



HAL
open science

Alkylsquarates as key intermediates for the rapid preparation of original drug-inspired compounds.

Julie Charton, Lise Charruault, Rebecca Déprez-Poulain, Benoit Déprez

► To cite this version:

Julie Charton, Lise Charruault, Rebecca Déprez-Poulain, Benoit Déprez. Alkylsquarates as key intermediates for the rapid preparation of original drug-inspired compounds.. *Combinatorial Chemistry and High Throughput Screening*, Bentham Science Publishers, 2008, 11 (4), pp.294-303. 10.2174/138620708784246013 . inserm-00281198

HAL Id: inserm-00281198

<https://www.hal.inserm.fr/inserm-00281198>

Submitted on 21 May 2008

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Alkylsquarates as key intermediates for the rapid preparation of original drug-inspired compounds.

Julie Charton,^{a,b,c} Lise Charruault,^{a,b,c} Rebecca Deprez-Poulain,^{a,b,c} Benoit Deprez.
a,b,c

^a*INSERM U761 Biostructures and Drug Discovery, Lille F-59006, France*

^b*Faculté de Pharmacie, Université Lille 2, Lille F-59006, France*

^c*Institut Pasteur de Lille, Lille F-59000, France*

Corresponding author: Address: 3 rue du Pr. Laguesse, 59006 Lille
Cedex, France. Tel.: +33 320 964 948; fax: +33 320 964 709; e-mail:
julie.charton@univ-lille2.fr

Abstract: Many natural privileged scaffolds contain a basic nitrogen atom, which often is a key element of pharmacophore and a chemically reactive centre as well. In our ongoing research program devoted to the design of targeted libraries based on acidic templates, we develop methods to convert privileged basic compounds -like natural alkaloids or drugs- into acidic compounds. This conversion leads to a profound alteration of the pharmacophore, without changing the overall shape and lipophilicity of the molecule. We expect such modifications to generate unexpected biological activities. Recently, we focused on derivatives of squaric acid, a vinylogous carboxylic acid. Two series were studied. First we describe a new, selective parallel synthesis of squaramic acids from a dissymmetric diester (3-tert-butoxy-4-ethoxy-cyclobut-3-en-1,2-dione). This efficient procedure avoids the synthesis of the undesired squaramides. Secondly we describe a microplate parallel synthesis (15 μ mol-scale) of squaric acid hydroxamate amides from a squaric hydroxamate ester.

Introduction

Privileged structures.

The construction of a library of “biologically” competent compounds is a cornerstone of HTS-based lead discovery. Recognition of frequently active templates (natural or synthetic) and published data on side-effects of known drugs provides guidelines for the selection of compounds.[1] In 1988, Evans introduced the concept of “privileged structure” to account for the outstanding recurrence of some scaffolds, such as benzodiazepines, in the world of bioactive compounds. Since then, numerous teams have focused on their use in medicinal chemistry.[2-5] More recently, IUPAC has given a structural definition that corresponds to the common denominator of Evans’ privileged structures.[3] According to that definition a privileged structure is substructure *“that often consists of a semi-rigid scaffold, which is able to present multiple hydrophobic residues without undergoing hydrophobic collapse”*.[4] This definition is useful for the construction of screening library because it offers selection criterias independent of any established biological activity. We ourselves have developed series of bio-inspired privileged structures: “spiro-compounds” and tropane-based compounds.[5-6] Among privileged structures that are also found in natural compounds, piperidine and piperazine in one hand, and phenethylamine, tryptamine, histamine derivatives (cyclized or not) in the other hand, are interesting because they contain a basic nitrogen atomⁱ.[7]

Drug-morphing and combinatorial synthesis of privileged structures

We have been interested into drug-morphing, *i.e.* transforming biologically active compounds on a target to related compounds active on new targets, by changes in pharmacophore. Wermuth and coll. have applied this concept to commercially available drugs and name it the “SOSA-Approach”.[8] We intend to modify the amine function of privileged compounds into new pharmacophores by simple chemical reactions. Recently, we focused on squaric acid as a key chemical intermediate that could serve the design of chemical libraries for screening. We use privileged bio-inspired amines and transform them into squaric acid derivatives. In particular, we

ⁱ For examples, see catalogs of building-blocks providers like ChemFiles® from Sigma-Aldrich.Inc or Optimer-Building Blocks® from Array biopharma.

aimed at addressing two key problems encountered in medicinal chemistry (Figure 1). First, these compounds can palliate the shortage of acidic compounds in screening libraries. Indeed, squaramic acid and squaric acid N-hydroxylamide amide derivatives are monobasic acid with pKa of 2-3 [9] and 8-9ⁱⁱ respectively. Secondly, these compounds display new chelating zing-binding groups (ZBGs) that are highly desirable in medicinal chemistry.

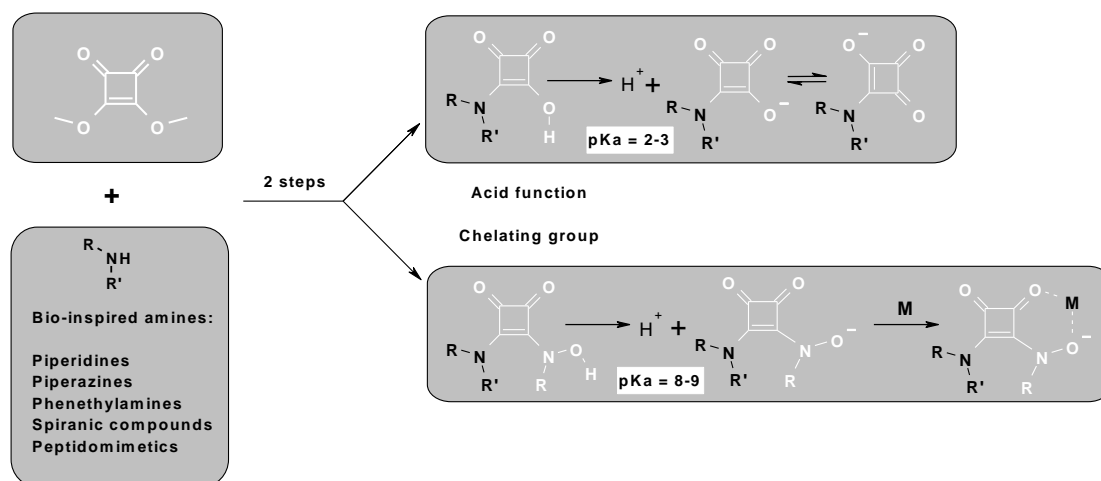


Figure 1: Examples of bio-inspired libraries of squaramic acids and squaric acid N-hydroxylamide amides

1. Squaric acid in medicinal chemistry

Squaric acid is a diacid that exhibits two acidic hydroxyl groups with pKa values of 0.54 and 3.48 as well as two highly polarized carbonyl groups.[10] This unique structure provides not only versatile proton acceptor sites [11] at the carbonyl function for hydrogen bonding but also binding sites to metal ions.[12,13] Since the pioneering work of Cohen [14] in 1959, many examples of the use of squaric template (Figure 2) have already been described particularly in the fields of bioorganic and medicinal chemistry.[15]

ⁱⁱ pKa of a prototypal compound was determined in DMSO/H₂O (58/42) by potentiometric titration using 0.025M NaOH.

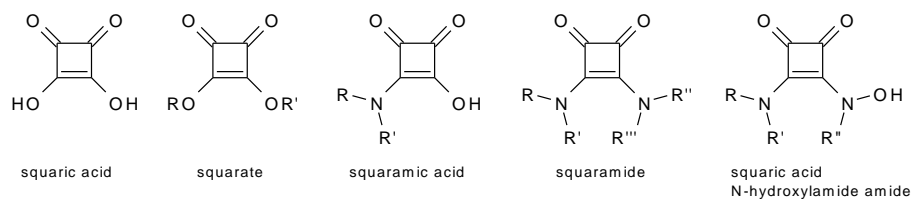


Figure 2. Nomenclature of squaric derivatives

The conjugate base of squaric acid can serve as a mimic of negatively charged groups that are common in biology such as carboxylates and phosphate mono- and diester. As a result, derivatives of squaric acid have been used as a replacement for these groups in medicinal applications. Sekine and co-workers have used a diamide of squaric acid as a replacement for one of the phosphate diester linkages in an oligodeoxynucleotide.[16] Squaric acid unit were also incorporated by Hanessian *et al.* in analogues of SAHA (Suberoyl Anilide Hydroxamic Acid, vorinostat).[17] Ishida *et al.* described the synthesis of amino-acid analogues bearing a squaryl group as a carboxylic acid surrogate.[18] Kinney and co-workers have reported the use of 3,4-diamino-3-cyclobutene-1,2-dione as a replacement group for the entire α -amino carboxylic acid functionality in various NMDA (N-methyl-D-aspartic acid) antagonists.[19] They also achieved the synthesis of C-linked squarate analogues of glycine, β -alanine and γ -aminobutyric acid.[20] Xie *et al.* demonstrated that squaric acid is an effective pharmacophore for the design of Tyrosin phosphatase inhibitors.[21]

Lee and co-workers have used a squaryldiamide as a new bioisostere of unsubstituted guanidine in the synthesis of peptidomimetic inhibitors of HIV-1 Tat–TAR interactions.[22] Diaminocyclobutenedione template was also used for bioisosteric replacement of the N-cyanoguanidine moiety of pinacidil and afforded a prototype for a novel series of K_{ATP} channel openers.[23]. Recently, a novel series of cyclobutenedione centered C(4)-alkyl substituted furanyl analogs was developed as potent CXCR2 and CXCR1 antagonists.[24] (Figure 3)

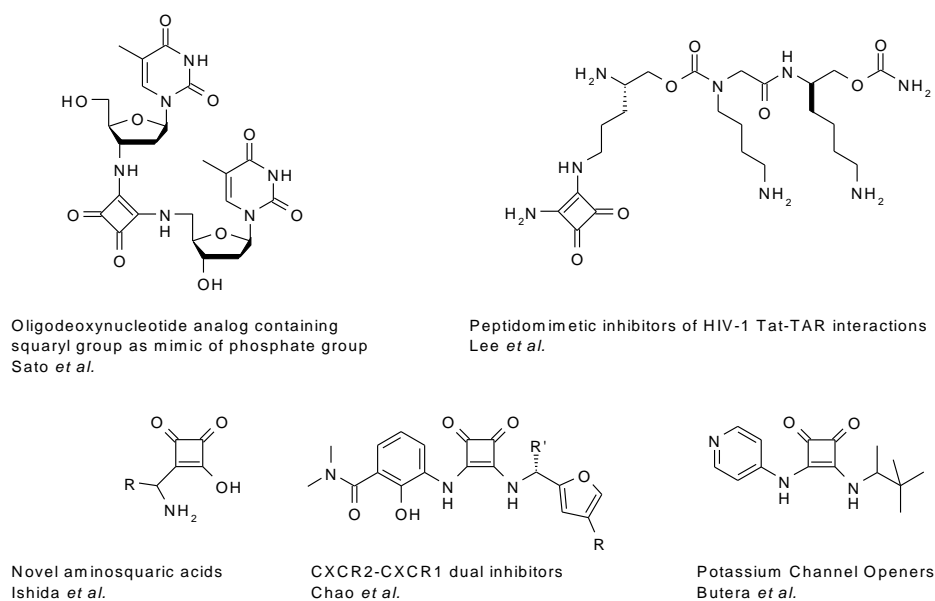


Figure 3. Examples of bioactive compounds displaying a squaric template.

Thus in the view of this growing interest of medicinal chemists in the use of squaric acid either as a linker, or as a precursor of acidic or metal binding functions, we tried to develop efficient parallel synthesis procedures for the incorporation of this structure into potentially bioactive compounds.

2. Converting basic compounds to acidic compounds

Evidencing the lack of acidic structures in screening libraries.

Among commercially available drugs, one can notice that acidic functions are essential for several important therapeutic classes like NSAIDs (Non Steroidal Anti-Inflammatory Drugs), sartans and glitazones (Figure 4). Interestingly, these drugs target very different protein classes: enzymes, GPCRs (G-protein coupled receptors) and nuclear hormone receptors. Carboxylic acid and bioisosters are thus important pharmacophoric groups. In agreement with this observation, Fesik *et al* identified carboxylic acid as a privileged structure using screening by NMR.[25]

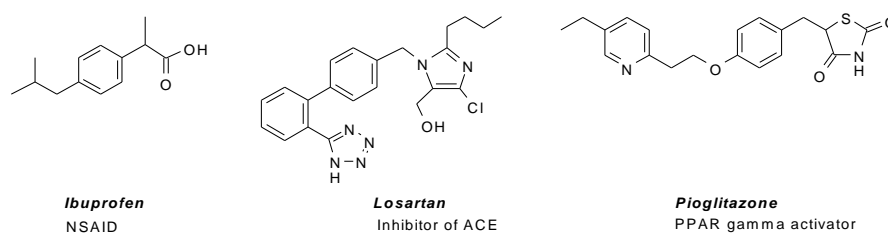


Figure 4. Examples of structures of acidic drug molecules.

However, a survey of MDL® CMC database reveals that acidic compounds are underrepresented in the chemical space of bioactive molecules as shown in Figure 5.ⁱⁱⁱ The same trend can be observed when analyzing the MDL® Drug Data Report. Indeed, among compounds in clinical phase or launched on the market, charge at pH 7.4 which reflects the acidic or basic behaviour of compounds is not evenly distributed.^{iv,v} Out of 2720 molecules, 53 % are neutral, 28 % are positively charged and only 19 % are negatively charged.

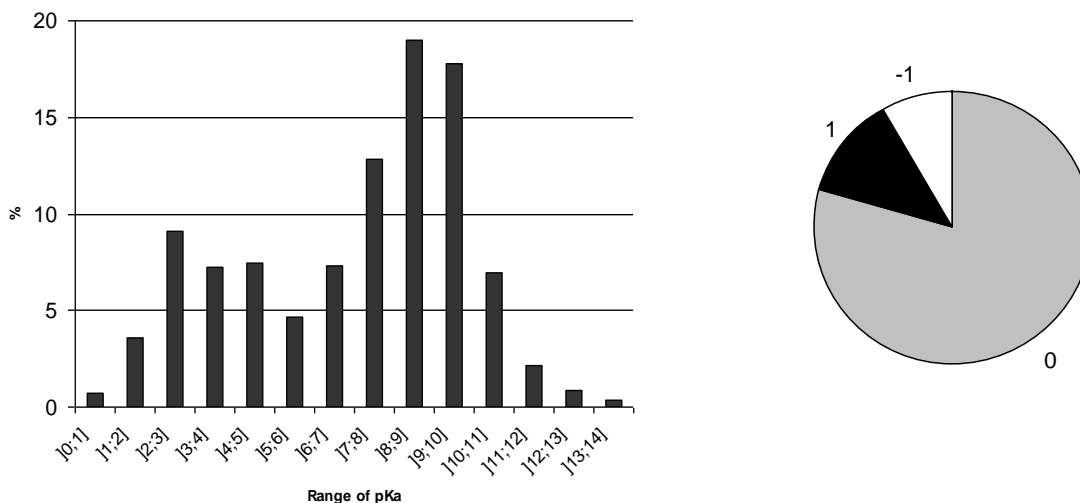
Since the beginning of high-throughput screening for lead discovery, the number of providers of chemical libraries has considerably increased. These libraries reflect either the history of the provider's sources and/or the ease of synthesis of compounds. Recently, the concept of targeted libraries has emerged to fill the diversity gaps. An analysis of databases of several chemical library providers reveals that libraries for High-Throughput Screening lack acidic compounds (Figure 5).^{vi} Thus, the relative lack of acidic compounds in bioactive molecules may only reflect the lack of acidic molecules available for screening and the relative difficulty of synthesis of such compounds.

ⁱⁱⁱ For this study, 893 compounds for which 1219 pKa values were available in the database were used. The MDL® Comprehensive Medicinal Chemistry (CMC-3D) database is an electronic version of Volume 6 of Comprehensive Medicinal Chemistry, published by Pergamon Press in March 1990. CMC-3D has been updated to include recently approved or registered drugs. Total number of compounds is 8000.

^{iv} The MDL Drug Data Report (MDDR) database is an online version of the Drug Data Report journal by Prous Science Publishers.

^v Ionization was performed using pKa value calculation of PipelinePilot TM V 6.0.2 from Scitegic.Inc

^{vi} Libraries analyzed were Asinex™(Gold) and Chembridge™.



A: Percent of compounds of MDL CMC™ database that have pKa(s) in the corresponding range

B: Charge of compounds at pH 7.4 : a survey of two different providers of chemical compounds (total of compounds : 602717)

Figure 5. Evidencing the lack of acidic structures in bioactive compounds (A) and in chemical libraries (B).^{vii}

We have been interested in the past few years in synthesizing acidic privileged structures. We focused on acidic heterocycles and hydroxamic acids, in order to supply our in-house collection with acidic compounds. [26-27] We now focus on squaric acid derivatives and are interested in incorporating squaric moiety in small lead- or drug-like molecules using a simple chemical group transformation for the conversion of rather common secondary or primary amines into a less common acidic group.

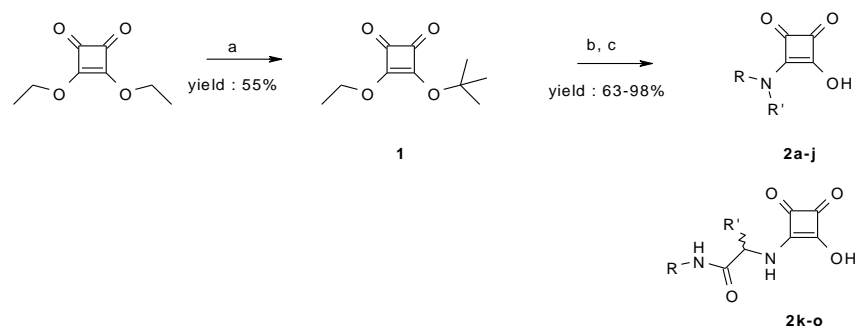
A simple procedure to convert drug-like amines into acidic compounds

a-Parallel synthesis

Squaric scaffold was introduced using a dissymmetric diester: 3-tert-butoxy-4-ethoxycyclobut-3-en-1,2-dione **1**, readily obtained from commercially available diethyl squarate (Scheme 1). The use of this intermediate avoids the formation of symmetrical squaramides resulting from a double substitution reaction by the

^{vii} When comparing graph A and B one must take into account that the bars on the left side of graph A contain weak bases not protonated at pH 7.4 (like pyridine : charge=0) and weak acids deprotonated at pH 7.4 (like carboxylic acids : charge =-1). Likewise, the bars on the right side of graph A contains weak bases protonated at pH 7.4 (like alkylamines : charge =+1) and weak acids not deprotonated at pH 7.4 (like phenols : charge =0).

amine.[28] Compound **1** reacted with a selection of secondary amines to provide tert-butyl squaramates in excellent purity without any chromatography. A final step of tert-butyl deprotection afforded the resulting squaramic acids.

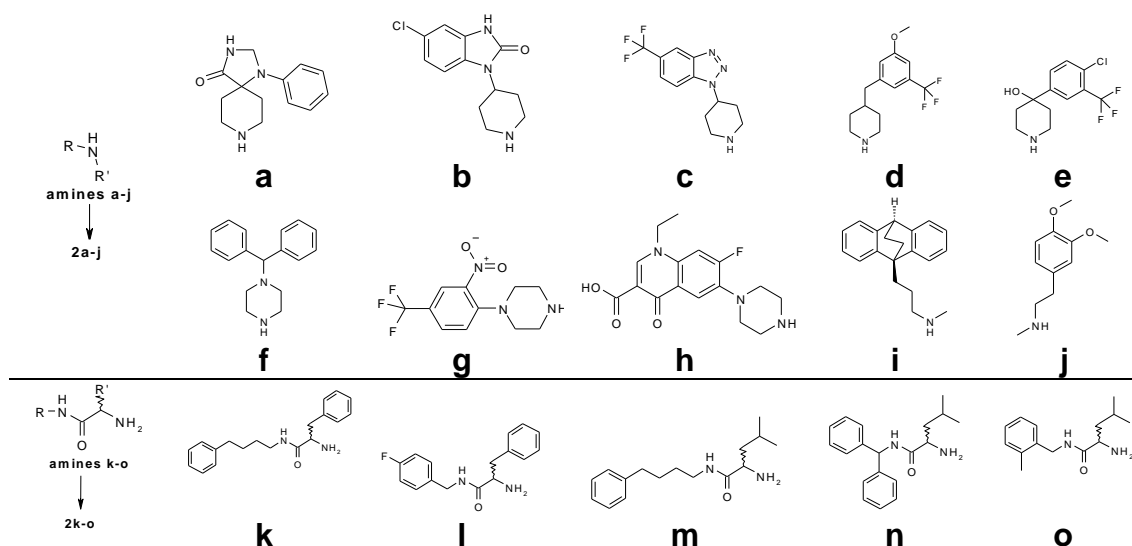


Scheme 1. Reaction conditions : a. t-BuOK, 1M in THF (1eq.), THF, 4°C ; b. RR'NH, NEt₃, EtOH, r.t.; c. TFA/dichloromethane (1/1 v/v), 4°C.

b-Choice of amines

Natural scaffolds may interact with multiple biological targets and can be regarded as embodying privileged structures. Many synthetic templates now considered as privileged structures derive from natural compounds. For example as far as nitrogen-heterocycles are concerned, piperidine and piperazine are heterocycles that are very frequent substructures in natural alkaloids [29] benzylpiperidines and spirocyclic compounds are also constrained analogues of endogenous bioactive monoamines (adrenaline, dopamine, tryptamine, histamine,...) that target GPCRs.[30-31] Diphenylmethyl, benzimidazole are other privileged structures found in natural compounds. [25] Taking all this into account, many natural products have given birth to ready-to-use building-blocks. [32] Figure 6 gathers all the selected structures that were incorporated for validation of our synthetic procedure. Amine building-blocks **a-e** contain a piperidine ring. Amines **f-h** display a piperazine moiety. Amines **i-j** as well as **a-e** can be considered as analogues of endogenous monoamines. Compounds **f,i** and **n** contain biphenylmethyl rings. Benzimidazole and its benzotriazole are represented respectively in compounds **b** and **c**. Finally, peptidomimetics derived from Boc-phenylalanine or Boc-leucine were used (**k-o**).

Figure 6: Bio-inspired secondary amines and peptidomimetic primary amines



Results observed for the conversion of the set of secondary amines into squaric acids are compiled in Table 1.

Piperidines were successfully converted into squaric amides (Table 1, **2a-2e**). The reaction was selective and amide functionalities did not react with the squaric ester (compounds **2a-2b**). Trifluoro-methyl derivatives afforded squaric acid with good to excellent yields (compounds **2c-2d**) and the presence of a potentially reactive alcohol was well tolerated (compound **2e**). Efficient reaction also occurred with piperazines diversely substituted in position 4 (Table 1, **2f-2h**). Diphenylmethyl piperazine was successfully converted into squaric acid **2f**. N-(2-nitro-4-trifluoromethylphenyl) piperazine was also an excellent substrate (compound **2g**). The reaction of norfloxacin proceeded with good yield (compound **2h**) and resulted in a complete change of the pharmacophore of this potent antibiotic. The same observation was made on the antidepressant maprotiline, that was converted with good yield into the corresponding squaric acid (compound **2i**). The squaric derivative of 2,4-dimethoxy-N-methylphenethylamine (compound **2j**) was obtained with a medium yield of 63%, since the protected intermediate was an oil that proved to be difficult to handle. The lower yields (below 80%) obtained for some compounds (**2a**; **2e**; **2g**; **2h**) were due to the more difficult substitution of squaric ester by the amine that eventually required to heat the reaction mixture and/or to add more equivalents of triethylamine. Tert-butyle deprotection was in all cases quantitative.

Table 1. Conversion of secondary amines to squaramic acids

Product	Yield (%) (2 steps)	Product	Yield (%) (2 steps)
2a	79	2f	92
2b	91	2g	74
2c	85	2h	77
2d	98	2i	86
2e	76	2j	63

The scope of this efficient procedure for preparation of squaramic acids was extended to the synthesis of some squaric peptidomimetic derivatives isolated with excellent yields (Table2).

Table 2. Preparation of squaric peptidomimetics

Product	Yield (%) (2 steps)
2k	81
2l	85
2m	93
2n	94
2o	90

3. Converting basic compounds to zinc chelating compounds

Evidencing the need for new Zinc-Binding Groups (ZBG)

Since long, Zn metallohydrolases have interested the medicinal chemistry community. They are important biological targets for drugs on the market or in clinical trials, such as inhibitors of angiotensin-converting enzyme carbonic anhydrase or more recently Histone Desacetylase [33-34-35] (Figure 7).

When targeting metalloproteases, a ZBG is necessary to bind to the Zinc ion (Figure 8) and sets the rest of the molecule in the active site. Using hydroxamate is convenient to achieve good activity at the screening stage because this function is one of the best Zn ligand. Nevertheless, a high binding to the target can be achieved with a “softer” ZBG, provided that the rest of the molecule fits nicely in the binding pocket (Figure 8).[36] Furthermore, because hydroxamic acids are often poorly

absorbed and are prone to metabolic degradation and glucuronidation, there has been considerable interest in discovering alternative groups that can be incorporated in the structures of metalloproteases inhibitors.[37] The search of relevant new zing binding groups is widely investigated. ZBG can be classified in two classes as shown in Figure 9: 1) monodentate that include thiols, carboxylic acids, acidic heterocycles, phosphinic acids...2) bidentate that include hydroxamate and hydroxypyridones recently published ZBG of Cohen *et al.* [38-39] Recent examples of the use of heterocyclic ZBGs include hydantoines, triazolones and imidazolones as inhibitors of TACE (TNF-alpha converting enzyme) or tetrazoles as inhibitors of metallo- β -lactamase.[40-41]

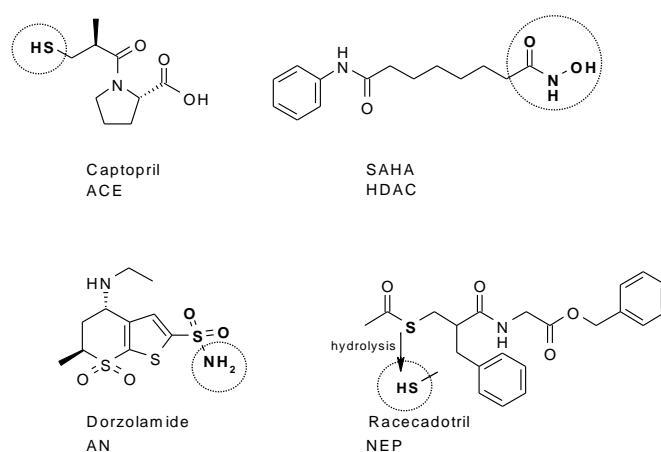


Figure 7: Examples of inhibitors of Zinc hydrolases on the market (each ZBG is circled)

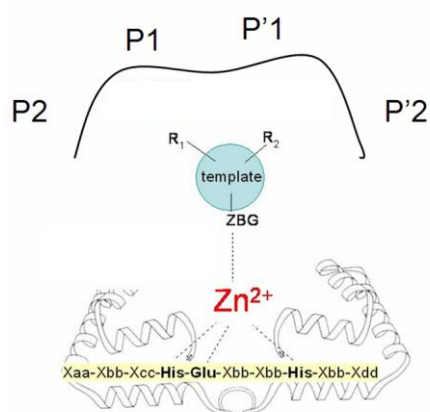


Figure 8: Orientating role of the Zn ion in the catalytic site of Zn metallo proteases.

Monodentates

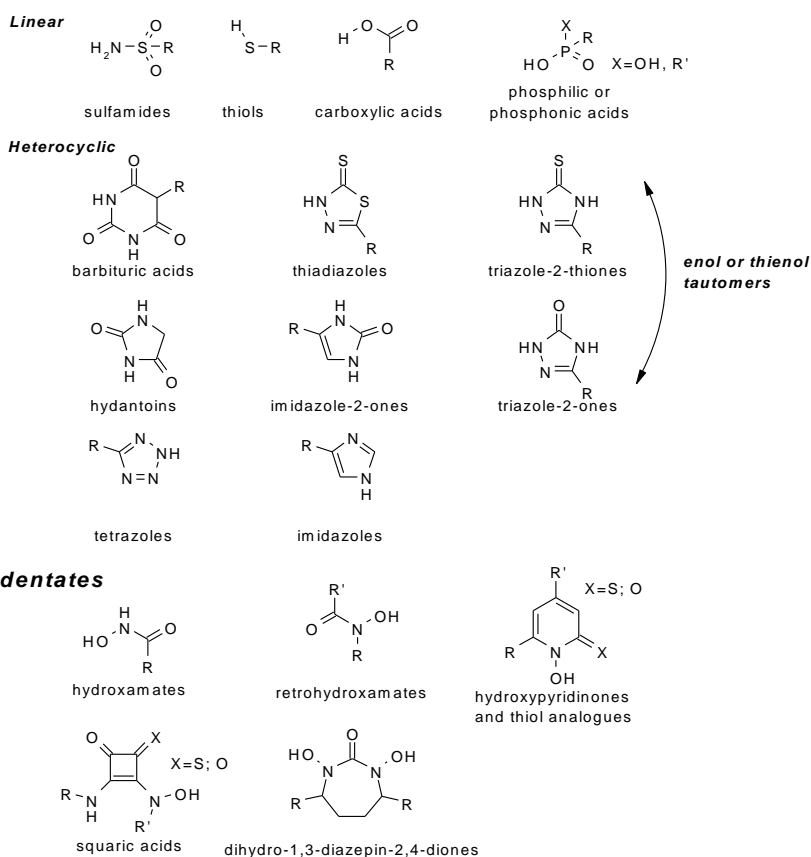


Figure 9: Classical and non-classical ZBGs classified by the Zinc-binding mode.

Selection of squaric Acid N-hydroxylamines template as Zn-chelating moiety.

Brucker and co-workers have demonstrated that vinylogous hydroxamic acids derived from squaric acids are good metal chelators (Figure 10) and squaric acid-based inhibitors of matrix metalloproteases were reported.[15a,42] Hanessian *et al.* also replaced the hydroxamic acid of SAHA by squaric acid and squaric hydroxamic acid.[17] In both cases (HDAC or MMP inhibitors) no inhibitory activity was observed below 1.0 μM and it was not clear whether the spatial requirements could be satisfied in the active sites of these enzymes.^{viii} The squaric/hydroxamic acid hybrids are generally not as potent as hydroxamic acid-based inhibitors, many of which have inhibition constants in the nM range but these hybrids nevertheless deserve

^{viii} Analogues of SAHA bearing either a squaric acid N-hydroxylamine or thio squaric derivatives or methylthioesters derivatives did not display activity below 1 μM .

screening to generate an alternative starting point for the design of inhibitors with perhaps improved pharmacological properties.

Nevertheless, very few squaric acid N-hydroxylamines amides have been prepared and described until now.[43]

a-Parallel synthesis

In our ongoing research program aiming at the synthesis of potent inhibitors of zinc-metalloproteases based on acidic templates, we investigated the synthesis of squaric acid N-hydroxylamide amides using simple convergent solution synthesis.^{ix}

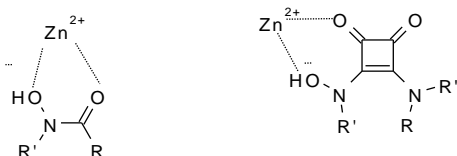
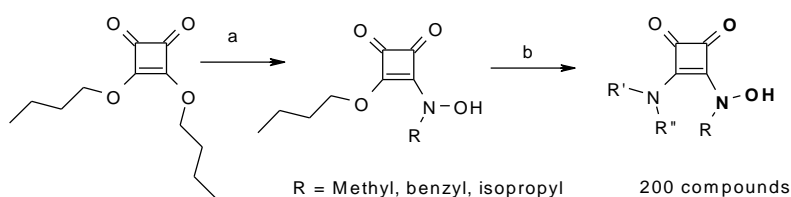


Figure 10. Known binding mode of hydroxamic acid and putative binding mode by squaric acid derivatives A (6-membered zinc chelation model).

The general solution phase method for parallel synthesis of the library members, using squaric acid inputs and amines is described in Scheme 2. Reaction of dibutyl squarate with a series of hydroxylamines gave 3 precursors. A subsequent reaction with various amines gave an array of 200 vinylogous hydroxamic acids.



Scheme 2. Reaction conditions : a. N-substituted hydroxylamine hydrochloride, 1.5 equiv., KOH, 1.5 equiv., MeOH, room temp., 5 h b. amines R'R''NH (1.1 equiv, 16.5 μ mol), MeOH, room temp., 5 h.

b-Choice of amines

Amines were chosen in order to generate a diversity of pharmacophore properties and geometries. Primary and secondary amines were selected. Among the primary

^{ix} Charton, J., Deprez-Poulain, R., Deprez, B. *Tetrahedron Lett.* submitted

amines (54 inputs, Figure 11), aliphatic amines, aromatic amines (benzylamines, phenethylamines, anilines...), amino-alcohol and amino-acids were incorporated. Among secondary amines (20 inputs, Figure 11), cyclic amines (piperidines, piperazines) and acyclic secondary amines were selected. As explained above, such building-blocks are expected to behave as privileged structures.

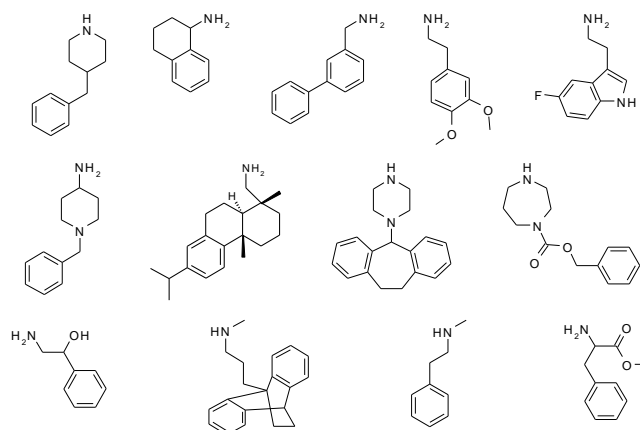


Figure 11: Some prototypal primary and secondary amines of the library.

Each compound was obtained with very good purity in a 15 μmol scale suitable for biological screening. Out of the 200 library members, 86 % displayed purity above 80% and were obtained in very good yield (75-100%).

Discussion-Conclusion

Recent attention has focused on the need to assess the potential for bioavailability problems of potential drug candidates early in the drug discovery cycle. Lipophilicity, hydrophilicity, hydrogen bonding and pKa are likely to be important factor for absorption, transport and excretion of compounds.[44] We compared the initial physico-chemical profile of amines with the final squaric acid derivatives either squaramic acids or squaric acid hydroxamate amides (Figure 12).^x Interestingly, these compounds differ mainly from amines by pKa and charge at physiological pH, and the presence of a potentially ZBG.

Using conventional Zn ligands and this original array of squaramides and squaramic acids we have recently started an *in vitro* screening campaign on six Zn

^x For ease of discussion, average values were attributed to initial amine buiding-blocks.

metalloproteases. Inhibitors will be used for the functional exploration of these enzymes in several biological setups.

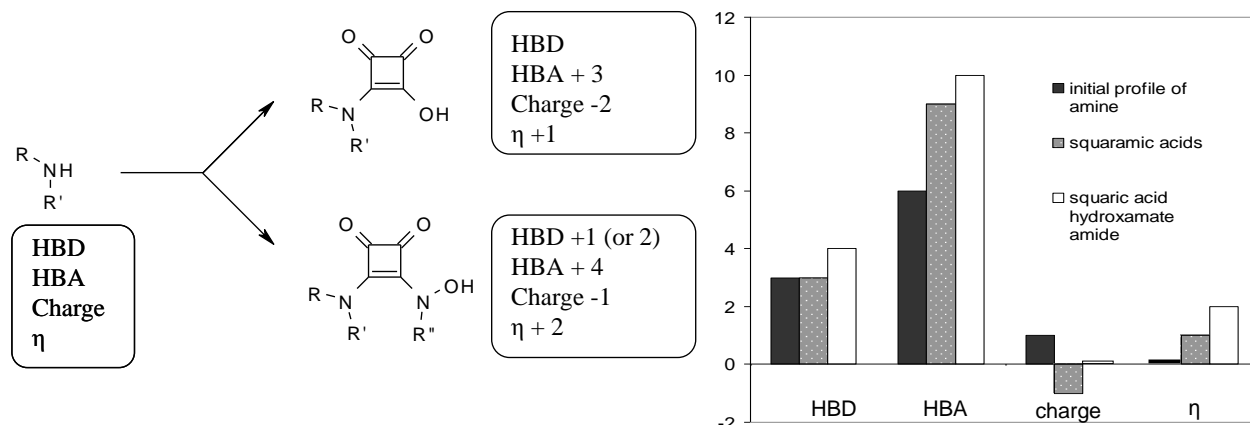


Figure 12: Comparison of the initial physico-chemical profile of amines and squaric acid derivatives (η represents the hapticity of the potential Zn ligand).

Acknowledgements: We are grateful to the institutions that support our laboratory (Inserm, Université de Lille2 and Institut Pasteur de Lille). Data management was performed using Pipeline Pilot™ from Scitegic. We thank also the following institutions or companies: CAMPLP and VARIAN.inc. This project was supported by the European Commission - ERDF funds, grant N° OBJ2 – 2006/364.1 N°302.

References and Notes

- [1] Deprez-Poulain, R. and Deprez, B. *Frontiers in Medicinal Chemistry* **2006**, 3, 653-673.
- [2] Nieto, M. J., Philip, A. E., Poupaert, J. H. and McCurdy, C. R. *J. Comb. Chem* **2005**, 7, 258-263.
- [3] Horton, D. A., Bourne, G. T. and Smythe, M. L. *Chem. Rev.* **2003**, 103, 893-930.
- [4] MacLean, D.; Baldwin, J.J.; Ivanov, V.T.; Kato, Y.; Shaw, A.; Schneider, P.; Gordon, E.M. *Pure Appl.Chem.*, **1999**, 71, 2349-2365.
- [5] (a) Deprez-Poulain, R., Willand, N., Boutillon, C., Nowogrocki, G., Azaroual, N. and Deprez, B. *Tetrahedron Lett.* **2004**, 45, 5287. (b)Willand, N., Beghyn, T., Nowogrocki, G., Gesquiere, J.-C. and Deprez, B. *Tetrahedron Lett.* **2004**, 45, 1051.

-
- [6] Willand, N., Folleas, B., Boutillon, C., Verbraeken, L., Gesquiere, J.-C., Tartar, A. and Deprez, B. *Tetrahedron Lett.* **2007**, *48*, 5007.
- [7] Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893-930
- [8] Camille G. Wermuth DDT, 2006, *11*, 160-164.
- [9] Seio, K.; Miyashita, T.; Sato, K.; Sekine, M. *Eur. J. Org. Chem.* **2005**, 5163–5170
- [10] Swartz, L. M.; Howard, L. O. *J. Phys. Chem.* **1971**, *75*, 1798-1803.
- [11] Terao, H.; Sugawara, T.; Kita, Y.; Kaho, E.; Takeda, S. *J. Am. Chem. Soc.* **2001**, *123*, 10468-10474.
- [12] Schmidt, A. H. *Synthesis* **1980**, 961-994.
- [13] West, R.; Niu, H. Y. *J. Am. Chem. Soc.* **1963**, *85*, 2589-2590.
- [14] a) Cohen, S.; Lacher, J. R.; Park, J. D. *J. Am. Chem. Soc.* **1959**, *81*, 3480. b) Park, J. D.; Cohen, S.; Lacher, J. R. *J. Am. Chem. Soc.* **1962**, *84*, 2919-2922. c) Cohen, S.; Cohen S. G. *J. Am. Chem. Soc.* **1966**, *88*, 1533-1536.
- [15] a) Onaran, M. B.; Comeau, A. B.; Seto, C. T. *J. Org. Chem.* **2005**, *70*, 10792-10803. b) Xu, Y.; Yamamoto, N.; Ruiz, D. I.; Kubitz, D. S.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 19, 4304-4307 c) Tevyashova, A.; Sztaricskai, F.; Batta, G.; Herczegh, P.; Jeney, A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 18, 4783-4789. d) Xie J, Comeau, A. B.; Seto, C. T. *Org. Lett.* **2004**, *6*, 1, 83-86. e) Porter, J. R.; Archibald, S. C.; Childs, K.; Critchley, D.; Head, J. C.; Linsley, J. M.; Parton, T. A.; Robinson, M. K.; Shock, A.; Taylor, R. J.; Warrellow, G. J.; Alexander, R. P.; Langham, B. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 7, 1051-1054.
- [16] a) Sato, K.; Seio, K.; Sekine, M. *J. Am. Chem. Soc.* **2002**, *124*, 12715-12724. b) Seio, K.; Miyashita, T.; Sato, K.; Sekine, M. *Eur. J. Org. Chem.* **2005**, 5163–5170
- [17] Hanessian, S.; Vinci, V.; Auzzas, L.; Marzi, M.; Giannini, G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 18, 4784-4787.
- [18] Ishida, T.; Shinada, T.; Ohfuné, Y. *Synthesis* **2005**, 2723-2729. Ishida, T.; Shinada, T.; Ohfuné, Y. *Tetrahedron Lett.* **2005**, *46*, 311-314.
- [19] Kinney, W. A.; Lee, N. E.; Garrison, D.T.; Podlesny, E. J.; Simmonds, Jr. J. T.; Bramlett, D.; Notvest, R. R.; Kowal, D. M.; Tasse, R.P. *J. Med. Chem.* **1992**, *35*, 4720-4726.

-
- [20] Campbell, E. F.; Park, A. K.; Kinney, W. A.; Fengl, R. W.; Liebeskind, L. S. *J. Org. Chem.* **1995**, *60*, 1470-1472.
- [21] Xie, J.; Comeau, A. B.; Seto, C. T. *Org. Lett.* **2004**, *6*, 83-86.
- [22] Lee, C. W.; Cao, H.; Ichiyama, K; Rana, T. M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 19, 4243-4246.
- [23] a) Butera, J. A.; Antane, M. M.; Antane, S. A.; Argentieri, T. M.; Freeden, C.; Graceffa, R. F.; Hirth, B. H.; Jenkins, D.; Lennox, J. R.; Matelan, E.; Norton, N. W.; Quagliato, D.; Sheldon, J. H.; Spinelli, W.; Warga, D.; Wojdan, A.; Woods, M. *J. Med. Chem.* **2000**, *43*, 6, 1187-1202. b) Gilbert, A. M.; Antane, M. M.; Argentieri, T. M.; Butera, J. A.; Francisco, G. D.; Freeden, C.; Gundersen, E. G.; Graceffa, R. F.; Herbst, D.; Hirth, B. H.; Lennox, J. R.; McFarlane, G.; Norton, N. W.; Quagliato, D.; Sheldon, J. H.; Warga, D.; Wojdan, A.; Woods, M. *J. Med. Chem.* **2000**, *43*, 6, 1203-1214, c) Butera, J. A.; Jenkins, D. J.; Lennox, J. R.; Sheldon, J. H.; Norton, N. W.; Warga, D.; Argentieri, T.M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 19, 2495-2501.
- [24] Chao, J. ; Taveras, A.G.; Chao, J.; Aki, C.; Dwyer, M.; Yu, Y.; Purakkattle, B.; Rindgen, D.; Jakway, J.; Hipkin, W.; Fosetta, J.; Fan, X.; Lundell, D.; Fine, J.; Minnicozzi, M.; Phillips, J.; Merritt, J.B. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3778–3783.
- [25] Hajduk, P. J., Bures, M., Praestgaard, J. and Fesik, S. W. *J. Med. Chem.* **2000**, *43*, 3443-3447.
- [26] Charton, J., Cousaert, N., Bochu, C., Willand, N., Deprez, B. and Deprez-Poulain, R. *Tetrahedron Lett.* **2007**, *48*, 1479-1483.
- [27] (a) Flipo, M., Beghyn, T., Charton, J., Leroux, V. A., Deprez, B. P. and Deprez-Poulain, R. F. *Bioorg. Med. Chem.* **2007**, *15*, 63-76. (b) Flipo, M., Beghyn, T., Leroux, V., Florent, I., Deprez, B. P. and Deprez-Poulain, R. F. *J. Med. Chem.* **2007**, *50*, 1322-1334.
- [28] Pirrung, M. C.; Han, H.; Chen, J. *J. Org. Chem.* **1996**, *61*, 4527-4531.
- [29] Escolano, C., Amat, M. and Bosch, J. *Chemistry - A European Journal* **2006**, *12*, 8198-8207.
- [30] Newman, D. J., Cragg, G. M. and Snader, K. M. *J. Nat. Prod.* **2003**, *66*, 1022-1037.

-
- [31] Mason, J. S., Morize, I., Menard, P. R., Cheney, D. L., Hulme, C. and Labaudiniere, R. F. *J. Med. Chem.* **1999**, *42*, 3251-3264.
- [32] Ortholand, J.-Y. and Ganesan, A. *Curr. Opin. Chem. Biol.* **2004**, *8*, 271.
- [33] Abbenante, G. and Fairlie, D. P. *Med Chem* **2005**, *1*, 71-104.
- [34] Supuran, C. T., Casini, A., Mastrolorenzo, A. and Scozzafava, A. *Mini Rev. Med. Chem.* **2004**, *4*, 625-632.
- [35] Grant, S., Easley, C. and Kirkpatrick, P. *Nat. Rev. Drug Discov.* **2007**, *6*, 21.
- [36] Wen, S., Carey, K. L., Nakao, Y., Fusetani, N., Packham, G. and Ganesan, A. *Org. Lett.* **2007**, *9*, 1105-1108.
- [37] a) Pikul, S.; Ohler, N. E.; Ciszewski, G.; Laufersweiler, M. C.; Almstead, N. G.; De, B.; Natchus, M. G.; Hsieh, L. C.; Janusz, M. J.; Peng, S. X.; Branch, T. M.; King, S. L.; Taiwo, Y. O.; Mieling, G. E. *J. Med. Chem.* **2001**, *44*, 2499–2502.
b) Suzuki, T.; Miyata, N. *Curr. Med. Chem.* **2005**, *12*, 2867.
- [38] For a recent review on Zinc-binding groups see : Faith E. Jacobsen, J. A. Lewis. Seth. M. Cohen. *ChemMedChem* **2007**, *2*, 152-171.
- [39] Puerta, D. T., Lewis, J. A. and Cohen, S. M. *J. Am. Chem. Soc.* **2004**, *126*, 8388-8389.
- [40] Sheppeck, J. E., 2nd, Gilmore, J. L., Tebben, A., Xue, C. B., Liu, R. Q., Decicco, C. P. and Duan, J. J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2769-2774.
- [41] Park, H. and Merz, K. M., Jr. *J. Med. Chem* **2005**, *48*, 1630-1637.
- [42] Lim, N. C.; Morton, M. D.; Jenkins, H. A.; Bruckner, C. *J. Org. Chem.* **2003**, *68*, 9233-9241.
- [43] Zinner, G.; Grünefeld, J. *Arch. Pharm. (Weinheim)*, **1985**, *318*, 977-983.
- [44] Martin C.M. *J. Med. Chem.* **2005**, *48*, 3164-3170.