd/C (10% w/w), MeOH, r.t., 94.7%-96.2%; (c) 3-(4-acetoxy-3-methoxyphenyl)acrylic acid, HATU, DIEA, DMF, r.t., 72.6%-74.5%; (d) NaOH (aq), MeOH, r.t., 92.6%-93.9%; (e) i) EDCI, HOBT, DMF, 0 ℃; ii) Hydrazinium hydroxide or Hydroxylamine hydrochloride, DIEA, DMF, 0 ℃, 69.2%-81.2%.

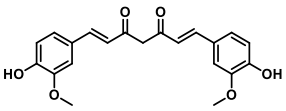
All of the compounds synthesized in this study were investigated for their inhibitory activities against LSD1 in vitro, and TCP was chosen as the positive control. As shown in Table 1, the β-diketone group is not essential for the biological activity of curcumin. It is possible to screen for more potential compounds by structural modification of monocarbonyl curcumin derivatives. Compared with compound **WA01**, the addition of substituents to the part A is beneficial to maintaining or enhancing the inhibitory activity of the compound against LSD1. Among them, **WA 02**–**06** showed that the electrical property and spatial position of the substituents had no significant effect on the pharmacological activity, with IC_{50} values ranging from 4.9 μM to 6.2 μM. **WA07-15** showed that when groups such as amides, oximes and hydrazines were introduced, the inhibitory activity of the compound was significantly increased after the carbon chain length was extended by one. However, among all the groups, the activity of the piperidine side chain was optimal, with an IC_{50} value of 1.4 μM for WA18, and its inhibitory activity was not significantly changed when the

carbon chain length of the piperidine side chain was increased, showing IC_{50} values ranging from 1.8 μM to 2.8 μM.

Table 1. In Vitro LSD1-Inhibitory activities of compounds WA01-20

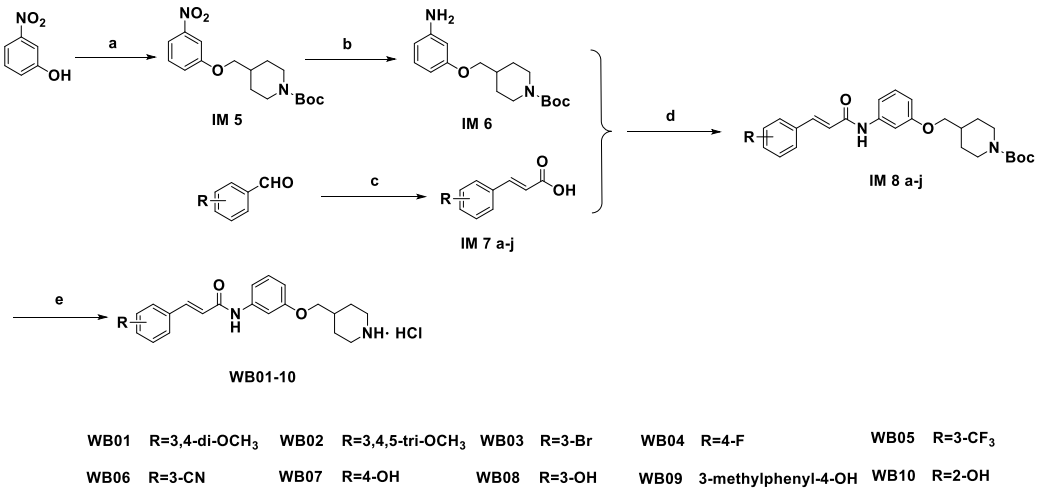


compound	R	IC_{50} (μM)[a]	compound	R	IC_{50} (μM)[a]
WA01		30±1.02	**WA10**		10.3±0.09
WA02		4.9±0.21	**WA11**		1.4±0.33
WA03		4.5±0.36	**WA12**		5.8±0.22
WA04		6.0±0.22	**WA13**		11.5±0.65
WA05		5.6±0.96	**WA14**		7.8±1.03
WA06		6.2±0.23	**WA15**		6.2±0.38
WA07		12.1±0.76	**WA17**		5.9±0.27
WA08		2.6±0.33	**WA18**		1.8±0.12
WA09		4.0±0.46	**WA19**		1.4±0.96
WA16					＞50
WA20					2.8±0.15

curcumin		9.6±0.68

[a] Data are presented as the means ± SDs of three independent experiments. $p < 0.05$.

After optimizing the structure of the part A, we began to focus on the structural modification of the benzene ring on the part B. Scheme **3** summarizes the initial approach to compounds WB01-10. A Mitsunobu reaction between o-nitropheno and *N*-Boc-4-piperidinemethanol produced **IM5**, which was reduced to give the anilino derivative **IM6**, a substituted benzaldehyde reacts with acetic anhydride to form intermediate **IM7**, and then condensates with **IM6** to form **IM8,** and **IM8** deprotected gives the final products WB01-10.

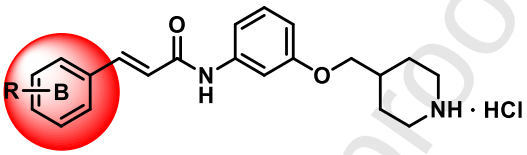


Scheme 3. Synthesis of compounds WB01-10. Reagents and conditions: (a) *N*-Boc-4-piperidinemethanol, DEAD, PPh_3, THF, -20°C, 55.5%; (b) Fe, NH_4Cl, H_2O, MeOH, r.t., 90.3%; (c) Pyridine, DMF, 90°C, 69.3%-81.5%; (d) HATU, DIEA, DMF, r.t., 75.6%-89.5%; (e) HCl-EtOH, r.t., 79.8%-88.3%

Comparing the results of enzyme inhibition activity of compounds WB01-10 (Table 2), it was found that the hydroxyl group is the key to the antitumor activity of the curcumin derivative at the 4 position of the phenyl ring, with an IC_{50} value of 0.8 μM for **WB07**, and the activity disappeared when other groups were introduced. Replacing the 3-methoxy group with a hydroxyl group is beneficial to activity, with

an IC_{50} value of 8.6 μM for **WB08**. In addition, we designed compounds WB09 and WB10, which considered with no LSD1 inhibition activity. This results indicating that changing the position of the hydroxyl group or blocking the hydroxyl group with a large steric block fragment will cause the activity to disappear, and the phenolic hydroxyl group in the structure of the compounds would not cause false positive problems.

Table 2. In Vitro LSD1-Inhibitory activities of compounds WB01-10



compound	R	IC_{50} (μM)[a]	compound	R	IC_{50} (μM)[a]
WB01	3,4-di-OCH_3	＞50[b]	WB06	4-CN	＞50[b]
WB02	3,4,5-tri-OCH_3	＞50[b]	WB07	4-OH	0.8±0.11
WB03	3-Br	33.9±0.85	WB08	3-OH	8.6±0.36
WB04	4-F	＞50[b]	WB09	3-methylphenyl -4-OH	**>** 50[b]
WB05	3-CF_3	＞50[b]	WB10	2-OH	49.6

[a] Data are presented as the means ± SDs of three independent experiments. $p < 0.05$.

[b] Considered with no LSD1 inhibition activity.

The docking results were evaluated by comparing the binding energy and docking poses via Glide SP mode. The docking results differing by <2.0 Å on the basis of a positional root mean square deviation (RMSD), were clustered together and were ranked on the basis of their free binding energy. Analysis of the results of the native docking simulations showed most binding energy scores could accurately forecast the ligand activities（all results were shown in table S1）. (The binding modes and 2D interaction maps of other inhibitors were shown in figure S1). Among the

series of **WA**, the inhibitory activity of the compounds increased due to alkaline group introduced, like amides, oximes, hydrazines and piperazine groups. Because they could form H-bond interactions with Asp 555 or Glu559. To our surprised, the tails of **WA17** formed hydrogen bond with Lys661, which also reported essential residue for LSD1 inhibitors. Meanwhile, phenyl ring is well important, compare the dock poses of **WB**, we can know that the compounds which have 4 position of the phenyl ring can well form aromatic−aromatic interaction between FAD and occupy the activity pocket of LSD1. When the phenolic hydroxyl group was substituted for big group like methoxy group and trifluoromethyl, the molecular could not generate comfortable docking poses to occupy the active site and less interactions at the active pocket. If replacing it with a halogen group, it is unfavorable to activity like **WB03** which got a lower docking score (Docking energy = -3.879 kcal/mol).

Preferred binding patterns of WB**07** within the binding site of LSD1 were shown in the Figure 2, which the binding energy of compound WB**07** (IC_{50} = 0.8 μM) was −7.33 kcal/mol. The tail of compound **WB07** extended towards an interesting cluster of negatively charged residues at Asp556 and Glu559 while there was an aromatic−aromatic interaction between FAD and the ring of benzamide. Meanwhile, the ring of the benzamide formed hydrophobic interactions with Ala539 and Tyr761. The head of **WB07** was located among residues Leu677, Leu679, and Tyr356. Due to the much interactions at the active pocket, **WB07** showed the highest activity in a series of curcumin analogues.

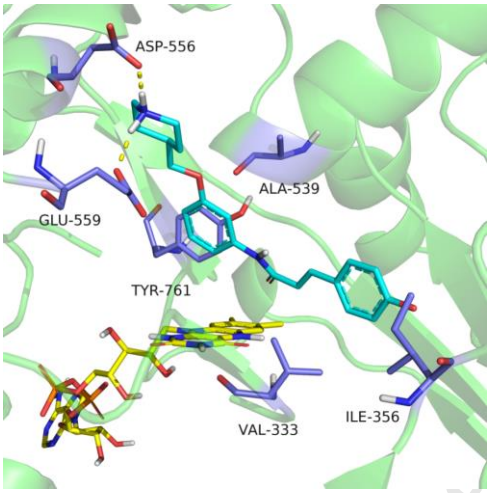
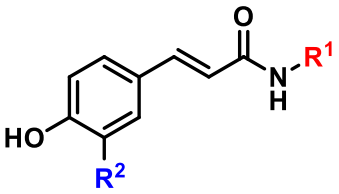


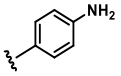
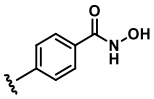
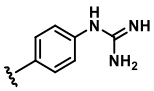
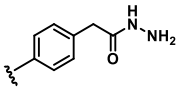
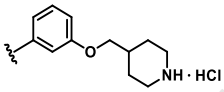
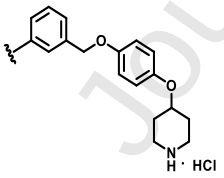
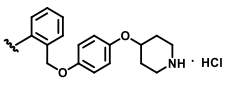
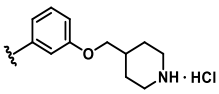
Figure 2. Binding models of WB07 (cyan) in active site. Key residues of LSD1 was showed in light blue, and the FAD of LSD1 was represented as yellow sticks.

To further confirm the cellular activity of the curcumin analogues, different concentrations of the target compounds (LSD1 IC_{50}<4.5 μM) were applied to the lung cancer cell line A549, which overexpresses LSD1, and the human glioblastoma cell line U87. As indicated in Table 3, in general, the tested compounds exhibited moderate activity in inhibition of the proliferation of these two cancer cells. Among them, compounds **WA03** and **WA09** had no activity on the A549 and U87 cell lines for unknown reasons, while compound **WA20**, which only showed a moderate inhibitory effect against LSD1 in the enzyme assay with an IC_{50} value of 2.80 μM, exhibited the best activity in inhibition of the growth of A549 cells, with an IC_{50} value of 4.14 μM. Also noteworthy is that compound **WA19** showed superior activity against the U87 human glioblastoma cell (Figure 3). Compounds **WA08**, **11**, **18**, and **19** also showed moderate inhibitory effects against LSD1 in the A549 cell line, ranging from 32.473±1.41 μM to 24.526±2.52 μM. Additionally, the ClogP of compounds were also calculated with Sybyl 6.91, showing that compounds **WA18-20**, **WB07** exhibited acceptable values (Table 3). The selectivity of the compounds **WA20**

and **WB07** were tested and the results showed that the two compounds exhibited excellent selectivity (Table 4**)**.

Table 3. Cellular activity and calculated ClogP-values of Partial compounds



compound	R^1	R^2	LSD1 IC_{50}(μM)	IC_{50} (μmol·L^{-1})[a]		ClogP[b]
				A549	U87	
WA03		OMe	4.5±0.36	>50	>50	1.6192
WA08		OMe	2.6±0.33	32.473 ± 1.41	>50	1.2536
WA09		OMe	4.0±0.46	>50	>50	1.2192
WA11		OMe	1.4±0.33	30.347 ± 3.03	49.255 ± 1.66	0.8482
WA18		OMe	1.8±0.12	24.526 ± 2.52	30.989 ± 6.19	3.1526
WA19		OMe	1.4±0.96	28.537 ± 0.59	>50	4.2342
WA20		OMe	2.8±0.15	4.419 ± 0.38	14.241 ± 1.07	3.5842
WB07		H	0.8±0.11	9.333 ± 1.09	>50	3.3034

[a] Data are presented as the means ± SDs of three independent experiments. $p < 0.05$.

[b] ClogP values were calculated using Sybyl 6.91.

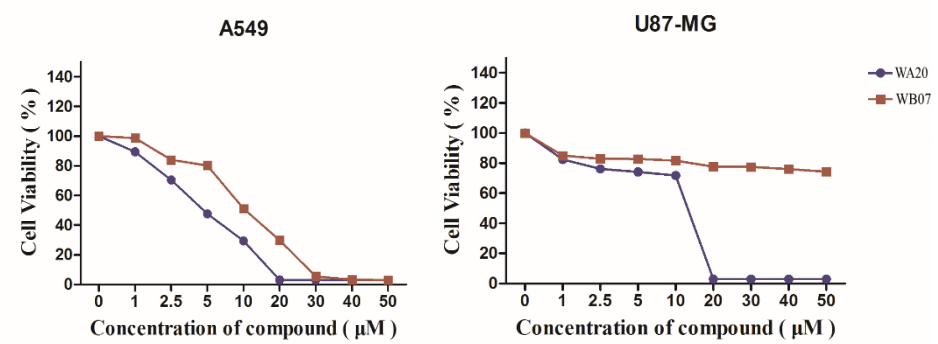


Table 4. MAO-A/B inhibitory activity of selected compounds.

Entry	Compound	MAO-A $IC_{50}(\mu M)^a$	MAO-B $IC_{50}(\mu M)^a$
1	TCP[b]	2.04 ± 0.100	0.72 ± 0.126
2	WA20	> 50	> 50
3	WB07	> 50	> 50

[a] Data are presented as the means ± SDs of three independent experiments. *p < 0.05.

[b] Used as a positive control.

In conclusion, on the basis of previously reported LSD1 inhibitors, a series of curcumin analogues containing a piperidine group were designed and synthesized. Based on biochemical assays, most of them exhibited in vitro inhibitory activities against LSD1. In particular, the inhibitory activity of compound **WB07** against LSD1 was nearly tenfold higher than that of curcumin, with an IC_{50} value reaching 0.8 μM. Furthermore, **WA20** showed potent inhibition against LSD1 in the A549 cells with IC_{50} values of 4.4 μM, while it showed no outstanding inhibitory activity against the U87 cells, which have low levels of LSD1 expression. This result indicates to some extent that the compound **WA20** specifically targeted LSD1. These curcumin analogues represent a novel class of LSD1 inhibitors, and our laboratory is carrying out further chemical modifications and anticancer activity evaluation of these compounds.

Acknowledgments

We gratefully acknowledge the Program for Innovative Research Team of the Ministry of Education, and the Program for Liaoning Innovative Research Team in University.

References and notes

[1] Yen C Y, Huang H W, Shu C W, et al. DNA methylation, histone acetylation and methylation of epigenetic modifications as a therapeutic approach for cancers[J]. Cancer Letters, 2016, 373(2):185-192.

[2] Shi Y, Lan F, Matson C, et al. Histone demethylation mediated by the nuclear amine oxidase homolog LSD1.[J]. Cell, 2004, 119(7):941-953.

[3] Chen Y, Jie W, Yan W, et al. Lysine-specific histone demethylase 1 (LSD1): A potential molecular target for tumor therapy.[J]. Critical Reviews in Eukaryotic Gene Expression, 2012, 22(1):53-59.

[4] Hayami S, Kelly J D, Cho H, et al. Overexpression of LSD1 contributes to human carcinogenesis through chromatin regulation in various cancers[J]. International Journal of Cancer Journal International Du Cancer, 2015, 128(3):574-586.

[5] Schulte J, Lim S A, Friedrichs N, et al. Lysine-specific demethylase 1 is strongly expressed in poorly differentiated neuroblastoma: implications for therapy.[J]. Cancer Research, 2010, 69(5):2065-2071.

[6] Yokoyama A, Takezawa S, Schüle R, et al. Transrepressive Function of TLX Requires the Histone Demethylase LSD1 †[J]. Molecular & Cellular Biology, 2008, 28(12):3995-4003.

[7] Lim S, Janzer A, Becker A, et al. Lysine-specific demethylase 1 (LSD1) is highly expressed in ER-negative breast cancers and a biomarker predicting aggressive biology[J]. Carcinogenesis, 2010, 31(3):512-20.

[8] Wang Y, Zhang H, Chen Y, et al. LSD1 is a subunit of the NuRD complex and targets the metastasis programs in breast cancer.[J]. Cell, 2009, 138(4):660-672.

[9] Milletti F, Cheng W Y, Maes T, et al. Abstract 4708: Neuroendocrine gene transcript expression is associated with efficacy to lysine-specific demethylase-1 inhibitor RG6016 in small cell lung cancer-derived cell lines[J]. Cancer Research, 2016, 76(14 Supplement):4708-4708.

[10] Mohammad H, Smitheman K, Kamat C, et al. A DNA Hypomethylation Signature Predicts Antitumor Activity of LSD1 Inhibitors in SCLC[J]. Cancer Cell, 2015, 28(1):57-69.

[11] Mohammad H, Smitheman K, Aller G V, et al. 212 Novel anti-tumor activity of targeted LSD1 inhibition by GSK2879552[J]. European Journal of Cancer, 2014, 50:72-72.

[12] Sang H L, Stubbs M, Liu X M, et al. Abstract 4712: Discovery of INCB059872, a novel FAD-directed LSD1 inhibitor that is effective in preclinical models of human and murine AML[J]. Cancer Research, 2016, 76(14 Supplement):4712-4712.

[13] Sang H L, Liu X M, Diamond M, et al. Abstract 4704: The evaluation of INCB059872, an FAD-directed inhibitor of LSD1, in preclinical models of human small cell lung cancer[J]. Cancer Research, 2016, 76(14 Supplement):4704-4704.

[14] Fu X , Zhang P , Yu B . Advances toward LSD1 inhibitors for cancer therapy[J]. Future medicinal chemistry, 2017, 9(11):1227-1242.

[15] Stazi G, Zwergel C, Valente S, et al. LSD1 inhibitors: a patent review (2010-2015)[J]. Expert Opinion on Therapeutic Patents, 2016:1-16.

[16] Xiao Z, Morris-Natschke S L, Lee K H. Strategies for the Optimization of Natural Leads to Anticancer Drugs or Drug Candidates[J]. Medicinal Research Reviews, 2016, 36(1):32-91.

[17] Hosseini A, Hosseinzadeh H. Antidotal or protective effects of Curcuma longa (turmeric) and its active ingredient, curcumin, against natural and chemical toxicities: A review[J]. Biomedicine & Pharmacotherapy, 2018, 99:411-421.

[18] Bhawana, Basniwal R K, Buttar H S, et al. Curcumin Nanoparticles: Preparation, Characterization, and Antimicrobial Study[J]. J Agric Food Chem, 2011, 59(5):2056-2061.

[19] Lee K H, Aziz F H A, Syahidaab A, et al. Synthesis and biological evaluation of curcumin-like diarylpentanoid analogues for anti-inflammatory, antioxidant and anti-tyrosinase activities[J]. European Journal of Medicinal Chemistry, 2009, 44(8):3195-3200.

[20] Khan M A, El-Khatib R, Rainsford K D, et al. Synthesis and anti-inflammatory properties of some aromatic and heterocyclic aromatic curcuminoids[J]. Bioorganic Chemistry, 2012, 40(1):30-38.

[21] Toda S, Miyase T, Arichi H, et al. Natural Antioxidants. III. Antioxidative Components Isolated from Rhizome of Curcuma longa L.[J]. Chemical & Pharmaceutical Bulletin, 1985, 33(4):1725-1728.

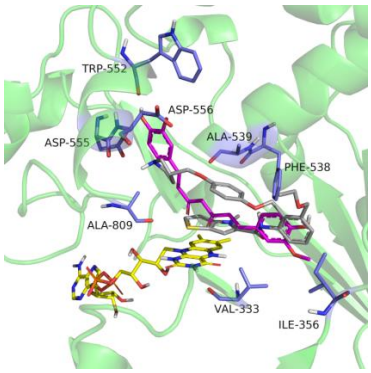
[22] Choudhuri T, Pal S, Agwarwal M L, et al. Curcumin induces apoptosis in human breast cancer cells through p53-dependent Bax induction. FEBS Lett[J]. Febs Letters, 2002, 512(1):334-340.

[23] Abdulla A, Zhao X, Yang F. Natural Polyphenols Inhibit Lysine-Specific Demethylase-1 in vitro.[J]. Journal of Biochemical & Pharmacological Research, 2013, 1(1):56.

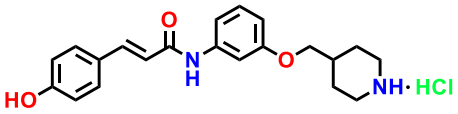
[24] Weber W M, Hunsaker L A, Abcouwer S F, et al. Anti-oxidant activities of curcumin and related enones.[J]. Bioorg Med Chem, 2005, 13(11):3811-3820.

[25] Wang Y J, Pan M H, Cheng A L, et al. Stability of curcumin in buffer solutions and characterization of its degradation products[J]. J Pharm Biomed Anal, 1997, 15(12):1867-1876.

[26] Rosemond M J, St J L, Yamaguchi T, et al. Enzymology of a carbonyl reduction clearance pathway for the HIV integrase inhibitor, S-1360: Role of human liver cytosolic aldo-keto reductases[J]. Chemico-Biological Interactions, 2004, 147(2):129-139.



curcumin IC_{50} = 9.6 μM



WB 07

IC_{50} = 0.8μM (LSD1)
= 9.3μM (A549)
> 50μM (MAO-A)
> 50μM (MAO-B)
ClogP = 3.3

Utilizing a structure-based drug design strategy, we designed and synthesized a series of curcumin analogues that were shown to be potent LSD1 inhibitors in the enzyme assay. Compound **WB07** displayed the most potent LSD1 inhibitory activity, with an IC_{50} value of 0.8 μM.

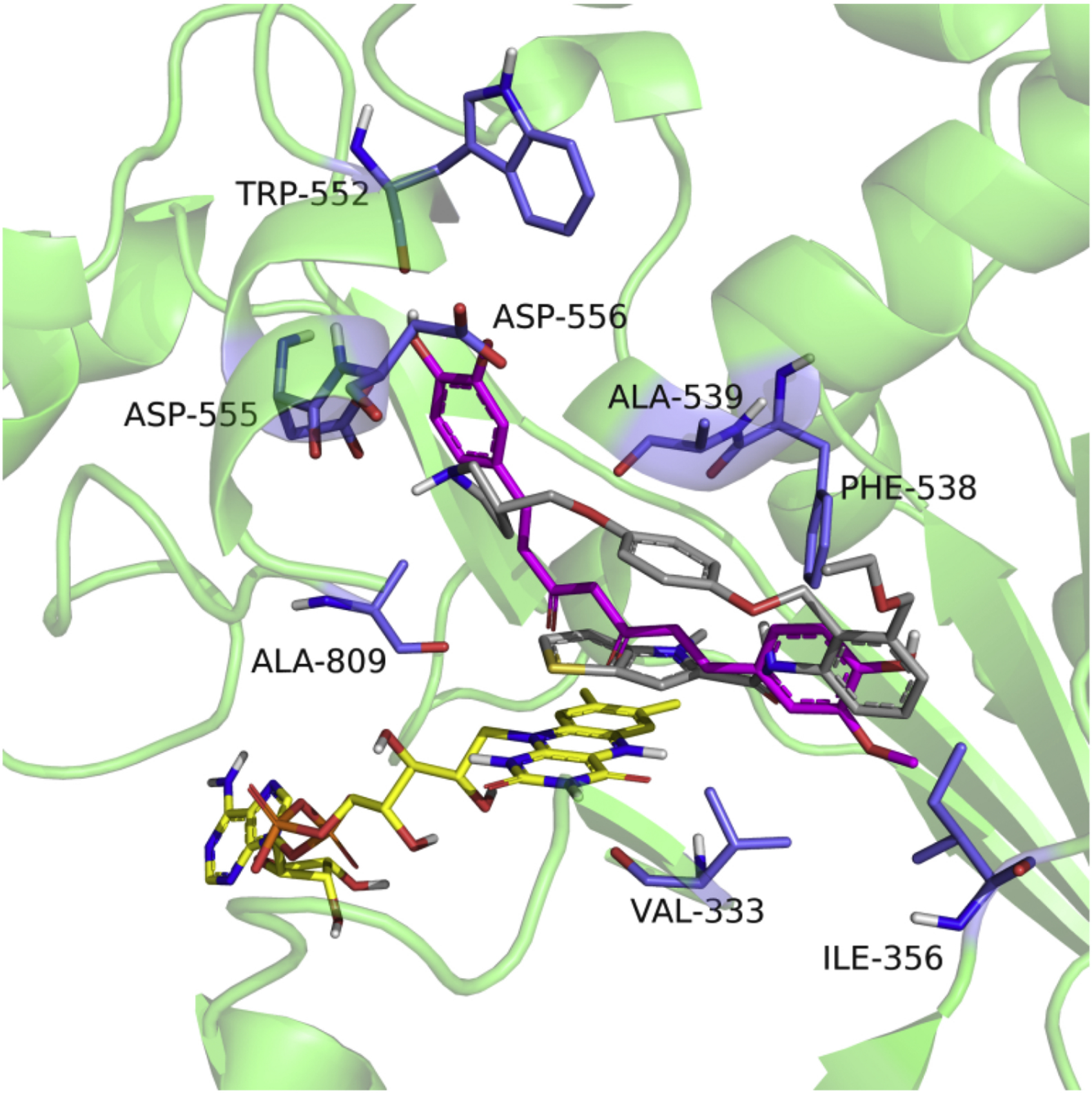


Figure 1

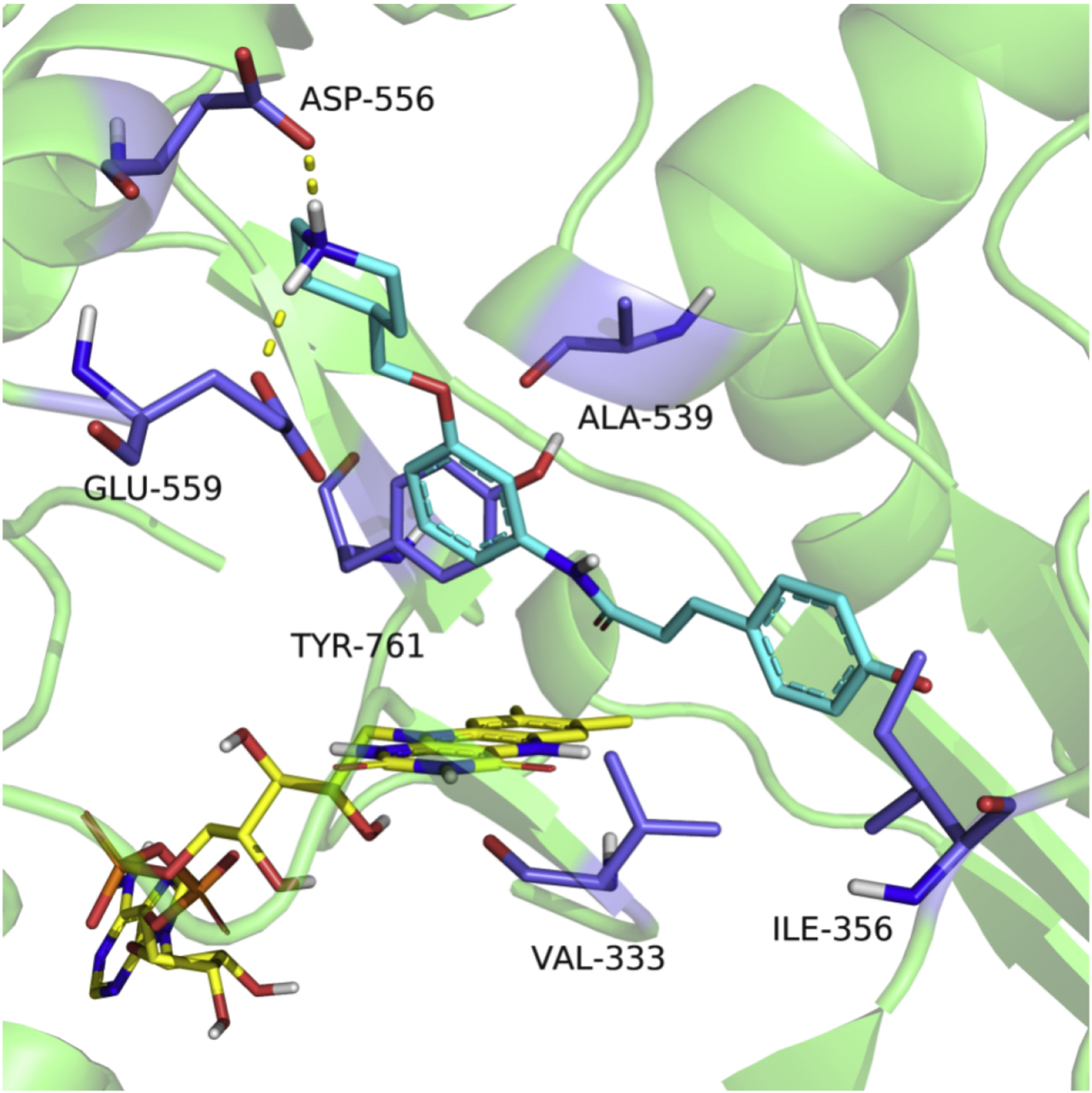


Figure 2

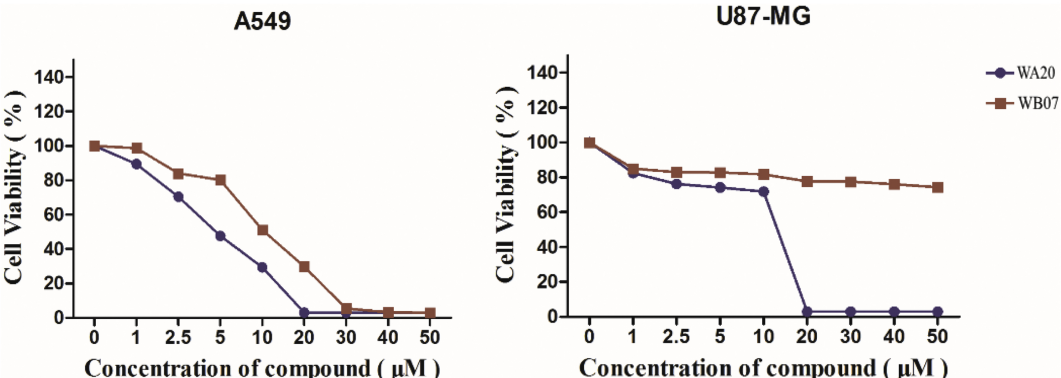

A549
U87-MG
Cell Viability (%)
140
120
100
80
60
40
20
0
0 1 2.5 5 10 20 30 40 50
Concentration of compound (μM)
WA20
WB07

Figure 3