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ARTICLE TYPE

Synthesis and biological evaluation of pentanedioic acid derivatives as farnesyltransferase inhibitors

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Structure-based virtual screening of a commercial library identified pentanedioic acid derivatives (6 and 13b) as a kind of novel scaffold farnesyltransferase inhibitors (FTIs). Chemical modifications of the lead compounds, biological assays and analysis of the structure-activity relationships (SAR) were conducted to discover more potent FTIs. Some of them displayed excellent inhibition against FTase, among them, the most active compound 13n with an IC_{50} value of 0.0029 μM and SAR analysis might be helpful to the discovery of more potent FTIs.

Post-translational modifications, including prenylation, proteolysis and carboxymethylation, are crucial biochemical features of a majority of Ras superfamily proteins.[1, 2] Among them, prenylation includes farnesylation and geranylgeranylation which were catalyzed by farnesyltransferase and geranylgeranyltransferase.[3, 4] Farnesyltransferase is a key zinc metalloenzyme, which facilitates the transfer of a 15-carbon farnesyl to cysteine residue on proteins. The cysteine residue is located at a conserved carboxyl-terminal CAAX motif where C is the farnesylated cysteine, A is an aliphatic amino acid and X is aserine, an alanine, a glutamine or a methionine.[5, 6] The farnesyl group of the farmesylated cysteine leads to the increase of hydrophobicity of Ras protein, thereby promoting its binding with the plasma membrane for signal transduction.[7] Since mutation of the Ras protein could make this protein overactivated which often result in some cancers, the inhibition of farnesyltransferase has been shown as a potential pharmacological target for cancer chemotherapies.[8]

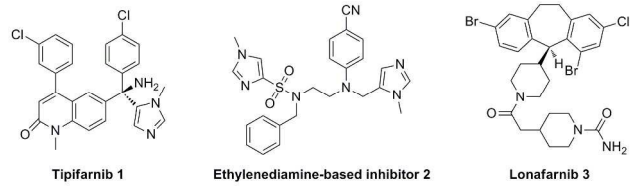


Fig. 1 Structures of reported FTIs in the clinical stage.

Although many peptidic and peptidomimetic FTIs have been reported in recent several decades, these FTIs are involved with several disadvantages, such as poor membrane permeability, instability towards proteases. Some of thiol-containing effective FTIs displayed some adverse effects caused by the presence of thiol moiety, which affected their further applications as therapeutic agents.[6, 9-11] Currently, a majority of non-peptidic FTIs have been developed,[12, 13] the typical ones are quinolinone scalfold Tipifarnib **1** (R115777),[14, 15] ethylenediamine scaffold such as compound **2**,[16, 17] tricyclic scaffold lonafarnib **3** (Fig. 1).[18] Some of them have been evaluated in the phase I and phase II clinical trials. For example, phase II study of FTI R115777 has been conducted in advanced melanoma, hematologic malignancies[19] and acute myelogenousleukemia (AML)[14]. But clinical data showed that the treatment of cancer such as solid tumoror hematological malignancies using FTIs caused various toxicities including myelosuppression, vomiting and gastrointestinal toxicity.[3, 19] Although these reported FTIs have some adverse effects and the molecular mechanism of FTIs is not entirely clear, the present inspiring facts of combining FTIs with other chemotherapies have put forward an urgent need to develop new non-peptide and thiol-free based FTIs with more potent for the therapeutic applications.[7, 20, 21]

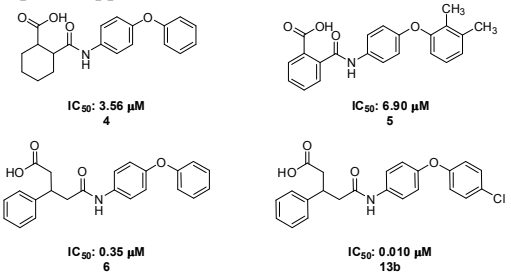


Fig. 2 Structures of compounds **4**, **5**, **6** and **13b**.

In our search for new FTIs by structure-based virtual screening, we have shown previously that the discovery of two di-acid derivatives **4** and **5** as FTIs (Fig. 2), in which the carboxyl

groups could coordinate with Zn^{2+} in the hydrophilic region of the binding site.[3] Here we report a series of novel non-peptide pentanedioic acid derivatives FTIs from structural optimization and biological evaluation of lead compounds **6** and **13b**. The predicted binding mode of the lead compound **13b** implied that carboxyl group could coordinate with Zn^{2+} and formed a hydrogen bond with Tyr861, the link amide moiety and phenyl ring A are stabilized by hydrophobic effects and Van der Waals force (VDW) interactions with the farnesyl moiety of farnesyldiphosphate (FPP). Moreover, chlorine-substituted phenyl ring B (**13b**) has aromatic interactions with aromatic hydrophobic pocket, which is composed of Trp602, Trp606, Tyr654, Trp803. Finally, phenyl ring A makes hydrophobic interaction with electronegative hydrophobic pocket, composing of Tyr593, Leu596, Trp606, Asp859 and Tyr861 (Fig. 3).

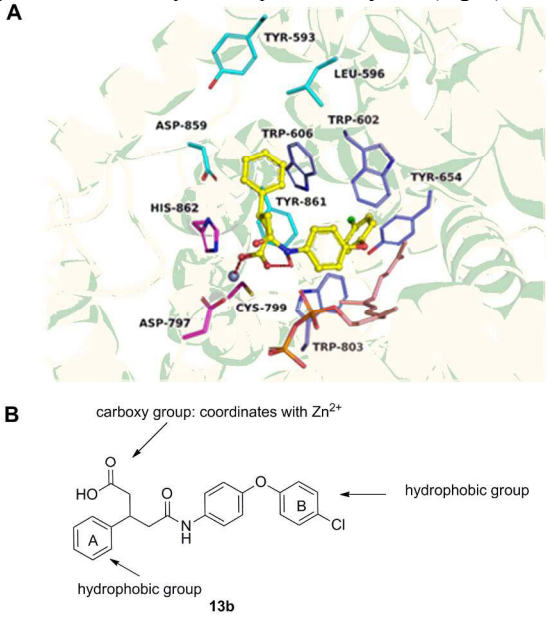
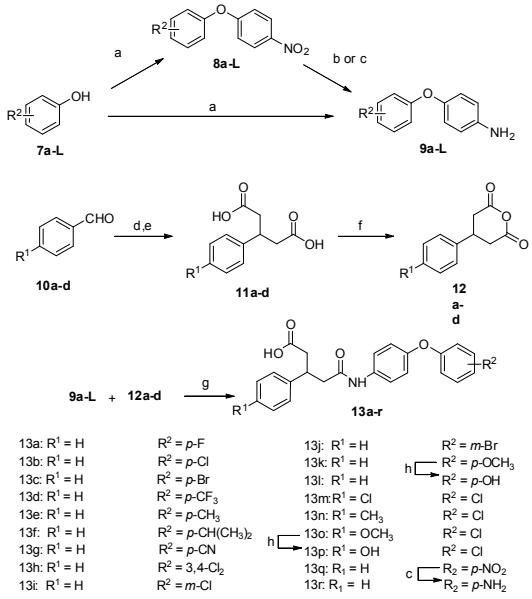


Fig. 3 A: Compound **13b** is shown as yellow stick and ball representation. FTase (PDB ID: 1LD8) is shown as pink cartoon. FPP is pink, Zn^{2+} is grey. Residues interacting with carboxylic acid, phenyl ring A, phenyl ring B are shown as magenta, cyan and purple, respectively; B: SAR studies on the compound **13b**.



Scheme 1. Synthesis route of compounds **13a-r**. Reagents and conditions: (a) 1-fluoro-4-nitrobenzene, K_2CO_3, DMSO, r.t., overnight; (b) con. HCl, $SnCl_2{\cdot}2H_2O$, 80°C, 6 h; (c) 10% Pd/C, H_2, ethanol, 6 h; (d) Ethyl acetoacetate (EAA), Piperidine, rt, 3 d; (e) KOH, H_2O, reflux, 4 h; (f) AcCl, reflux, 2 h; (g) dioxane, TEA, rt, 8 h; (h) BBr_3, DCM, 0 °C→rt, 30 min.

Results and Discussion

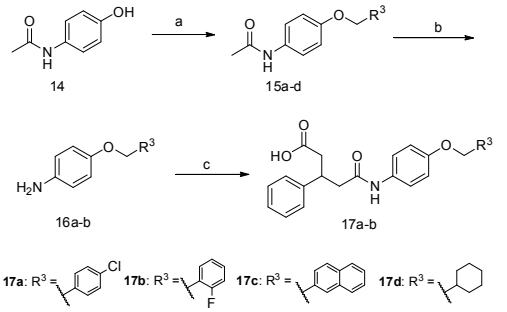
Compound **13b** with the farnesyltransferase inhibition IC_{50} 0.01 μM was identified by structure-based virtual screening and biological assays. In order to search novel FTIs with improved activities and explicate structure-activity relationships, a series of derivatives were designed on the basis of the proposed binding model described above by introducing diverse substituents into phenyl ring B such as small hydrophobic or hydrophilic moieties; some substituents modifications in para-position of phenyl ring A; and the replacement of carboxyl with esters, amide or sulfamide (Fig. 3A).

The formation of amide from compound **13b** was carried out by 3-substituted glutaricanhydride derivatives and aniline derivatives in the presence of TEA.[22] And, as reported, glutaricanhydride derivatives **12a-d** have been successfully synthesized by the reaction of corresponding substituted benzaldehyde **10a-d** with ethyl acetoacetate, followed by hydrolysis with an aqueous solution of KOH (20 M) to form the pentanedioic acid scaffold **11a-d**, then heating in the presence of acetyl chloride.[23] The following synthesis step of the key aniline intermediates **9a-l** were from nucleophilic substituted reactions of substituted phenols and 1-fluoro-4-nitrobenzene, followed by reduction of nitro (Scheme 1). Compounds **13k** and **13o** were treated with BBr_3 as demethylation reagent to obtain compounds **13l** and **13p**. Synthesis of **9l** was different from **9a-k**, which was directly obtained from 1-fluoro-4-nitrobenzene and 4-aminophenol.

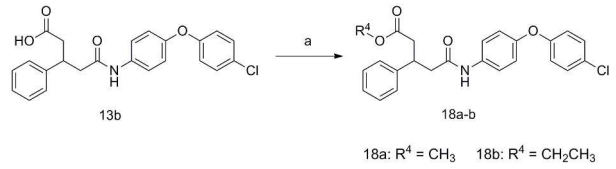
As docking suggested, the segment of chlorobenzene in compound **13b** was located in a hydrophobic pocket of FTase. To test the size and the orientation of this pocket, the insertion of a methylene in diphenyl ether was carried out in order to clarify the depth and width of the pocket, four compounds **17a-d** have been

prepared in three steps from commercially available materials starting from 4-acetamido phenol as Scheme 2.

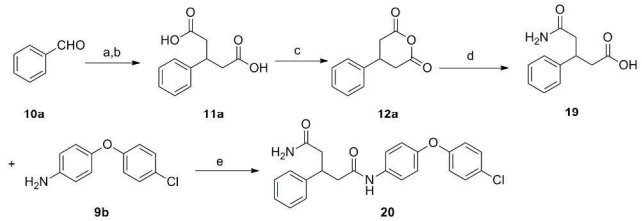
To explore the significance of carboxyl in the compound **13b**, compound **18a** and **18b** were obtained by esterification of compound **13b** as Scheme 3, and by amidation of compound **13b** and compound **20** as Scheme 4. To the best of our knowledge, sulfamide is a special functional group which could coordinate with Zn^{2+}, which might be effective for the biological activity of FTIs.[24] In order to construct FTIs with segment of sulfamide, four compounds **30a-d** were synthesized through some complicated reactions as Scheme 5.[25] First, intermediate **23** was prepared by reductive amination and protection of methylsulfonyl. Compound **23** was treated with LiHMDS and diethyl chlorophosphate followed by the addition of benzaldehyde derivatives to form alkenylsulfonamide **25**, and then Michael addition reaction was carried out with dimethyl malonate to form compound **26**, followed by Krapcho decarboxylation to obtain the ester **27**.[26] Acid **28** was obtained through hydrolysis of the ester **27**, then coupled with aniline derivatives to obtain target compounds described as above.



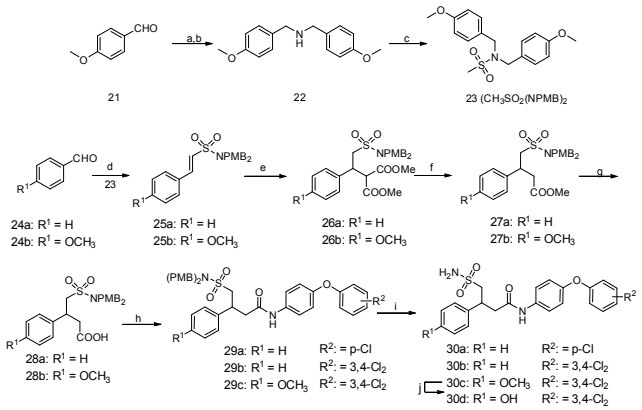
Scheme 2. Reagents and conditions: (a) arylhalide, K_2CO_3, DMSO, rt, overnight; (b) KOH, CH_3OH, H_2O, reflux, 18 h; (c) glutaric anhydride (**12a**), dioxane, TEA, rt, 8 h.



Scheme 3. Methyl or ethyl esterification of compound **13b**. Reagents and conditions: $SOCl_2$, CH_3OH, 0 °C→rt, 1 h.



Scheme 4. Reagents and conditions: (a) Ethyl acetoacetate (EAA), Piperidine, rt, 3 d; (b) KOH (20 M), H_2O, reflux, 4 h;(c) AcCl, reflux, 2 h; (d) NH_3, THF, r.t., overnight; (e) HBTU, DIPEA, DMF, r.t., overnight.



Scheme 5. Reagents and conditions: (a) 4-methoxybenzylamine, Ethanol, 2 h; (b) $NaBH_4$, reflux, 2 h; (c) MsCl, TEA, DCM, 0 °C→rt, 5h.(d) **23**, LiHMDS, $ClPO(OEt)_2$, THF, –20 °C to rt, 1 h; (e) DMM, NaOMe–MeOH, MeCN, 2 d, reflux; (f) DMF, NaCl, H_2O, reflux, 6 h; (g) $LiOH{\cdot}H_2O$, CH_3OH, H_2O, 3 h; (h) HBTU, DIPEA, DMSO, rt, overnight; (i) TFA, DCM, 10 h; (j) BBr_3, DCM, 0 °C→rt, 30 min.

The human FTase expression plasmid pRSF-Duet1-FTase (a kind gift from Professor Gerrit J. K. Praefcke) was verified by DNA sequencing and used to generate FTase. The expression and purification of recombinant human FTase was performed as published protocols.[27] The fluorescent assays were performed as previously described.[3] Compounds **31**, **32** and **33** were purchased (SPECS datebase) because of the similarity of their structures with the compound **13b** to some degree. Inhibition ratios of these compounds are all less than 50%, which reveals that phenyl ring A is an essential part for maintaining the activity. This significant variety might be caused by the abatement of flexibility of carboxyl in the presence of benzene and hence increase the interaction between carboxyl and Zn^{2+}. We next discuss the SAR of synthetic compounds from modification of three parts as suggested above：diverse substituents into phenyl ring B such as small hydrophobicity or hydrophily moieties; modifications of carboxyl into esters, amide or sulfamide; para-position modifications of phenyl ring A.

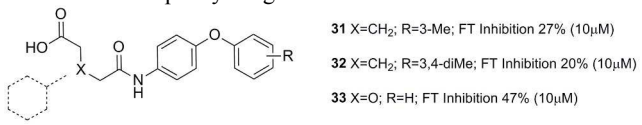
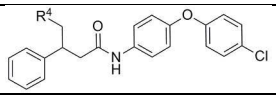


Fig. 4. Structures and inhibition ratio of compounds **31**, **32** and **33**.

First, FTase inhibition data in Table 1 showed that compounds **18a**, **18b** and **20** obtained through esterification and amidation of compound **13b** resulted in the complete loss of the activity, which further certify our hypothesis that carboxyl group on compound **13b** was the key zinc binding groups. Then, we focused on compounds **30a-d** (Table 4) from the modification of carboxyl group with another zinc binding group sulfamide. To our disappointment, compound **30a** (0.71 μM) showed less potency than that of compound **13b** (0.010μM). To some extent, compound **30b** displayed better FTase inhibition (IC_{50} 0.038μM), which showed that sulfamide group in this series really coordinated with zinc of FTase, but the affinity with zinc was weaker than that of the carboxyl group.

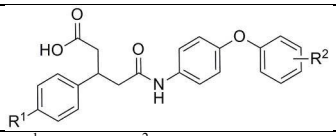
Table 1 Inhibitory activities of target compounds against human FTase (*h*FTase)



Compound	R^4	IC_{50} (μM)	Inhibition ratio
18a	$-COOCH_3$	-	-19%
18b	$-COOCH_2CH_3$	-	-24%
20	$-CONH_2$	-	6%

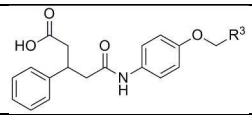
Comparing compound **6** with compound **13b** (Fig. 2), the removal of 4-Cl from the phenyl ring B resulted in a 35-fold decrease in potency against FTase, this significant variety might be caused by preferable steric complementation with hydrophobic pocket composing of Trp602, Trp606, Tyr654 and Trp803. we next developed compounds **13a-13r** by introducing different substituents onto the phenyl B (Table 2). First, compounds **13a, 13b, 13c** resulted from introducing F, Cl, Br atom onto the 4-position of the phenyl ring B all showed good bioactivities against FTase with an IC_{50} value at about 10 nM, 4-Cl and 4-Br (**13b, 13c**) were a little better than that of 4-F (**13a**). Second, introduction of Cl, Br onto the 3-position of the phenyl ring B showed the similar phenomenon. A gradual potency improvement also was observed for those with halogen atom at the para-position of the phenyl ring B (compound **13a, 13b, 13c**), which correlated well with increased hydrophobicity and size (Br>Cl>F). The similar phenomenon could be observed from compounds **13i** and **13j**. By substitution with two chlorine atoms at 2,4-positions, compound **13h** was the best one in this series of compounds with an IC_{50} of 0.0072 μM. Some larger substitutions, such as methyl (**13e**), trifluoromethyl (**13d**), cyan (**13g**), isopropyl (**13f**), methoxyl (**13k**), nitro(**13q**) in the para-position were sterically less tolerated, leading to a huge loss of activity. Meanwhile, compounds **13l** and **13r** with introduction of hydrophilic groups OH and NH_2 into para-position, resulted in a complete loss of activity which further verifies that para-position substitution of small non-polar groups was more preferential.

Table 2. Inhibitory activities of target compounds against human FTase (*h*FTase)



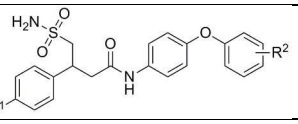
Compound	R^1	R^2	IC_{50} (μM)	Inhibition ratio
13a	H	*p*-F	0.015	94.44
13b	H	*p*-Cl	0.010	99.24
13c	H	*p*-Br	0.0096	99.00
13d	H	*p*-CF_3	0.071	96.93
13e	H	*p*-CH_3	0.027	98.95
13f	H	*p*-$CH(CH_3)_2$	0.58	89.34
13g	H	*p*-CN	7.1	51.95
13h	H	*3,4*-Cl_2	0.0072	96.19
13i	H	*m*-Cl	0.032	96.12
13j	H	*m*-Br	0.013	96.66
13k	H	*p*-OCH_3	2.27	69.13
13l	H	*p*-OH	-	0.04
13m	Cl	*p*-Cl	0.45	86.98
13n	CH_3	*p*-Cl	0.0029	97.16
13o	OCH_3	*p*-Cl	1.94	79.11
13p	OH	*p*-Cl	-	21.45
13q	H	*p*-NO_2	0.91	93.65
13r	H	*p*-NH_2	-	13.35

Table 3 Inhibitory activities of target compounds against human FTase (*h*FTase)



Compound	R^3	IC_{50} (μM)	Inhibition ratio
17a		0.017	98.75
17b		0.023	98.62
17c		0.15	88.14
17d		0.24	88.79

Table 4 Inhibitory activities of target compounds against human FTase (*h*FTase)



Compound	R^1	R^2	IC_{50} (μM)	Inhibition ratio
30a	H	*p*-Cl	0.71	77.23
30b	H	*3,4*-Cl_2	0.038	95.99
30c	OCH3	*3,4*-Cl_2	-	35.03
30d	OH	*3,4*-Cl_2	-	-6.52

To further explore the SAR in this hydrophobic valume, we next focus our efforts on the modification of diphenyl ether. The strategy was performed by the insertion of methylene between oxygen atom and phenyl ring to form benzyl ether (Table 3). Compounds **17a** (0.017 μM) and **17b** (0.023 μM) derived from lead compound **13b** had resulted in a little decrease in activity against FTase, which might be resulted from the increased structural flexibility caused by an inserted CH_2 in diphenyl ether.

Besides the variation of flexibility, steric effect should be considered. For example, compound **17c**, with the replacement of naphthylmethylene, showed a greatly reduced activity against FTase, which was possible due to collision with that small hydrophobic pocket.

Finally, we focus on the effects of substituents on phenyl ring A. As illustrated in the predicted binding mode of compound **13b**, this phenyl ring was pointed toward a small hydrophobic cavity formed by residues Tyr593, Leu596, Trp606, Asp859 and Tyr861. The introduction of hydrophilic group OH (**13o**) and OCH_3 (**13p**) resulted in a sharp reduction in activity in comparison with compound **13b**, which demonstrated that polar and large functional group was relatively less acceptable. The similar results could be seen in compounds **30c** and **30d**. On the contrary, compound **13n** from the introduction of methyl, displayed stronger activity against FTase with an IC_{50} value of 0.0029 μM than that of compound **13b**. We speculated the results possibly suggested that methyl was suitable to occupy the hydrophobic cavity to form better hydrophobic interaction (Fig. 5).

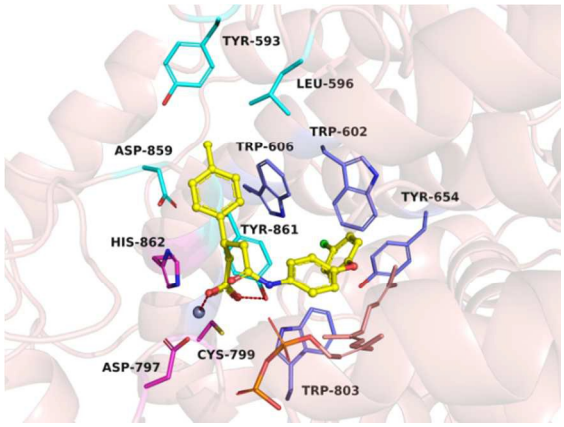


Fig. 5. Predicted binding modes of compound **13n** in the active site of FTase (PDB code:1LD8).

Conclusions

In this study, a series of pentanedioic acid derivatives as a kind of novel scaffold farnesyltransferase inhibitors from lead compounds **6** and **13b** were obtained. Some of them displayed good inhibitory activity, among them, compound **13n** with an IC_{50} value of 0.0029 μM was the most active one in these series, which might lead to the discovery of new FTIs. Chemical modifications of the lead compounds, biological assays and analysis of the structure-activity relationships (SAR) were conducted. Some valuable structural optimization suggestions were obtained to discover more potent FTIs.

Acknowledgements

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