PROLINAMIDE CONTAINING DIAMIDES OF SQUARIC ACID - SYNTHESIS AND STRUCTURAL CHARACTERIZATION

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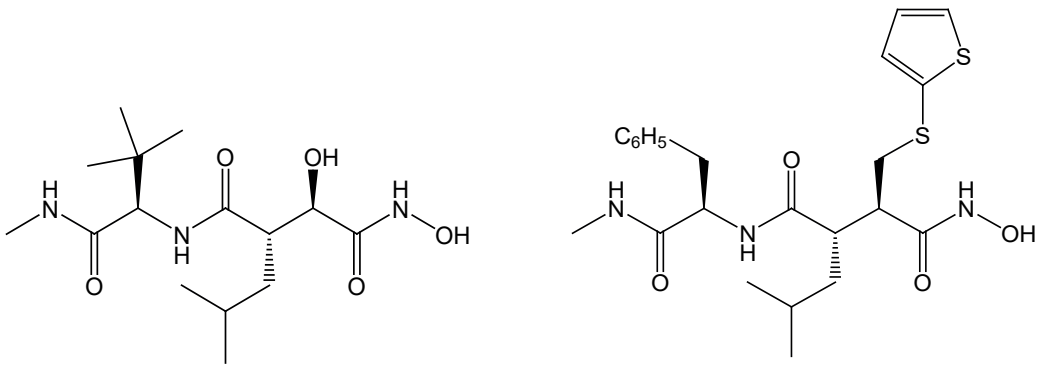
Abstract. A series of diamides of squaric acid bearing prolinamide fragment were synthesized by condensation reaction of prolinamide esteramide of squaric acid with different amino acid amides. Structures of the newly synthesized compounds were confirmed by elemental analyses, IR and ^{1}H NMR, ^{13}C NMR spectra. The investigation included theoretical study of the molecular structures of the compounds by a DFT method. The theoretical analysis showed that molecules of the compounds were stabilized by intramolecular hydrogen bonding.

Keywords: diamide of squaric acid, prolinamide, IR, DFT calculations;

Introduction

The matrix metalloproteinases (MMPs) are zinc-dependent neutral endopeptidases [1]. MMPs are thought to be essential for the diverse invasive processes of angiogenesis and tumor metastasis, therefore development of MMP inhibitors has generated considerable interest as a possible anticancer strategy [1-4]. Various MMP inhibitors were designed by maintaining the basic protein backbone of collagen and replacing the amide bond by a zinc-binding group, for instance marimastat and batimastat (Scheme 1) [5]. Both drugs are potent broad-spectrum inhibitors of all major MMPs and have been shown to prevent or reduce spread and growth of a number of different malignant tumors in numerous animal models [2].



I **II**

Scheme 1. Hydroxamate-based MMP inhibitors: marimastat **(I)** and batimastat **(II)**

All inhibitors containing a hydroxamate (-CONHOH) group that binds the zinc atom in the active site of the MMP enzyme are called hydroxamate-based MMP inhibitors. They have been extensively studied as small molecule drug candidates for anticancer therapy, but the toxicity risk associated with some hydroxamic acids and insufficient selectivity towards the enzyme targets implies the need of new modified hydroxamate-based MMP inhibitors. Hence, diverse MMP inhibitors are designed and synthesized by structural modifications of the hydroxamate zinc-binding group [6-9].

Amides of H_2Sq are considered as isosters of hydroxamic acid [10] and were studied as metal chelators for the inhibition of matrix metalloprotease enzymes [11-12]. A 200-member library of squaramides was recently synthesized and the screening of their potency against metalloprotease ADAMTS-5 led to the identification of two structurally related inhibitors with IC_{50} in low micromolar range [13].

This motivated us to synthesize a new series of squaric acid-peptide conjugates as potential MMP inhibitors. The structure of the peptide fragment of the inhibitors helps target them to the active site of zinc proteases [11], therefore we incorporated prolinamide and various other amino acid residues in the squramide structure. In order to get more information about their molecular structure the newly synthesized compounds were studied by theoretical methods.

Materials and Methods

General Information: Hydrochlorides of the amino acid amides were purchased from Bachem AG. Diethyl ester of squaric acid, ethanol and triethylamine were purchased from Sigma-Aldrich.

The IR spectra were measured on a Bruker Tensor 27 FTIR spectrometer.
In all cases the spectra were recorded at a resolution of 2 cm^{-1} (64 scans). The NMR spectra were recorded on a Bruker 600 spectrometer in solvent DMSO–d_6 using TMS as internal standard. Standard Bruker pulse sequences and software were used to record and process the spectra. The elemental analyses were carried out according to the standard procedures for C and H (as CO_2, and H_2O) and N (by the Dumas method). Thin layer chromatography (TLC) was performed on aluminum sheets pre-coated with Merck Kieselgel 60 F254 0.25 mm (Merck). All density functional theory (DFT) computations were performed with the Gaussian 09 program package [14] employing the B3LYP (Becke's three-parameter non-local exchange correlation functional) [15,16] and 6-311++G** basis set. Molinspiration software [17] was used to calculated parameters such as miLogP, topological polar surface area (TPSA), hydrogen bond donors and acceptors, rotatable bonds, number of atoms, molecular weight, and violations of Lipinski's rule of five.

Synthesis of prolinamide containing diamides of squaric acid

Aqueous ethanolic solution (1:4) of corresponding hydrochloride of amino acid amide (1 mmol) was mixed with exess of Et_3N (5 mmol) and the mixture was stirred for 10 minutes at room temperature. After that ethanol solution of prolinamide estermide of H_2Sq (1 mmol) was added. The mixture was stirred at room temperature to complete the reaction. The products were isolated by precipitation and purified by recrystallization.

3a: 1- [2 - (1 - Carbamoyl - 2 - methyl - propylamino) - 3,4 - dioxo-cyclobut - 1-enyl] - pyrrolidine - 2 - carboxylic acid amide
Mr = 308.3; Anal. Calcd. for $C_{14}H_{20}N_4O_4$ *(Pro/Val)*: C 54.5, H 6.5, N 18.1. Found: C 54.2, H 6.7, N 18.0;
^{1}H NMR (DMSO– d_6, 600 MHz), δ (ppm): 7.57 (s, 1H, NH_2), 7.51 (s, 1H, NH_2), 7.17(m, 3H, NH, NH_2), 4.67 (d, J= 6.8 Hz, 1H, CH), 4.52 (t, J= 8.1, 7.9 Hz, 1H, CH), 3.87 (s, 1H, CH_2), 3.71 (s, 1H, CH_2), 1.86 (m, 4H, $2CH_2$), 1.16 (m, 1H, CH), 0.92 (m, 6H, $2CH_3$);
^{13}C NMR (DMSO-d_6, 600 MHz), δ (ppm): 182.75, 182.15, 182.10, 173.21, 172.34, 172.24, 167.31, 166.68, 61.56, 56.03, 49.14, 30.37, 23.23, 19.00, 18.58, 17.91

3b: 1 - [2 - (1 - Carbamoyl - 2 - methyl - butylamino) - 3,4 - dioxo - cyclobut - 1 - enyl] - pyrrolidine - 2 - carboxylic acid amide
Mr = 322.4; Anal. Calcd. for $C_{15}H_{22}N_4O_4$ *(Pro/Ile):* C 55.8, H 6.8, N 17.3. Found: C 55.5, H 6.8, N 17.6
^{1}H NMR (DMSO– d_6, 600 MHz), δ (ppm): 7.50 (s, 2H, NH_2), 7.18 (d, J= 45.5 Hz, 2H, NH_2), 4.66 (q, J= 2.8, 5.6, 2.9 Hz, 1H, CH), 4.55 (t, J= 8.3, 8.2 Hz, 1H, CH), 3.85 (m, 1H, CH_2), 3.68 (s, 1H, CH_2), 2.14 (m, 1H, CH), 1.86 (m, 4H, $2CH_2$), 1.50 (s, 1H, CH), 1.15 (m, 1H, CH), 0.92 (m, 6H, $2CH_3$);
^{13}C NMR (DMSO-d_6, 600 MHz), δ (ppm): 182.69, 182.14, 173.22, 172.46, 167.21, 166.70, 166.66, 61.58, 61.55, 61.11, 49.15, 30.38, 24.07, 23.20, 15.14, 11.06;

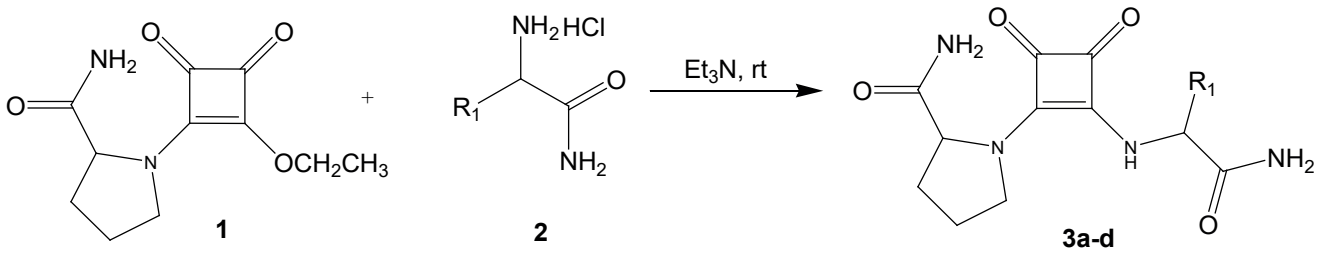
3c: 1 - [2 - (1 - Carbamoyl - 3 - methylsulfanyl - propylamino) - 3,4 - dioxo - cyclobut - 1 - enyl] - pyrrolidine - 2-carboxylic acid amide
Mr = 340.40; Anal. Calcd. for $C_{14}H_{20}N_4O_4S$ *(Pro/Met) (%):* C 49.4, H 5.9, N 16.4, S 9.4. Found: C 49.6, H 5.8, N 16.7, S 9.3;
^{13}C NMR (DMSO– d_6, 400 MHz), δ (ppm): 182.65, 182.25, 173.20, 172.14, 167.25, 166.93, 166.60, 60.73, 55.29, 49.20, 34.56, 30.25, 28.61, 25.03, 14.70

3d: 1 - {2 - [1 - Carbamoyl - 2 - (4 - hydroxy - phenyl) - ethylamino] - 3,4 - dioxo - cyclobut - 1 - enyl} - pyrrolidine - 2 - carboxylic acid amide
Mr = 372.4; Anal. Calcd. for $C_{18}H_{20}N_4O_5$ *(Pro/Tyr):* C 58.0, H 5.4, N 15.0. Found: 58.4, H 5.4, N 15.5
^{1}H NMR (DMSO– d_6, 600 MHz), δ (ppm): 9.40 (s, 1H, OH), 7.96 (s, 2H, NH_2), 7.50 (s, 2H, NH_2), 7.19 (s, 1H, NH), 7.05 (d, J= 8.4 Hz, 2H, Ar), 6.71 (d, J= 1.8 Hz, 2H, Ar) 4.50 (m, 2H, 2CH), 3.86 (t, J= 6.8, 6.6 Hz, 2H, CH_2), 2.88 (dd, J= 7.1, 6.8, 2H, CH_2), 1.18 (m, 4H, $2CH_2$)

The structures of the synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analyses. The results were consistent with the assigned structures.

Results and Discussion

Prolinamide containing diamides of squaric acid (H_2Sq) **3a-d** were prepared by condensation reaction of prolinamide esteramide of H_2Sq (**1**) and amino acid amides (**2**) under mild conditions according to Scheme 2. The synthesis, spectral and structural properties of prolinamide esteramide of squaric acid **1** were described by Kolev et al. [18].



Scheme 2. Synthesis of prolinamide containing diamides of H_2Sq **(3a-d)**

The products were isolated by precipitation and purified by recrystalization in high yields (Table 1).

Table1. Prolinamide diamides of squaric acid obtained according to the Scheme 2.

3	R_1	Reaction conditions*	Yield (%)	M.p. (°C)
a	$-CH(CH_3)_2$ (Val)	r.t, 36 h, $EtOH/H_2O$	84	260-262
b	$-CH(CH_3)CH_2CH_3$ (Ile)	r.t, 32 h, $EtOH/H_2O$	96	264-266
c	$-CH_2CH_2SCH_3$ (Met)	r.t, 24 h, $EtOH/H_2O$	80	oil
d	$-CH_2C_6H_4OH$ (Tyr)	r.t, 32 h, $EtOH/H_2O$	70	oil

*temperature, reaction time, solvent

Vibrational analysis

The most important vibrational frequencies for the elucidated compounds were the stretching vibrations of primary and secondary amino groups, $\nu^{as}C{=}O$, $\nu^{s}C{=}O$, $\nu C{=}C$ from the squaric fragment (Sq), Amide I($\nu C{=}O$), Amide II(δNH_2) and deformation vibrations of NH groups.

In the experimental IR spectra of the prolinamide containing diamides of H_2Sq stretching vibrations of NH_2 and NH groups were observed in the region region 3386-3100 cm^{-1} (Table2). The theoretical method predicts higher frequencies for these vibrations (3516-3320 cm^{-1}). This is due to the fact that the calculations were performed in gas phase, without taking into account intermolecular hydrogen bonding, while the IR spectra were measured in solid state, where the formation of hydrogen bonds is possible.

With regard to the bands belonging to the $\nu^{s}C{=}O$, $\nu^{as}C{=}O$, $\nu C{=}C$ of Sq, they were observed at 1800 cm^{-1}, 1700 cm^{-1} and 1590 cm^{-1} (theor.range -1780-1570 cm^{-1}). The Amide I band was shifted to higher frecuency – around 1683 cm^{-1} in comparison with Met-containing diamides of H_2Sq (1660-1670 cm^{-1}) [19]. Additionally, the Amide II band has an average intensity commensurate with this of the asymmetric stretching vibration of C=O groups from Sq fragment. The intensities of the remaining bands in the spectra of the prolinamide containing diamides of H_2Sq were similar to those obtained in the spectra of the Met-containing diamides of H_2Sq [18].

Table 2. Selected experimental vibrational frequencies (v in cm^{-1}) of **3a-d**

№	**Assignment**[a]	ν			
		3a	**3b**	**3c**	**3d**
1.	ν_{OH}	–	–	-	3460sh
2.	ν^{as}_{NH2}	3371;3320sh	3367; 3325sh	3368,3334	3386; 3336sh
3.	ν_{NH}	3251sh	3261	3272	3278
4.	ν^{s}_{NH2}	3191	3203; 3152sh	3172,3162	3212; 3203
5.	$\nu^{s}_{C=O(Sq)}$	1800	1799	1806	1797
6.	$\nu^{as}_{C=O(Sq)}$	1705	1704	1704	1704
7.	$\nu_{C=O}$ (Amide I)	1683; 1676	1683	1675,1660	1677
8.	$\nu_{C=C(Sq)}$	1586	1593; 1589	1590	1596
9.	δ_{NH2} (Amide II)	1654	1662	1654	1624sh
10.	δ_{NH}	1521	1518	1517	1513
11.	ρ_{NH}	1113; 1103	1122; 1097	1119,1090	1128; 1101

[a]Vibrational modes: v, stretching; δ, bending

NMR analysis

In ^{1}H NMR spectra of **3a-d**, NH and NH_2 protons appeared in the region 7.96-7.18 ppm. The chemical shift of the NCH_2 protons of prolinamide residue were observed as two signals at 3.87 and 3.71-3.68 ppm, in the case of **3d** there was only one signal at 3.86 ppm. The protons of the asymmetric carbon atoms were detected around 4.50 ppm as a triplet and 4.65 ppm as doublet to quintet. In the experimental ^{13}C NMR spectra the signals of the asymmetric carbon atoms were observed at 55-56 ppm and 61 ppm, similarly to those of Met-containing diamides. The signals for the C-atoms of the cyclobutene fragment and carbonyl C-atoms from amide moiety appeared around 167 ppm, 182 ppm and 172-173 ppm. The carbon atoms from C=C bond in diamides are shifted to higher fields than those of esteramides.

Computational analysis

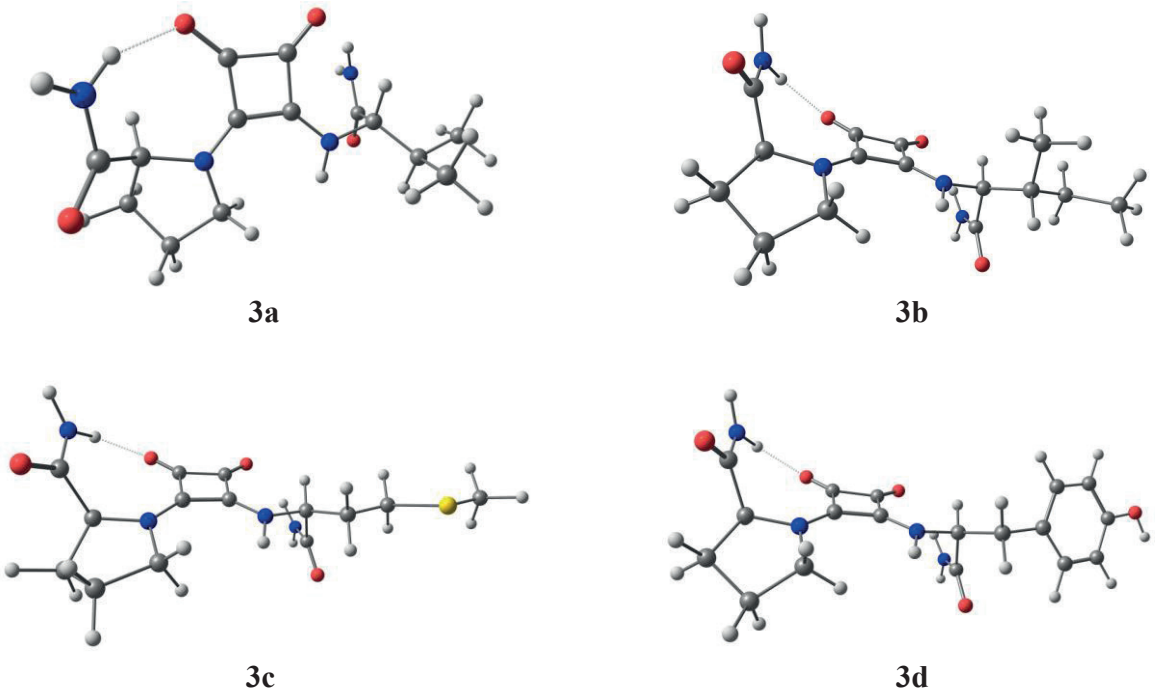
In order to characterize and understand the molecular structures of the newly synthesized diamides of H_2Sq computational analysis was performed. All the structures were optimized at the DFT level with B3LYP functional and 6-311++G** basis set. The optimized structures of the compounds **(3a-d)** are presented in Figure 1.

Theoretically found structural parameters for the prolinamide part and Sq fragment of the molecules were compared with the corresponding data from the X-ray analysis for prolinamide esteramide and diamide of H_2Sq [18]

and theoretical data for methioninamide containing diamides of H_2Sq [19].

The azacyclopentane ring has envelope conformation in which the amide group is in axial position relative to the pyrrolidine ring. The plane of squaramide and those of amide groups are almost perpendicularly oriented to each other in the investigated compounds.

Due to limited rotation around the C-N bond, the angle between the squaramide plane and those of the amide group of the proline residue is in the range 63-65°.



3a **3b**

3c **3d**

Figure 1. Molecular structure of prolinamide containing diamides of H_2Sq, optimized at DFT/B3LYP/6-311++G** level

The compounds are stabilized by intramolecular hydrogen bond between the NH_2 from amide group and C=O group from Sq fragment with a length of 2.93 Å and angle 154.9°. Similar results were obtained by X-ray studies of prolinamide esteramide and diamide of H_2Sq [18].

The compounds **(3a-d)** were characterized by bond lengths and angles similar to those found for prolinamide and methioninamide containing diamides of H_2Sq [18,19].

Comparing the theoretical results for the compounds **3a-d** with experimental data of the prolinamide esteramide and diamide of H_2Sq, it becomes apparent that the theoretical method predicts with particularly good accuracy the lengths of the C=O (theor. 1.21 Å, exp. 1.23Å) and C=C (theor. 1.41 Å, exp. 1.41 Å) bonds in the cyclobutene ring. The predicted distance of squaramide bond C-N that connects the Sq fragment to the prolinamide residue is 1.33 Å. In the experimentally studied prolinamide diamide of H_2Sq, this bond was slightly shorter – by 0.01Å.

Physico-chemical properties

For pharmacological application the studied compounds should be able to cross physiological barriers and to be quickly transported into the cells. For this reason, the physico-chemical properties of the studied compounds were assessed by calculating logP, molecular size, flexibility and the presence of hydrogen-donor and acceptors with a Molinspiration tool (Table 3) [17]. The method is very robust and is able to process practically all organic and organometa-

lic compounds. It enables the design of lots of compounds that can be screened and determines the most capable ones [20-22].

Table 3. Physico-chemical properties of synthesized compounds **3a-d** and prolinamide esteramide of squaric acid, calculated using Molinspiration tool

Compound	LogP < 5	MW <500	N_{ON}[a] <10	N_{OHNH}[b] <5	N_{rotb}[c]	N_{viol}[d]	Vol.[e]	TPSA
3a	0.49	308.3	8	5	6	0	276.1	135.6
3b	0.99	322.4	8	5	7	0	292.9	135.6
3c	0.16	340.4	8	5	8	0	294.4	135.6
3d	0.69	372.4	9	6	7	1	322.4	155.8
1	-0.01	238.2	6	2	4	0	209.0	89.7

[a]number of hydrogen-bond acceptors (O and N atoms); [b]number of hydrogen-bond donors (OH and NH groups); [c]number of rotatable bonds; [d] Number of "Rule of five" violations; [e] molecular volume; TPSA- topological surface area

LogP value is a measure of lipophilicity and it is used to predict the solubility of a potential drug. All compounds possesses low lipophilicity with values of logP < 1, therefore they will have a good solubility in water and other polar liquids as blood and blood plasma. The molecular weight gives information for the size of the molecules. The calculated molecular weight is between 308.3 and 372.4 and the molecules are suitable for drugs. The number of rotatable bonds and the number of hydrogen-bond acceptors and donors indicate sufficient solubility and permeability of the studied compounds. An important factor for the oral bioavailability as well as the efficient bonding of receptors and channels is the number of rotatable bonds. The diamides **3a-d** have 6 to 8 rotatable bonds which means that the molecules are flexible enough for oral bioavailability. Total polar surface area (TPSA) is a very good predictor for the oral bioavailability [23], drug transport properties such as intestinal absorption [24] and blood brain barrier penetration. The compounds **(3a-c)** show a TPSA of slightly less than 140 Å^2, indicating a good permeability in the cellular plasma. The diamide with hydroxyl group **(3d)** show TPSA slightly higher than 150 Å^2, which indicate that it might have poorer oral bioavailability through the membrane.

Conclusions

Through condensation reaction of amino acid amides and prolinamide esteramide of H_2Sq four new diamides of H_2Sq containing prolinamide residue were synthesized. The structures of the newly synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analyses. The molecular optimization showed that the plane of squaramide and those of amide groups were almost perpendicular to each other. The investigated compounds were characterized by bond lengths and angles similar to those found for the other diamides of H_2Sq. The calculated molecular properties indicate that compounds have a good solubility in water and other polar liquids as blood and blood plasma and a good permeability in the cellular plasma membrane.

Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication.

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