Alkylsquarates as Key Intermediates for the Rapid Preparation of Original Drug-Inspired Compounds

Julie Charton*, Lise Charruault, Rebecca Deprez-Poulain and Benoit Deprez

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

Faculté de Pharmacie, Université Lille 2, F-59006 Lille, France

Institut Pasteur de Lille, F-59000 Lille, France

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 developed methods to convert privileged basic compounds -like natural alkaloids or drugs into acidic compounds. This conversion led 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 µmol-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 a 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 criteria 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 the privileged structures that are also found in natural compounds, piperidine and piperazine on one hand, and phenethylamine, tryptamine, and histamine derivatives (cyclized or not) on the other hand, are interesting because they contain a basic nitrogen atom [7][i].

*Address correspondence to this author at the Faculté de Pharmacie, Université Lille 2, 3 rue du Pr. Laguesse, F-59006 Lille, Cedex, France; Tel: +33 320 964 948; Fax: +33 320 964 709;
E-mail: julie.charton@univ-lille2.fr

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

Drug-Morphing and Combinatorial Synthesis of Privileged Structures

We have been interested in drug-morphing, *i.e.* transforming biologically active compounds on a target to related compounds active on new targets, by changes in pharmacophore. Wermuth and colleagues have applied this concept to commercially available drugs and named it as the "SOSA-Approach" [8]. We intended 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 used privileged bio-inspired amines and transformed them into squaric acid derivatives. In particular, we aimed at addressing two key problems encountered in medicinal chemistry (Fig. **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 8-9[ii], respectively. Secondly, these compounds display new chelating zing-binding groups (ZBGs) that are highly desirable in medicinal chemistry.

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 polarised 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 (Fig. **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/H_2O (58/42) by potentiometric titration using 0.025 M NaOH.

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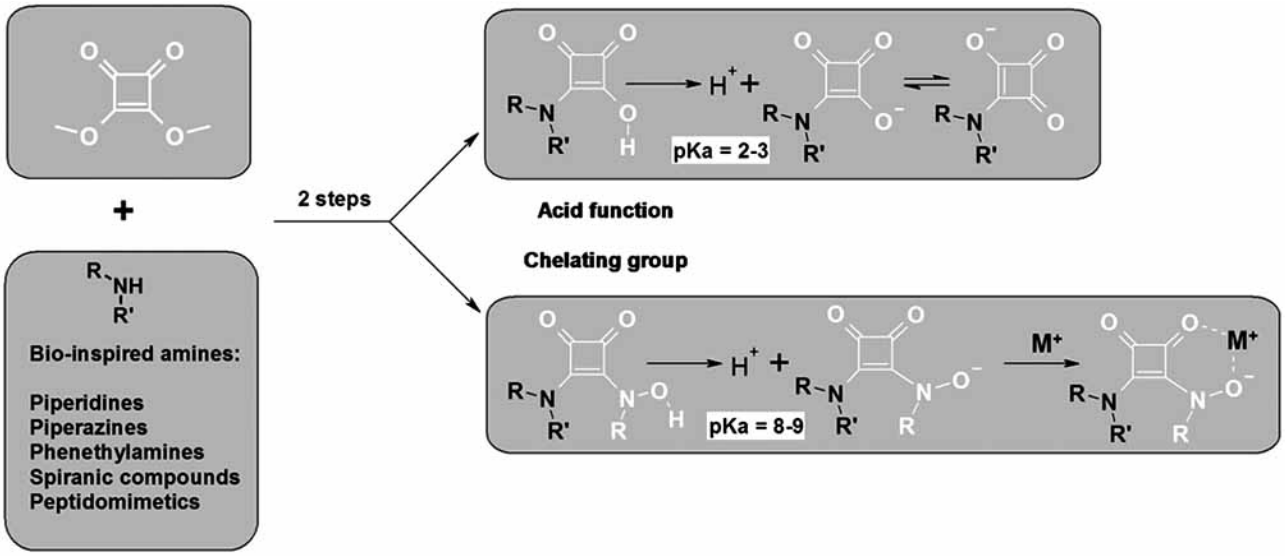


Fig. (1). Examples of bio-inspired libraries of squaramic acids and squaric acid N-hydroxylamide amides.

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 was 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 tyrosine phosphatase inhibitors [21].

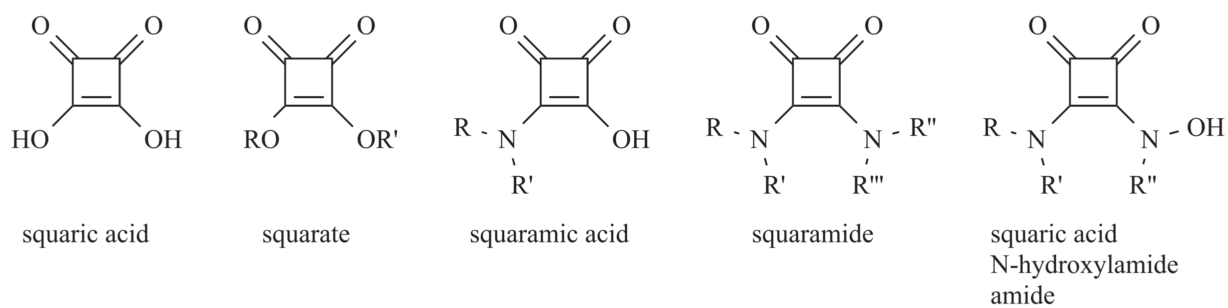


Fig. (2). Nomenclature of squaric derivatives.

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] (Fig. **3**).

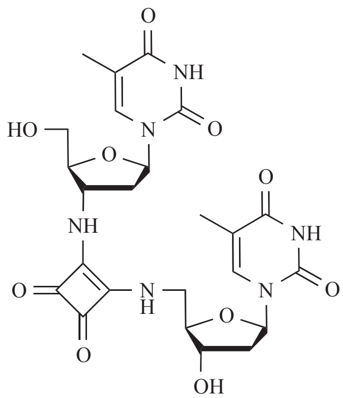
Thus, in the view of this growing interest of medicinal chemists in the use of squaric acid either as a linker or as a precursor of acidic or metal binding functions, we tried to develop efficient parallel synthesis procedures for the incorporation of this structure into potentially bioactive compounds.

2. Converting Basic Compounds to Acidic Compounds

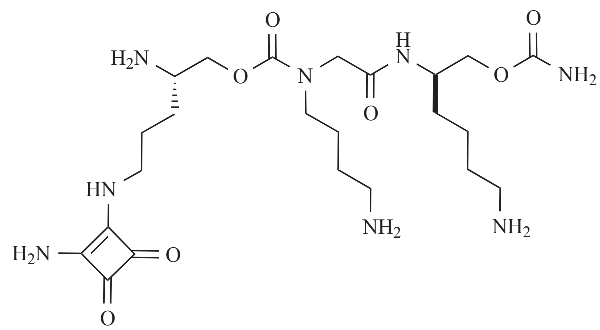
<u>Evidencing the Lack of Acidic Structures in Screening Libraries</u>

Among the 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 (Fig. **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].

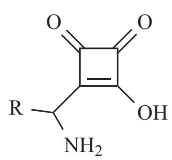
However, a survey of MDL® CMC database revealed that acidic compounds are underrepresented in the chemical



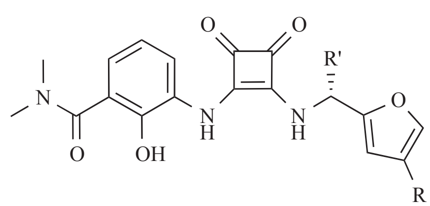
Oligodeoxynucleotide analog containing squaryl group as mimic of phosphate group
Sato *et al.*



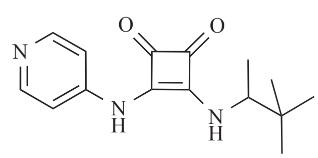
Peptidomimetic inhibitors of HIV-1 Tat-TAR interactions
Lee *et al.*



Novel aminosquaric acids
Ishida *et al.*

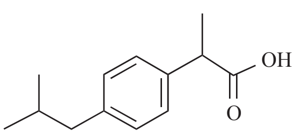


CXCR2-CXCR1 dual inhibitors
Chao *et al.*

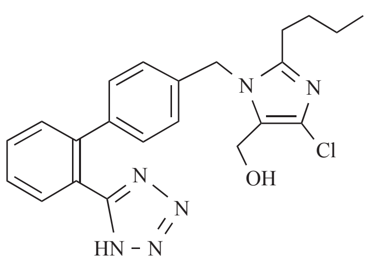


Potassium Channel Openers
Butera *et al.*

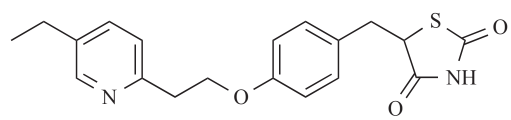
Fig. (3). Examples of bioactive compounds displaying a squaric template.



Ibuprofen
NSAID



Losartan
Inhibitor of ACE



Pioglitazone
PPAR gamma activator

Fig. (4). Examples of structures of acidic drug molecules.

space of bioactive molecules as shown in Fig. **5**[iii]. This trend can be observed when analysing 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 the 2720 molecules, 53% are neutral, 28% are positively charged and only 19% are negatively charged.

[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.

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 revealed that libraries for high-throughput screening lack acidic compounds (Fig. **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.

We have been interested in the past few years in synthesising 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

[vi]Libraries analyzed were AsinexTM(Gold) and ChembridgeTM.

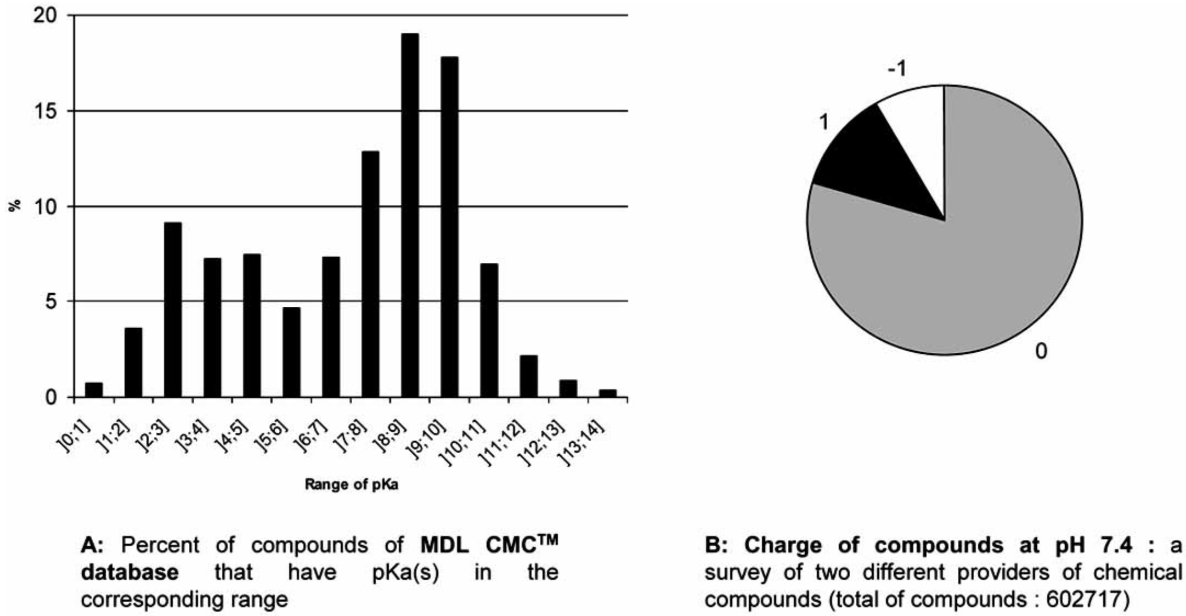


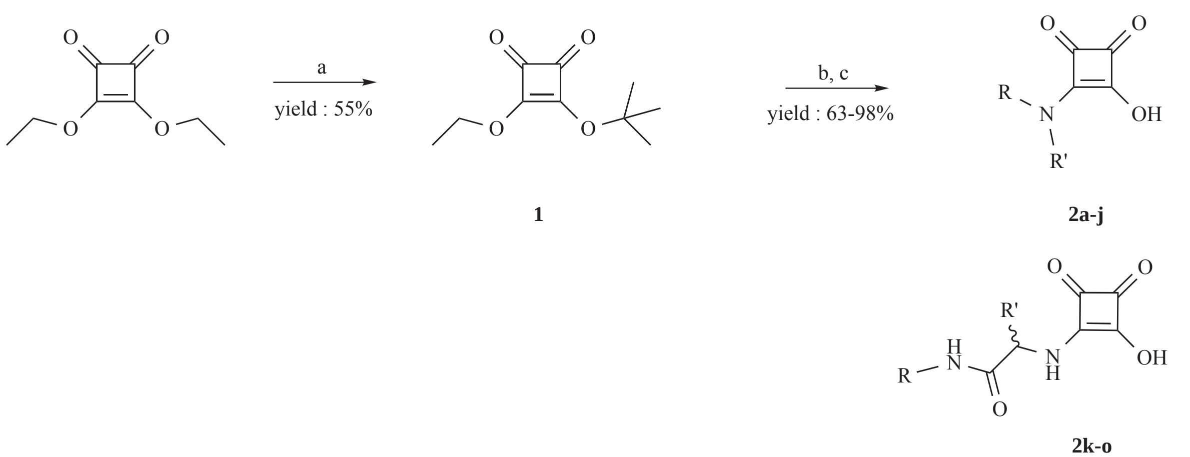
Fig. (5). Lack of acidic structures in bioactive compounds (**A**) and in chemical libraries (**B**)[vii].

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

The squaric scaffold was introduced using a dissymmetric diester: 3-*tert*-butoxy-4-ethoxy-cyclobut-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 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, 1 M in THF (1 eq.), THF, 4°C; b) RR'NH, NEt_3, EtOH, r.t.; and 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 have derived 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 monamines (adrenaline, do-

[vii] When comparing graphs 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).

pamine, tryptamine, histamine,…) that target GPCRs [30, 31]. Diphenylmethyl and 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]. Fig. **6** shows 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** displayed a piperazine moiety. Amines **i-j** as well as **a-e** can be considered to be analogues of endogenous mono-amines. Compounds **f**, **i** and **n** contained biphenylmethyl rings. Benzimidazole and its benzotriazole were represented respectively in compounds **b** and **c**. Finally, peptidomimetics derived from Boc-phenylalanine or Boc-leucine were used (**k-o**). Results observed for the conversion of the set of secondary amines into squaramic 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 squaramic 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 squaramic 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 squaramic 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 heating the reaction mixture and/or adding more equivalents of triethylamine. *Tert*-butyl 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 the preparation of squaramic acids was extended to the synthesis of some squaric peptidomimetic derivatives isolated with excellent yields (Table **2**).

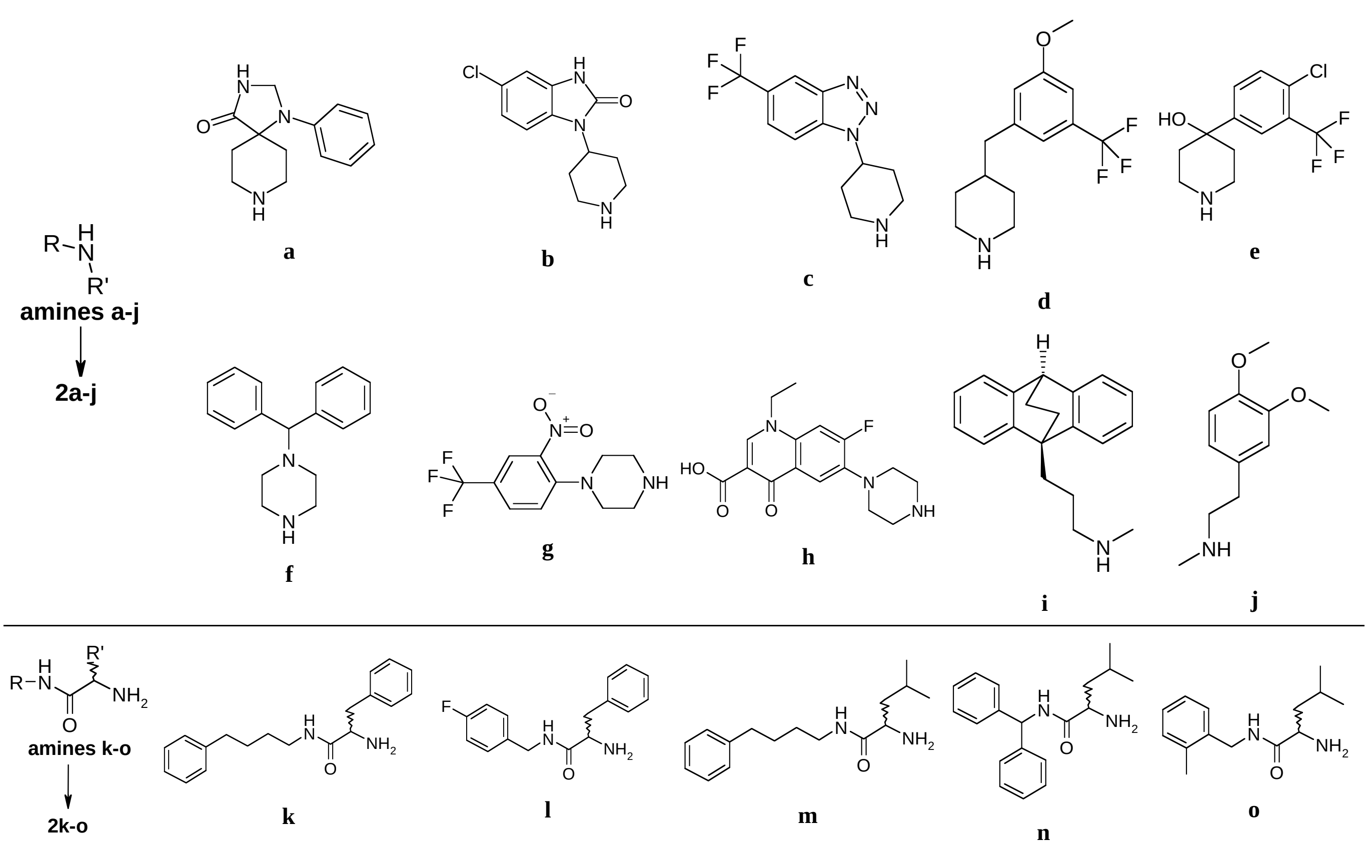


Fig. (6). Bio-inspired secondary amines and peptidomimetic primary amines.

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

The Need for New Zinc-Binding Groups (ZBG)

For some time, 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, NEP, carbonic anhydrase or more recently histone deacetylase [33-35] (Fig. **7**). When targeting metalloproteases, a ZBG is necessary to bind to the Zinc ion (Fig. **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 ligands. 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 (Fig. **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 in progress. ZBG can be classified in two classes as shown in Fig. **9**: 1) monodentate that include thiols, carboxylic acids, acidic heterocycles, phosphinic acids…; and 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].

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 (Fig. **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 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].

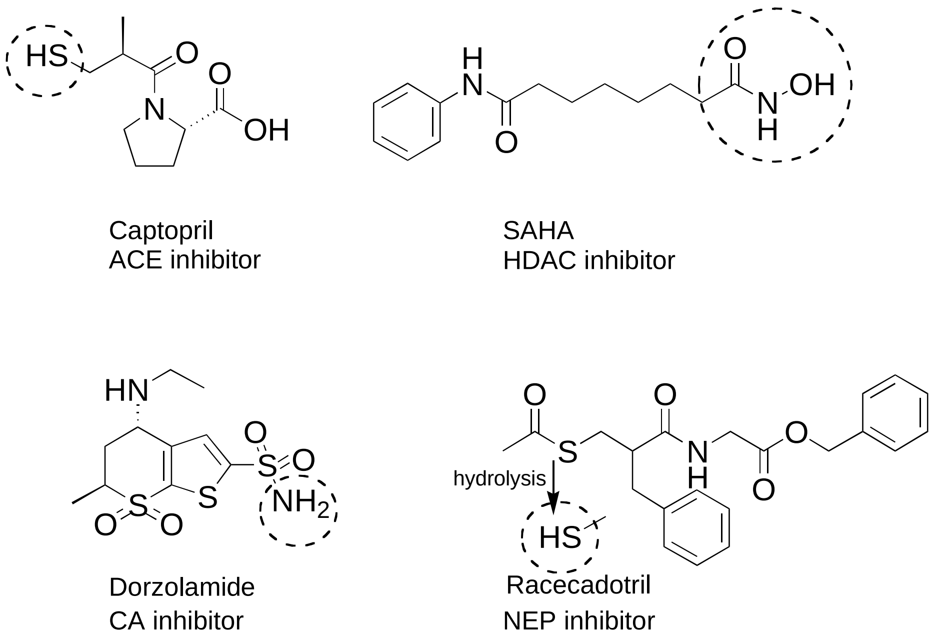


Fig. (7). Examples of inhibitors of Zinc hydrolases on the market (each ZBG is circled).

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].

[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.

[ix]Charton, J., Deprez-Poulain, R., Deprez, B. *Tetrahedron Lett*. submitted

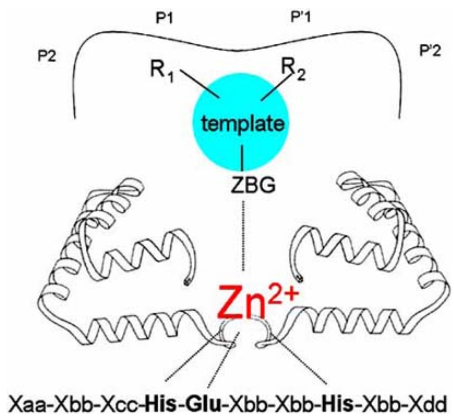


Fig. (8). Orientating role of the Zn ion in the catalytic site of Zn metalloproteases.

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.

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

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 AND CONCLUSIONS

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 factors for absorption, transport and excretion of

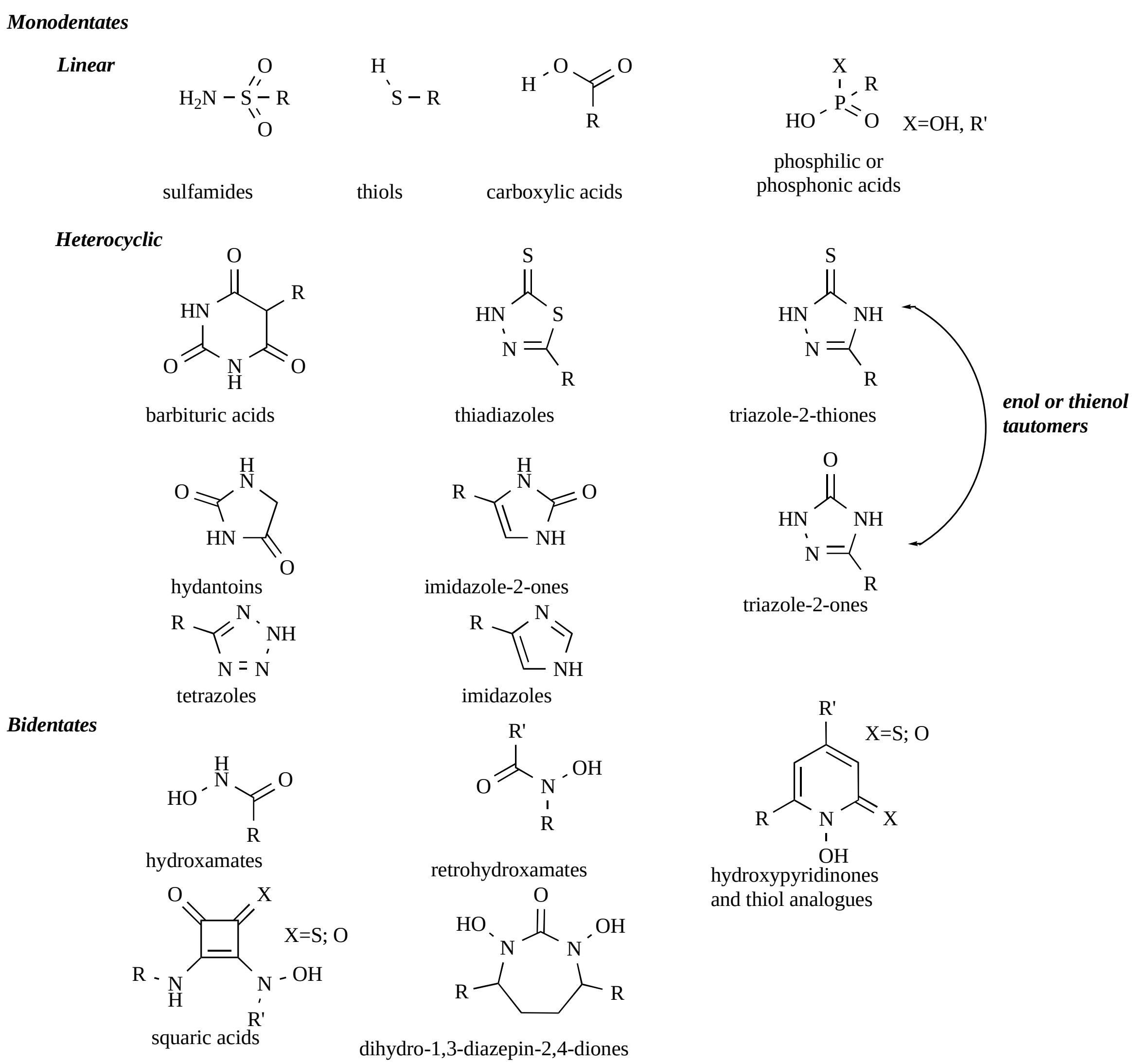


Fig. (9). Classical and non-classical ZBGs classified by the zinc-binding mode.

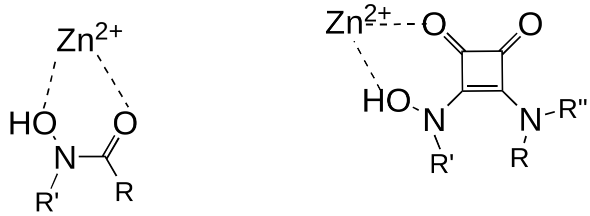
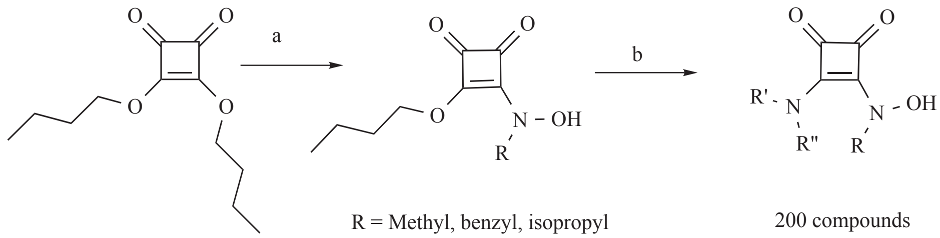


Fig. (10). Known binding mode of hydroxamic acid and putative binding mode by squaric acid derivatives A (6-membered zinc chelation model).



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 μmol), MeOH, room temp., 5 h.

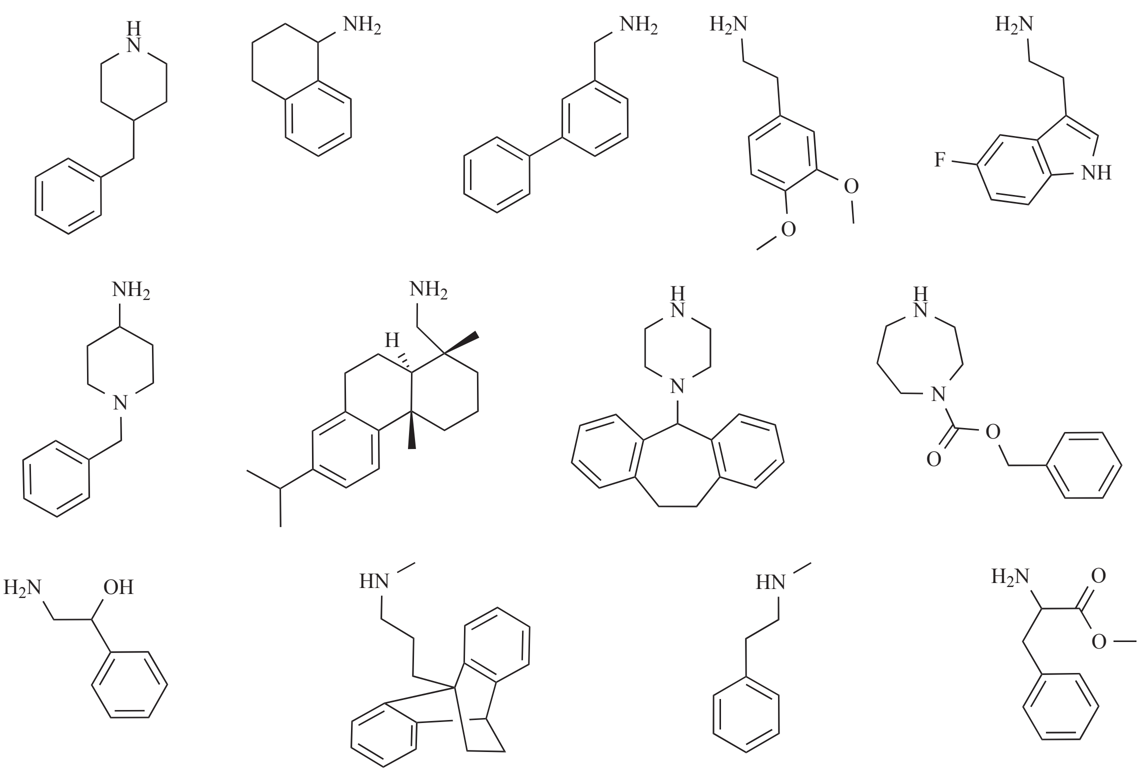


Fig. (11). Some prototypal primary and secondary amines of the library.

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

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

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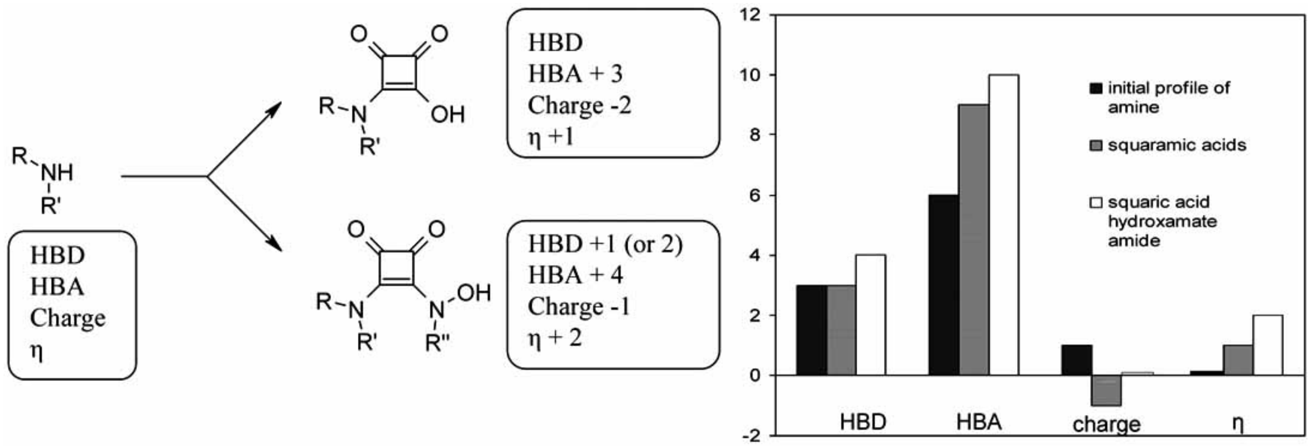

Fig. (12). Comparison of the initial physico-chemical profile of amines and squaric acid derivatives (η represents the hapticity of the potential Zn ligand).

REFERENCES

[1] Deprez-Poulain, R.; Deprez, B. *Frontiers Med. Chem.*, **2006**, *3*, 653-673.
[2] Nieto, M.J.; Philip, A.E.; Poupaert, J.H.; McCurdy, C.R. *J. Comb. Chem.*, **2005**, *7*, 258-263.
[3] Horton, D.A.; Bourne, G.T.; 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.; Deprez, B. *Tetrahedron Lett.*, **2004**, *45*, 5287. (b)Willand, N.; Beghyn, T.; Nowogrocki, G.; Gesquiere, J.-C.; Deprez, B. *Tetrahedron Lett.*, **2004**, *45*, 1051.
[6] Willand, N.; Folleas, B.; Boutillon, C.; Verbraeken, L.; Gesquiere, J.-C.; Tartar, A.; Deprez, B. *Tetrahedron Lett.*, **2007**, *48*, 5007.
[7] Horton, D.A.; Bourne, G.T.; Smythe, M.L. *Chem. Rev.*, **2003**, *103*, 893-930
[8] Wermuth, C.G. *Drug Discov. Today*, **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*, 4304-4307 c) Tevyashova, A.; Sztaricskai, F.; Batta, G.; Herczegh, P.; Jeney, A. *Bioorg. Med. Chem. Lett*., **2004**, *14*, 4783-4789. d) Xie J, Comeau, A.B.; Seto, C.T. *Org. Lett.*, **2004**, *6*, 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*, 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*, 4784-4787.
[18] Ishida, T.; Shinada, T.; Ohfune, Y. *Synthesis*, **2005**, 2723-2729. Ishida, T.; Shinada, T.; Ohfune, 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*, 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, 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, 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*, 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.; Fesik, S.W. *J. Med. Chem.*, **2000**, *43*, 3443-3447.
[26] Charton, J.; Cousaert, N.; Bochu, C.; Willand, N.; Deprez, B.; Deprez-Poulain, R. *Tetrahedron Lett.*, **2007**, *48*, 1479-1483.
[27] (a) Flipo, M.; Beghyn, T.; Charton, J.; Leroux, V.A.; Deprez, B.P.; Deprez-Poulain, R.F. *Bioorg. Med. Chem.*, **2007**, *15*, 63-76. (b) Flipo, M.; Beghyn, T.; Leroux, V.; Florent, I.; Deprez, B.P.; 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.; Bosch, J. *Chem. - A Eur. J.*, **2006**, *12*, 8198-8207.
[30] Newman, D.J.; Cragg, G.M.; Snader, K.M. *J. Nat. Prod.*, **2003**, *66*, 1022-1037.
[31] Mason, J.S.; Morize, I.; Menard, P.R.; Cheney, D.L.; Hulme, C.; Labaudiniere, R.F. *J. Med. Chem.*, **1999**, *42*, 3251-3264.
[32] Ortholand, J.-Y.; Ganesan, A. *Curr. Opin. Chem. Biol.*, **2004**, *8*, 271.
[33] Abbenante, G.; Fairlie, D.P. *Med. Chem.*, **2005**, *1*, 71-104.
[34] Supuran, C.T.; Casini, A.; Mastrolorenzo, A.; Scozzafava, A. *Mini Rev. Med. Chem.*, **2004**, *4*, 625-632.
[35] Grant, S.; Easley, C.; Kirkpatrick, P. *Nat. Rev. Drug Discov.*, **2007**, *6*, 21.
[36] Wen, S.; Carey, K. L.; Nakao, Y.; Fusetani, N.; Packham, G.; 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: Jacobsen, F.E., Lewis, J.A.; Cohen, S.M. *ChemMedChem.,* **2007**, *2*, 152-171.
[39] Puerta, D.T.; Lewis, J.A.; 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.; Duan, J.J. *Bioorg. Med. Chem. Lett.,* **2007**, *17*, 2769-2774.
[41] Park, H.; 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.

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