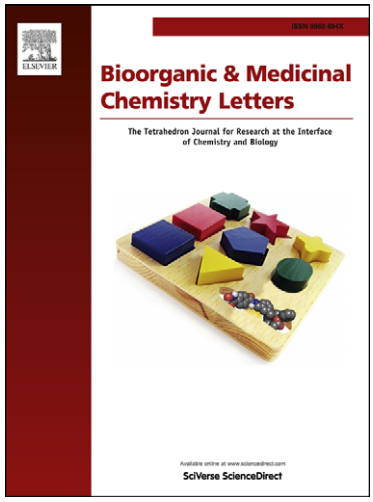
# Accepted Manuscript




A series of thiazole derivatives bearing thiazolidin-4-one as non-competitive ADAMTS-5 (Aggrecanase-2) inhibitors

Masakazu Atobe, Naomi Maekawara, Noriko Ishiguro, Shinya Sogame, Yoshihito Suenaga, Masashi Kawanishi, Hiroko Suzuki, Norimasa Jinno, Eiichi Tanaka, Shiro Miyoshi

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## Graphical Abstract

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**A series of thiazole derivatives bearing thiazolidin-4-one as non-competitive ADAMTS-5(Aggrecanase-2) inhibitors**

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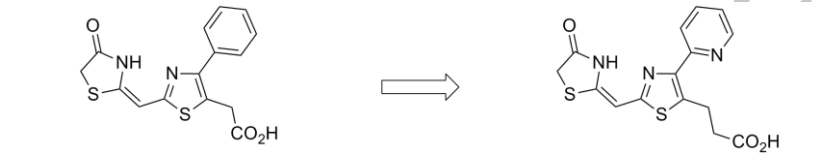


ADAMTS-5 $IC_{50}$: 1.2 μM
Ex vivo cartilage explant $IC_{50}$: No Inhibition

ADAMTS-5 $IC_{50}$: 0.23 μM
Ex vivo cartilage explant $IC_{50}$: 22 μM

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# A series of thiazole derivatives bearing thiazolidin-4-one as non-competitive ADAMTS-5 (Aggrecanase-2) inhibitors

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ABSTRACT

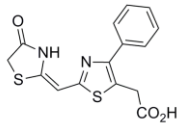
A series of thiazole bearing thiazolidin-4-one was discovered via high-throughput screening as non-competitive inhibitors of ADAMTS-5. Compound **31** appeared to give the best ADAMTS-5 inhibition and good selectivity over other metalloproteases.



Osteoarthritis (OA) is a degenerative joint disease characterized by loss of joint cartilage and bone thickening, possibly leading to bony outgrowths[1]. The prevalence of OA globally is 11.3%, or approximately 85 million people, and this is expected to increase from 85 million in 2009 to 122 million in 2017. A significant increase in OA incidence has occurred in recent years[2].

The pathogenesis of OA is poorly understood, but a major feature is the loss of two most important components of cartilage extracellular matrix (ECM); Type II collagen and aggrecan. Aggrecan loss resulting from decreased synthesis by chondrocytes and activation of enzymes that degrade cartilage is recognized as one of the earliest processes in the course of OA; thus aggrecan appears to have an additional role in collagen protection from degradation[3]. Therefore, inhibition of aggrecanases has evolved as a potential drug target for treatment of OA. Recent evidence that ADAMTS-5 knockout mice are protected from cartilage destruction in OA model shows that ADAMTS-5 may have a major role in OA[4]. Furthermore, AGG-523, a specific aggrecanase inhibitor developed by Pfizer, reduced the release of aggrecanase-generated aggrecan fragments into rat joints in a rat model of meniscal tear-induced joint instability[5]. Thus, ADAMTS-5 inhibitors may protect cartilage from OA progression. The vast majority of reported ADAMTS-5 inhibitors can be viewed as zinc chelating compounds via bidentate zinc chelators such as hydroxamic acid[6], reverse hydroxamamate[7], carboxylic acid[8] and other structures[9]. However, in the development of new therapeutic agents targeting ADAMTS-5, there remains considerable room for new structural classes not coordinating the active site zinc atom.

On screening our in-house compound library, a thiazole bearing thiazolidin-4-one **1** was identified as having potent inhibitory activity against ADAMTS-5 (Fig. 1).




**1**

**Figure 1**. Hit compound of HTS

Compound **1** was then tested for its ability to inhibit ADAMTS-4, -13, MMP-2, -3, 14 and TACE[10]. As listed in Table 1, **1** showed excellent ADAMTS-5 selectivity over other Zn metalloproteases.

**Table 1.** Activity of thiazolidin-4-one **1**

| ADAMTS-5 | ADAMTS-4 | ADAMTS-13 | MMP-2 | MMP-3 | MMP-14 | TACE |
|---|---|---|---|---|---|---|
| 1.2 μM | >10 μM | 12 μM | >30 μM | >30 μM | >30 μM | 16 μM |

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Based on studies in MMP-2[11], -3[12] and -14[13] knockout mice, inhibition of MMP-2, -3 and -14 appears to facilitate proteoglycan degradation. In addition, investigation of ADAMTS-4 knockout mice confirmed that ADAMTS-4 is not responsible for aggrecan degradation in murine osteoarthritis[14]. ADAMTS-13 cleaves the Tyr1605-Met1606 bond of a von Willebrand factor subunit and plays a key role in the pathogenesis of thrombotic thrombocytopenic purpura[15]. Furthermore, TACE-deficient mice die shortly after birth[16]. Therefore, we reasoned that a selective ADAMTS-5 inhibitor would constitute an ideal OA therapeutic agent.

Next, we speculated that mode of ADAMTS-5 inhibition elicited by compound **1** differs from that of known competitive inhibitors. Indeed, Lineweaver-Burk plot analysis showed that **1** is a non-competitive inhibitor (Fig. 2). Therefore, we focused on investigating the structure-activity relationships (SAR) to optimize this lead compound.

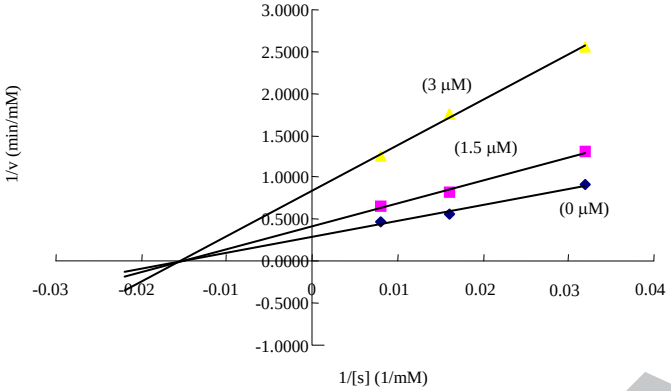



**Figure 2**: Lineweaver-Burk plot analysis the inhibition of ADAMTS-5 by **1**

Our initial investigation focused on replacement of thiazolidin-4-one (Table 2). When $R^1$ = H (**2**), 3-pyridyl (**3**), $R^1$ = (**4**), 3,5-dimethyl-4-isoxazolyl (**5**) or 2-methyl-5-thiazolyl (**6**), no ADAMTS-5 inhibition was seen. The corresponding 3-methyl 2-benzimidazolyl analog (**7**) and 4-methyl 2-thiazolyl analog (**8**) showed moderate ADAMTS-5 inhibition (2.8 or 2.9 μM). These results suggested that thiazolidin-4-one forms strong interactions with ADAMTS-5.

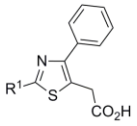


**Table 2.** Modification of thiazolidin-4-one

| Compound | $R^1$ | ADAMTS-5 %inh (10μM) | ADAMTS-5 $IC_{50}$ |
|---|---|---|---|
| **1** |  | | 1.2 μM |
| **2** |  | 8% | |
| **3** |  | 17% | |
| **4** |  | 21% | |
| **5** |  | 4.7% | |
| **6** |  | 19% | |
| **7** |  | | 2.8 μM |
| **8** |  | | 2.9 μM |

In the SAR exploration of the phenyl group at the 4-position of the thiazole ring (Table 3), replacement of the hydroxyl group decreased ADAMTS-5 inhibition. Optimal $R^2$ substituents are seen in **10** (4-Cl-phenyl $IC_{50}$: 6.4 μM), **11** (4-Me-phenyl $IC_{50}$: 0.72 μM) and **12** (4-MeO-phenyl $IC_{50}$: 1.0 μM). Biphenyl moiety **13** appears to give increased ADAMTS-5 inhibition ($IC_{50}$: 0.43 μM). We prepared compounds bearing 2-thiophene **14** and 5-bromo-2-thiophene **15** and found that these compounds had decreased ADAMTS-5 activity. However, a compound bearing 3-bromo-2-thiophene **16** showed improved ADAMTS-5 activity ($IC_{50}$: 0.47 μM); ortho substitution was favored over para. The best compounds were in this series; 2-pyridine **17** and 4-bromo pyridine **18** appeared to provide more potent inhibition with $IC_{50}$ values of 0.4 μM or 0.84 μM.

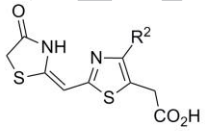
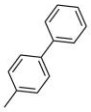


**Table 3.** Modification of phenyl group

| Compound | $R^2$ | ADAMTS-5 $IC_{50}$ |
|---|---|---|
| **1** |  | 1.2 μM |
| **9** |  | 4.2 μM |
| **10** |  | 6.4 μM |
| **11** |  | 0.72 μM |
| **12** |  | 1.0 μM |
| **13** |  | 0.43 μM |
| **14** |  | 4.0 μM |
| **15** |  | 3.0 μM |
| **16** |  | 0.47 μM |
| **17** |  | 0.4 μM |
| **18** |  | 0.84 μM |

SAR of the carboxymethyl groups at the 5-position on the thiazole was investigated (Table 4). When $R^3$ = H (**19**), ADAMTS-5 inhibition was decreased. When $R^3$ = Me (**20**), $R^3$ = Et (**21**), $R^3$ = iPr (**22**) and $R^3$ = n-Pr (**23**), ADAMTS-5 inhibition was retained. *N*,*N*-dimethylamide group (**24**) showed decreased ADAMTS-5 activity. We prepared demethyl carboxyl group (**25**),

2-methyl analog (**26**), carboxyethyl group (**27**) and carboxyl-propyl group (**28**), and found that **27** showed the most potent ADAMTS-5 activity.

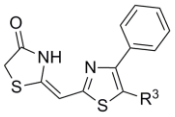


**Table 4.** Modification of methylcarboxy group

| Compound | $R^3$ | ADAMTS-5 $IC_{50}$ |
|---|---|---|
| **1** |  | 1.2 μM |
| **19** |  | 7.0 μM |
| **20** |  | 1.2 μM |
| **21** |  | 1.3 μM |
| **22** |  | 0.83 μM |
| **23** |  | 1.4 μM |
| **24** |  | 2.2 μM |
| **25** |  | 1.2 μM |
| **26** |  | 0.73 μM |
| **27** |  | 0.42 μM |
| **28** |  | 0.5 μM |

We then focused on optimization of **27** derivatives by a combination of substituents at the 4-position of the thiazole ring (Table 5). Optimal $R^4$ substituents are seen in **29** (biphenyl $IC_{50}$: 0.43 μM), **30** (4-bromo-thiophene $IC_{50}$: 0.72 μM) and **32** (4-bromo-pyridine $IC_{50}$: 0.63 μM). Finally, compounds bearing pyridine (**31**) appeared to give the best ADAMTS-5 inhibition ($IC_{50}$: 0.23 μM).

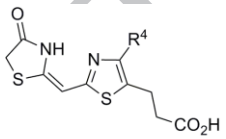
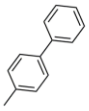


**Table 5.** Modification of phenyl group

| Compound | $R^4$ | ADAMTS-5 $IC_{50}$ |
|---|---|---|
| **27** |  | 0.42 μM |
| **29** |  | 0.43 μM |
| **30** |  | 0.42 μM |
| **31** |  | 0.23 μM |
| **32** |  | 0.63 μM |

Compound **31** was tested for its ability to inhibit ADAMTS-4 and -13, MMP-2, -3 and -14 and TACE. As shown in Table 6, **31** showed excellent ADAMTS-5 selectivity over other metalloproteases. The *in vitro* ADME profile of **31** was also determined. Compound **31** was found to be intrinsically stable in plasma (human CLint: 2.7 ml/min/kg; rat CLint: 0 ml/min/kg). **31** displayed moderate apparent permeability as measured by flux through MDCK cells in transwell culture (A/B Papp = $5.55 \times 10^{-6}$ cm/s).

**Table 6.** Activity of thiazolidin-4-one **1** and **31**

| Compound | ADAMTS-5 | ADAMTS-4 | ADAMTS-13 | MMP-2 | MMP-3 | MMP-14 | TACE |
|---|---|---|---|---|---|---|---|
| **1** | 1.2 μM | >10 μM | 12 μM | >30 μM | >30 μM | >30 μM | 16 μM |
| **31** | 0.23 μM | 23 μM | 20 μM | >30 μM | >30 μM | 24 μM | >30 μM |

*Ex vivo* cartilage explant studies using compound **31** were then performed[17]. As a positive control, the published multi-MMP inhibitor 1-benzyl-4-((4-(4-chlorophenoxy) phenyl)-sulfonyl)-N-hydroxypiperidine-4-carboxamide (**33**, Figure 4)[18], which has an $IC_{50}$ of 0.42 μM against ADAMTS-5 and 1.0 μM against ADAMTS-4, demonstrated highly potent activity in the surgical OA rabbit model at 15 mg/kg. This compound was shown to inhibit spontaneous aggrecan degradation in IL-1-stimulated bovine cartilage (91% inhibition at 10 μM), and compound **31** showed 66% inhibition at 10 μM ($IC_{50}$: 22 μM). These data support the hypothesis that protection of cartilage aggrecan leads to preservation of aggrecanase activity (Fig. 3).

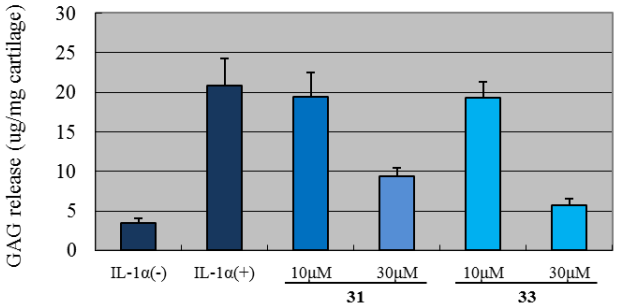
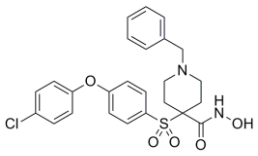


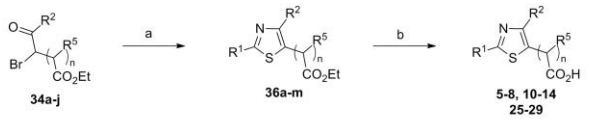

**Figure 3**: Ex vivo cartilage explant studies of **31** and **33**



**33**

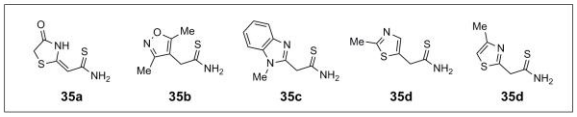
**Figure 4**. Structure of **33**

The synthesis of thiazole derivatives (**5-18** and **21-32**) is shown in Scheme 1-6. Compounds **1-4**, **19** and **20** were commercially available. As shown in Scheme 1, reaction of 3-bromo-4-oxo-4-phenylbutanoic acid derivatives **34a-j** and arylmethyl thioamide **35a-e** in ethanol under reflux (Hanzsch reaction) produced thiazoleacetate **36a-m**, followed by hydrolysis to give **5-8**, **10-14** or **25-29**.



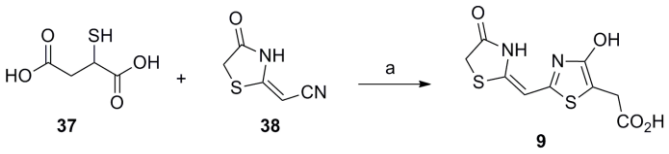

**34a**: $R^2$ = Ph, $R^5$ = H, n = 1
**34b**: $R^2$ = 4-Cl-Ph, $R^5$ = H, n = 1
**34c**: $R^2$ = 4-Me-Ph, $R^5$ = H, n = 1
**34d**: $R^2$ = 4-MeO-Ph, $R^5$ = H, n = 1
**34e**: $R^2$ = 4-Phenyl-Ph, $R^5$ = H, n = 1
**34f**: $R^2$ = 2-thienyl, $R^5$ = H, n = 1
**34g**: $R^2$ = Ph, $R^5$ = H, n = 0
**34h**: $R^2$ = Ph, $R^5$ = Me, n = 1
**34i**: $R^2$ = Ph, $R^5$ = H, n = 2
**34j**: $R^2$ = Ph, $R^5$ = H, n = 3
**34k**: $R^2$ = 4-Pheyl-Ph, $R^5$ = H, n = 2

**36a**: $R^1$ = (3,5-dimethylisoxazol-4-yl)methyl, $R^2$ = Ph, $R^5$ = H, n = 1
**36b**: $R^1$ = (1-methyl-1*H*-benzo[*d*]imidazol-2-yl)methyl, $R^2$ = Ph, $R^5$ = H, n = 1
**36c**: $R^1$ = (2-methylthiazol-5-yl)methyl, $R^2$ = Ph, $R^5$ = H, n = 1
**36d**: $R^1$ = (4-methylthiazol-5-yl)methyl, $R^2$ = Ph, $R^5$ = H, n = 1
**36e**: $R^1$ = (*E*)-4-(4-oxothiazolidin-2-ylidene)methyl, $R^2$ = 4-Cl-Ph, $R^5$ = H, n = 1
**36f**: $R^1$ = (*E*)-4-(4-oxothiazolidin-2-ylidene)methyl, $R^2$ = 4-Me-Ph, $R^5$ = H, n = 1
**36g**: $R^1$ = (*E*)-4-(4-oxothiazolidin-2-ylidene)methyl, $R^2$ = 4-MeO-Ph, $R^5$ = H, n = 1
**36h**: $R^1$ = (*E*)-4-(4-oxothiazolidin-2-ylidene)methyl, $R^2$ = 4-Phenyl-Ph, $R^5$ = H, n = 1
**36i**: $R^1$ = (*E*)-4-(4-oxothiazolidin-2-ylidene)methyl, $R^2$ = 2-thienyl, $R^5$ = H, n = 1
**36j**: $R^1$ = (*E*)-4-(4-oxothiazolidin-2-ylidene)methyl, $R^2$ = Ph, $R^5$ = H, n = 0
**36k**: $R^1$ = (*E*)-4-(4-oxothiazolidin-2-ylidene)methyl, $R^2$ = Ph, $R^5$ = Me, n = 1
**36l**: $R^1$ = (*E*)-4-(4-oxothiazolidin-2-ylidene)methyl, $R^2$ = Ph, $R^5$ = H, n = 2
**36m**: $R^1$ = (*E*)-4-(4-oxothiazolidin-2-ylidene)methyl, $R^2$ = Ph, $R^5$ = H, n = 3
**36n**: $R^1$ = (*E*)-4-(4-oxothiazolidin-2-ylidene)methyl, $R^2$ = 4-Pheyl-Ph, $R^5$ = H, n = 2



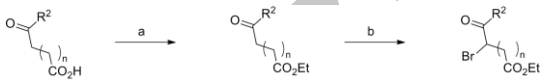

**Scheme 1.** Reagents and conditions: (a) **35a-e**, EtOH, reflux (**36a**: 67%, **36b**: 58%, **36c**: 37%, **36d**: 94%, **36e**: 50%, **36f**: 75%, **36g**: 84%, **36h**: 81%, **36i**: 72%, **36j**: 89%, **36k**: 68%, **36l**: 99%, **36m**: 98%, **36n**: 84%); (b) 1M NaOH, MeOH, r.t. (**5**: 32%, **6**: 36%, **7**: 76%, **8**: 38%, **10**: 93%, **11**: 82%, **12**: 92%, **13**: 62%, **14**: 12%, **15**: 65%, **25**: 89%, **26**: 99%, **27**: 69%, **28**: 70%, **29**: 43%)

Compound **9** was prepared by condensation reaction between 2-mercaptosuccinic acid **37** and nitrile **38** (Scheme 2).




**Scheme 2.** Reagents and conditions: (a) Pyridine, reflux (24%)

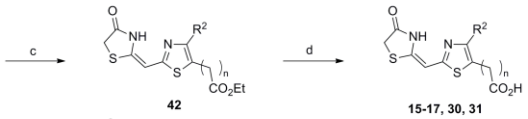
As shown in Scheme 3, commercially available carboxylic acid **39a-f** was esterified to give the ethyl ester **40a-f**, which underwent bromine-mediated bromination to provide **41a-f**. Hanzsch reaction with **35a** and basic hydrolysis provided **15-17**, **30** or **31**.




**39a**: $R^2$ = 4-Bromo-2-thienyl, n =1
**39b**: $R^2$ = 2-Bromo-2-thienyl, n =1
**39c**: $R^2$ = 2-Py, n =1
**39d**: $R^2$ = 4-Bromo-2-thienyl, n =2
**39e**: $R^2$ = 2-Py, n =2

**40a**: $R^2$ = 4-Bromo-2-thienyl, n =1
**40b**: $R^2$ = 2-Bromo-2-thienyl, n =1
**40c**: $R^2$ = 2-Py, n =1
**40d**: $R^2$ = 4-Bromo-2-thienyl, n =2
**40e**: $R^2$ = 2-Py, n =2

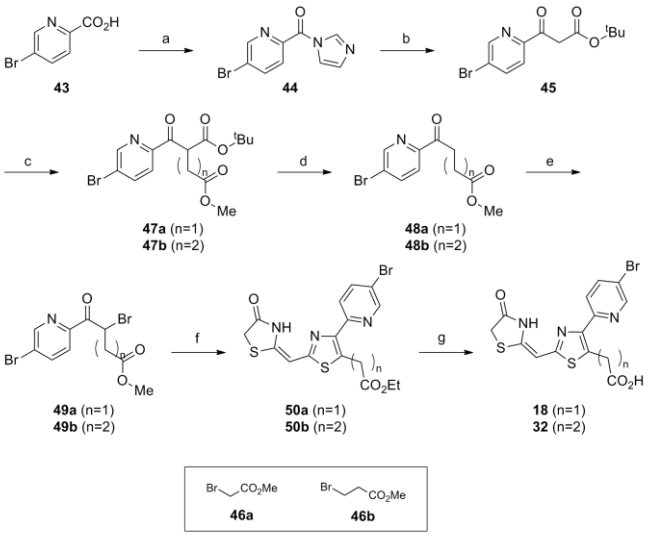
**41a**: $R^2$ = 4-Bromo-2-thienyl, n =1
**41b**: $R^2$ = 2-Bromo-2-thienyl, n =1
**41c**: $R^2$ = 2-Py, n =1
**41d**: $R^2$ = 4-Bromo-2-thienyl, n =2
**41e**: $R^2$ = 2-Py, n =2




**42a**: $R^2$ = 4-Bromo-2-thienyl, n =1
**42b**: $R^2$ = 2-Bromo-2-thienyl, n =1
**42c**: $R^2$ = 2-Py, n =1
**42d**: $R^2$ = 4-Bromo-2-thienyl, n =2
**42e**: $R^2$ = 2-Py, n =2

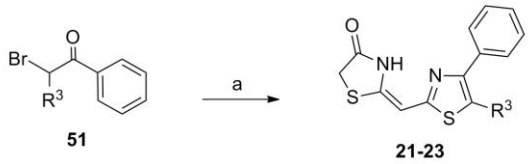
**Scheme 3.** Reagents and conditions: (a) conc $H_2SO_4$, EtOH, 85°C (**39a**: 99%, **39b**: 94%, **39c**: 78%, **39d**: 99%, **39e**: 99%); (b) $Br_2$, AcOH , 0°C (**40a**: 56%, **40b**: 98%, **40c**: 65%, **40d**: 99%, **40e**: 60%); (c) **35a**, EtOH, reflux (**41a**: 83%, **41b**: 81%, **41c**: 76%, **41d**: 99%, **41e**: 65%); (d) 1M NaOH, MeOH, r.t. (**15**: 99%, **16**: 56%, **17**: 99%, **30**: 52%, **31**: 72%,

Compounds **18** and **32** were synthesized according to Scheme 4. The reaction between 5-bromopicolinic acid (**43**) and carbodiimidazole, and the subsequent reaction with lithium reagent at -78°C resulted in the formation of β-ketoester **45**. C-alkylation with the appropriate bromide and NaH and then decarboxylation of **47** under acidic conditions gave ketone **48**. Bromination and Hanzsch reaction led to a thiazole ring, followed by hydrolysis to give **18** or **32**.



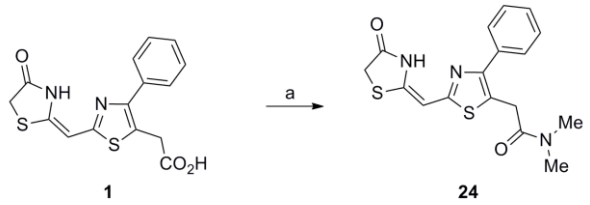

**Scheme 4.** Reagents and conditions: (a) Carbodiimidazole, THF, 40°C; (b) LDA, *tert*-butyl acetate, THF, 40°C (2 steps 48%); (c) NaH, DMF, 0°C, then **46**, 40°C (**47a**: 51%, **47b**: 58%); (d) p-TsOH, toluene, reflux (**48a**: 91%, **48b**: 75%); (e) $Br_2$, AcOH , 100°C (**49a**: 93%, **49b**: 35%); (f) **35a**, EtOH, reflux (**50a**: 99%, **50b**: 99%); (g) 1M NaOH, MeOH, r.t. (**18**: 99%, **32**: 52%)

As shown in Scheme 5, Compound **21-23** was prepared by Hanzsch reaction.




**Scheme 5.** Reagents and conditions: (a) **35a,** EtOH, reflux (**21**: 99%, **22**: 99%, **23**: 75%).

Scheme 6 shows the synthesis of **24** via amidation of **1** under peptide formation conditions.




**Scheme 6.** Reagents and conditions: (a) 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride, HOBt, $Et_3N$, DMF, r.t. (99%).

In conclusion, we presented a series of thiazoles bearing thiazolidin-4-one as non-competitive inhibitors of ADAMTS-5. Compound **31** appeared to give the best ADAMTS-5 inhibition and good selectivity over other metalloproteases. **31** was also shown to inhibit the spontaneous aggrecan degradation in IL-1-stimulated bovine cartilage. The continued development of selective ADAMTS-5 inhibitors is currently underway and will be reported in the near future.

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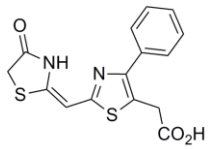
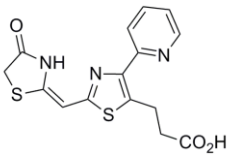



ADAMTS-5 $IC_{50}$: 1.2 μM
Ex vivo cartilage explant $IC_{50}$: No Inhibition




ADAMTS-5 $IC_{50}$: 0.23 μM
Ex vivo cartilage explant $IC_{50}$: 22 μM