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Identification of BR102910 as a selective fibroblast activation protein (FAP) inhibitor

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ABSTRACT

Fibroblast activation protein (FAP) belongs to the family of prolyl-specific serine proteases and displays both exopeptidase and endopeptidase activities. FAP expression is undetectable in most normal adult tissues, but is greatly upregulated in sites of tissue remodeling, which include fibrosis, inflammation and cancer. Due to its restricted expression pattern and dual enzymatic activities, FAP inhibition is investigated as a therapeutic option for several diseases. In the present study, we described the structure–activity relationship of several synthesized compounds against DPPIV and prolyl oligopeptidase (PREP). In particular, BR102910 (compound **24**) showed nanomolar potency and high selectivity. Moreover, the *in vivo* FAP inhibition study of BR102910 (compound **24**) using C57BL/6J mice demonstrated exceptional profiles and satisfactory FAP inhibition efficacy. Based on excellent *in vitro* and *in vivo* profiles, the potential of BR102910 (compound **24**) as a lead candidate for the treatment of type 2 diabetes is considered.

Fibroblast activation protein (FAP, FAP-α, separase) is a type II transmembrane glycoprotein consisting of 760 amino acids, which is inducible in cultured fibroblasts using the monoclonal antibody (mAb) F19.[1] It belongs to the family of post-proline dipeptidyl aminopeptidases, which mainly cleave peptide substrates after proline residues.[2] Dipeptidyl peptidases (DPP2, DPP4, DPP8, DPP9) and prolyl oligopeptidases (PREP, POP) are also parts of this family.[3] FAP is a serine protease that has all of the activities of endopeptidase, and is known to be highly expressed in various lesion tissues such as epithelial cancer, cirrhosis and pulmonary fibrosis.[4] Since FAP is mainly expressed in fibroblasts, it induces tumor development by cancer growth and the invasion into normal tissues.[5] Moreover, FAP is known to affect type 2 diabetes and obesity through the inactivation of FGF21 (fibroblast growth factor 21) by the N- and C-terminal cleavage process.[6] As shown in Fig. 1, FGF21 is a hormone secreted from liver and adipose tissues to regulate sugar and lipid metabolism.[7] In the case of human FGF21, the C-terminal portion of FGF21 is readily cleaved by FAP, and the biological action of FGF21 is reduced by about 400 times.[8] In addition, the inactivation of FGF21 is involved in the accumulation of triglycerides and improvement of inflammation in the liver. Therefore, it is expected to be a crucial target for the treatment of non-alcoholic steatohepatitis (NASH).[9] Moreover, FGF21 is highly related with the control of insulin sensitivity, fat browning, and glucose uptake. Therefore, the development of FAP inhibitor could be a promising therapeutic approach for type 2 diabetes alternative to the recombinant FGF21 therapies.[10]

With the growing interest on FAP inhibition in drug discovery, various FAP inhibitors have been reported.[11] For examples, a non-selective inhibitor, Val-boroPro (**1**) reached up to the phase II clinical trial for cancer treatment. However, it was withdrawn due to both safety and efficacy issues (Fig. 2).[12] Linagliptin (**2**) was clinically approved as a DPPIV inhibitor though it shows significant FAP affinity.[13] Recently, ARI-3099 (**3**) with a boronic acid moiety was also found as a FAP inhibitor.[14] The selectivity of this compound is more than 350-fold towards FAP over PREP. The affinity of this compound is negligible for the DPPs. It is noted that a dipeptide linker between pyrrolidine moiety and heterocycle framework is very crucial for improved FAP affinity.[14] In fact, the installations on dipeptide linker led to the loss in potency toward FAP and the increased selectivity for PREP rather than FAP. It was also observed that addition of halo substituents (F and Cl) to the pyridine ring improved potency against FAP.

Compound **4** containing a quinolinoylglycyl(2-cyano-4,4-difluoropyrrolidine) backbone has been recognized as one of the most potent FAP inhibitors.[15] Notably, the preferential accommodation of 2-cyanopyrrolidine moiety with minimal steric bulk in the FAP's S1 pocket

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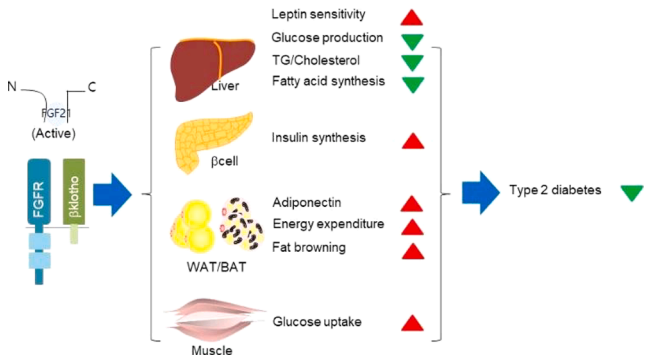


Fig. 1. Biological action of human FGF21.

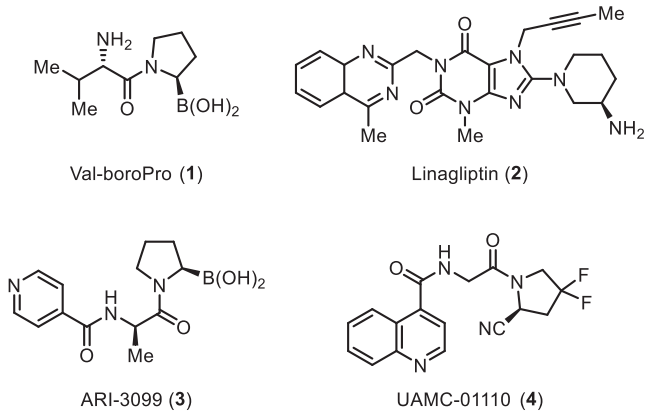


Fig. 2. Selected FAP inhibitors.

was described.[16] The potency and selectivity of the synthesized compounds were significantly decreased by exchanging cyano group into other functional groups such as boronic acid and chloromethyl ketone. More importantly, the improved hydrophobicity arising out of difluorination might be playing an important role for high FAP inhibitory potency, proficient ligand efficiency and superior FAP/PREP selectivity of compound **4** (Table 1).

Taking into consideration the structure activity relationship of reference compounds **3** and **4**, we conceived a general structure with three fragments to design the novel and selective FAP inhibitors (Fig. 3). Firstly, the 2-cyano-4,4-difluoropyrrolidine tail was retained in the newly designed compounds. A *N*-oxoglycyl group as a second fragment was selected to link a tail with a heterocycle framework. Then we started the synthesis and evaluation of various aryl-substituted 5- and 6-membered heterocycles, which have been rarely explored as the heterocyclic fragment. Moreover, different kind of linkers consisting of alkyl and heteroalkyl moieties between aryl and heteroaryl rings were also screened to identify the influence on the FAP inhibition.

Table 1
IC_{50} values for reference compounds **1**–**4**.

Compounds	IC_{50} (μM)				
	FAP	DPP-4	PREP	DPP-2	DPP-9
1	0.07 ± 0.01	0.022 ± 0.001	0.98 ± 0.06	0.086 ± 0.0007	N.D.[a]
2	0.37 ± 0.002	0.0020 ± 0.00002	>100	>100	>100
3	0.025 ± 0.001	>100	0.99 ± 0.04	>100	>100
4	0.0033 ± 0.0004	>100	1.8 ± 0.2	>100	>12.5

[a] N.D. = not determined.

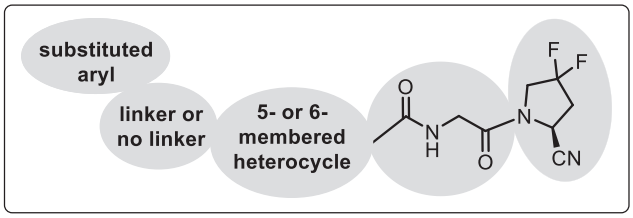


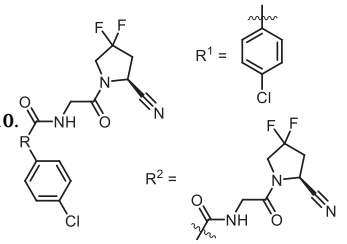
Fig. 3. General structure of synthesized FAP inhibitors.

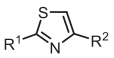
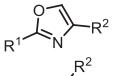
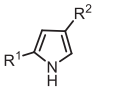
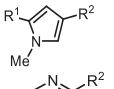
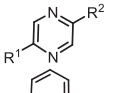
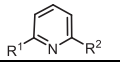
All the compounds listed in Tables 2–5 were prepared according to the general synthetic routes summarized in Scheme 1. The key intermediate, 4,4-difluoro-2-glycylcyclopentane-1-carbonitrile **53**, was prepared in two steps from 4,4-difluoropyrrolidine-2-carbonitrile **51** via amide formation followed by deprotection of Boc group under acidic conditions. The Pd(0)-catalyzed Suzuki coupling of azolyl chloride **54** with aryl boronic acids provided the corresponding adducts **55**. Subsequently, hydrolysis of ester group and EDC-catalyzed amidation reaction furnished difluoropyrrolidines **5**–**16**.

Acyl chlorination of phenylacetic acids **56** with oxalyl chloride and consecutive amination by ammonia afforded the corresponding phenylacetamides **57**, which was converted to the corresponding thioamides by treatment with Lawesson's reagent. The intermediate thioamides were subjected into intermolecular annulation with ethyl-3-bromo-2-oxopropanoate to give 2-benzyl thiazoles **58**. Difluoropyrrolidines **17**–**38** were obtained from the benzyl thiazoles **58** via basic hydrolysis and amide formation in a similar manner as stated before. Sulfinyl **35** and sulfonyl **36** derivatives were obtained through oxidation of compound **34** with *m*-CPBA. Substituted acetic acids **59** were transformed into difluoropyrrolidines **39**–**50** by adopting a similar sequence as that for compounds **17**–**38**.

Compounds **5**–**10** containing a *para*-chlorophenyl ring were first evaluated against inhibitory effects on FAP and PREP, as shown in

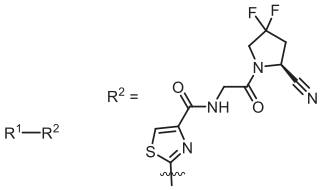
Table 2
In vitro potency and selectivity of compounds **5**–**10**.

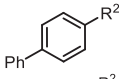
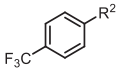
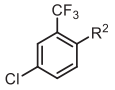
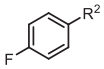
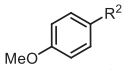
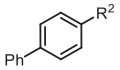
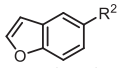
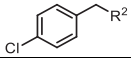


Entry	R	% Inhibition[†]	IC_{50}[‡] (μM)		SI*
		1uM	FAP	PREP	
5		86.74	0.148	26.84	181.4
6		88.71	0.093	3.997	43.0
7		57.75	0.550	3.623	6.6
8		85.31	0.104	0.624	6.0
9		63.98	0.795	0.197	0.2
10		80.64	0.100	0.108	1.1

*SI means selectivity index (calculated as [IC_{50}(PREP)/IC_{50}(FAP)]).
[†] Competitive binding assay (TR-FRET).
[‡] IC_{50} values by fluorometric assay using AMC substrates.

Table 3
IC_{50} values of compounds (**5** and **11**–**17**) with a thiazole scaffold.



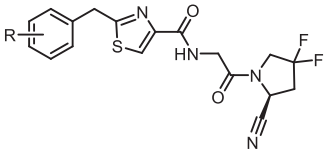
Entry	R^1	% Inhibition†	IC_{50}‡ (μM)			SI*
		1uM	FAP	DPP-4	PREP	
5		86.74	0.148	N.D	26.84	181.4
11		98.96	0.077	>100	1.377	17.9
12		94.64	0.06	>100	0.154	2.6
13		90.49	0.087	N.D	1.597	18.4
14		76.45	0.214	N.D	1.182	5.5
15		84.75	0.414	N.D	10	24.2
16		83.38	0.446	N.D	10	22.4
17		98.58	0.021	>100	0.182	8.7

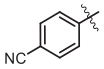
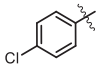
*SI means selectivity index (calculated as [IC_{50}(PREP)/IC_{50}(FAP)]).
† Competitive binding assay (TR-FRET).
‡ IC_{50} values by fluorometric assay using AMC substrates.

Table 2. After critically analyzing the inhibitory potency and selectivity of the compounds comprising of 5- or 6-membered heterocycle, compound **5** containing a thioazole ring was identified to display selectivity more than 100 folds for FAP than PREP. Introduction of an oxazole or pyrrole moiety (compounds **6**–**8**) could not provide any significant advantage to overall activity and selectivity. Major loss of selectivity was observed with the increase in ring size in case of compounds **9** and **10** containing pyrazine and pyridine moieties respectively. Hence, the thiazole moiety was chosen for further investigation based on the selectivity of inhibition criteria.

Next, the effect of the substituents on the aryl ring attached to thiazole was evaluated, and the results are given in Table 3. A CF_3-group on compounds **11** and **12** increased the FAP inhibitory activity, but caused a sharp reduction in the SI value compared to **5**. Similar effect was recorded in case of compound **13** with a 4-fluorophenyl substituent. Decrease in both activity and selectivity were found for *para*-methoxy and *para*-phenyl groups (compounds **14** and **15**). Replacement of the phenyl ring with a fused benzofuran ring in compound **16** could not offer any improvement in this trend. Interestingly, *para*-chlorobenzyl thiazole substituent in compound **17** dramatically enhanced the FAP inhibitory potency (0.021 μM). Determining the best scaffold with specific regard to affinity for FAP, regardless of selectivity, was the primary goal of second step of scaffold optimization. Therefore, the next series of compounds were constructed with benzyl thiazole as the heterocyclic part and the derivatives were synthesized with different substitution of various size and electronic properties at the phenyl ring (Table 4). The IC_{50} values for FAP, DPPIV, and PREP inhibitions were determined for these compounds. In general, monohalo-substituted compounds demonstrated high potency and selectivity varied according to the position (compounds **17**–**21**). Particularly, loss of selectivity was observed

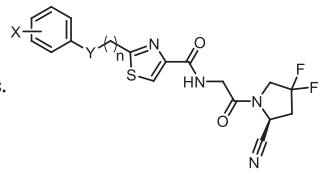
Table 4
IC_{50} values of compounds **17**–**38** with various substituents on aryl rings.



Entry	R	% Inhibition†	IC_{50}‡ (μM)			SI* (PREP/FAP)
		1uM	FAP	DPP-4	PREP	
17	4-Cl	98.58	0.021	>100	0.182	8.7
18	2-Br	93.71	0.050	0.20	0.009	0.2
19	3-Br	97.52	0.035	52.02	0.159	4.5
20	4-Br	99.96	0.016	>100	0.108	6.8
21	2-I	90.64	0.078	>100	0.001	0.0
22	4-OMe	97.95	0.026	>100	0.005	0.2
23	2-naphthyl	99.35	0.004	>100	0.026	6.6
24	3,4-di-Cl	98.97	0.002	>100	49.00	24.5
25	2,4-di-Cl	97.20	0.001	>100	0.001	1.0
26	2,5-di-Cl	94.47	0.055	>100	0.016	0.3
27	3,4-di-F	95.42	0.047	>100	0.474	10.1
28	2-Cl, 4-F	95.87	0.060	>100	0.048	0.8
29	4-Me	97.84	0.037	68.85	0.107	2.9
30	4-OCF_3	86.32	0.022	>100	0.200	9.1
31	4-CN	99.27	0.014	>100	3.204	27.6
32		98.70	0.012	>100	0.103	8.6
33		93.84	0.145	>100	0.464	3.2
34	4-SMe	99.02	0.025	>100	0.060	2.4
35	4-SOMe	95.00	0.390	4.12	1.205	3.1
36	4-SO_2Me	98.03	0.020	10.110	0.048	2.4
37		98.84	0.023	>100	0.076	3.3
38		98.31	0.028	18.71	0.410	14.6

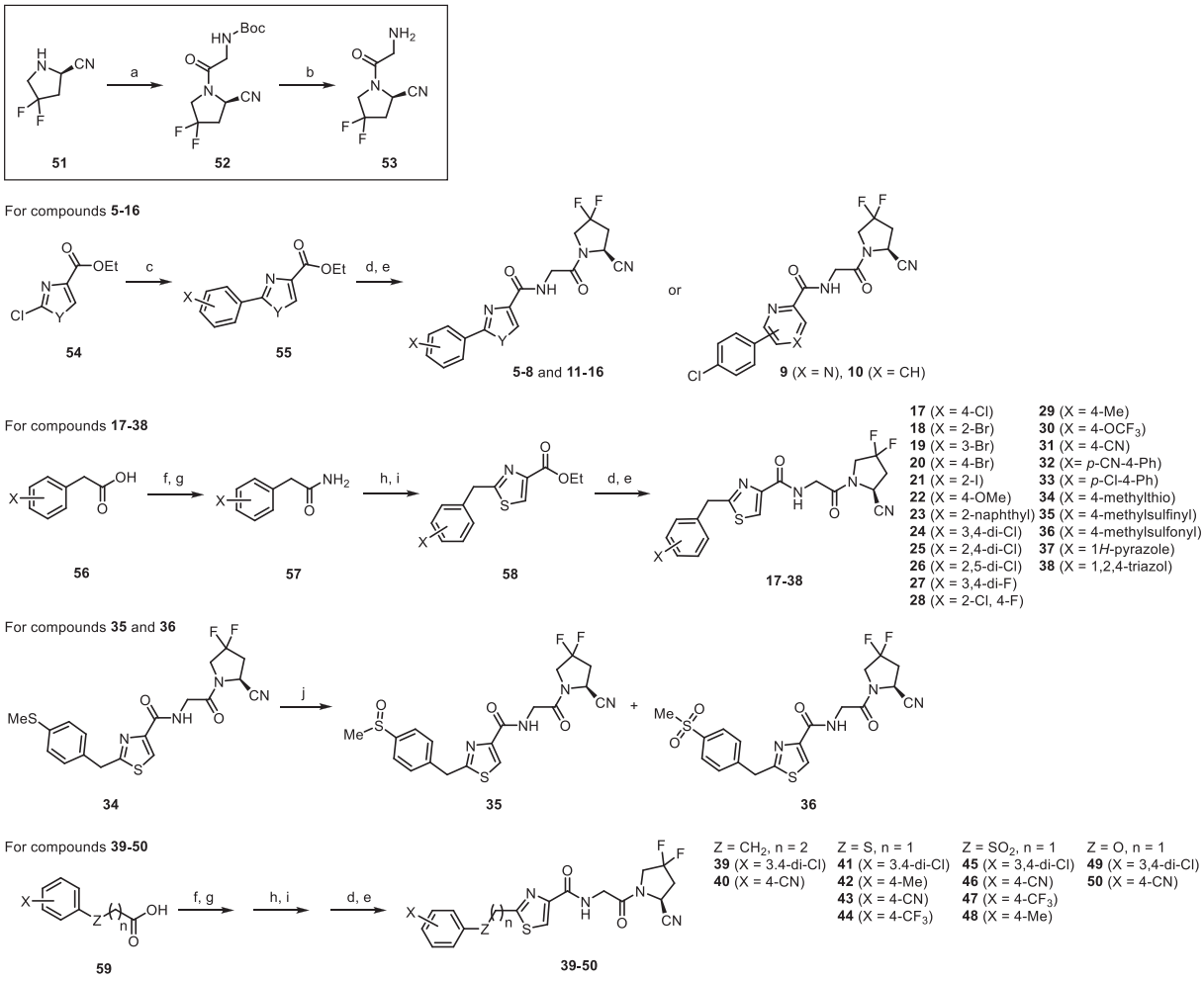
*SI means selectivity index (calculated as [IC_{50}(PREP)/IC_{50}(FAP)]).
† Competitive binding assay (TR-FRET).
‡ IC_{50} values by fluorometric assay using AMC substrates.

Table 5
IC_{50} values of compounds **24** and **39**–**50** with modified linkers.



Entry	X	Y	n	IC_{50}† (μM)			SI* (PREP/FAP)
				FAP	DPP-4	PREP	
24	3,4-di-Cl	CH_2	0	0.002	>100	49.00	24.5
39	3,4-di-Cl	CH_2	1	0.051	>100	0.387	7.6
40	4-CN	CH_2	1	0.021	82.53	0.051	2.4
41	3,4-di-Cl	S	1	0.119	>100	0.001	0.74
42	4-Me	S	1	0.005	>100	0.121	24.2
43	4-CN	S	1	0.024	44.56	0.138	5.8
44	4-CF_3	S	1	0.011	>100	0.508	46.2
45	3,4-di-Cl	SO_2	1	0.019	>100	0.368	19.4
46	4-CN	SO_2	1	0.009	76.790	0.077	8.6
47	4-CF_3	SO_2	1	0.005	>100	0.151	30.3
48	4-Me	SO_2	1	0.020	>100	0.163	8.2
49	3,4-di-Cl	O	1	0.035	>100	0.269	7.7
50	4-CN	O	1	0.007	>100	0.070	10.0

*SI means selectivity index (calculated as [IC_{50}(PREP)/IC_{50}(FAP)]).
† IC_{50} values by fluorometric assay using AMC substrates.



Scheme 1. Reagents and conditions: (a) (*tert*-butoxycarbonyl)glycine, EDCI, HOBt, NMP, DMF; (b) TFA, rt; (c) $Pd(PPh_3)_4$, DPPF, K_2CO_3, aryl boronic acid, toluene, 90 ℃; (d) $LiOH{\cdot}H_2O$, THF/H_2O, 80 ℃; (e) **53**, EDCI, HOBt, NMP, DMF; (f) oxalyl chloride, CH_2Cl_2, DMF (cat.), rt; (g) NH_3, THF, rt; (h) Lawesson's reagent, THF, 80 ℃; (i) ethyl-3-bromo-2-oxopropanoate, EtOH, 80 ℃; (j) *m*-CPBA, CH_2Cl_2, rt.

in *ortho*-halo compounds **18** and **21**, and *para*-halo congeners **17** and **20** were found most active as well as selective. Particularly, the *para*-bromo compound **20** displayed the highest percent inhibition value in this series. Although an electron-donating *para*-methoxy group on compound **22** could impart good activity against FAP, this analog almost lost selectivity over PREP whereas the analog with an *ortho*-naphthyl group on **23** displayed higher potency and selectivity in contrast to the *ortho*-halo compounds. Among the dihalo derivatives **24**–**28**, *meta*- and *para*-substituted analogs were found to be more selective. Dichloro-substituted compounds **24** and **25** were recorded to be highly active with single-digit nanomolar FAP inhibitory concentration. It is noted that 3,4-dichloro-substituted compound **24** was far more selective to FAP than 2,4-dichloro isomer **25**, which showed equal preference to bind with FAP and PREP. An electron donating methyl group at the *para*-position of compound **29** decreased the FAP activity, but increase in selectivity was observed with respect to the *para*-methoxy analog **22**. Electron-withdrawing groups such as trifluoromethoxy and cyano at the *para*-position (compounds **30** and **31**) could not improve the activity compared to **24**, but *para*-cyano derivative **31** was found to be very selective to FAP with the highest SI index in this series and a percent inhibition value of 99.27. A better FAP potency was observed for *para*-cyano phenyl substituted compound **32** though the SI index was similar to that of *para*-chloro substituted compound **17**. Significant loss of activity and selectivity was observed for *para*-chloro phenyl substituted compound **33**. Remarkably, the FAP potency of the *para*-thiomethyl derivative **34** was close to that of *para*-methoxy derivative **22**, and SI index was near to that of *para*-methyl derivative **29**. The monoxide derivative **35** showed manifold-diminished FAP inhibitory potency, while the sulfone derivative **36** was more potent as compared to compound **35**. Pyrazole substituted compound **37** exhibited nearly same potency to that of triazole substituted analog **38** regarding FAP inhibition. Taking into account both activity and selectivity, 3,4-dichloro-substituted compound **24** was found to be the most suitable candidate in this series.

The influence of different linkers between the 5-membered thiazole and 6-membered phenyl rings at the heterocyclic fragment was investigated. Therefore, the effect of various linkers consisting of alkyl and heteroalkyl moieties was screened and the results are listed in Table 5. Additionally, some of the compounds with satisfactory potency and selectivity from the former series were also evaluated with a modified linker to analyze the effect in comparison with compound **24**. Increasing the length of the carbon chain was not beneficial. The immediate homologues **39** and **40** were found to be much inferior against FAP as compared to the lower homologues **24** and **31**, respectively. The thiomethylene linker in **41** induced superior PREP inhibition and selectivity, but FAP potency was measured to be negligible with respect to PREP. Remarkably, replacing a methylene group with a thiomethylene group made the analog **42** approximately 7-fold more active and 8-fold more selective compared to **29**. Contrasting outcome was recorded in case of compound **43**. The *para*-trifluoromethyl phenyl derivative **44** with a thiomethylene linker stood out as the most selective (SI = 46.2) with moderate FAP inhibitory action compared to **24**. Generally, introduction

of sulfone in place of sulfur produced enhancement of FAP potency in the compounds with electron withdrawing substituents, and reverse impact was observed in case of compounds **45**–**48** with electron-donating substituents. Intriguingly, complete oxidation of the thiomethylene linker in **41** brought about an abrupt change in selectivity making the sulfone derivative **45**, a favorable inhibitor of FAP. The dioxide derivatives **47** was also found to be highly active and selective. Loss of both activity and selectivity were observed in case of compound **48** as compared to **42**. Replacement of sulfur with oxygen also provided a drastic modification in affinity towards FAP in compound **49** as compared to **41**. The *para*-cyano derivative **50** containing a methyleneoxy linker exhibited maximum FAP inhibitory potency and selectivity among the similar members (**40**, **43**, **46** and **50**).

To evaluate the *in vivo* therapeutic effect of BR102910 (compound **24**) as a FAP inhibitor, C57BL/6J mice (n = 5 per group) were orally administered with two dosages such as 10 and 30 mg/kg. Blood samples were collected, and the FAP inhibition was measured at five time intervals. As shown in Fig. 4, BR102910 (compound **24**) showed significant FAP inhibition in a dose dependent manner.

In order to confirm the effect in treating type 2 diabetes, compound **24** was studied in oral glucose tolerance test (OGTT), as shown in Fig. 5. Single oral administration of **24** with dosages as 20 and 50 mg/kg in two groups of 8 weeks-old ob/ob mice, 60 min prior to glucose challenge reduced the subsequent plasma glucose levels in a dose-dependent manner compared to the control group (Fig. 5A). Since the cleavage by FAP does not take place in mice, rhFGF21 was administered by intraperitoneal injection into the control group after treating with vehicle to figure out the reaction in actual human body. It is reported that the amount of undigested FGF21 is augmented when the C-terminal cleavage of FGF21 is inhibited. As shown in Fig. 5B, we observed the similar result on the FAP inhibition effect in *in vivo* experiment by using ob/ob mice. These results indicate that the FAP inhibition by treatment of BR102910 (compound **24**) is a promising therapeutic approach for type 2 diabetes.

The binding mode of BR102910 (compound **24**) in the x-ray crystal structure of human fibroblast activation protein-α was also predicted using the Schrödinger program. Four main interactions are observed as shown in Fig. 6. One of hydrogen bonding interactions is observed between the nitrogen of cyanide at the pyrrolidine ring of **24** and hydroxyl of the amino acid (AA) residue S624 of FAP. Second hydrogen bonding interaction is between the oxygen of carbonyl group attached to thiazole moiety and one amine of guanidine at the AA residue R123. A third hydrogen bonding interaction can be observed between the carbonyl oxygen attached to the pyrrolidine ring of **24** and iminium hydrogen of the histidine734 AA residue. The fourth interaction is a π-stacking interaction between thiazole ring of **24** and indole moiety of amino acid residue W623.

In summary, we have successfully identified a novel FAP inhibitor, BR102910 (compound **24**), with high FAP inhibitory activity and selectivity (PREP/FAP, SI = 24.5). In addition, BR102910 (compound **24**) demonstrated excellent level of *in vivo* FAP inhibition activity. Moreover, this compound displayed the reduction of blood glucose

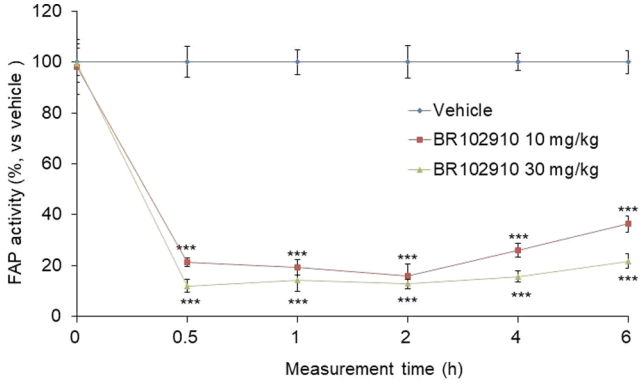


Fig. 4. Plasma FAP profile of compound **24** in C57BL/6J mice.

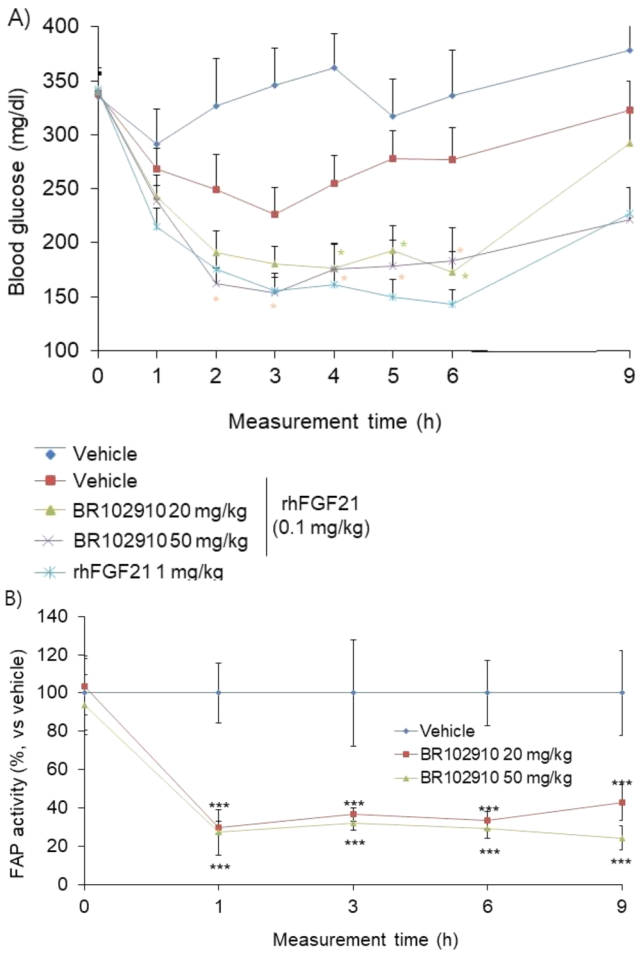


Fig. 5. Blood glucose profiles in *ob/ob* mice via FAP inhibition by compound **24**. 8-Week-old *ob/ob* mice were treated with compound **24** (BR102910) or vehicle before *ip* treatment of rhFGF21. (A) Non fasting blood glucose levels were measured at the indicated time points. (B) Plasma FAP activity was measured by fluorometric assay using AMC substrate at 1, 3, 6 and 9 h.

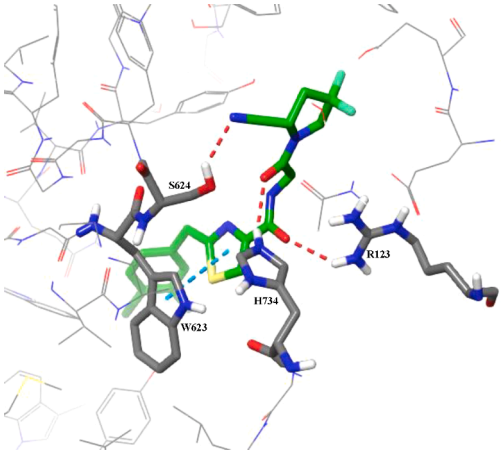


Fig. 6. Predicted binding mode of BR102910 in crystal structure of human FAP (PDB code: 1Z68). Hydrogen bonding interactions are shown in red and π-stacking interaction in cyan. Docked molecule and the interacting AA residues are highlighted by stick model.

levels in animal model. Based on excellent in vitro and *in vivo* profiles, BR102910 (compound **24**) can be developed as a lead candidate for the treatment of type 2 diabetes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2021.127846.

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