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Transamidation reactions of 2-(2-sulfonylguanidino)acetamides

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Dedicated to Professor Ramón Mestres on occasion of his retirement

Abstract—The reactivity of a series of sulfonylguanidinoacetamides **2A–E** towards amines is reported. Guanidinoacetamides **2A–C**, containing the arylsulfonylimino moiety, undergo a facile transamidation to give substituted carboxamides **4A–C**, through the imidazolidinone intermediate **3**. Acetamide **2D**, having a methanesulfonylimino substituent, affords the imidazolidinone **3D** and no transamidated carboxamides **4** are detected. In the case of guanidinoacetamide **2E**, with a *p*-nitrobenzenesulfonylimino substituent, a Smiles rearrangement was observed.
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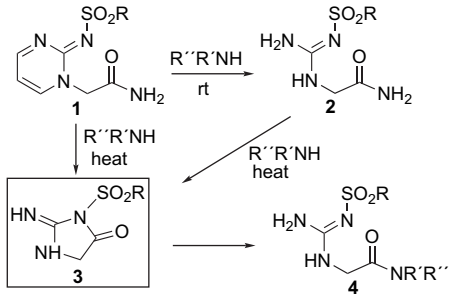
1. Introduction

In a previous paper[1] we reported that 1,2-dihydro-2-tosyliminopyrimidine **1A** undergoes a facile ring cleavage with primary amines at room temperature to give 2-(2-tosylguanidino)acetamide **2A** with high yield (70%). In a subsequent communication[2] we showed that the reaction of either **1A** or **2A** at reflux temperature with propylamine afforded the substituted carboxamide **4Aa** with moderate to good yield (50–80%, respectively). The transamidation reaction was postulated to occur through the 2-iminoimidazolidin-4-one intermediate **3**, which was isolated by the reaction of acetamide **2A** with dimethylamine at reflux temperature. Treatment of imidazolidinone **3A** with propylamine at 50 °C gave almost quantitatively the transamidated carboxamide **4Aa** (Scheme 1).

Direct transamidation is known to be a difficult reaction and it is restricted to special conditions and requirements like ring expansion of lactams[3] and oxosultams,[4] lower carboxamides,[5] intramolecular processes,[6] activated amides,[7] catalytic conditions,[8] high temperatures[9] and critical pH.[10]



A: R = *p*-$C_6H_4CH_3$, **a**: R´ = Pr, R´´= H

Scheme 1.

Amide exchange has also been described in solid-phase synthesis.[11] The transamidation reported in our previous work[2] with conversion of sulfonylguanidinoacetamide **2A** into the substituted carboxamide **4Aa**, through the formation of the 2-imino-3-sulfonylimidazolidin-4-one ring system **3A**, would have some similarity with other intermolecular transamidation reactions reported in the literature, which take place through an intramolecular substrate activation.[6f] Nevertheless, the mechanism we propose for the formation of imidazolidinones **3**,[12] through a ring closure reaction that supposes a sulfonamide–amide intramolecular interaction, with the displacement of the sulfonylamino group as a leaving group,[4,11b,13] has no precedents in the literature.

Keywords: Transamidation; Guanidines; Acetamides; Dihydropyrimidines; Imidazolidinones.
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2. Results and discussion

In order to study the role of the tosyl group in the observed transamidation reaction of compound **2A**,[1] we prepared the guanidinoacetamide derivatives **2B–E**, containing different sulfonylimino substituents, and we examined their reactivity towards primary and secondary amines at reflux temperature (Scheme 2).

The results obtained by reaction of carboxamides **2** with propylamine, ethylamine and dimethylamine at reflux temperature are shown in Table 1. In general, the reaction of the compounds **2** with amines to afford the transamidated products **4** relies on the sulfonylimino substituent, independent of the amine reagent, and the yields obtained follow the order **2B** (R=*p*-C_6H_4Br)≥**2A** (R=*p*-$C_6H_4CH_3$)>**2C** (R=*p*-$C_6H_4OCH_3$), in the experiments carried out with propylamine (entries 1–3), ethylamine/MeOH (entries 7–9) and dimethylamine/MeOH (entries 13–15). These results are in agreement with the leaving group character of the sulfonamido group in the ring opening reaction of imidazolidinones **3**. It is noteworthy that in the case of mesylguanidinoacetamide **2D** (R=CH_3), the transamidated product **4D** was not observed (entries 4, 10, 16), even under long reaction periods, in accordance with a poorer leaving character of this iminosulfonyl substituent in the ring opening reaction. No transamidated products **4E** were detected in the reaction of **2E** (R=*p*-nitrobenzenesulfonylimino group) with ethylamine/MeOH and dimethylamine/MeOH (entries 11 and 17), similar to **2D**. However, in the reaction of sulfonylguanidinoacetamide **2E** with propylamine, a Smiles rearrangement[14,15] took place and 2-(4-nitrophenylamino)-*N*-propylacetamide **5** was isolated.

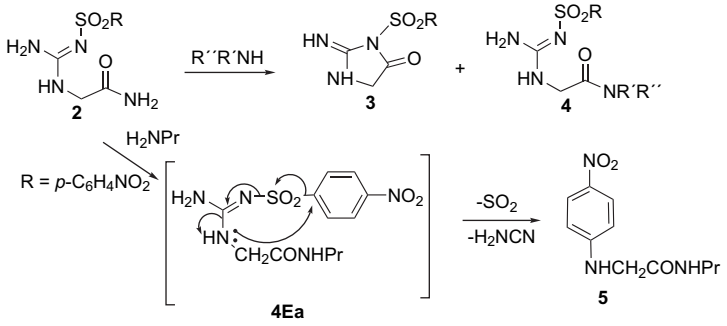
We also found that in addition to the effect of the sulfonylimino substituent, the amine and the solvent play an important role in the transamidation. As shown in Table 1, the best results in the transamidation of acetamides **2A–C** were achieved when the reaction was performed with propylamine (entries 1–3), whereas in the reaction of **2A–C** with ethylamine/MeOH (entries 7–9) lower yields of the transamidated products **4A–C** were obtained. When a secondary amine as dimethylamine/MeOH was used, the transamidated products **4A**,**B** were also isolated with low yields (entries 13 and 14) and, in the case of 4-methoxybenzenesulfonylguanidinoacetamide **2C**, the transamidated compound **4C** was not detected (entry 15).

Table 1. Reaction of acetamides **2A–E** with amines[a,b]

Entry	2	Amine	2 (%)	3 (%)	4 (%)	5 (%)	Solvent
1	**2A**	H_2NPr	—	—	80	—	H_2NPr
2	**2B**	H_2NPr	—	8	85	—	H_2NPr
3	**2C**	H_2NPr	30	7	50	—	H_2NPr
4	**2D**	H_2NPr	86	7	—		H_2NPr
5	**2E**	H_2NPr	—	—	—	89	H_2NPr
6	**2A**	H_2NPr	52	—	12	—	THF
7	**2A**	H_2NEt	—	9	60	—	MeOH
8	**2B**	H_2NEt	—	6	50	—	MeOH
9	**2C**	H_2NEt	25	36	19	—	MeOH
10	**2D**	H_2NEt	75	10	—	—	MeOH
11	**2E**	H_2NEt	53	14	—	—	MeOH
12	**2A**	H_2NEt	68	—	10	—	THF
13	**2A**	Me_2NH	—	50	42	—	MeOH
14	**2B**	Me_2NH	—	35	47	—	MeOH
15	**2C**	Me_2NH	20	60	—	—	MeOH
16	**2D**	Me_2NH	30	49	—	—	MeOH
17	**2E**	Me_2NH	63	15	—	—	MeOH

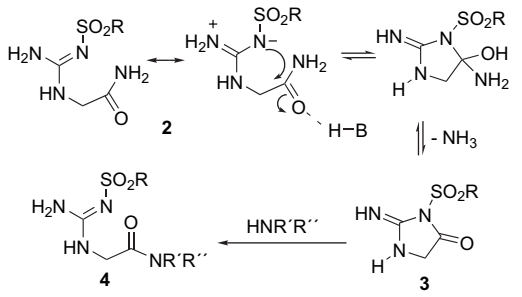
[a] Reaction conditions: reflux temperature.
[b] Yields obtained after purification.

The results in these comparative experiments suggest that the solvent also significantly affects the transamidation reaction of acetamides **2** (Scheme 3). Thus, the ring closure reaction with conversion of the acetamides **2** into imidazolidinones **3** is favoured by the electrophilic assistance of the protic solvent (propylamine as a solvent and experiments with ethyl and dimethylamine in methanol). When methanol is used as solvent, the nucleophilicity of the amine is decreased by hydrogen bonding with methanol, affording lower yields of the ring opening products **4** in comparison with the experiments with propylamine without methanol (entries 7–9, 13, 14). The effect of the solvent in the transamidation was confirmed by the reaction of tosylguanidinoacetamide **2A** with propylamine and ethylamine using an aprotic solvent such as THF (Table 1, entries 6 and 12). In this case the formation of the intermediate imidazolidinone **3** is not favoured because of the lack of solvent assistance in the ring closure reaction, and the small amounts of imidazolidinone **3** are completely converted into the transamidated guanidines **4**.



A: R = *p*-$C_6H_4CH_3$, **B**: R = *p*-C_6H_4Br, **C**: R = *p*-$C_6H_4OCH_3$, **D**: R = CH_3, **E**: R = *p*-$C_6H_4NO_2$;
a: R´ = Pr, R´´= H; **b**: R´ = Et, R´´= H; **c**: R´ =CH_3, R´´= CH_3

Scheme 2.



Scheme 3.

In summary, we report on interesting transamidation reactions of appropriately substituted *N*-sulfonylguanidinoacetamides as a useful synthetic procedure for the preparation of secondary and tertiary amides. This reaction with acetamides **2** as starting materials proceeds through imidazolidinones **3** as intermediates, and is strongly dependent on the sulfonylimino substituent and the solvent.

3. Experimental

3.1. General methods

All reagents were used without purification unless otherwise stated. DMF was distilled with 4 Å sieves under reduced pressure. All experiments were performed under nitrogen atmosphere. Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Flash column chromatography was performed using silica gel (Merck 60, 70–230 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 instrument. Chemical shifts (δ values) and coupling constants (J values) are given in parts per million and Hertz, respectively. MS and HRMS were obtained using a VG Autospec TRIO 1000 instrument. The ionization mode used in mass spectra was electron impact (EI) or fast atom bombardment (FAB). ^{1}H and ^{13}C NMR assignments have been confirmed by homonuclear two-dimensional correlations and DEPT experiments. Compounds **1A** and **2A** were obtained as described in the literature.[1]

3.2. General procedure for the preparation of dihydropyrimidines 1B–E

To a stirred suspension of the corresponding 2-sulfonamidopyrimidine[16] (3.6 mmol) in dry DMF (12 mL), diisopropylethylamine (0.65 mL, 3.6 mmol) was added dropwise under nitrogen and after 40 min iodoacetamide (0.66 g, 3.6 mmol) was added. The reaction mixture was stirred at room temperature for 16 h and then poured onto water (100 mL). The resulting solid was collected, air dried and purified by recrystallization or column chromatography.

3.2.1. 2-[2-{(4-Bromobenzenesulfonyl)imino}pyrimidin-1(2*H*)-yl]acetamide 1B. Yield 85%. Mp: 235–240 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 4.77 (2H, s); 6.90 (1H, dd, J=6.4, 4.1); 7.46 (1H, br); 7.68 (2H, d, J=8.6); 7.74 (2H, d, J=8.6); 7.86 (1H, br); 8.39 (1H, dd, J=6.4, 1.9); 8.64 (1H, dd, J=4.1, 1.9) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 54.9 (CH_2); 108.0 (CH); 125.0 (C); 129.2 (CH); 131.5 (CH); 143.3 (C); 152.2 (CH); 154.8 (C═N); 164.8 (CH); 167.2 (C═O) ppm. HRMS (FAB$^+$): m/z calcd for $C_{12}H_{12}BrN_4O_3S$ 370.9813; found 370.9809.

Starting sulfonamide: 4-bromo-*N*-pyrimidin-2-ylbenzenesulfonamide. Yield 60%. Mp: 218–220 °C, lit.[17] 212–214 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.06 (1H, t, J=5); 7.52 (1H, s); 7.79 (2H, d, J=8.6); 7.90 (2H, d, J=8.6); 8.50 (2H, d, J=5) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 116.1 (CH); 127.1 (C); 130.0 (CH); 132.3 (CH); 140.1 (C); 157.0 (C); 158.7 (CH) ppm.

3.2.2. 2-[2-{(4-Methoxybenzenesulfonyl)imino}pyrimidin-1(2*H*)-yl]acetamide 1C. Yield 58%. Mp: 196–200 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.78 (s, 3H); 4.73 (2H, s); 6.82 (1H, dd, J=6.7, 4.1); 6.96 (2H, d, J=9.0); 7.43 (1H, br); 7.75 (2H, d, J=9.0); 7.83 (1H, br); 8.33 (1H, dd, J=6.7, 2.2); 8.60 (1H, dd, J=4.1, 2.2) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 54.7 (CH_2); 55.1 (CH_3); 108.0 (CH); 113.6 (CH); 129.1 (CH); 136.0 (C); 152.0 (CH); 154.7 (C═N); 161.4 (C); 164.9 (CH); 167.2 (C═O) ppm. HRMS (IE$^+$): m/z calcd for $C_{13}H_{15}N_4O_4S$ 323.0814; found 323.0775.

Starting sulfonamide: 4-methoxy-*N*-pyrimidin-2-ylbenzenesulfonamide. Yield 90%. Mp: 193–195 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.78 (3H, s); 7.03 (1H, t, J=4.8); 7.07 (2H, d, J=8.9); 7.92 (2H, d, J=8.9); 8.49 (2H, d, J=4.8); 11.62 (1H, br) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 56.0 (OCH_3); 114.3 (CH); 116.1 (CH); 120.2 (CH); 132.2 (C); 157.8 (C); 158.7 (CH); 162.8 (C) ppm. HRMS (FAB$^+$): m/z calcd for $C_{11}H_{12}N_3O_3S$ 266.0599; found 266.0607.

3.2.3. 2-[2-[(Methylsulfonyl)imino]pyrimidin-1(2*H*)-yl]acetamide 1D. Recrystallized from ethanol. Yield 50%. Mp: 273–274 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.96 (3H, s); 4.71 (2H, s); 6.87 (1H, dd, J=6.6, 4.3); 7.38 (1H, br); 7.81 (1H, br); 8.36 (1H, dd, J=6.6, 2.2); 8.74 (1H, dd, J=4.3, 2.2) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 40.7 (CH_3); 54.3 (CH_2); 107.5 (CH); 152.0 (CH); 154.9 (C); 164.6 (CH); 167.2 (C═O) ppm. HRMS (FAB$^+$): m/z calcd for $C_7H_{11}N_4O_3S$ 231.0551; found 231.0540.

Starting sulfonamide: *N*-pyrimidin-2-ylmethanesulfonamide. Yield 64%. Mp: 240–244 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.36 (3H, s); 7.13 (1H, t, J=4.9); 8.61 (1H, d, J=4.9); 11.33 (1H, br) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 41.6 (CH_3); 116.1 (CH); 157.9 (C); 158.9 (CH) ppm. HRMS (IE$^+$): m/z calcd for $C_5H_7N_3O_2S$ 173.0258; found 173.0258.

3.2.4. 2-[2-{(4-Nitrobenzenesulfonyl)imino}pyrimidin-1(2*H*)-yl]acetamide 1E. Eluent: EtOAc/MeOH (9:1). Yield 48%. Mp: 250–251 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 4.71 (2H, s); 6.92 (1H, dd, J=6.1, 4.1); 7.48 (1H, br); 7.88 (1H, br); 8.04 (2H, d, J=9); 8.28 (2H, d, J=9); 8.43 (1H, dd, J=6.1, 2.2); 8.63 (1H, dd, J=4.1, 2.2) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 55.1 (CH_2); 109.1 (CH); 124.0 (CH); 128.5 (CH); 149.0 (C); 149.7 (C); 152.3 (CH); 154.9 (C═N); 164.9 (CH); 167.2 (C═O) ppm. HRMS (IE$^+$): m/z calcd for $C_{12}H_{12}N_5O_5S$ 338.0559; found 338.0553.

Starting sulfonamide: 4-nitro-*N*-pyrimidin-2-ylbenzenesulfonamide. Yield 68%. Mp: 274–278 °C, lit.[18] 278–280 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.11 (1H, t, J=4.9); 8.24 (2H, d, J=9); 8.43 (2H, d, J=9); 8.56 (2H, d, J=4.9); 11.33 (1H, br) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 115.4 (CH); 124.5 (CH); 129.3 (CH); 146.8 (C); 150.0 (C); 157.9 (C); 158.6 (CH) ppm.

3.3. Synthesis of sulfonylguanidinoacetamides 2B–E

Procedure A: a solution of dihydropyrimidine **1** (1.63 mmol) in propylamine (5 mL) was stirred at room temperature overnight. The excess of amine was removed under reduced pressure and the residue was purified by column chromatography or recrystallized.

Procedure B: to a solution of dihydropyrimidine **1** (1.63 mmol) in methanol (20 mL) was added ethylamine 2 M in methanol (5 mL) and the reaction mixture was stirred at room temperature overnight. The remaining oil was purified by flash column chromatography.

3.3.1. 2-[2-(4-Bromobenzenesulfonyl)guanidino]acetamide 2B. Procedure A: yield 48%. Eluent: EtOAc/MeOH (9:1). Mp: 190–195 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.77 (2H, d, J=4.3); 6.87 (2H, br); 6.99 (1H, br); 7.13 (1H, br); 7.45 (1H, br); 7.69 (4H, s) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 43.5 (CH_2); 125.1 (C); 128.1 (CH); 132.0 (CH); 143.8 (C); 156.9 (C=N); 170.5 (C=O) ppm. HRMS (IE$^+$): m/z calcd for $C_9H_{12}N_4O_3SBr$ 334.9813; found 334.9796.

3.3.2. 2-[2-(4-Methoxybenzenesulfonyl)guanidino]acetamide 2C. Procedure A: yield 70%. Eluent: EtOAc/MeOH (4:1). Mp: 152–156 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.70 (2H, d, J=4.9); 3.79 (s, 3H); 6.82 (3H, br); 6.99 (2H, d, J=9.0); 7.13 (1H, br); 7.40 (1H, br); 7.68 (2H, d, J=9.0) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 43.4 (CH_2); 55.8 (OCH_3); 114.0 (CH); 127.9 (CH); 136.7 (C); 156.6 (C=N); 161.5 (C); 170.5 (C=O) ppm. HRMS (IE$^+$): m/z calcd for $C_{10}H_{15}N_4O_4S$ 287.0814; found 287.0812.

3.3.3. 2-[2-(Methylsulfonyl)guanidino]acetamide 2D. Procedure A: yield 60%. Recrystallized from EtOAc. Mp: 198–200 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.96 (3H, s); 3.94 (2H, d, J=5); 6.90 (3H, br); 7.35 (1H, br); 7.96 (1H, br) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 41.7 (CH_3); 43.5 (CH_2); 157.1 (C=N); 170.6 (C=O) ppm. HRMS (IE$^+$): m/z calcd for $C_4H_{10}N_4O_3S$ 194.0473; found 194.0427.

3.3.4. 2-[2-(4-Nitrobenzenesulfonyl)guanidino]acetamide 2E. Procedure B: yield 46%. Eluent: EtOAc/MeOH (4:1). Mp: 164–167 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.73 (2H, d, J=5); 6.96 (2H, br); 7.12 (2H, br); 7.46 (1H, br); 8.01 (2H, d, J=9); 8.32 (2H, d, J=9) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 43.5 (CH_2); 123.8 (CH); 124.5 (CH); 149.2 (C); 150.0 (C); 157.1 (C=N); 170.6 (C=O) ppm. HRMS (IE$^+$): m/z calcd for $C_9H_{12}N_5O_5S$ 302.0559; found 302.0540.

3.4. Reaction of sulfonylguanidinoacetamides 2A–E with amines

Procedure A: a solution of sulfonylguanidinoacetamide **2** (1.63 mmol) in propylamine (5 mL) was heated to reflux for 6 h. The excess of amine was removed under reduced pressure and the residue was purified by column chromatography.

Procedure B: to a solution of sulfonylguanidinoacetamide **2** (1.63 mmol) in methanol (20 mL) was added ethylamine 2 M in methanol or dimethylamine 2 M in methanol (5 mL). The reaction mixture was heated to reflux for 6 h and then concentrated under reduced pressure. The remaining oil was purified by flash column chromatography.

The yields obtained in the reactions are described in Table 1.

3.4.1. 2-Imino-3-(4-methylbenzenesulfonyl)-imidazolidin-4-one 3A. Eluent: hexane/AcOEt (1:4). Mp: 205–208 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.37 (3H, s); 4.03 (2H, s); 7.35 (2H, d, J=8.1); 7.74 (2H, d, J=8.1); 8.63 (1H, br); 11.37 (1H, br) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 21.2 (CH_3); 49.2 (CH_2); 126.3 (CH); 129.7 (CH); 140.3 (C); 142.6 (C); 157.9 (C=N); 173.1 (C=O) ppm. HRMS (IE$^+$): m/z calcd for $C_{10}H_{11}N_3O_3S$ 253.0521; found 253.0532.

3.4.2. 3-(4-Bromobenzenesulfonyl)-2-iminoimidazolidin-4-one 3B. Eluent: hexane/EtOAc (1:4). Mp: 225–230 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 4.04 (2H, s); 7.77 (4H, s); 8.74 (1H, br); 11.4 (1H, br) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 49.2 (CH_2); 126.2 (C); 128.4 (CH); 132.4 (CH); 142.3 (C); 158.2 (C=N); 173.0 (C=O) ppm. HRMS (IE$^+$): m/z calcd for $C_9H_8N_3O_3SBr$ 316.9469; found 316.9475.

3.4.3. 2-Imino-3-(4-methoxybenzenesulfonyl)imidazolidin-4-one 3C. Eluent: hexane/EtOAc (1:4). Mp: 181–183 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.82 (3H, s); 4.02 (2H, s); 7.06 (2H, d, J=9.0); 7.79 (2H, d, J=9.0); 8.6 (1H, br); 11.37 (1H, br) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 49.2 (CH_2); 55.9 (CH_3); 114.0 (CH); 128.4 (CH); 135.0 (C); 157.7 (C=N); 162.2 (C); 173.3 (C=O) ppm. HRMS (IE$^+$): m/z calcd for $C_{10}H_{11}N_3O_4S$ 269.0470; found 269.0381.

3.4.4. 2-Imino-3-(methylsulfonyl)imidazolidin-4-one 3D. Eluent: EtOAc. Mp: 205–207 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.98 (3H, s); 4.06 (2H, s); 8.5 (1H, br); 11.0 (1H, br) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 41.8 (CH_3); 49.0 (CH_2); 157.8 (C=N); 173.2 (C=O) ppm. HRMS (EI$^+$): m/z calcd for $C_4H_7N_3O_3S$ 177.0208; found 177.0206.

3.4.5. 2-Imino-3-(4-nitrobenzenesulfonyl)imidazolidin-4-one 3E. Eluent: hexane/EtOAc (1:4). Mp: 228–232 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 4.06 (2H, s); 8.17 (2H, d, J=9); 8.36 (2H, d, J=9); 8.89 (1H, br); 11.36 (1H, br) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 49.3 (CH_2); 124.7 (CH); 127.8 (CH); 148.4 (C); 149.7 (C); 158.4 (C=N); 173.1 (C=O) ppm. HRMS (EI$^+$): m/z calcd for $C_9H_8N_4O_5S$ 284.0215; found 284.0223.

3.4.6. *N*-Propyl-2-(2-tosylguanidino)acetamide 4Aa. Eluent: hexane/EtOAc (3:7). Mp: 145–146 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.82 (3H, t, J=7.3); 1.38 (2H, sextet, J=7.3); 2.34 (3H, s); 3.00 (2H, q, J=7.3); 3.71 (2H,

d, J=5.2); 6.82 (2H, br); 6.92 (1H, br); 7.28 (2H, d, J=8.1); 7.63 (2H, d, J=8.1); 7.94 (1H, br) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 11.3 (CH_3); 20.8 (CH_3); 22.3 (CH_2); 40.3 (CH_2); 43.3 (CH_2NH); 125.6 (CH); 129.0 (CH); 141.1 (C); 141.5 (C); 156.5 (C═N); 168.0 (C═O) ppm. HRMS (EI$^+$): m/z calcd for $C_{13}H_{20}N_4O_3S$ 312.1256; found 312.1265. Anal. Calcd for $C_{13}H_{20}N_4O_3S$: C, 49.98; H, 6.40; N, 17.92; S, 10.26. Found: C, 50.06; H, 6.57; N, 17.92; S, 10.25.

3.4.7. 2-[2-(4-Bromobenzenesulfonyl)guanidino]-*N*-propylacetamide 4Ba. Eluent: hexane/EtOAc (1:4). Mp: 202–205 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.85 (3H, t, J=7.1); 1.40 (2H, sextet, J=7.1); 3.04 (2H, q, J=6.7); 3.76 (2H, d, J=5.2); 6.91 (2H, br); 7.05 (1H, br); 7.72 (4H, s); 7.97 (1H, t, J=5.2) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 11.7 (CH_3); 22.6 (CH_2); 40.7 (CH_2); 43.7 (CH_2NH); 125.1 (C); 128.1 (CH); 132.0 (CH); 143.9 (C); 157.0 (C═N); 168.3 (C═O) ppm. HRMS (EI$^+$): m/z calcd for $C_{12}H_{17}N_4O_3SBr$ 376.0204; found 376.0199.

3.4.8. 2-[2-(4-Methoxybenzenesulfonyl)guanidino]-*N*-propylacetamide 4Ca. Eluent: EtOAc/MeOH (9:1). Mp: 147–149 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.82 (3H, t, J=7.1); 1.38 (2H, sextet, J=7.1); 3.01 (2H, q, J=7.1); 3.72 (2H, d, J=5.2); 3.80 (3H, s); 6.82 (2H, br); 6.92 (1H, br); 6.99 (2H, d, J=8.6); 7.68 (2H, d, J=8.6); 7.94 (1H, t, J=5.2) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 11.7 (CH_3); 22.6 (CH_2); 40.7 (CH_2); 43.7 (CH_2NH); 55.8 (OCH_3); 114.0 (CH); 127.9 (CH); 136.7 (C); 156.6 (C═N); 161.6 (C); 168.2 (C═O) ppm. HRMS (EI$^+$): m/z calcd for $C_{13}H_{20}N_4O_4S$ 328.1205; found 328.1219.

3.4.9. *N*-Ethyl-2-(2-tosylguanidino)acetamide 4Ab. Eluent: EtOAc/MeOH (9:1). Mp: 158–160 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.99 (3H, t, J=7.1); 2.33 (3H, s); 3.08 (2H, quintet, J=7.1); 3.71 (2H, d, J=5.2); 6.85 (2H, br); 6.97 (1H, br); 7.27 (2H, d, J=8.0); 7.64 (2H, d, J=8.0); 7.95 (1H, t, J=5.2) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 15.0 (CH_3); 21.2 (CH_3); 33.8 (CH_2); 43.7 (CH_2NH); 126.0 (CH); 129.3 (CH); 141.5 (C); 141.9 (C); 157.0 (C═N); 168.2 (C═O) ppm. HRMS (EI$^+$): m/z calcd for $C_{12}H_{18}N_4O_3S$; 298.1099; found 298.1069.

3.4.10. 2-[2-(4-Bromobenzenesulfonyl)guanidino]-*N*-ethylacetamide 4Bb. Eluent: EtOAc. Mp: 110–114 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.98 (3H, t, J=7.1); 3.07 (2H, quintet, J=7.1); 3.70 (2H, d, J=5.2); 6.87 (2H, br); 7.01 (1H, br); 7.69 (4H, s); 7.95 (1H, t, J=5.2) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 15.0 (CH_3); 33.8 (CH_2); 43.7 (CH_2NH); 125.1 (C); 128.1 (CH); 132.0 (CH); 143.9 (C); 157.0 (C═N); 168.2 (C═O) ppm. HRMS (EI$^+$): m/z calcd for $C_{11}H_{16}N_4O_3SBr$ 363.0126; found 363.0130.

3.4.11. *N*-Ethyl-2-[2-(4-methoxybenzenesulfonyl)guanidino]acetamide 4Cb. Eluent: EtOAc/MeOH (9:1). Mp: 136–139 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.99 (3H, t, J=7.1); 3.07 (2H, quintet, J=7.1); 3.69 (2H, d, J=5.2); 3.8 (3H, s); 6.82 (3H, br); 6.99 (2H, d, J=9.0); 7.68 (2H, d, J=9.0); 7.95 (1H, br) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 14.9 (CH_3); 33.8 (CH_2); 43.7 (CH_2NH); 55.8 (OCH_3); 114.0 (CH); 127.9 (CH); 136.7 (C); 156.8 (C═N); 161.6 (C); 168.2 (C═O) ppm. HRMS (EI$^+$): m/z calcd for $C_{12}H_{19}N_4O_4S$ 315.1127; found 315.1125.

3.4.12. *N*,*N*-Dimethyl-2-(2-tosylguanidino)acetamide 4Ac. Eluent: EtOAc/MeOH (9:1). Mp: 192–194 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.33 (3H, s); 2.84 (3H, s); 2.89 (3H, s); 3.93 (2H, d, J=4.1); 6.90 (2H, br); 7.28 (2H, d, J=8.2); 7.44 (1H, br); 7.64 (2H, d, J=8.2) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 35.4 (CH_3); 35.8 (CH_3); 42.4 (CH_2NH); 126.0 (CH); 129.3 (CH); 141.5 (C); 142.6 (C); 156.7 (C═N); 168.0 (C═O) ppm. HRMS (FAB$^+$): m/z calcd for $C_{12}H_{19}N_4O_3S$ 299.1177; found 299.1181.

3.4.13. 2-[2-(4-Bromobenzenesulfonyl)guanidino]-*N*,*N*-dimethylacetamide 4Bc. Eluent: EtOAc/MeOH (9:1). Oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.81 (3H, s); 2.95 (3H, s); 3.95 (2H, d, J=5.2); 6.88 (2H, br); 7.0 (1H, br); 7.75 (4H, s) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 35.4 (CH_3); 35.9 (CH_3); 42.5 (CH_2NH); 125.1 (C); 125.1 (CH); 128.2 (CH); 143.8 (C); 156.3 (C═N); 168.1 (C═O) ppm. HRMS (EI$^+$): m/z calcd for $C_{11}H_{15}BrN_4O_3S$ 362.0048; found 362.0013.

3.4.14. 2-(4-Nitrophenylamino)-*N*-propylacetamide 5. Eluent: hexane/EtOAc (3:7). Mp: 140–142 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.80 (3H, t, J=7.35); 1.40 (2H, sextet, J=7.35); 3.04 (2H, q, J=7.35); 3.82 (2H, d, J=6); 6.63 (2H, d, J=9.4); 7.49 (1H, t, J=6); 7.99 (2H, d, J=9); 8.10 (1H, t, J=4) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 11.6 (CH_3); 22.7 (CH_2); 40.7 (CH_2); 46.0 (CH_2NH); 111.5 (CH); 126.3 (CH); 136.5 (C); 154.7 (C); 168.8 (C═O) ppm. HRMS (EI$^+$): m/z calcd for $C_{11}H_{16}N_3O_3$ 238.1191; found 238.1251.

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