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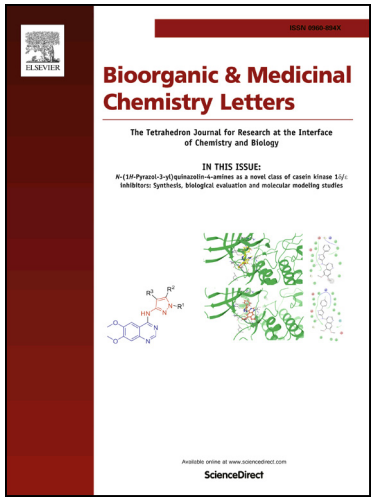

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Design, synthesis and biological evaluation of Lenalidomide derivatives as tumor angiogenesis inhibitor

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ABSTRACT

Lenalidomide is a type of immunomodulatory agent with anti-tumor activity by mainly expressed in the anti-angiogenesis. In order to enhance the pharmacological activity of Lenalidomide, a series of Lenalidomide derivatives were designed as tumor angiogenesis inhibitors. The potential anti-angiogenesis targets of Lenalidomide derivatives were virtual screened on Auto-Dock 4.0 by using reverse docking method. The six target proteins, such as vascular endothelial growth factor receptor, epidermal growth factor receptor, fibroblast growth factor receptor, BCR-ABL tyrosine kinase, p38 mitogen activated protein kinase and metal protein kinase, were chosen as the targets. The Lenalidomide derivatives were synthesized by alkylated, acylated or sulfonylated Lenalidomide and verified by the ^{1}H-NMR, ^{13}C-NMR and LC-MS. Their anti-cancer activities were detected by using CCK-8 in the esophageal carcinoma cell line EC9706. The results indicate that the inhibitory activities of Lenalidomide derivatives were higher than that of Lenalidomide.

Angiogenesis, which is regulated by a host of growth factors in the microenvironment, plays an important role in the tumour growth, invasion and metastasis.[1,2] Inhibition of tumour angiogenesis, through small molecules acting on endothelial cell surface receptors to cut the signal downstream to block up blood vessels, has been widely used for treatment of malignant tumour.[3] The FDA has approved drugs that have anti-angiogenic activity, including Thalidomide and Erlotinib et al **(Fig. 1)**.[4]

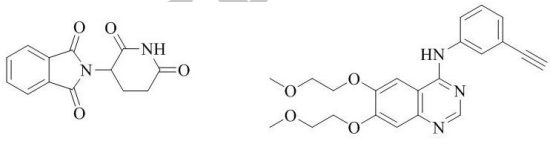
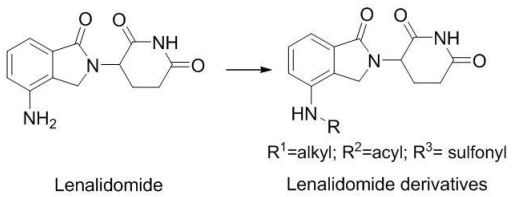


Fig. 1 Chemical structures of Thalidomide and Erlotinib

Lenalidomide, [3-(4-Amino-1-oxo-1,3-dihydro-2H-isoindol-2-yl)piperidine-2,6-dione], is a derivative of Thalidomide introduced in 2004. It was initially intended as a treatment for multiple myeloma. Now, it has been used to successfully treat for inflammatory disorders and tumors, such as myelodysplastic syndromes, Hodgkin's lymphoma and some solid cancers.[5] Lenalidomide has various activities, including direct anti-tumor effect, inhibition of angiogenesis and immunomodulatory role. It induces tumor cell apoptosis directly and indirectly by inhibition of bone marrow stromal cell support.[6] Clinical studies have shown that Lenalidomide manifests fewer side effects and almost no neurological toxicity and teratogenicity, compared with Thalidomide.[7,8] It has been increasingly used in combination with other chemotherapy drugs in a variety of hematopathy and solid tumors.[9-14]

In order to enhance the pharmacological activity of Lenalidomide, a series of Lenalidomide derivatives **(Scheme 1)** were designed by the reverse virtual screening of the molecular targets of anti-angiogenesis on Auto-Dock 4.0. The Lenalidomide derivatives (**1**, **2** and **3**) were synthesized by the alkylation, acylation and sulfonylation of Lenalidomide. CCK-8 was used to detect the inhibitory activity in the esophageal carcinoma cell line EC9706.



Scheme 1 Lenalidomide and its derivatives

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Initially, the reverse virtual screening was utilized to identify the potential anti-angiogenesis targets of Lenalidomide on Auto-Dock 4.0. The six target proteins, such as Vascular endothelial growth factor receptor (VEGFR-2, PDB: 1Y6A),[15] Epidermal growth factor receptor (erbB-3, PDB: 3LMG),[16] Fibroblast growth factor receptor (FGFR-4, PDB: 4QQ5),[17] BCR-ABL tyrosine kinase (ABL, PDB: 3CS9),[18] p38 Mitogen activated protein kinase (p38MAPK, PDB: 2NPQ),[19] and Metal protein kinase (MMP-3, PDB: 2JT5),[20] were chosen as the research targets. The screening results **(Table 1)** indicated that the angiogenesis molecular target of Lenalidomide was FGFR-4 for the lowest binding energy and inhib constant (ΔG=-7.05 kcal/mol, Ki=3.86 μM) among the 6 targets and even lower than that of FIIN-2 **(Fig. 2)** (ΔG=-6.63 kcal/mol, Ki=5.12 μM) the original ligand in crystal structure of FGFR-4 (PDB: 4QQ5).

Table 1

Reverse virtual screening results of Lenalidomide

Target (PDB)	Original ligand		Lenalidomide	
	ΔG (kcal/mol)	Ki (μM)	ΔG (kcal/mol)	Ki (μM)
VEGFR-2 (1Y6A)	-7.66	5.88	-3.55	1683
ErbB-3 (3LMG)	-6.96	7.91	-3.53	28.62
FGFR-4 (4QQ5)	-6.63	5.12	-7.05	3.86
ABL (3CS9)	-6.81	9.63	-3.54	1285
MMP-3 (2JT5)	-7.11	6.42	-2.56	4536
p38 MAPK (2NPQ)	-7.64	8.48	-2.99	3620

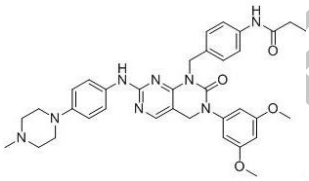


Fig. 2 Chemical structures of FIIN-2

The original ligand FIIN-2, which in the complex (PDB number: 4QQ5) was re-docked with the FGFR-4 to give the docking mode as shown **(Fig 3)**. The green molecule (FIIN-2) is the lowest energy conformation of interaction with FGFR-4; the purple and green areas on the surface indicate the hydrogen bond between FIIN-2 and FGFR-4. Nitrogen-containing heterocyclic ring in FIIN-2 molecule has the common hydrophobicity and Van der Waals force with Lenalidomide to LEU478, ALA634, ASP635, GLU525, LYS508, LEU555 residues.

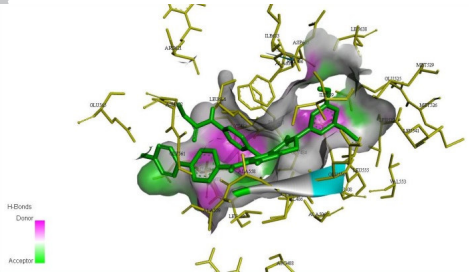


Fig. 3 Binding models of FIIN-2 in the FGFR-4(PDB: 4QQ5) active site

Further detailed computational analysis of Lenalidomide binding mode to the FGFR-4 **(Fig. 4)** shows that the Lenalidomide molecule is completely encapsulated by structural cavities consisting of amino acid residues LAL558, GLU556, LEU478, CYS557, ILE539, LEU624, ALA634, ASP635, GLU525, LYS508, LEU555, ALA506. The red molecule (Lenalidomide) is the lowest energy conformation of interaction with FGFR-4; the purple and green areas on the surface indicate the hydrogen bond between FIIN-2 and FGFR-4. The oxygen atoms and hydrogen atoms of the lactam carbonyl groups in the lenalidomide molecule interact with the amino acid residues ALA558 and GLU556, respectively, and form hydrogen bonds. The structure of the isoindolone interacts with the amino acid residues LEU478, CYS557, ILE539, LEU624, ALA634, ASP635, GLU525, LYS508, LEU555, ALA506 by Van der Waals and hydrophobic interactions and fit in the FGFR-4 cavity inside.

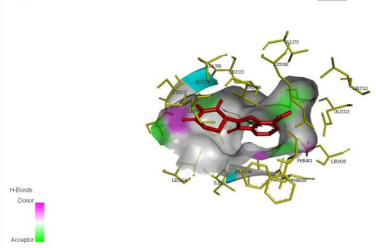


Fig. 4 Binding models of Lenalidomide in the FGFR-4(PDB: 4QQ5) active site

The docking models of Lenalidomide with FGFR-4, via Van der Waals and hydrophobic forces, were the same as the original ligand FIIN-2. It was confirmed by the binding ability of lenalidomide to FGFR-4 (ΔG=-7.05 kcal/mol, Ki=3.86 μM) was better than the original ligand (ΔG=-6.63 Kcal/mol, Ki=5.12μM) from the reverse molecular docking results. But the stacked plots of Lenalidomide and FIIN-2 in the binding mode reveal that there was an unoccupied pocket adjacent to ALY481, ALU480 and LEU624 **(Fig. 5)**. A series of Lenalidomide derivatives which the amino group of Lenalidomide was modified have been reported by Robarge, Michael J. et al.[21] Modification may fill the unoccupied pocket and enhance its interaction with amino acid residues on FGFR-4. More alkylation, acylation and sulfonylation of Lenalidomide derivatives were designed **(Scheme 1)**. The docking study on the Lenalidomide derivatives was carried out with FGFR-4 and results shown in Table 2.

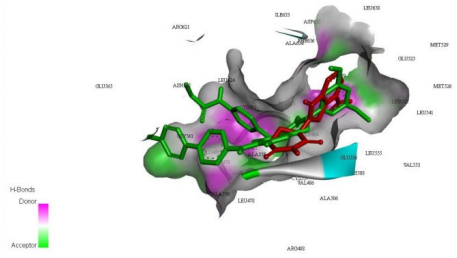
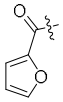
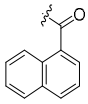
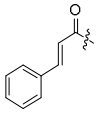
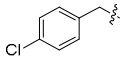
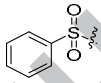
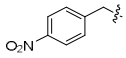
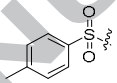
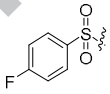
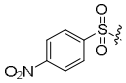
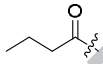
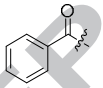
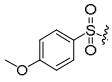
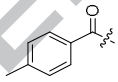
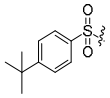
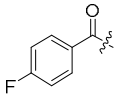
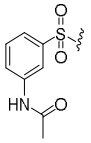
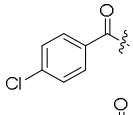
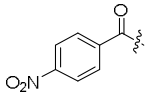
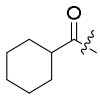


Fig. 5 Stacked plots of Lenalidomide and FIIN-2 in the binding mode

Table 2

Docking results of Lenalidomide derivatives

Compd	R	*ΔG* (kcal/mol)	*Ki* (μM)	Compd	R	*ΔG* (kcal/mol)	*Ki* (μM)
1a		-5.47	97.01	**2j**		-6.28	24.87
1b		-5.65	71.78	**2k**		-7.99	1.40
1c		-6.83	9.82	**2l**		-6.62	14.11
1d		-7.19	5.46	**3a**		-5.36	116.31
1e		-7.12	3.31	**3b**		-8.39	0.71
1f		-7.23	0.95	**3c**		-8.40	0.63
1g		-7.95	1.49	**3d**		-8.34	4.14
2a		-5.37	115.58	**3e**		-8.95	0.28
2b		-7.07	6.54	**3f**		-11.11	0.072
2c		6.07	35.51	**3g**		-8.68	0.44
2d		-7.51	3.21	**3h**		-8.88	2.35
2e		-7.68	5.62	**3i**		-7.85	1.74
2f		-7.56	5.59	**3j**		-6.68	9.39
2g		-7.78	4.26	**3k**		-7.03	7.08
2h		-7.28	3.82	**FIIN-2**		-6.63	5.12
2i		-7.80	1.93	**10**	H	-7.05	3.86

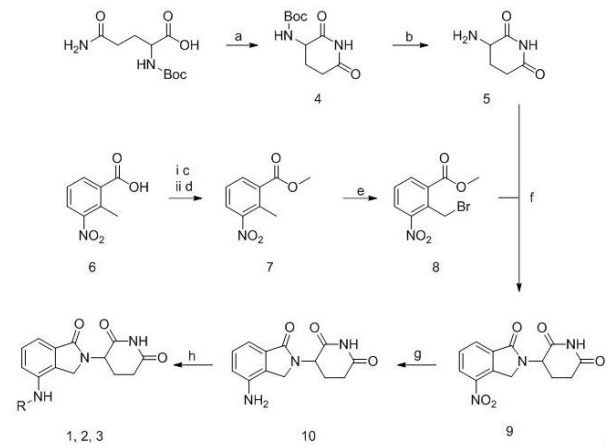
From the molecular docking results of Lenalidomide derivatives listed in Table 2, the values of *ΔG* are mainly between -11.11 kcal/mol and -5.37 kcal/mol, the values of *Ki* are from 0.072 μM to 115 μM. The value *ΔG* of the original ligand molecule FIIN-2 on FGFR-4 is -6.63 kcal/mol and the *Ki* is 5.12 μM. The values of most Lenalidomide derivatives are in the same order of magnitude or even better than the FIIN-2.

The sulfonylated derivatives **(3)** are more effective than the alkylated **(1)** and acylated derivatives **(2)**. **3b** (*ΔG*=-8.39 kcal/mol) is better than **1c** (*ΔG*=-6.83 kcal/mol) or **2d** (*ΔG*=-7.51 kcal/mol). The *ΔG* values are mostly below -7.00 kcal/mol and the lowest even reaches -11.11 kcal/mol, and the *Ki* values are mostly below 3.00 μM and the lowest is 7.20 nM. Among the 30 compounds, compounds with nitro groups, such as **1f** (*ΔG*=-7.23 kcal/mol), **2h** (*ΔG*=-7.28 kcal/mol), **3e** (*ΔG*=-8.95 kcal/mol), **3f** (*ΔG*=-11.11 kcal/mol) and **3g** (*ΔG*=-8.68 kcal/mol), performance outstanding effect. The sulfonyl derivatives **3e**, **3f** and **3g**, which the Ki value reached "nM "Level, and the *ΔG* values were all less than -8.0 kcal/mol.

It was found that the docking effect of the derivatives with aryl, most of the *ΔG* below -7.00 kcal/mol and the *Ki* also small, were better than that of the derivatives with aliphatic groups, most of the *ΔG* is in the range of -6.00 Kcal/mol or more, *Ki* significantly larger. The result may due to the docking modes are dominated by Van der Waals forces and hydrophobic forces, and the hydrogen bond is relatively less important. When the R group were designed with an aryl groups, such as phenyl, naphthyl, thienyl or furyl, the strong Van der Waals force and hydrophobic interaction resulting in a significant reduction of the *ΔG*, most of the *ΔG* was below -7.00 kcal/mol lower than those of aliphatic groups of R.

The synthetic routes of target compounds are detailed in **Scheme 2**. The key intermediate **5** was prepared by the deprotection of intermediate **4**, which was derived from the lactamization of commercially available *N*-(tert-Butoxycarbonyl)-L-glutamine in the presence of DCC and 4-DMAP. The intermediate **7** was prepared form acid **6** in the presence of thionyl chloride, followed by treating with methanol to give ester, then **7** was bromination with bromine in carbon tetrachloride to afford intermediate **8**. The intermediate **8** was connected with **5** by nucleophilic substitution then ammonolysis of ester in the presence of potassium hydrogen carbonate in acetonitrile, followed by reduction reaction of intermediate **9** under hydrogen atmosphere in methanol catalyzed by Pd-C afforded the Lenalidomide **10**.

The Lenalidomide derivatives were obtained by alkylated with differently substituted halogenated hydrocarbons in acetonitrile catalyticed by KI to give lenalidomide alkylated derivatives **1**; acid chlorides were prepared by different substituted carboxylic acid in presence of thionyl chloride, then Lenalidomide was acylated in THF which TEA as deacid reagent to yield Lenalidomide acylated derivatives **2** and lenalidomide was sulfonylated with different substituted sulfonyl chloride in THF to get lenalidomide sulfonyl derivatives **3**. All synthesized compounds were verified by the ^{1}H-NMR, ^{13}C-NMR and LC-MS.



Scheme 2 Synthesis of Lenalidomide derivatives.

Reagents and conditions: (a) DCC, 4-DMAP, ACN, r.t.; (b) TFA, DCM, r.t.; (c) $SOCl_2$, DCM, reflux; (d) MeOH, DCM, reflux; (e) Br_2, CCl_4, r.t.; (f) $KHCO_3$, ACN, reflux; (g) H_2, Pd/C, MeOH, r.t.; (h) 1: KI, K_2CO_3, CAN, reflux; 2: i $SOCl_2$, DCM, reflux, ii TEA, THF, r.t.; 3: Pyr, THF, r.t.

CCK-8 was used to detect the anti-tumor activity of Lenalidomide and its derivatives in the esophageal carcinoma cell line EC9706.[22] Inhibiting ratio of 4 compounds on EC9706 **(Fig. 6)** shows that at the concentration of 150 μg/mL, there is a clear different inhibiting ratio between them. With the increase of concentration, the inhibitory activity gradually increases and the different shrink. When the concentration reach to 600.0 μg/mL or more, the inhibition rate substantially 100%. From the results of analysis, inhibitory activity of alkylation, acylation and sulfonylation derivatives are stronger than Lenalidomide **(10)**.

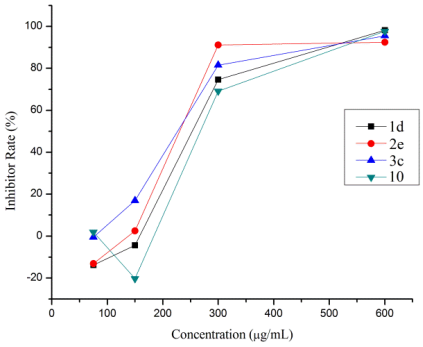


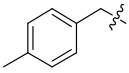
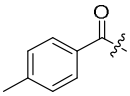
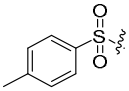
Fig. 6 Inhibiting ratio of compounds on EC9706

The results indicate that the inhibitory activity IC_{50} of Lenalidomide was 340.3 μg/mL and the inhibitory activity IC_{50} of its derivatives **1d**, **2e** and **3c** were 261.8 μg/mL, 309.5 μg/mL and 225.2 μg/mL, it shows that the Lenalidomide derivatives have better inhibitory activity than Lenalidomide. As can be seen from **Table 4**, all of Lenalidomide derivative have stronger inhibitory activity for esophageal cancer EC9706 cells than Lenalidomide. Substituent on the amino filling the pocket and forming π-π interaction enhanced affinity between ligand and receptor. Inhibitory activity of sulfonyl derivative **(3c)** is higher than inhibitory activity of acylated derivative **(2e)** or than inhibitory activity of alkylated derivative **(1d)**. This may be due to three types of Lenalidomide derivatives obtained these functional groups via modified amino group to occupy the pocket. These

functional groups have different angle with Lenalidomide lead to different activity. Structure of sulfonyl derivative is more suitable with FGFR-4 molecules, also the molecular docking result. The consistent of anti-tumor activity on EC9706 with that of molecular docking, shown that the angiogenesis docking is feasible and the FGFR-4 is the potential target for Lenalidomide derivatives.

Table 4

Inhibitory activity of Lenalidomide derivatives on EC9706

Compd	R	IC_{50} (μg/mL)	ΔG (kcal/mol)[a]
1d		309.5	-7.19
2e		261.8	-7.68
3c		225.2	-8.40
Lenalidomide	H	340.3	-7.05

[a:] Calculated

In this paper, a series of Lenalidomide derivatives were designed by the virtual screening of the molecular targets of anti-tumor angiogenesis. The results show that the angiogenesis molecular target of Lenalidomide is innitialy FGFR-4. The Lenalidomide derivatives were designed by modification of the amino group of Lenalidomide. The intended structures of Lenalidomide derivatives were identified as the alkylation, acylation and sulfonylation of Lenalidomide with a binding free energy ΔG values between -11.11 kcal/mol and -5.37 kcal/mol, inhibition rate constant Ki values from 0.072 μM to 115 μM. The Lenalidomide derivatives were synthesized and verified by the ^{1}H-NMR, ^{13}C-NMR and LC-MS. CCK-8 was used to detect the inhibitory activity of Lenalidomide derivatives in the esophageal carcinoma cell line EC9706. The results indicate that the inhibitory activity IC_{50} of Lenalidomide derivatives **1d**, **2e** and **3c** were 261.8 μg/mL, 309.5 μg/mL and 225.2 μg/mL. It shows that the Lenalidomide derivatives have better angiogenesis inhibitory than Lenalidomide (IC_{50}=340.3 μg/mL).

Acknowledgments

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A Supplementary data

Supplementary data associated with this article can be found, in the online version, at XXX Including methods of docking synthesis and activity testing of compounds described in this article, and data of ^{1}H-NMR, ^{13}C-NMR and LC-MS.

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Graphical Abstract

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Design, synthesis and biological evaluation of Lenalidomide derivatives as tumor angiogenesis inhibitor

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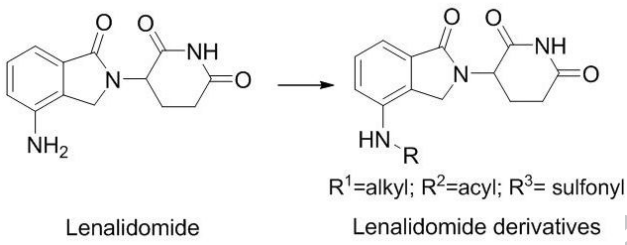
Shengquan Hu[a], Libin Yuan[a], Hong Yan[a,*] and Zhigang Li[b]



R^1=alkyl; R^2=acyl; R^3= sulfonyl

Lenalidomide

Lenalidomide derivatives