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Bioorganic & Medicinal Chemistry Letters
ELSEVIER
Bioorganic & Medicinal Chemistry Letters 14 (2004) 1119–1121

New heteroarylbenzenesulphonamides as matrix metalloproteinase inhibitors

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Received 23 July 2003; revised 17 December 2003; accepted 22 December 2003

Abstract—A series of derivatives of 2,4- and 2,5-thiazolyl- or oxazolylbenzenesulphonamides has been prepared and evaluated as potential MMP inhibitors. The thiazole **15b** have been found to exhibit MMP-2 and MMP-9 inhibitions higher than reference compounds GI 129471 and CGS 27023A.

Degradation of extracellular matrix is crucial for malignant tumour growth, invasion, metastatis and angiogenesis.[1,2] Matrix metalloproteinases (MMPs) are a family of zinc-dependent neutral endopeptidases which regulate many biologic processes[3] and have long been associated with cancer-cell invasion and metastasis.[4]

For at least 30 years, MMPs and specially gelatinases[5,6] have been heralded as promising targets for cancer therapy on the basis of their massive up regulation in malignant tissues and their unique ability to degrade all components of the extracellular matrix.[7] Synthetic metalloproteinase inhibitors (MPIs) were rapidly developed and routed into human clinical trials[8–12] but the results of these trials have been disappointing.

However, recent studies[6,13,14] showed that the MMPs have functions other than promotion of invasion, substrates other than components of the extracellular matrix, and that they function before invasion in the development of cancer. Use of MPIs in the clinic can therefore be rethinked: new knowledges on how and where MMPs effect occurs, can have an impact on the management of patients affected by malignancies.[15]

Then, design of new compounds more efficient, for therapeutic intervention either on their own or in conjunction with cytotoxic treatments, is still needed, since it was observed that targeting and inactivating MMPs may enhance the apoptotic activity of DNA-damaging anticancer drugs via regulation of Fas/FasL system.[16]

Among the compounds whose MMP inhibition has been evaluated, benzenesulphonamides constitute a main family.[17,18] In this view, we have prepared a series of thiazolyl and oxazolylbenzenesulphonamides which seem to be good candidates against MMPs in comparison with computational studies. Recent publication of patents prompts us to report our results.[19–21]

The 2,4-diarylthiazoles were prepared as shown in Scheme 1. We used the Stille coupling reaction[22] between the iodide **1** and the organostannane **4** to obtain compounds **5** in good yields (50% for **5a**; 75% for **5b**). Commercially available 4-iodobenzenesulfonyl chloride was condensed with the amino group of the aminoesters derived from Val or Glu to afford **1**. 4-Methoxy-α-bromoacetophenone **2** was converted[23] to 1-(4-methoxyphenyl)-2-thiocyanatoethanone **3** which was cyclized[24] with hydrobromic acid to 2-bromo-4-methoxyphenylthiazole. Lithiation of the later with *n*-butyllithium and quenching with tributylstannyl chloride gave compounds **4**. Alternatively the derivatives **5** could be obtained by reaction of methoxy-α-bromoacetophenone **2** with the thiobenzamide **7a** (50% for **1a**).

Keywords: MMP inhibitors; Benzenesulphonamides; Thiazoles; Oxazoles.
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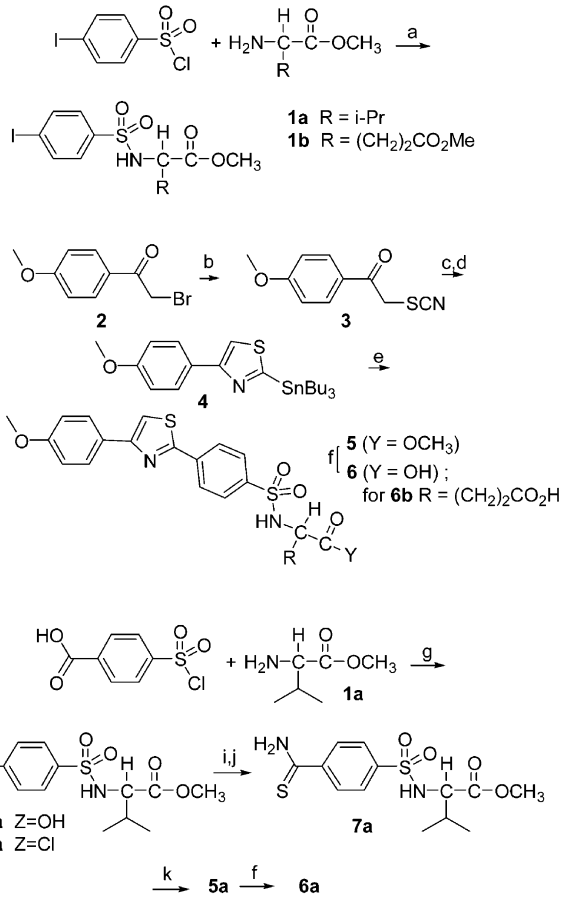
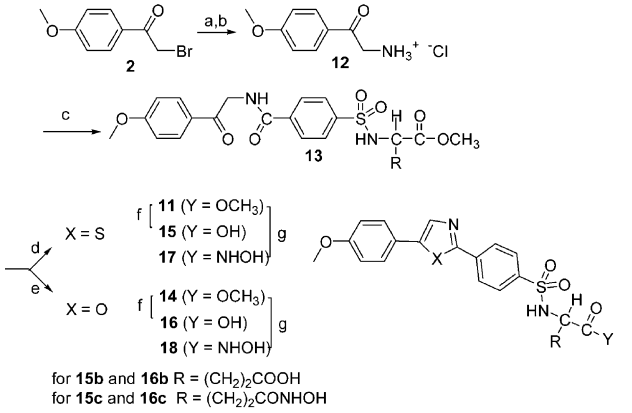
doi:10.1016/j.bmcl.2003.12.076



Scheme 1. Reagents and conditions: (a) Et_3N, CH_2Cl_2, reflux, 2 h, 50–70%; (b) KSCN, EtOH, reflux, 2 h, 98%; (c) HBr gas, Et_2O, 20 °C, 2 h, 62%; (d) *n*-BuLi, Et_2O–hexane, −78 °C, 1 h then Bu_3SnCl, −78 °C/1 h and 20 °C/2 h, 95%; (e) **1**, $PdCl_2(PPh_3)_2$, DMF, 70 °C, 8 h.; (f) NaOH, MeOH or DMSO, 20 °C, 100%; (g) $NaHCO_3$, H_2O, 3 h, 20 °C, 63%; (h) $SOCl_2$, CH_2Cl_2, reflux, 2 h, 86%; (i) NH_4OH, $CHCl_3$, 20 °C, 60%; (j) Lawesson's reagent, THF, reflux, 2 h, 72%; (k) **2**, EtOH, reflux, 3 h.

4-Chlorosulfonylbenzoic acid was transformed into the sulphonamide **8a**. The carboxylic acid part of **8a** was converted with thionyl chloride into acyl chloride **9a** which reacted with ammonia to afford the carboxamide **10a**. Lawesson's reagent[25] converted **10a** into the thioamide **7a**. Esters **5** were easily saponified to the carboxylic acids **6.**

Another synthetic strategy was used to obtain the 2,5-diarylthiazoles **11** as described in Scheme 2. The aminoketone **12** resulted from the action of sodium diformylamide with the bromoketone **2** followed by an acid-catalyzed hydrolysis according to Yinglin and Hongwen.[26] Acyl chloride **9** (**9a** or **b**) was condensed[27] with **12** to afford the β-ketoamide **13** which was cyclized by phosphorus pentasulfide[28] to the thiazole **11** (20% for **11a** and 33% for **11b**). Similarly, the 2,5-diaryloxazoles **14** arose from the cyclization of **13** with phosphorous oxychloride (25% for **14a** and 39% for **14b**). Esters **11** and **14** were easily saponified respectively to the carboxylic acids **15** and **16** or converted respectively to the hydroxamic acids **17** and **18**.



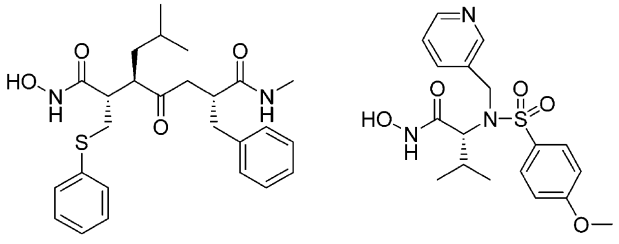
Scheme 2. Reagents and conditions: (a) $NaN(CHO)_2$, CH_3CN, 20 °C, 3 h, 96%; (b) HCl 12N, MeOH, 20 °C, 2 days, 92%; (c) **9**, $NaHCO_3$–H_2O, $PhCH_3$, 20 °C, 1 h, 90%; (d) P_2S_5, pyridine, 100 °C, 1 h; (e) $POCl_3$, reflux, 2 h; (f) NaOH, MeOH, 20 °C, 5 h, 100%; (g) NH_2OH, MeOH, 50 °C/30 min then 20 °C/2 h, 91%.

The inhibitory activity of test compounds against MMP-2 and MMP-9 (purchased from Sigma) was determined by using semi quantitative zymographic analysis (Table 1). MMPs were electrophoresed on a SDS-PAGE separating gel containing 0.1% gelatine. Gels were then incubated overnight at 37 °C in activation buffer supplemented with different concentrations of test compounds, stained with Coomassie blue for 1 h and destained with methanol:acetic acid:water (40:10:50) (Scheme 3).

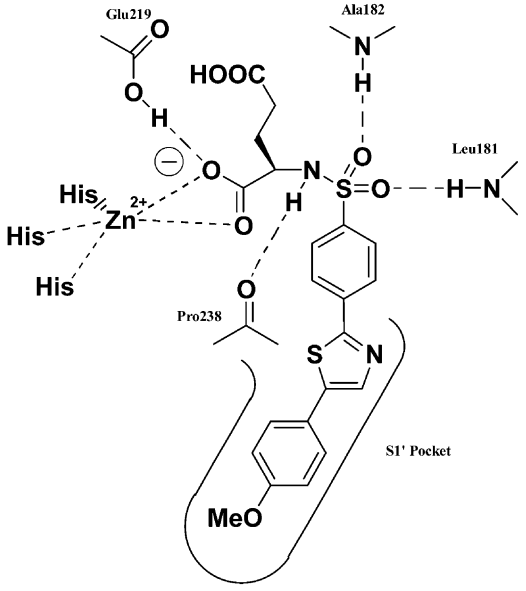
Table 1. Inhibitory activities of diarylthiazolyl- or diaryloxazolyl-benzenesulphonamides against MMP-2 and MMP-9

Compd	IC_{50} (μM)[a]	
	MMP-2	MMP-9
GI 129471[b]	0.2	0.2
CGS 27023 A[b]	3	3
6a	—	—
6b	—	—
15a	0.2	0.7
15b	0.05	0.05
17a	0.4	0.9
16a	1	1
16b	10	10
18a	1	1

[a] Concentration required for 50% inhibition of enzyme activity.
[b] See Scheme 3.



Scheme 3. Reference compounds for evaluation of inhibitory activity of new heteroarylbenzenesulphonamides.



Scheme 4. Polar interactions of the inhibitor docked into MMP-9-A16 model described by Kiyama et al.[19]

Areas of protease activity appear as clear bands against a dark blue background where the protease has digested the substrate. For each test compound, assays were carried out twice and then mean value was calculated as inhibitory activity. The results obtained in the 2,5-thiazole series suggest that the longer C–S bonds better fit with the enzyme structure than C–N (2,4-thiazole series) or C–O (2,5-oxazole series). The aryl group on the 5-position of the heterocyclic moiety is directed towards the S'1 pocket.

We have observed an enhanced inhibitory potency not with an hydroxamate zinc-binding group as currently observed with MMPs inhibitors but with the ε-carboxylic acid group of the glutamic acid (Scheme 4). In the absence of molecular modelling, several proposals may be put forward among which we retain those that present a five-coordinated zinc ion with the three histidines of the protein and a bidentate group of the inhibitor (carboxylate, hydroxamate, dithiolate...)[31–33]: the coordination of the metal by the two monodentate carboxylate and ε-carboxylic groups is not favourable, no more than the formation of an hydrogen bond between the carboxylate and the ε-carboxylic group in place of Glu219. A weak bond between the ε-carboxylic group and another residue of the protein could be a possible explanation of the observed enhanced inhibitory potency.

Acknowledgements

This work was supported by the Association pour la Recherche sur le Cancer.

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