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Synthesis of the Substituted 3-Cyclobutene-1,2-diones

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Abstract: A convenient synthesis of the novel squaric acid derivatives is reported. Unsymmetrically substituted 3,4-diamino-3-cyclobutene-1,2-diones and 3-amino-4-hydroxy-3-cyclobutene-1,2-diones were prepared by interaction of diethyl squarate with different nucleophilic reagents such as alkali, primary and secondary amines and amino acids. Substituted 3-amino-4-aryl-3-cyclobutene-1,2-diones were synthesized by interaction of squaryl dichloride with different arenes followed by arylsquarylation of amines. Efficient procedures were developed for consequent substitution of ethoxy groups in diethyl squarate and chlorine atoms in squaryl dichloride. The synthesized compounds have a great potential of bioactivity and are useful objects for biomedicinal screening.

Keywords: Friedel-Crafts alkylation, squarates, squaric acid, squarylation

INTRODUCTION

The 3-cyclobutene-1,2-dione structural motif can be found in a large number of pharmaceutical agents with a diverse range of biological properties. The majority of bioactive 3-cyclobutene-1,2-diones are substituted 3,4-diamino

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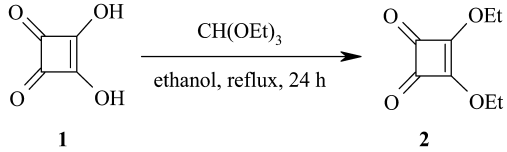
derivatives. They are documented as inhibitors of transactivation responsive RNA of HIV-1,[1] antagonists of VLA-4 integrin[2] and histamine H2,[3,4] K(ATP) channel activators[5] and NMDA antagonists.[6] Some squaric acid peptide conjugates were reported as inhibitors of matrix metalloprotease-1.[7] Ability of some 3-cyclobutene-1,2-diones to give colored complexes with transition metal cations causes their use as dyes[8] and chemosensors for iron (III).[9] A number of 3-aryl-3-cyclobutene-1,2-diones were described in literature as inhibitors of protein tyrosine phosphatases.[10] The 3-cyclobutene-1,2-dione fragment ("squaryl") containing substituted amino groups can be considered as a bioisostere of various fragments in amino acids.[1,2] Combination of squaryl and amino acid fragments can be very useful approach in the design of novel bioactive compounds.

In this article, we describe the results of our systematic studies in the area of synthesis and characterization of amino- and aryl-substituted 3-cyclobutene-1,2-diones.

As a part of our studies of chemistry of substituted 3-cyclobutene-1,2-diones, we explored two different approaches to the synthesis of the novel 3-cyclobutene-1,2-diones. The first approach features generation of diethyl squarate (**2**) from squaric acid (**1**) (Scheme 1) followed by interaction of the resulting diethyl squarate with different nucleophilic reagents (Schemes 2, 3). This approach leads to unsymmetrical 3,4-diamino derivatives.

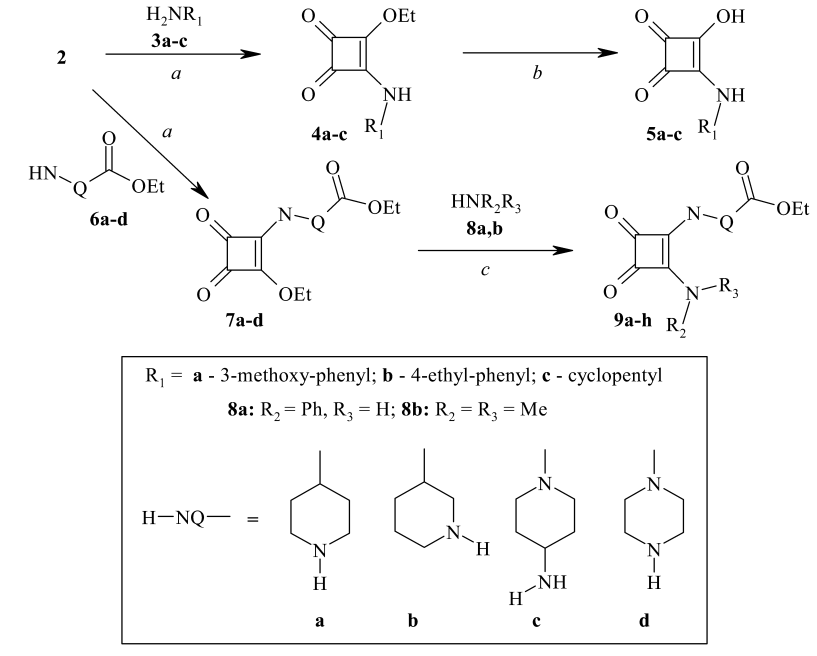
Diethyl squarate (**2**) was obtained by interaction of squaric acid (**1**) with triethyl orthoformate in a solution of boiling ethanol in 80% yield and served as a precursor for the synthesis of amino derivatives. Substitution of the first ethoxy group with amines (**3a**–**c**) proceeded in parallel in ethanol solution at room temperature for 24 h or with amino acid ethyl esters (**6a**–**d**) at the same reaction conditions. The resulting compounds (**4a**–**c**) were transformed into 3-substituted squaric acids (**5a**–**c**) by alkaline hydrolysis of the remaining ethoxy group. The hydrolysis proceeded in a water solution of NaOH at 90°C. The resulting solutions of the corresponding sodium salts were neutralized with hydrochloric acid to afford the desired acids (**5a**–**c**).

Ethyl ethers (**7a**–**d**) were used as precursors for the synthesis of the substituted squaryl diamines (**9a**–**h**) by interaction with amines (**8a,b**) in parallel. This interaction proceeds smoothly in alcohol solution in the presence of triethylamine (TEA) at room temperature. At higher temperature, the yields of the desired 3,4-diamino derivatives were decreased because of side reactions.

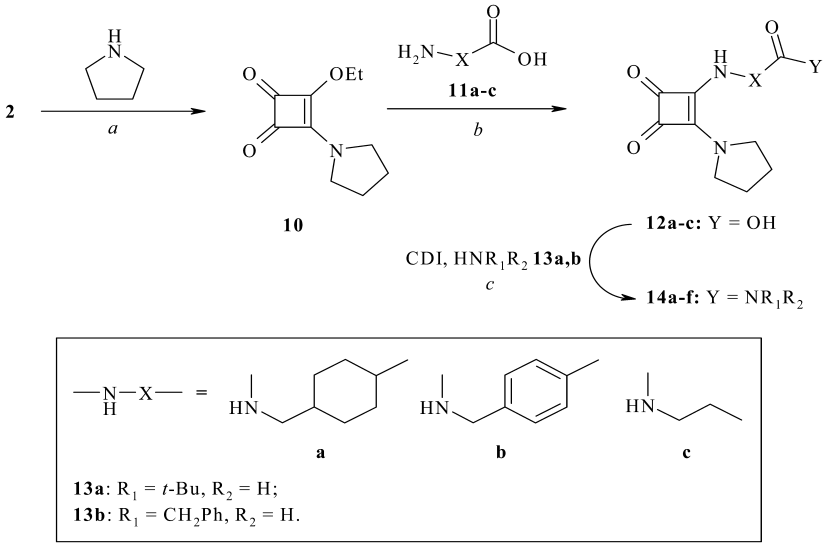


1 **2**

Scheme 1. Synthesis of 3,4-diethoxy-3-cyclobutene-1,2-dione.



Scheme 2. Substitution of ethoxy groups in 3,4-diethoxy-3-cyclobutene-1,2-dione with amines (*a*—ethanol, 20°C, 24 h; *b*—water, NaOH, 100°C, 15 min; *c*—TEA, ethanol, 20°C, 24 h).

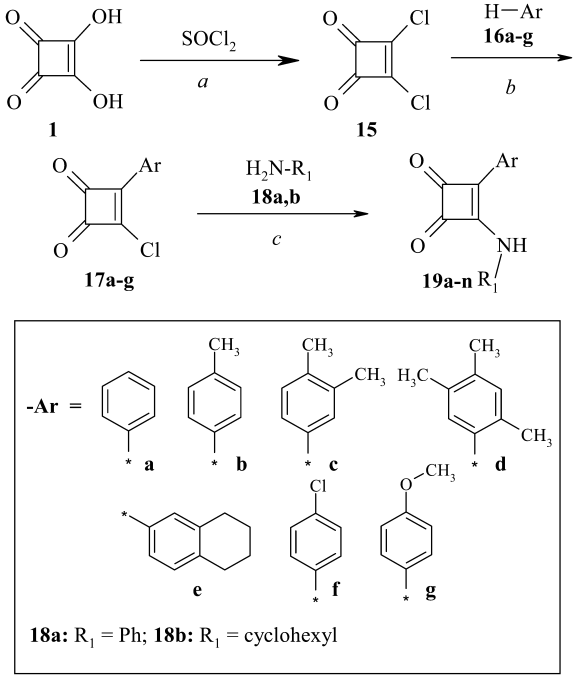


Scheme 3. Substitution of ethoxy group with amino acids (*a*—ethanol, 20°C, 24 h; *b*—TEA, ethanol, reflux, 24 h; *c*—dry DMF, reflux, 3 h).

Reaction of diethyl squarate (**2**) with pyrrolidine proceeded at the same reaction conditions as with primary amines (**3a–c**) and afforded compound (**10**). We explored its interaction with zwitterionic amino acids (**11a–c**) and developed an efficient procedure for preparation of the corresponding carboxylic acids (**12a–c**). The desired reaction products were obtained in good yields by reaction of **10** with amino acids (**11a–c**) in refluxing ethanol solution in the presence of TEA as a deprotonating agent for 24 h. The resulting acids (**12a–c**) were used as precursors for the synthesis of amides (**14a–f**) in parallel.

A second synthetic approach features transformation of squaric acid (**1**) to the corresponding dichloride, 3,4-dichloro-3-cyclobutene-1,2-dione (**15**), by treatment of squaric acid (**1**) with thionyl chloride under reflux for 2 h (Scheme 4). The resulting dichloro derivative (**15**) was used for squarylation of arenes (**16a–g**) in the presence of $AlCl_3$ in chloroform solution. The resulting chlorides (**17a–g**) were treated with amines (**18a,b**) in parallel to obtain the substituted 3-amino-4-aryl-3-cyclobutene-1,2-diones (**19a–n**), which are novel and useful objects for biomedicinal screening.

All the squaric acid derivatives within these series were characterized by ^{1}H NMR and LC MS analysis. The ^{1}H NMR spectra were clean, and mass



Scheme 4. Squarylation of arenes (*a*—reflux, 2 h; *b*—$AlCl_3$, chloroform, 10–20°C, 3 h; *c*—ethanol, 20°C, 24 h).

spectral data obtained on an liquid chromatography/mass spectrometry (LC/MS) instrument were also satisfactory. The suggested direction of the squarylation was confirmed by ^{1}H NMR spectral data.

EXPERIMENTAL

Melting points were measured with a Buchi B-520 melting-point apparatus and are not corrected. ^{1}H NMR spectra were recorded on Bruker DRX-500 spectroscope in DMSO-d_6 using TMS as an internal standard. LC MS spectra were recorded with PE SCIEX API 150EX liquid chromatograph equipped with a UV detector (λ_{max} 215 and 254 nm) and using a C_{18} column (100 × 4 mm). Elution started with water, ended with acetonitrile/water (95:5, v/v) and used a linear gradient at a flow rate of 0.15 mL/min and an analysis cycle time of 25 min.

3,4-Diethoxy-3-cyclobutene-1,2-dione (2) was obtained using the procedure introduced by Liu et al.[11]

General Procedure for Synthesis of 3-Amino-4-ethoxy-3-cyclobutene-1,2-diones (4a–c, 10)

A solution of 2 mmol of corresponding amine (**3a**–**c**) or pyrrolidine and 0.34 g (2 mmol) of diethyl squarate (**2**) in ethanol (5 mL) was stirred at room temperature for 24 h and then evaporated to dryness. The residue was treated with water; the white precipitate was collected by filtration, washed with diethyl ether, and dried to afford pure reaction product (**4a**–**c**, **10**).

3-Ethoxy-4-(3-methoxy-phenylamino)-3-cyclobutene-1,2-dione (**4a**)

This compound was obtained in 85% yield, mp 227–229°C (2-propanol). LC MS m/z 247 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 1.50 (t, 3H, J = 7.4 Hz, CH_3), 3.78 (s, 3H, OCH_3), 4.83 (q, 2H, J = 7.4 Hz, OCH_2), 6.55 (d, 1H, J = 8.1 Hz, ArH), 6.92–6.99 (m, 2H, ArH), 7.15 (dd, 1H, J_1 = 8.1 Hz, J_2 = 8.3 Hz, ArH), 10.57 (s, 1H, NH).

3-(Cyclopentylamino)-4-ethoxy-3-cyclobutene-1,2-dione (**4b**)

This compound was obtained in 78% yield, mp 90–92°C (2-propanol). LC MS m/z 209 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 1.41 (t, 3H, J = 7.4 Hz, CH_3), 1.72–1.78 (m, 8H, $4CH_2$), 3.92–4.02 (m, 1H, NCH), 4.65 (q, 2H, J = 7.4 Hz, OCH_2), 8.64 (d, 1H, J = 5.3 Hz, NH).

3-Ethoxy-4-(4-ethyl-phenylamino)-3-cyclobutene-1,2-dione (**4c**)

This compound was obtained in 92% yield, mp 192–195°C (2-propanol). LC MS m/z 245 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 1.21 (t, 3H, $J = 7.8$ Hz, CH_3), 1.48 (t, 3H, $J = 7.4$ Hz, CH_3), 2.52 (q, 2H, $J = 7.8$ Hz, $ArCH_2$), 4.80 (q, 2H, $J = 7.4$ Hz, OCH_2), 7.05 (d, 2H, $J = 7.3$ Hz, ArH), 7.22 (d, 2H, $J = 7.3$ Hz, ArH), 10.54 (s, 1H, NH).

3-Ethoxy-4-pyrrolidino-3-cyclobutene-1,2-dione (**10**)

This compound was obtained in 82% yield, mp 175–178°C (2-propanol). LC MS m/z 195 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 1.46 (t, 3H, $J = 7.4$ Hz, CH_3), 1.95–1.99 (m, 4H, $2CH_2$), 3.60–3.67 (m, 2H, NCH_2), 3.72–7.77 (m, 2H, NCH_2), 4.70 (q, 2H, $J = 7.4$ Hz, OCH_2).

General Procedure for Synthesis of 3-Amino-4-hydroxy-3-cyclobutene-1,2-diones (5a–c)

Compound (**4a–c**) (1 mmol) was suspended in a solution of NaOH (2.5 mmol) and ethanol (2 mL) in water (10 mL). The mixture was stirred at 90°C until the solid was completely dissolved. The resulting solution was cooled down to room temperature and acidified with 5% hydrochloric acid. The formed precipitate was collected by filtration, washed with water, dried, and crystallized from 1,4-dioxane to afford the pure reaction product (**5a–c**).

3-Hydroxy-4-(3-methoxy-phenylamino)-3-cyclobutene-1,2-dione (**5a**)

This compound was obtained in 75% yield, mp 275–277°C (2-propanol). LC MS m/z 219 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 3.78 (s, 3H, OCH_3), 6.55 (d, 1H, $J = 8.1$ Hz, ArH), 6.92–6.99 (m, 2H, ArH), 7.15 (dd, 1H, $J_1 = 8.1$ Hz, $J_2 = 8.3$ Hz, ArH), 10.57 (s, 1H, NH); OH is in exchange.

3-(Cyclopentylamino)-4-hydroxy-3-cyclobutene-1,2-dione (**5b**)

This compound was obtained in 79% yield, mp 180–183°C (2-propanol). LC MS m/z 181 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 1.72–1.78 (m, 8H, $4CH_2$), 3.92–4.02 (m, 1H, NCH), 8.64 (d, 1H, $J = 5.3$ Hz, NH); OH is in exchange.

3-(4-Ethyl-phenylamino)-4-hydroxy-3-cyclobutene-1,2-dione (**5c**)

This compound was obtained in 88% yield, mp 255–257°C (2-propanol). LC MS m/z 217 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 1.48 (t, 3H,

$J = 7.4$ Hz, CH_3), 2.52 (q, 2H, $J = 7.8$ Hz, $ArCH_2$), 7.05 (d, 2H, $J = 7.3$ Hz, ArH), 7.22 (d, 2H, $J = 7.3$ Hz, ArH), 10.54 (s, 1H, NH); OH is in exchange.

General Procedure for Synthesis of 4-Ethoxy-3-cyclobutene-1,2-dione-3-amino Acids Ethyl Ethers (7a–d)

A solution of 2 mmol of corresponding amino acid ethyl ether (**6a**–**d**) and 0.34 g (2 mmol) of diethyl squarate (**2**) in ethanol (5 mL) was stirred at room temperature for 24 h and then evaporated to dryness. The residue was treated with water; the white precipitate was collected by filtration, washed with diethyl ether, and dried to afford the pure reaction product (**7a**–**d**).

Ethyl 1-(2-Ethoxy-3,4-dioxo-cyclobut-1-enyl)-piperidine-4-carboxylate (**7a**)

This compound was obtained in 71% yield, mp 98–100°C (2-propanol). LC MS m/z 281 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 1.23 (t, 3H, $J = 7.4$ Hz, CH_3), 1.49 (t, 3H, $J = 6.8$ Hz, CH_3), 1.71–1.78 (m, 4H, $2CH_2$), 3.55–3.61 (m, 2H, NCH_2), 3.69–3.71 (m, 1H, CH) 3.82–3.88 (m, 2H, NCH_2), 4.04 (q, 2H, $J = 6.8$ Hz, OCH_2), 4.73 (q, 2H, $J = 7.4$ Hz, OCH_2).

Ethyl 1-(2-Ethoxy-3,4-dioxo-cyclobut-1-enyl)-piperidine-3-carboxylate (**7b**)

This compound was obtained in 69% yield, mp 94–97°C (2-propanol). LC MS m/z 281 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 1.23 (t, 3H, $J = 7.4$ Hz, CH_3), 1.48 (t, 3H, $J = 6.8$ Hz, CH_3), 1.67–1.72 (m, 4H, $2CH_2$), 3.55–3.61 (m, 2H, NCH_2), 3.65–3.69 (m, 1H, CH) 3.85–3.89 (m, 2H, NCH_2), 4.05 (q, 2H, $J = 6.8$ Hz, OCH_2), 4.73 (q, 2H, $J = 7.4$ Hz, OCH_2).

Ethyl 4-[(2-Ethoxy-3,4-dioxo-1-cyclobutenyl)amino]-piperidine-1-carboxylate (**7c**)

This compound was obtained in 69% yield, mp 102–104°C (2-propanol). LC MS m/z 296 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 1.25 (t, 3H, $J = 7.4$ Hz, CH_3), 1.47 (t, 3H, $J = 6.8$ Hz, CH_3), 1.55–1.59 (m, 2H, CH_2), 1.84–1.89 (m, 2H, CH_2), 2.95–3.02 (m, 2H, CH_2), 3.59–3.62 (m, 1H, NCH), 4.02–4.11 (m, 2H, CH_2), 4.06 (q, 2H, $J = 6.8$ Hz, OCH_2), 4.71 (q, 2H, $J = 7.4$ Hz, OCH_2), 8.82 (d, 1H, $J = 7.5$ Hz, NH).

Ethyl 4-(2-Ethoxy-3,4-dioxo-1-cyclobutenyl)-piperazine-1-carboxylate (**7d**)

This compound was obtained in 73% yield, mp 119–122°C (2-propanol). LC MS m/z 282 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 1.26 (t, 3H, $J = 7.2$ Hz, CH_3), 1.45 (t, 3H, $J = 6.8$ Hz, CH_3), 3.52–3.59 (m, 6H, $3CH_2$),

3.79–3.84 (m, 2H, CH_2), 4.08 (q, 2H, $J = 6.8$ Hz, OCH_2), 4.72 (q, 2H, $J = 7.2$ Hz, OCH_2).

General Procedure for Synthesis of 3-Amino-3-cyclobutene-1,2-dione-4-amino Acids Ethyl Ethers (9a–h)

Corresponding amine (**8a,b**) (1 mmol) was added to a solution of 1 mmol of compound (**7a–d**) and 0.17 mL (1.2 mmol) of TEA in 10 mL of ethanol. The mixture was stirred at room temperature for 24 h. The formed precipitate was collected by filtration, dried, and crystallized from a mixture of ethanol and hexane to afford the pure reaction product (**9a–h**).

Ethyl 1-(3,4-Dioxo-2-phenylamino-cyclobut-1-enyl)-piperidine-4-carboxylate (**9a**)

This compound was obtained in 81% yield, mp 205–207°C (2-propanol). LC MS m/z 328 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 1.48 (t, 3H, $J = 6.8$ Hz, CH_3), 1.71–1.78 (m, 4H, $2CH_2$), 3.55–3.61 (m, 2H, NCH_2), 3.69–3.71 (m, 1H, CH), 3.82–3.88 (m, 2H, NCH_2), 4.05 (q, 2H, $J = 6.8$ Hz, OCH_2), 7.51–7.57 (m, 5H, Ph), 10.11 (s, 1H, NH).

Ethyl 1-(2-Dimethylamino-3,4-dioxo-cyclobut-1-enyl)-piperidine-4-carboxylate (**9b**)

This compound was obtained in 78% yield, mp 198–200°C (2-propanol). LC MS m/z 280 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 1.49 (t, 3H, $J = 6.8$ Hz, CH_3), 1.71–1.78 (m, 4H, $2CH_2$), 3.52 (s, 6H, $2NCH_3$), 3.55–3.61 (m, 2H, NCH_2), 3.69–3.71 (m, 1H, CH) 3.82–3.88 (m, 2H, NCH_2), 4.05 (q, 2H, $J = 6.8$ Hz, OCH_2).

Ethyl 1-(3,4-Dioxo-2-phenylamino-cyclobut-1-enyl)-piperidine-3-carboxylate (**9c**)

This compound was obtained in 79% yield, mp 195–197°C (2-propanol). LC MS m/z 328 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 1.48 (t, 3H, $J = 6.8$ Hz, CH_3), 1.67–1.72 (m, 4H, $2CH_2$), 3.55–3.61 (m, 2H, NCH_2), 3.65–3.69 (m, 1H, CH), 3.85–3.89 (m, 2H, NCH_2), 4.05 (q, 2H, $J = 6.8$ Hz, OCH_2), 7.51–7.57 (m, 5H, Ph), 10.12 (s, 1H, NH).

Ethyl 1-(2-Dimethylamino-3,4-dioxo-cyclobut-1-enyl)-piperidine-4-carboxylate (**9d**)

This compound was obtained in 75% yield, mp 164–166°C (2-propanol). LC MS m/z 280 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 1.47 (t, 3H,

$J = 6.8$ Hz, CH_3), 1.67–1.72 (m, 4H, $2CH_2$), 3.54 (s, 6H, $2NCH_3$), 3.55–3.61 (m, 2H, NCH_2), 3.65–3.69 (m, 1H, CH) 3.85–3.89 (m, 2H, NCH_2), 4.08 (q, 2H, $J = 6.8$ Hz, OCH_2).

Ethyl 4-(3,4-Dioxo-2-phenylamino-cyclobut-1-enylamino)-piperidine-1-carboxylate (**9e**)

This compound was obtained in 84% yield, mp 237–239°C (2-propanol). LC MS m/z 343 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 1.46 (t, 3H, $J = 6.8$ Hz, CH_3), 1.55–1.59 (m, 2H, CH_2), 1.84–1.89 (m, 2H, CH_2), 2.95–3.02 (m, 2H, CH_2), 3.59–3.62 (m, 1H, NCH), 4.02–4.11 (m, 2H, CH_2), 4.09 (q, 2H, $J = 6.8$ Hz, OCH_2), 7.51–7.57 (m, 5H, Ph), 8.82 (d, 1H, $J = 7.5$ Hz, NH), 10.21 (s, 1H, NH).

Ethyl 4-(2-Dimethylamino-3,4-dioxo-cyclobut-1-enylamino)-piperidine-1-carboxylate (**9f**)

This compound was obtained in 77% yield, mp 221–224°C (2-propanol). LC MS m/z 295 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 1.47 (t, 3H, $J = 6.8$ Hz, CH_3), 1.55–1.59 (m, 2H, CH_2), 1.84–1.89 (m, 2H, CH_2), 2.95–3.02 (m, 2H, CH_2), 3.53 (s, 6H, $2NCH_3$), 3.59–3.62 (m, 1H, NCH), 4.02–4.11 (m, 2H, CH_2), 4.06 (q, 2H, $J = 6.8$ Hz, OCH_2), 8.82 (d, 1H, $J = 7.5$ Hz, NH).

Ethyl 4-(3,4-Dioxo-2-phenylamino-cyclobut-1-enyl)-piperazine-1-carboxylate (**9g**)

This compound was obtained in 87% yield, mp 287–289°C (2-propanol). LC MS m/z 329 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 1.47 (t, 3H, $J = 6.8$ Hz, CH_3), 3.52–3.59 (m, 6H, $3CH_2$), 3.79–3.84 (m, 2H, CH_2), 4.08 (q, 2H, $J = 6.8$ Hz, OCH_2), 7.51–7.57 (m, 5H, Ph), 10.12 (s, 1H, NH).

Ethyl 4-(2-Dimethylamino-3,4-dioxo-cyclobut-1-enyl)-piperazine-1-carboxylate (**9h**)

This compound was obtained in 81% yield, mp 263–267°C (2-propanol). LC MS m/z 281 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 1.47 (t, 3H, $J = 6.8$ Hz, CH_3), 3.50 (s, 6H, $2NCH_3$), 3.52–3.59 (m, 6H, $3CH_2$), 3.79–3.84 (m, 2H, CH_2), 4.08 (q, 2H, $J = 6.8$ Hz, OCH_2).

General Procedure for Synthesis of 3-Amino-3-cyclobutene-1,2-dione-4-amino Acids (12a–c)

Amino acid (**11a–c**) (0.11 mol) was added to a solution of compound (**10**) (0.1 mol) and 17 mL (0.12 mol) of TEA in 100 mL of ethanol. The reaction

mixture was refluxed for 24 h and then evaporated to dryness. The residue was treated with diethyl ether. The formed precipitate was collected by filtration and dried to afford pure reaction product (**12a–c**).

4-({[3,4-Dioxo-2-(1-pyrrolidinyl)-1-cyclobutenyl]amino}methyl)-1-cyclohexanecarboxylic Acid (**12a**)

This compound was obtained in 81% yield, mp 278–282°C (2-propanol). LC MS m/z 306 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 0.95–1.11 (m, 2H, CH_2), 1.32–1.42 (m, 2H, CH_2), 1.87–1.93 (m, 8H, $4CH_2$), 2.06–2.12 (m, 1H, CH), 3.38–3.43 (m, 2H, NCH_2), 3.69–3.74 (m, 4H, $2NCH_2$), 7.35 (t, 1H, $J = 5.1$ Hz, NH), 11.62 (s, 1H, COOH).

4-[(2-Pyrrolidino-3,4-dioxo-1-cyclobutenyl)amino]methylbenzoic Acid (**12b**)

This compound was obtained in 64% yield, mp 232–234°C (2-propanol). LC MS m/z 302 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 1.65–1.71 (m, 4H, $2CH_2$), 4.08–4.13 (m, 4H, $2CH_2$), 4.84 (d, 2H, $J = 6.2$ Hz, NCH_2), 7.40 (d, 2H, $J = 7.3$ Hz, ArH), 7.92 (d, 2H, $J = 7.3$ Hz, ArH), 7.95 (t, 1H, $J = 6.2$ Hz, NH); OH is in exchange.

3-(3,4-Dioxo-2-pyrrolidin-1-yl-cyclobut-1-enylamino)-propionic Acid (**12c**)

This compound was obtained in 71% yield, mp 212–215°C (2-propanol). LC MS m/z 238 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 1.60–1.70 (m, 4H, $2CH_2$), 4.02 (t, 2H, $J = 5.3$ Hz, CH_2), 4.06–4.11 (m, 4H, $2CH_2$), 4.15 (m, 2H, NCH_2), 7.35 (t, 1H, $J = 5.0$ Hz, NH); OH is in exchange.

General Procedure for Synthesis of 3-Amino-3-cyclobutene-1,2-dione-4-amino Acids Amides (14a–f)

Acid (**12a–c**) (1 mmol) was added to a solution of CDI (1 mmol) in dry DMF (5 mL). The mixture was stirred at 80°C for 1 h. Then corresponding amine (**13a,b**) (1 mmol) was added to the reaction mixture. The solution was refluxed for 2 h, cooled down to room temperature, and poured into water. The formed precipitate was collected by filtration, washed with water, dried, and purified by crystallization from a mixture of ethanol and DMF to afford pure reaction product (**14a–f**).

4-[(3,4-Dioxo-2-pyrrolidin-1-yl-cyclobut-1-enylamino)-methyl]-cyclohexanecarboxylic acid *tert*-butylamide (**14a**)

This compound was obtained in 45% yield, mp 245–247°C (2-propanol). LC MS m/z 361 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 0.95–1.11

(m, 2H, CH_2), 1.32–1.42 (m, 2H, CH_2), 1.78 (s, 9H, $3CH_3$), 1.87–1.93 (m, 8H, $4CH_2$), 2.06–2.12 (m, 1H, CH), 3.38–3.43 (m, 2H, NCH_2), 3.69–3.74 (m, 4H, $2NCH_2$), 7.35 (t, 1H, $J = 5.1$ Hz, NH), 8.11 (s, 1H, NH).

4-[(3,4-Dioxo-2-pyrrolidin-1-yl-cyclobut-1-enylamino)-methyl]-cyclohexanecarboxylic Acid Benzylamide (**14b**)

This compound was obtained in 53% yield, mp 259–261°C (2-propanol). LC MS m/z 395 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 0.95–1.11 (m, 2H, CH_2), 1.32–1.42 (m, 2H, CH_2), 1.87–1.93 (m, 8H, $4CH_2$), 2.06–2.12 (m, 1H, CH), 3.38–3.43 (m, 2H, NCH_2), 3.69–3.74 (m, 4H, $2NCH_2$), 4.83 (d, 2H, $J = 6.1$ Hz, NCH_2), 7.35 (t, 1H, $J = 5.1$ Hz, NH), 7.50–7.54 (m, 5H, Ph), 7.97 (t, 1H, $J = 6.1$ Hz, NH).

N-tert-Butyl-4-[(3,4-dioxo-2-pyrrolidin-1-yl-cyclobut-1-enylamino)-methyl]-benzamide (**14c**)

This compound was obtained in 62% yield, mp 221–223°C (2-propanol). LC MS m/z 355 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 1.65–1.71 (m, 4H, $2CH_2$), 1.78 (s, 9H, $3CH_3$), 4.08–4.13 (m, 4H, $2CH_2$), 4.84 (d, 2H, $J = 6.2$ Hz, NCH_2), 7.40 (d, 2H, $J = 7.3$ Hz, ArH), 7.92 (d, 2H, $J = 7.3$ Hz, ArH), 7.95 (t, 1H, $J = 6.2$ Hz, NH), 8.13 (s, 1H, NH).

N-Benzyl-4-[(3,4-dioxo-2-pyrrolidin-1-yl-cyclobut-1-enylamino)-methyl]-benzamide (**14d**)

This compound was obtained in 67% yield, mp 234–237°C (2-propanol). LC MS m/z 389 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 1.65–1.71 (m, 4H, $2CH_2$), 4.08–4.13 (m, 4H, $2CH_2$), 4.81 (d, 2H, $J = 6.1$ Hz, NCH_2), 4.84 (d, 2H, $J = 6.2$ Hz, NCH_2), 7.40 (d, 2H, $J = 7.3$ Hz, ArH), 7.50–7.54 (m, 5H, Ph), 7.92 (d, 2H, $J = 7.3$ Hz, ArH), 7.95 (t, 1H, $J = 6.2$ Hz, NH), 7.97 (t, 1H, $J = 6.1$ Hz, NH).

N-tert-Butyl-3-(3,4-dioxo-2-pyrrolidin-1-yl-cyclobut-1-enylamino)-propionamide (**14e**)

This compound was obtained in 53% yield, mp 211–213°C (2-propanol). LC MS m/z 293 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 1.65–1.71 (m, 4H, $2CH_2$), 1.78 (s, 9H, $3CH_3$), 4.02 (t, 2H, $J = 5.3$ Hz, CH_2), 4.08–4.13 (m, 4H, $2CH_2$), 4.15 (m, 2H, NCH_2), 7.35 (t, 1H, $J = 5.0$ Hz, NH), 8.10 (s, 1H, NH).

N-Benzyl-3-(3,4-dioxo-2-pyrrolidin-1-yl-cyclobut-1-enylamino)-propionamide (**14f**)

This compound was obtained in 57% yield, mp 231–233°C (2-propanol). LC MS m/z 327 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 1.65–1.71 (m, 4H, $2CH_2$), 4.02 (t, 2H, $J = 5.3$ Hz, CH_2), 4.08–4.13 (m, 4H, $2CH_2$), 4.15 (m, 2H, NCH_2), 4.81 (d, 2H, $J = 6.1$ Hz, NCH_2), 7.35 (t, 1H, $J = 5.0$ Hz, NH), 7.50–7.54 (m, 5H, Ph), 7.99 (t, 1H, $J = 6.1$ Hz, NH).

3,4-Dichloro-3-cyclobutene-1,2-dione (**15**) was obtained using the procedure introduced by Masatomi et al.[12]

General Procedure for Synthesis of 3-Aryl-4-chloro-3-cyclobutene-1,2-diones (17a–g)

Compound (**16a–g**) (0.1 mol) was added to a solution of 1.51 g (0.1 mol) of compound (**15**) in 10 mL of dry chloroform. The mixture was cooled down to 10°C. Then 13.4 g (0.1 mol) of anhydrous $AlCl_3$ was added to the reaction mixture. The suspension was stirred at room temperature for 3 h and then poured onto crushed ice. The formed precipitate was extracted with chloroform (three portions per 15 mL). The organic layers were combined, dried over $CaCl_2$, and evaporated to dryness. The residue was treated with diethyl ether, collected by filtration, and dried to afford reaction product (**17a–g**) in 70–80% yields.

General Procedure for Synthesis of 3-Amino-4-aryl-3-cyclobutene-1,2-diones (19a–n)

Compound (**17a–g**) (1 mmol) was added to a solution of corresponding amine (**18a,b**) (1 mmol) and TEA (1.2 mmol) in dioxane (3 mL) at 0–5°C under stirring. The mixture was stirred at 45–50°C for 4 h, cooled down to room temperature, and poured into water. The formed precipitate was collected by filtration, washed with water, dried, and purified by crystallization from a mixture of ethanol and DMF to afford pure reaction product (**19a–n**).

3-Phenyl-4-phenylamino-cyclobut-3-ene-1,2-dione (**19a**)

This compound was obtained in 78% yield, mp 177–179°C (2-propanol). LC MS m/z 249 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 7.51–7.54 (m, 5H, Ph), 7.58–7.61 (m, 5H, Ph), 10.12 (s, 1H, NH).

3-Cyclohexylamino-4-phenyl-cyclobut-3-ene-1,2-dione (**19b**)

This compound was obtained in 72% yield, mp 157–159°C (2-propanol). LC MS m/z 255 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 0.95–1.11

(m, 2H, CH_2), 1.32–1.44 (m, 8H, $4CH_2$), 3.59–3.62 (m, 1H, NCH), 7.51–7.54 (m, 5H, Ph), 8.54 (d, 1H, $J = 5.8$ Hz, NH).

3-Phenylamino-4-*p*-tolyl-cyclobut-3-ene-1,2-dione (**19c**)

This compound was obtained in 81% yield, mp 197–199°C (2-propanol). LC MS m/z 263 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 1.87 (s, 3H, CH_3), 7.13 (d, 2H, $J = 8.2$ Hz, ArH), 7.50–7.58 (m, 5H, Ph), 7.65 (d, 2H, $J = 8.2$ Hz, ArH), 10.12 (s, 1H, NH).

3-Cyclohexylamino-4-*p*-tolyl-cyclobut-3-ene-1,2-dione (**19d**)

This compound was obtained in 74% yield, mp 155–158°C (2-propanol). LC MS m/z 269 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 0.95–1.11 (m, 2H, CH_2), 1.32–1.44 (m, 8H, $4CH_2$), 1.87 (s, 3H, CH_3), 3.59–3.62 (m, 1H, NCH), 7.13 (d, 2H, $J = 8.2$ Hz, ArH), 7.65 (d, 2H, $J = 8.2$ Hz, ArH), 8.54 (d, 1H, $J = 5.8$ Hz, NH).

3-(3,4-Dimethyl-phenyl)-4-phenylamino-cyclobut-3-ene-1,2-dione (**19e**)

This compound was obtained in 71% yield, mp 151–153°C (2-propanol). LC MS m/z 277 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 1.86 (s, 3H, CH_3), 1.89 (s, 3H, CH_3), 6.95 (d, 1H, $J = 8.1$ Hz, ArH), 7.36 (s, 1H, ArH), 7.50–7.58 (m, 5H, Ph), 7.80 (d, 1H, $J = 8.1$ Hz, ArH), 10.21 (s, 1H, NH).

3-Cyclohexylamino-4-(3,4-dimethyl-phenyl)-cyclobut-3-ene-1,2-dione (**19f**)

This compound was obtained in 68% yield, mp 164–167°C (2-propanol). LC MS m/z 283 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 0.95–1.11 (m, 2H, CH_2), 1.32–1.44 (m, 8H, $4CH_2$), 1.86 (s, 3H, CH_3), 1.89 (s, 3H, CH_3), 3.62 (m, 1H, NCH), 6.95 (d, 1H, $J = 8.1$ Hz, ArH), 7.36 (s, 1H, ArH), 7.80 (d, 1H, $J = 8.1$ Hz, ArH), 8.54 (d, 1H, $J = 5.8$ Hz, NH).

3-Phenylamino-4-(2,4,5-trimethyl-phenyl)-cyclobut-3-ene-1,2-dione (**19g**)

This compound was obtained in 67% yield, mp 193–195°C (2-propanol). LC MS m/z 291 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 1.86 (s, 6H, $2CH_3$), 1.89 (s, 3H, CH_3), 6.95 (s, 1H, ArH), 7.36 (s, 1H, ArH), 7.50–7.58 (m, 5H, Ph), 10.18 (s, 1H, NH).

3-Cyclohexylamino-4-(2,4,5-trimethyl-phenyl)-cyclobut-3-ene-1,2-dione (**19h**)

This compound was obtained in 62% yield, mp 171–173°C (2-propanol). LC MS m/z 297 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 0.95–1.11

(m, 2H, CH_2), 1.32–1.44 (m, 8H, $4CH_2$), 1.86 (s, 6H, $2CH_3$), 1.89 (s, 3H, CH_3), 3.62 (m, 1H, NCH), 6.95 (s, 1H, ArH), 7.36 (s, 1H, ArH), 8.54 (d, 1H, $J = 5.8$ Hz, NH).

3-Phenylamino-4-(5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclobut-3-ene-1,2-dione (**19i**)

This compound was obtained in 58% yield, mp 161–162°C (2-propanol). LC MS m/z 303 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 1.77–1.82 (m, 4H, $2CH_2$), 2.20–2.26 (m, 2H, CH_2), 2.55–2.59 (m, 2H, CH_2), 6.50 (dd, 1H, $J_{3-4} = 6.7$ Hz, $J_{3-1} = 0.8$ Hz, ^{3}CH), 6.77 (d, 1H, $J_{4-3} = 6.7$ Hz, ^{4}CH), 6.96 (d, 1H, $J_{1-3} = 0.8$ Hz, ^{1}CH), 7.50–7.58 (m, 5H, Ph), 10.22 (s, 1H, NH).

3-Cyclohexylamino-4-(5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclobut-3-ene-1,2-dione (**19j**)

This compound was obtained in 51% yield, mp 142–145°C (2-propanol). LC MS m/z 309 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 0.95–1.11 (m, 2H, CH_2), 1.32–1.44 (m, 8H, $4CH_2$), 1.77–1.82 (m, 4H, $2CH_2$), 2.20–2.26 (m, 2H, CH_2), 2.55–2.59 (m, 2H, CH_2), 3.62 (m, 1H, NCH), 6.50 (dd, 1H, $J_{3-4} = 6.7$ Hz, $J_{3-1} = 0.8$ Hz, ^{3}CH), 6.77 (d, 1H, $J_{4-3} = 6.7$ Hz, ^{4}CH), 6.96 (d, 1H, $J_{1-3} = 0.8$ Hz, ^{1}CH), 8.54 (d, 1H, $J = 5.8$ Hz, NH).

3-(4-Chloro-phenyl)-4-phenylamino-cyclobut-3-ene-1,2-dione (**19k**)

This compound was obtained in 84% yield, mp 201–203°C (2–propanol). LC MS m/z 283 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 7.13 (d, 2H, $J = 8.0$ Hz, ArH), 7.50–7.58 (m, 5H, Ph), 8.12 (d, 2H, $J = 8.0$ Hz, ArH), 10.24 (s, 1H, NH).

3-(4-Chloro-phenyl)-4-cyclohexylamino-cyclobut-3-ene-1,2-dione (**19l**)

This compound was obtained in 74% yield, mp 197–199°C (2-propanol). LC MS m/z 289 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 0.95–1.11 (m, 2H, CH_2), 1.32–1.44 (m, 8H, $4CH_2$), 3.59–3.62 (m, 1H, NCH), 7.12 (d, 2H, $J = 8.2$ Hz, ArH), 8.11 (d, 2H, $J = 8.2$ Hz, ArH), 8.53 (d, 1H, $J = 5.8$ Hz, NH).

3-(4-Methoxy-phenyl)-4-phenylamino-cyclobut-3-ene-1,2-dione (**19m**)

This compound was obtained in 71% yield, mp 200–203°C (2-propanol). LC MS m/z 279 (M + 1); ^{1}H NMR (500 MHz, DMSO-d_6): 3.97 (s, 3H,

CH_3), 7.13 (d, 2H, $J = 8.2$ Hz, ArH), 7.50–7.58 (m, 5H, Ph), 8.42 (d, 2H, $J = 8.2$ Hz, ArH), 10.12 (s, 1H, NH).

3-Cyclohexylamino-4-(4-methoxy-phenyl)-cyclobut-3-ene-1,2-dione (**19n**)

This compound was obtained in 69% yield, mp 185–187°C (2-propanol). LC MS m/z 285 $(M + 1)$; ^{1}H NMR (500 MHz, DMSO-d_6): 0.95–1.11 (m, 2H, CH_2), 1.32–1.44 (m, 8H, $4CH_2$), 3.96 (s, 3H, CH_3), 3.59–3.62 (m, 1H, NCH), 7.13 (d, 2H, $J = 8.2$ Hz, ArH), 7.65 (d, 2H, $J = 8.2$ Hz, ArH), 8.54 (d, 1H, $J = 5.8$ Hz, NH).

REFERENCES

1. Lee, C. W.; Cao, H.; Ichiyama, K.; Rana, T. M. Design and synthesis of a novel peptidomimetic inhibitor of HIV-1 Tat-TAR interactions: Squaryldiamide as a new potential bioisostere of unsubstituted guanidine. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4243–4246.
2. Porter, J. R.; Archibald, S. C.; Childs, K.; Critchley, D.; Head, J. S.; Linsley, J. M.; Parton, T. A.; Robinson, M. K.; Shock, A.; Taylor, R. J.; Warrellow, G. J.; Alexander, R. P.; Langham, B. Squaric acid derivatives as VLA-4 integrin antagonists. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1051–1054.
3. Cavanagh, R. L. BMY-25368. *Drugs Fut.* **1985**, *10*, 890.
4. Prous, J.; Castañer, J. IT-066. *Drugs Fut.* **1990**, *15*, 1181.
5. 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. Design and SAR of novel potassium channel openers targeted for urge urinary incontinence, 2: Selective and potent benzylamino cyclobutenediones. *J. Med. Chem.* **2000**, *43*, 1203–1214.
6. Kinney, W. A.; Abou-Gharbia, M.; Garrison, D. T.; Schmid, J.; Kowal, D. M.; Bramlett, D. R.; Miller, T. L.; Tasse, R. P.; Zaleska, M. M.; Moyer, J. A. Design and synthesis of [2-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)-ethyl]phosphonic acid (EAA-090), a potent N-methyl-D-aspartate antagonist, via the use of 3-cyclobutene-1,2-dione as an achiral alpha-amino acid bioisostere. *J. Med. Chem.* **1998**, *41*, 236–246.
7. Onaran, M. B.; Comeau, A. B.; Seto, C. T. Squaric acid-based peptidic inhibitors of matrix metalloprotease—1. *J. Org. Chem.* **2005**, *70*, 10792–10802.
8. Yagi, S.; Fujie, Y.; Hyodo, Y.; Nakazumi, H. Synthesis, structure, and complexation properties with transition metal cations of a novel methine-bridged bisquarylium dye. *Dyes Pigm.* **2002**, *52*, 245–252.
9. Lim, N. C.; Morton, M. D.; Jenkins, H. A.; Brückner, C. Squaric acid *N*-hydroxylamides: Synthesis, structure, and properties of vinylogous hydroxamic acid analogues. *J. Org. Chem.* **2003**, *68*, 9233–9241.
10. Xie, J.; Comeau, A. B.; Seto, C. T. Squaric acids: A new motif for designing inhibitors of protein tyrosine phosphatases. *Org. Lett.* **2004**, *6*, 83–86.
11. Liu, H.; Tomooka, C. S.; Moore, H. W. An efficient general synthesis of squarate esters. *Synth. Commun.* **1997**, *27*, 2177–2180.

12. Masatomi, O.; Yoshihiko, Y.; Yuhichi, S.; Shoji, E. Synthesis of squaric acid derivatives by Lewis acid-catalysed reaction of its dichloride, methyl ester chloride, diethylamide chloride, and ethyl diester with unsaturated organosilanes: New method for C-C bond formation on cyclobutenedione. *J. Chem. Soc., Perkin Trans. 1* **1993**, *2*, 263–271.