

Full Paper

Synthesis and Analgesic Activity Evaluation of Some Agmatine Derivatives

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Abstract: A series of *N,N'*-disubstituted-2-nitroethene-1,1-diamine and *N,N'*-disubstituted-*N''*-cyanoguanidine derivatives were prepared and evaluated for *in vivo* analgesic activity. The blood brain barrier (BBB) VolSurf model was used to predict the BBB permeation profiles of our synthesized compounds. Some compounds show both remarkable analgesic activity and good BBB permeation profiles, and these compounds might be developed for treatment of opioid tolerance and dependence.

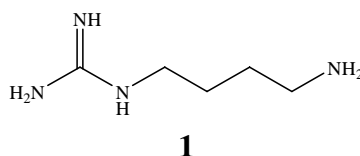
Keywords: Agmatine derivatives; synthesis; analgesic activity; blood-brain barrier; opioid dependence.

Introduction

Agmatine (**1**, Figure 1) is an endogenous ligand of imidazoline receptors [1], and is biologically active in the nervous system and many other tissues in mammals [2]. Previous research indicates that this compound, which is not able to interact with opioid receptors, plays an important role in regulating the pharmacological actions of opioids [3-6]. Agmatine has weak analgesic effects and shows biphasic modulation on opioid functions, which enhance opioid analgesia, but inhibit tolerance

to and substance dependence on opioids. The mechanisms associated with the analgesic effect and biphasic modulation on opioid functions is by activation of imidazoline receptors on central nervous system [7-8]. These results suggest that agmatine might be developed for treatment of opioid tolerance and dependence, but the pharmacokinetic profile of agmatine, such as its low ability to cross the blood-brain barrier and its fast excretion (mostly due to its hydrophilicity), restricts its potential drug use [9-10].

Figure 1.



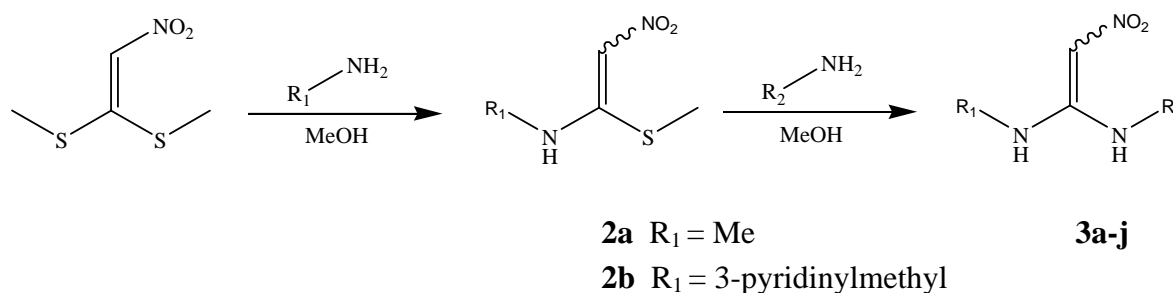
It is known that lipophilicity is an essential feature for the penetration of a molecule through the blood-brain barrier [11], consequently, the purpose of the present work was to synthesize several structurally-related agmatine derivatives with better lipophilicity and biological activity. We synthesized some derivatives of agmatine by substituting guanidine with 2-nitroethene-1,1-diamine or N-cyanoguanidine, and tested their analgesic activity in mice in order to find new potent compounds for treatment of opioid tolerance and dependence.

Results and Discussion

Chemistry

We used 1,1-bis(methylthio)-2-nitroethene as starting material, which was refluxed with one equivalent of amine to give the corresponding N-substituted-1-(methylthio)-2-nitroethenamines **2a-b**. Then compounds **2** were reacted with the appropriate amine to obtain the corresponding N,N'-disubstituted -2-nitroethene-1,1-diamine derivatives **3a-j** (Scheme 1) [12-13].

Scheme 1. The synthesis of N,N'-disubstituted -2-nitroethene-1,1-diamines.



The preparation of N,N'-disubstituted-N''-cyanoguanidine derivatives **5a-l** was similar to that of **3a-j**. First, dimethyl N-cyanodithioiminocarbonate was refluxed with one equivalent of amine to give the corresponding methyl N'-cyano-N-substituted-imidothiocarbamates **4a-d**. Then compounds **4a-d** were reacted with the second amine to give the derivatives **5a-l** (Scheme 2) [14-15]. The structures of the compounds are presented in Table 1.

The model was able to correctly predict the BBB range for more than 75% of the compounds. Bearing in mind that BBB permeation is not only dependent on passive diffusion but also on active transport and metabolism, the results are very encouraging.

Table 2. Inhibition on acetic acid-induced mice writhing and BBB profile as predicted by Volsurf.

Compd	inhb.rate (%)	BBB prediction by Volsurf	Compd	inhb.rate (%)	BBB prediction by Volsurf
Saline	0		5a	27.0	0.79
Morphine	100		5b	57.3	-0.51
Agmatine	55.3	-0.64	5c	19.9	-0.47
3a	35.8*	0.95	5d	54.1**	-0.34
3b fumarate	37.7	-0.28	5e	53.1	-0.28
3c fumarate	46.5	-0.18	5f fumarate	56.2*	0.08
3d fumarate	52.0*	-0.12	5g fumarate	37.3	-0.74
3e	33.6*	0.83	5h fumarate	51.3	-0.69
3f	23.9	0.82	5i fumarate	38.4*	-0.28
3g	35.4	-0.35	5j fumarate	24.8	-0.21
3h	60.6*	0.64	5k fumarate	4.14	-0.38
3i fumarate	47.9	-0.64	5l fumarate	16.1*	-0.46
3j fumarate	27.8	-0.58			

** P < 0.01, * P < 0.05, saline and morphine is the control.

Conclusions

Ten compounds **3a-j** and twelve compounds **5a-l** were prepared as shown in Schemes 1 and 2. Compounds **3d**, **3h** and **5f** present notable analgesic activity and good blood-brain barrier permeation profiles. Further research on these compounds and their potential use for treatment of opioid tolerance and dependence will be report in due course.

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Experimental

General

¹H-NMR (400 MHz) and ¹³C-NMR (100 MHz) spectra were recorded on a JNM-ECA-400 spectrometer in the solvents indicated. Mass spectral analyses were carried out using a Micromass

ZabSpec or an API3000 mass spectrometer. Elemental analysis was carried at the CarloErba-1106 instrument. Melting points were recorded on an Electrothermal digital capillary melting point apparatus and are uncorrected. Column chromatography was performed with silica gel H (250-400 mesh).

General procedure for the preparation of compounds 2a-b

A solution of 1,1-bis(methylthio)-2-nitroethene (50 mmol) in absolute methanol (200 mL) was refluxed with one equivalent of amine for 8 h. After cooling to room temperature, the solvent was evaporated and the residue was recrystallized from ethanol/diethyl ether (1:6) to yield **2a-b**.

N-Methyl-1-(methylthio)-2-nitroethenamine (**2a**) [19]: Yield 65%; mp: 113-115°C.

1-(Methylthio)-2-nitro-*N*-[(pyridin-3-yl)methyl]ethenamine (**2b**) [20]: Yield 67%; mp: 130-132°C; EI-MS: 225.0 (M)⁺.

General procedure for the preparation of compounds 3a-j and their fumarates

A mixture of *N*-substituted-1-(methylthio)-2-nitroethenamine **2** (1 mmol) and MeOH (15 mL) containing 1.5 equivalents of the appropriate amine was refluxed for 6h. After cooling to room temperature, the solvent was evaporated and the residue was purified by column chromatography to afford the product **3**. One equivalent each of fumaric acid and **3** were dissolved in EtOH and then refluxed for 2 min. After cooling to room temperature diethyl ether was slowly added to the solution. The precipitate formed was filtered off to give the fumarate of **3**.

*N*¹,*N*¹,2,2-Tetramethyl-*N*³-[1-(methylamino)-2-nitrovinyl]propane-1,3-diamine (**3a**): Yield 69%; mp: 99-100°C. ¹H-NMR (D₂O) δ: 0.97 (s, 6H), 2.26 (s, 6H), 2.36 (s, 2H), 2.90 (s, 3H), 3.14 (s, 2H), 6.86 (s, 1H); EI-MS: 231.1 (M+1)⁺; Anal. Calcd. for C₁₀H₂₂N₄O₂: C, 52.15; H, 9.63; N, 24.33. Found: C, 51.96; H, 9.73; N, 24.16.

*N*¹-[1-(Methylamino)-2-nitrovinyl]butane-1,4-diamine (**3b**). Yield 56%; mp: 104-106°C; mp fumarate: 110-112 °C; ¹H-NMR (D₂O) δ: 1.47-1.62 (m, 4H), 2.65 (s, 2H), 2.90 (s, 3H), 3.28 (t, 2H), 6.88 (s, 1H); FAB-MS: 189.0 (M+1)⁺.

*N*¹-[1-(Methylamino)-2-nitrovinyl]pentane-1,5-diamine (**3c**). Yield 57 %; mp: 110-112°C; ¹H-NMR (D₂O) δ: 1.35-1.48 (m, 6H), 2.61 (t, 2H), 2.89 (s, 3H), 3.26 (t, 2H), 6.87 (s, 1H); EI-MS: 203.0 (M+1)⁺; Anal. Calcd. for fumarate C₈H₁₈N₄O₂·C₄H₄O₄: C, 45.28; H, 6.97; N, 17.60. Found: C, 44.94; H, 6.98; N, 17.26.

*N*¹-[1-(Methylamino)-2-nitrovinyl]hexane-1,6-diamine (**3d**) [21]. Yield 55 %; mp: 111-113°C; ¹H-NMR (D₂O) δ: 1.15-1.45 (m, 8H), 2.61 (t, 2H), 2.89 (s, 3H), 3.26 (t, 2H), 6.87 (s, 1H); EI-MS: 217.2

(M+1)⁺; Anal. Calcd. for fumarate C₉H₂₀N₄O₂·C₄H₄O₄: C, 46.98; H, 7.28; N, 16.86. Found: C, 46.73; H, 7.33; N, 16.58.

N-Methyl-2-nitro-*N*'-pentylethene-1,1-diamine (**3e**). Yield: 69 %; mp: 78-80°C; ¹H-NMR (DMSO-D₆) δ: 0.84 (m, 4H), 1.30 (t, 3H), 1.62 (s, 2H), 2.90 (s, 3H), 3.24 (t, 2H), 6.88 (s, 1H); EI-MS: 187.2 (M)⁺.

N-Methyl-2-nitro-*N*'-[4-(piperidin-1-yl)butyl]ethene-1,1-diamine (**3f**). Yield 39%; mp: 139-140°C; ¹H-NMR (CDCl₃) δ: 1.57-1.68 (m, 10H), 2.38 (s, 6H), 2.88 (d, 3H), 3.20 (s, 2H), 5.53 (s, 1H), 5.90 (s, 1H), 6.60 (s, 1H); FAB-MS: 257.2 (M+1)⁺.

*N*¹-[1-(Methylamino)-2-nitrovinyl]but-2-yne-1,4-diamine (**3g**). Yield 43%; mp: 146-147°C; ¹H-NMR (D₂O) δ: 2.96 (s, 3H), 3.41 (s, 2H), 4.13 (s, 2H), 6.97 (s, 1H); FAB-MS: 185.2 (M+1)⁺.

N-Methyl-2-nitro-*N*'-[pyridin-3-ylmethyl]ethene-1,1-diamine (**3h**) [22]. Yield: 61%; mp: 161-163°C; ¹H-NMR (D₂O) δ: 2.94 (s, 3H), 4.52 (s, 2H), 6.73 (s, 1H), 7.38 (dd, 1H), 7.73 (d, 1H), 8.41 (d, 2H); ESI-MS: 209.2 (M+1)⁺; Anal. Calcd. for C₉H₁₂N₄O₂: C, 51.92; H, 5.81, N 26.91. Found: C, 51.88; H, 5.92; N, 26.67.

*N*¹-[1-((Pyridin-3-yl)methylamino)-2-nitrovinyl]butane-1,4-diamine (**3i**). Yield: 61%; mp fumarate: 197-198°C; ¹H-NMR (D₂O) δ: 1.53 (s, 4H), 2.84 (s, 2H), 3.22 (s, 2H), 4.46 (s, 2H), 6.34 (s, 1H), 7.30 (t, 1H), 7.65 (d, 1H), 8.32 (s, 2H); EI-MS: 266.0 (M+1)⁺; Anal. Calcd. for fumarate C₁₂H₁₉N₅O₂·1/2 C₄H₄O₄: C, 52.00; H, 6.55; N, 21.66. Found: C, 51.89; H, 6.61; N, 21.40.

*N*¹-[1-((Pyridin-3-yl)methylamino)-2-nitrovinyl]pentane-1,5-diamine (**3j**). Yield: 55 %; mp fumarate: 182-184°C; ¹H-NMR (D₂O) δ: 1.48 (s, 6H), 2.79 (s, 2H), 3.19 (s, 2H), 4.47 (s, 2H), 6.34 (s, 1H), 7.31 (t, 1H), 7.66 (d, 1H), 8.33 (s, 2H). EI-MS: 280.0 (M+1)⁺.

General procedure for the preparation of **4a-d**

A solution of dimethyl *N*-cyanodithioiminocarbonate (50 mmol) in absolute methanol (200 mL) was refluxed with one equivalent of amine (50 mmol) for 6 h. After cooling to room temperature, the solvent was evaporated and the residue was recrystallized from ethanol/diethyl ether (1:6) to yield **4a-l**.

Methyl N'-cyano-*N*-methyl-imidothiocarbamate (**4a**) [23]: Yield: 59 %; mp: 202-203°C.

Methyl N'-cyano-*N*-[(pyridin-3-yl)methyl]-imidothiocarbamate (**4b**) [24]: Yield: 63%; mp: 155-157°C; ¹H-NMR (DMSO-D₆) δ: 2.62 (s, 3H), 4.51 (s, 2H), 7.36 (dd, 1H), 7.70 (d, 1H), 8.48-8.52 (m, 2H), 8.91 (s, 1H).

Methyl N'-cyano-*N*-isobutyl-imidothiocarbamate (**4c**) [25]: Yield: 67 %; mp: 119-121°C.

Methyl N'-cyano-*N*-phenylethyl-imidothiocarbamate (**4d**): Yield: 61 %; mp: 173-174°C (Lit. [26] 172-175°C).

General procedure for the preparation of 5a-l and their fumarates

A mixture of methyl *N'*-cyano-*N*-substituted-imidothiocarbamate **4a-d** (1 mmol) and MeOH (15 mL) containing 1.5 equivalent of amine was refluxed for 6h. After cooling to room temperature, the solvent was evaporated and the residue was purified by column chromatography to afford the products **5a-l**. One equivalent each of fumaric acid and **5a-l** was dissolved in EtOH and then refluxed for 2 min. After cooling to room temperature diethyl ether was added slowly to the solution. The precipitate formed was filtered off to give the corresponding fumarate of **5a-l**.

N''-Cyano-*N*-[3-(dimethylamino)-2,2-dimethylpropyl]-*N'*-methylguanidine (**5a**): Yield 73%; mp: 124-126°C; ¹H-NMR (D₂O) δ: 0.97 (s, 6H), 2.33 (s, 6H), 2.36 (s, 2H), 2.77 (s, 3H), 3.09 (s, 2H); EI-MS: 211.1 (M)⁺; Anal. Calcd. for C₁₀H₂₁N₅: C, 56.84; H, 10.02; N, 33.14. Found: C, 57.00; H, 10.26; N, 33.13.

N-(4-Aminobutyl)-*N''*-cyano-*N'*-methylguanidine (**5b**) [27]: Yield 57%; mp: 113-115°C; ¹H-NMR (D₂O) δ: 1.50-1.58 (m, 4H), 2.67 (t, 2H), 2.78 (s, 3H), 3.30 (t, 2H); EI-MS: 169.0 (M)⁺; Anal. Calcd. for C₇H₁₅N₅: C, 49.68; H, 8.93; N, 41.38. Found: C, 49.99; H, 8.99; N, 41.18.

N-(5-Aminopentyl)-*N''*-cyano-*N'*-methylguanidine (**5c**): Yield 56%; mp: 112-114 °C; ¹H-NMR (D₂O) δ: 1.35-1.37 (m, 2H), 1.50-1.57 (m, 4H), 2.64 (t, 2H), 2.77 (s, 3H), 3.18 (t, 2H); EI-MS: 182.0 (M-1)⁺; Anal. Calcd. for C₈H₁₇N₅: C, 52.43; H, 9.35; N,38.22. Found: C, 52.66; H, 9.46; N, 38.02.

N-(6-Aminohexyl)-*N''*-cyano-*N'*-methylguanidine (**5d**): Yield 53%; mp: 78-80°C; ¹H-NMR (D₂O) δ: 1.35 (m, 4H), 1.48-1.55 (m, 4H), 2.62 (t, 2H), 2.78 (s, 3H), 3.18 (t, 2H); EI-MS: 197.0 (M)⁺.

N-(7-Aminoheptyl)-*N''*-cyano-*N'*-methylguanidine (**5e**): Yield 49%; mp: 83-86°C; ¹H-NMR (D₂O) δ: 1.17-1.33 (m, 10H), 2.41 (t, 2H), 2.58 (s, 3H), 2.98 (t, 2H); EI-MS: 211.0 (M)⁺; Anal. Calcd. for C₁₀H₂₁N₅: C, 56.84; H, 10.02; N, 33.14. Found: C, 56.69; H, 10.17; N, 32.66.

N''-Cyano-*N*-[3-(dimethylamino)-2,2-dimethylpropyl]-*N'*-[(pyridin-3-yl)methyl]guanidine (**5f**): Yield 68%; mp fumarate: 119-120°C; ¹H-NMR (D₂O) δ: 0.74 (s, 6H), 2.70-2.76 (m, 8H), 3.00 (s, 2H), 4.43 (s, 2H), 6.33 (m, 2H), 7.59 (m, 1H), 8.05 (m, 1H), 8.39-8.44 (m, 2H); EI-MS: 288.0(M)⁺;

N-(6-Aminohexyl)-*N''*-cyano-*N'*-[(pyridin-3-yl)methyl]guanidine (**5g**): Yield 61%; mp fumarate: 158-159°C; ¹H-NMR (D₂O) δ: 1.13 (m, 4H), 1.36-1.43 (m,4H), 2.75 (t, 2H), 3.03 (t, 2H), 4.40 (s, 2H), 6.38 (s, 2H), 7.62 (m, 1H), 8.04 (m,1H) , 8.41 (m, 2H); EI-MS: 274.2 (M)⁺; Anal. Calcd. for fumarate C₁₄H₂₂N₆·C₄H₄O₄: C, 55.37; H, 6.71; N, 21.52. Found: C, 55.24; H, 6.85; N, 21.42.

N-(7-Aminoheptyl)-*N''*-cyano-*N'*-[(pyridin-3-yl)methyl]guanidine (**5h**): Yield 66%; mp fumarate: 149-150°C; ¹H-NMR (D₂O) δ: 1.11 (m, 6H), 1.32-1.45 (m, 4H), 2.75 (t, 2H), 3.02 (t, 2H), 4.38 (s, 2H), 6.36 (s, 2H), 7.55 (m, 1H), 7.96 (m, 1H) , 8.38 (m, 2H); EI-MS: 288.4 (M)⁺; Anal. Calc. for fumarate C₁₅H₂₄N₆·C₄H₄O₄: C, 56.42; H, 6.98; N, 20.78. Found: C, 56.56; H, 7.20; N, 21.22.

N-(6-Aminohexyl)-*N*''-cyano-*N*'-isobutylguanidine (**5i**): Yield 57%; mp fumarate: 154-157°C; ¹H-NMR (D₂O) δ: 0.74 (d, 6H), 1.22 (m, 4H), 1.40-1.50 (m, 4H), 1.52 (m, 1H), 2.84 (dd, 4H), 3.05 (t, 2H), 6.41 (s, 2H); EI-MS: 239.2 (M)⁺; Anal. Calcd. for fumarate C₁₂H₂₅N₅·C₄H₄O₄: C, 54.07; H, 8.22; N, 19.70. Found: C, 54.60; H, 8.09; N, 19.97.

N-(7-Aminoheptyl)-*N*''-cyano-*N*'-isobutylguanidine (**5j**): Yield 51%; mp fumarate: 113-115°C; ¹H-NMR (D₂O) δ: 0.74 (d, 6H), 1.21 (s, 4H), 1.39-1.51 (m, 4H), 1.69 (m, 1H), 2.84 (dd, 4H), 3.05 (t, 2H), 6.54 (s, 2H); EI-MS: 253.2 (M)⁺; Anal. Calcd. for fumarate C₁₃H₂₇N₅·C₄H₄O₄: C, 55.27; H, 8.46; N, 18.96. Found: C, 55.11; H, 8.55; N, 19.14.

N-(5-Aminopentyl)-*N*''-cyano-*N*'-phenethylguanidine (**5k**): Yield 55%; mp fumarate: 155-156°C; ¹H-NMR (D₂O) δ: 1.09-1.22 (m, 4H), 1.42 (dd, 2H), 2.67-2.87 (m, 6H), 3.28 (t, 2H), 6.49 (s, 2H), 7.09-7.19 (m, 5H); EI-MS: 273.2 (M)⁺; Anal. Calc. for fumarate C₁₅H₂₃N₅·C₄H₄O₄: C, 58.60; H, 6.99; N, 17.98. Found: C, 58.06, H, 7.09; N, 17.72.

N-(7-Aminoheptyl)-*N*''-cyano-*N*'-phenethylguanidine (**5l**): Yield 60%; mp fumarate: 165-166°C; ¹H-NMR (D₂O) δ: 1.13-1.20 (m, 8H), 1.45 (m, 2H), 2.67-2.85 (m, 6H), 3.28 (t, 2H), 6.49 (s, 2H), 7.08-7.19 (m, 5H); EI-MS: 301.2 (M)⁺; Anal. Calcd. for fumarate C₁₇H₂₇N₅·C₄H₄O₄: C, 60.41; H, 7.48; N, 16.77; Found: C, 60.16; H, 7.61; N, 16.76.

Analgesic activity

Male and Female (1:1) Kunming mice (weighing 18-22 g) were used to test the analgesic activity. The tests were carried out by administering the compounds orally at a dose of 40 mg/kg, and each compound was tested on 10 mice. Thirty minutes later, the animals were injected intraperitoneally (ip) with 0.4 mL/mouse of a 0.6% acetic acid solution and writhes were counted during the following 15 min. The mean number of writhes for each experimental group and percent decrease compared with control group (10 mice treated with saline) were calculated.

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