Synthesis of 3-(2-Guanidinoethyl) and 3-[2-(*S*-Methylisothioureidoethyl)] Analogs of 5-Isopropyl 2,6-Dimethyl-1,4-dihydro-4-(2,3-dichlorophenyl)pyridine-3,5-dicarboxylate as a Respective Releaser of Nitric Oxide and Inhibitor of Nitric Oxide Synthase

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The Hantzsch condensation of 2-azidoethyl acetoacetate with 2,3-dichlorobenzaldehyde and isopropyl 3-aminocrotonate afforded 3-(2-azidoethyl) 5-isopropyl 2,6-dimethyl-1,4-dihydro-4-(2,3-dichlorophenyl)pyridine-3,5-dicarboxylate (**7**). Reduction of the 3-(2-azidoethyl) moiety of **7** using 5% palladium-on-calcium carbonate and hydrogen gas gave the 3-(2-aminoethyl) derivative **8**, which was subjected to guanylation using 1*H*-pyrazole-1-carboxamidine hydrochloride to yield the target 3-(2-guanidinoethyl) analog **9**. The 3-(2-aminoethyl) product **8** was elaborated to the title compound 3-[2-(*S*-methylisothioureidoethyl)] 5-isopropyl 2,6-dimethyl-1,4-dihydro-4-(2,3-dichlorophenyl)pyridine-3,5-dicarboxylate hydrochloride (**12**) *via* the intermediate 3-(2-thioureidoethyl) compound **10**. The 3-(2-guanidinoethyl **9** and 3-[2-(*S*-methylisothioureidoethyl)] **12** compounds were about 116- and 23-fold less potent calcium channel antagonists, respectively relative to the reference drug nifedipine.

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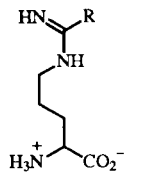
Introduction.

The significant therapeutic potential associated with the rational control of nitric oxide (•NO) synthesis has stimulated intense pharmaceutical interest in this area of research [1,2]. Nitric oxide synthase (NOS) catalyzes the molecular oxygen and NADPH-dependent five electron oxidation of L-arginine to L-citrulline and •NO [3]. The biological actions of •NO relate directly to the tissue and cell type in which it is produced. Thus, when •NO is synthesized in the vascular endothelium, it induces relaxation of adjacent smooth muscle *via* activation of the enzyme guanylate cyclase that is present in vascular smooth muscle. Production of •NO by immune system cells such as macrophages and neutrophils utilizes the toxic properties of •NO to kill or inhibit the growth of invading pathogenic organisms and tumor cells [4]. Two approachs to regulate the physiological level and function of •NO action include the design of NOS inhibitors and •NO-releasing drugs to decrease and elevate the physiological levels of •NO, respectively. NOS inhibitors have potential therapeutic value to treat endotoxic shock where levels of •NO exceed normal physiological levels [5]. In contrast, •NO-releasing drugs could be of value to inhibit platelet aggregation and adhesion [6].

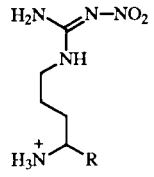
A number of N^G-substituted-L-arginine analogs **1a-c, 2a-b**, *N*-(iminoethyl)-L-ornithine (**1d**) [1] and *S*-methyl-L-thiocitrulline (**1e**) [7] have been characterized as NOS inhibitors. Ogawa *et al.* [8] prepared a class of 1,4-dihydropyridines **3a** containing a 2-nitrooxyethyl moiety at the C-3 ester position that increased femoral and vertebral arterial blood flow relative to the calcium channel (CC) antagonist nifedipine. A related class of 3-(1,3-dinitrooxy-2-propyl) analogs **3b**, which exhibit potent CC antagonist activity [9], were investigated that could also serve as potential releasers of •NO *in vivo* [2]. It was therefore of interest to develop hybrid molecules which could exhibit CC antagonist activity due to the presence of the CC antagonist 1,4-dihydropyidine moiety that possess a C-3 ester substituent which simultaneously release •NO *in vivo* (guanidinoethyl), or confer NOS inhibitory activity (*S*-methylisothioureidoethyl). We now report the synthesis and CC antagonist activities of the 3-(2-guanidinoethyl) **9** and 3-[2-(*S*-methylisothioureidoethyl)] **12** derivatives of 5-isopropyl 2,6-dimethyl-1,4-dihydro-4-(2,3-dichlorophenyl)pyridine-3,5-dicarboxylate.

Chemistry.

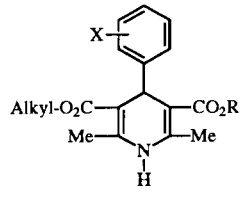
Reaction of 2-azidoethanol (**5**), prepared by the reaction of 2-chloroethanol (**4**) and sodium azide, with diketene



1a, R = NHMe (L-NMA)
1b, R = $NHNH_2$ (L-NAA)
1c, R = NH-cylcopropyl (L-CPA)
1d, R = Me (L-NIO)
1e, R = SMe (L-NTMC)



2a, R = CO_2^- (L-NNA)
2b, R = CO_2Me (L-NAME)



3a, R = $CH_2CH_2ONO_2$
3b, R = $CH(CH_2ONO_2)_2$

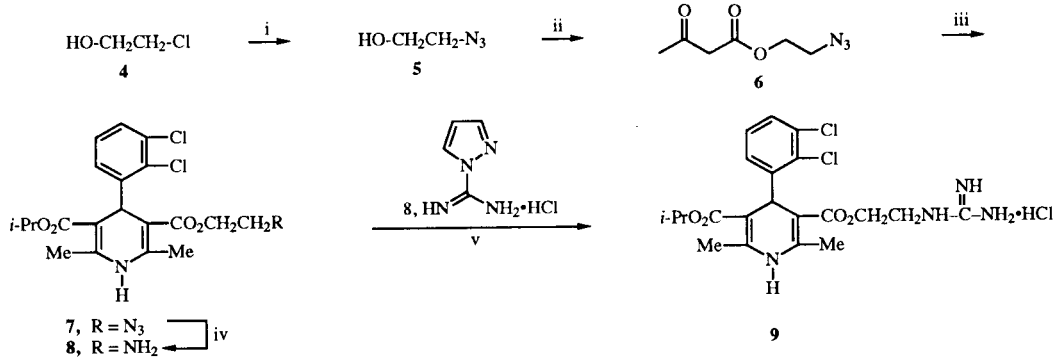
afforded 2-azidoethyl acetoacetate (**6**) in 60% yield, as illustrated in Scheme 1. Condensation of **6** with 2,3-dichlorobenzaldehyde and isopropyl 3-aminocrotonate, using a modified Hantzsch reaction [10] yielded 3-(2-azidoethyl) 5-isopropyl 2,6-dimethyl-1,4-dihydro-4-(2,3-dichlorophenyl)pyridine-3,5-dicarboxylate (**7**, 54% yield). Reduction of **7** with 5% palladium-on-calcium carbonate and hydrogen gas afforded the 3-(2-aminoethyl) derivative **8**, (26%). Guanylation of the 3-(2-aminoethyl) compound **8** using 1*H*-pyrazole-1-carboxamidine hydrochloride [11] yielded the target product 3-(2-guanidinoethyl) 5-isopropyl 2,6-dimethyl-1,4-dihydro-4-(2,3-dichlorophenyl)pyridine-3,5-dicarboxylate hydrochoride (**9**, 34% yield).

uct 3-[2-(*S*-methylisothioureidoethyl)] 5-isopropyl 2,6-dimethyl-1,4-dihydro-4-(2,3-dichlorophenyl)pyridine-3,5-dicarboxylate hydrochloride (**12**, 88% yield).

Biological Results.

The *in vitro* calcium channel (CC) antagonist activities of compounds **9** and **12**, determined as the molar concentration of test compound causing a 50% decrease in the slow component, or tonic contractile response, (IC_{50} ± SEM, n = 3) in guinea pig ileum longitudinal smooth muscle (GPILSM) by the muscarinic agonist carbachol (1.6×10^{-7} *M*), were determined graphically from the dose-response curves [12]. Compounds **9** (IC_{50} = 1.67 ±

Scheme 1[a]

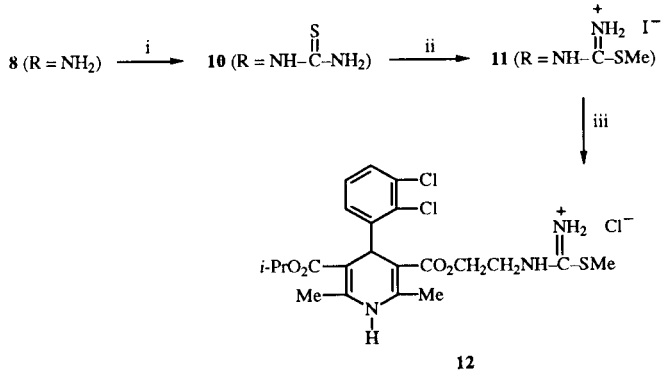


[a] Reagents and conditions: i, NaN_3, 110°, 24 h; ii, diketene, Et_3N, 80°, 1 h; iii, 2,3-dichlorobenzaldehyde, isopropyl 3-aminocrotonate, *i*-PrOH, reflux, 6 h; iv, 5% $Pd/CaCO_3$, H_2 gas, 25°, 1 h; v, 1*H*-pyrazole-1-carboxamidine. HCl, $(i\text{-Pr})_2NEt$, DMF, 25°, 24 h.

The two-step reaction of the 3-(2-aminoethyl) compound **8** with thiophosgene in the presence of calcium carbonate, and then the subsequent reaction with ammonia in methanol yielded the 3-(2-thioureidoethyl) product **10** in 20% yield, as illustrated in Scheme 2.

Treatment of **10** with iodomethane in acetonitrile gave the 3-[2-(*S*-methylisothioureidoethyl)] hydroiodide product **11** (85% yield) that was elaborated to the target prod-

Scheme 2[a]



[a] Regents and conditions: i, thiophosgene, $CaCO_3$, $CHCl_3$-H_2O, 25°, 20 h and then NH_3, MeOH, 20°, 3 h; ii, MeI, MeCN, 25°, 16 h; iii, $NaHCO_3$, dioxane, 25°, 5 min and then 4N HCl, dioxane, 25°, 1 h.

0.05 x 10^{-6} *M*) and **12** (IC_{50} = 3.32 ± 0.08 x 10^{-7} *M*) were less potent CC antagonists than the reference drug nifedipine [3,5-dimethyl 2,6-dimethyl-1,4-dihydro-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate] which exhibited an IC_{50} value of 1.43 ± 0.38 x 10^{-8} *M*. It has been observed that the 3-(2-guanidinoethyl) compound **9** enhances polychromatic light induced relaxation (photorelaxation) of rat aortic tissue pre-contracted with phenylephrine [13].

The 3-(2-guanidinoethyl) compound **9** warrants evaluation as a nitric oxide (•NO) releasing drug if it serves as a substrate, like L-arginine, for nitric oxide synthase (NOS) [2], whereas the 3-[2-(*S*-methylisothioureidoethyl)] compound **12**, based on a structural similarity to *S*-methylthiocitrulline (**1e**), is a potential NOS inhibitor [7]. The 3-(2-azidoethyl) compound (**7**) may be of value as a biochemical tool to photolabel the α_1-subunit binding site of the L-type calcium channel receptor [14].

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover capilliary apparatus and are uncorrected. Nuclear magnetic reso-

nance spectra (^{1}H nmr) were recorded on a Bruker AM-300 spectrometer. The assignment of exchangeable protons (NH, NH_2) was confirmed by the addition of deuterium oxide. Infrared spectra were acquired using a Nicolet 5DX-FT spectrometer. Silica gel column chromatography was carried out using Merck 7734 (60-200 mesh) silica gel. Diketene, 2,3-dichlorobenzaldehyde and isopropyl 3-aminocrotonate were purchased from the Aldrich Chemical Co. 1*H*-Pyrazole-1-carboxamidine hydrochloride was prepared according to the reported procedure [11].

2-Azidoethanol (**5**).

Sodium azide (7.15 g, 0.11 mole) was added to 2-chloroethanol (8.05 g, 0.1 mole), the reaction was allowed to proceed at 110° for 24 hours with stirring and the resulting precipitate was removed by filtration. Removal of the solvent from the filtrate and distillation of the residue obtained afforded **5** as an oil (7.0 g, 80%), bp 80°/10 mm (lit [15] bp 60°/8 mm); ir (neat): ν 3344 (OH), 2106 (N_3) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.27 (s, 1H, OH), 3.47 (t, J = 6 Hz, 2H, CH_2N_3), 3.75-3.80 (m, 2H, CH_2OH). This product was used immediately in the subsequent reaction.

2-Azidoethyl Acetoacetate (**6**).

Diketene (4.2 g, 50 mmoles) was added dropwise with stirring to 2-azidoethanol (4.35 g, 50 mmoles) containing a catalytic amount of triethylamine (4-5 drops) that was preheated to 60°. Diketene was added at a rate such that the temperature of the reaction mixture did not exceed 80°, and the reaction was allowed to proceed at 80° for one additional hour. Removal of the solvent *in vacuo* gave a residue which was purified by silica gel column chromatography using ethyl acetate-hexane (1:1, v/v) as eluent to afford **6** as an oil (5.2 g, 60%); ir (neat): ν 2114 (N_3), 1745 and 1720 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.28 (s, 3H, CH_3), 3.48 (m, 4H, CH_2N_3, $COCH_2CO_2$), 4.30 (t, J = 6 Hz, 2H, $CO_2CH_2CH_2$).

Anal. Calcd. for $C_6H_9N_3O_3$: C, 42.11; H, 5.30. Found: C, 42.45; H, 5.30.

3-(2-Azidoethyl) 5-Isopropyl 2,6-Dimethyl-1,4-dihydro-4-(2,3-dichlorophenyl)pyridine-3,5-dicarboxylate (**7**).

A mixture of 2,3-dichlorobenzaldehyde (3.50 g, 20 mmoles), 2-azidoethyl acetoacetate (**6**, 3.42 g, 20 mmoles) and isopropyl 3-aminocrotonate (2.84 g, 20 mmoles) in 2-propanol (30 ml) was heated at reflux for six hours. Removal of the solvent *in vacuo* and purification of the residue obtained by silica gel column chromatography using ethyl acetate-hexane (60:40, v/v) as eluent afforded **7** as a viscous oil (4.9 g, 54%); ir (neat): ν 3336 (NH), 2106 (N_3), 1687 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.04 and 1.25 (two d, $J_{CH,Me}$ = 6 Hz, 3H each, $CHMe_2$), 2.33 (s, 6H, C-2 and C-6 *Me's*), 3.38-3.56 (m, 2H, CH_2N_3), 4.12-4.28 (m, 2H, CO_2CH_2), 4.98 (sept, $J_{CH,Me}$ = 6 Hz, 1H, $CHMe_2$), 5.46 (s, 1H, H-4), 5.70 (br s, 1H, N*H*), 7.08 (t, J = 8 Hz, 1H, aryl H-5), 7.25-7.30 (m, 1H, aryl H-6), 7.34 (dd, $J_{4,5}$ = 8, $J_{4,6}$ = 2 Hz,1H, aryl H-4).

Anal. Calcd. for $C_{20}H_{22}Cl_2N_4O_4$: C, 52.99; H, 4.89. Found: C, 53.15; H, 5.11.

3-(2-Aminoethyl) 5-Isopropyl 2,6-Dimethyl-1,4-dihydro-4-(2,3-dichlorophenyl)pyridine-3,5-dicarboxylate (**8**).

5% Palladium-on-calcium carbonate (0.1 g) was added to a solution of **7** (4.53 g, 10 mmoles) in 98% ethanol (20 ml). The reaction flask was flushed with hydrogen gas and an inflated balloon containing hydrogen gas was connected to the reaction flask. The reaction was allowed to proceed for one hour with stirring at 25°, the solid which was removed by filtration was discarded, and the solvent was removed *in vacuo*. The residue obtained was purified by silica gel column chromatography using ethyl acetate-hexane (9:1, v/v) as eluent to yield **8** (1.1 g, 26%), mp 75° after recrystallization from ethyl acetate-hexane; ir (potassium bromide): ν 3254 (NH), 1687 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.05 and 1.25 (two d, $J_{CH,Me}$ = 6 Hz, 3H each, $CHMe_2$), 2.28-2.36 (m, 8H, C-2 and C-6 *Me's*, NH_2), 2.95 (t, J = 6 Hz, 2H, CH_2NH_2), 4.04-4.17 (m, 2H, CO_2CH_2), 4.98 (sept, J = 6 Hz, 1H, $CHMe_2$), 5.43 (s, 1H, H-4), 5.77 (br s, 1H, N*H*), 7.09 (t, J = 8 Hz, 1H, aryl H-5), 7.22-7.30 (m, 1H, aryl H-6), 7.33 (dd, J = 8, J = 2 Hz, 1H, aryl H-4).

Anal. Calcd. for $C_{20}H_{24}Cl_2N_2O_4$: C, 56.21; H, 5.66. Found: C, 56.19; H, 5.71.

3-(2-Guanidinoethyl) 5-Isopropyl 2,6-Dimethyl-1,4-dihydro-4-(2,3-dichlorophenyl)pyridine-3,5-dicarboxylate Hydrochloride (**9**).

Diisopropylethylamine (151 mg, 1.17 mmoles) and 1*H*-pyrazole-1-carboxamidine hydrochloride (171 mg, 1.17 mmoles) were added to a solution of **8** (0.5 g, 1.17 mmoles) in dimethylformamide (2 ml) and the reaction was allowed to proceed at 25° under a nitrogen atmosphere for 24 hours with stirring. Diethyl ether (10 ml) was added to precipitate the solid product which was removed by filtration and washed with cold diethyl ether. Purification of this solid by silica gel column chromatography using ethyl acetate-ethanol (80:20, v/v) as eluent gave **9** as an amorphous solid (200 mg, 34%), mp 60°; ir (potassium bromide): ν 3385 (NH), 1663 (C=O) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 0.83 and 1.16 (two d, $J_{CH,Me}$ = 6 Hz, 3H each, $CHMe_2$), 2.22 (s, 6H, C-2 and C-6 *Me's*), 2.50 (br s, 1H, CH_2NH), 3.30-3.40 (m, 2H, CH_2NH), 3.88-4.00 and 4.02-4.10 (two m, 1H each, CO_2CH_2), 4.81 (sept, J = 6 Hz, 1H, $CHMe_2$), 5.28 (s, 1H, H-4), 7.00-7.40 (m, 6H, *H*Cl, NH_2, aryl hydrogens), 7.59 (br s, 1H, =N*H*), 9.0 (br s, 1H, dihydropyridine N*H*); uv (98% ethanol): λ (log ε) 205 (4.51), 237 (4.32), 362 (3.75) nm.

Anal. Calcd. for $C_{21}H_{27}Cl_3N_4O_4$: C, 49.86; H, 5.38; N, 11.08. Found: C, 49.60; H, 5.60; N, 10.95.

3-(2-Thioureidoethyl) 5-Isopropyl 2,6-Dimethyl-1,4-dihydro-4-(2,3-dichlorophenyl)pyridine-3,5-dicarboxylate (**10**).

A solution of **8** (427 mg, 1 mmole) in chloroform (5 ml) was added to a solution of calcium carbonate (285 mg) and thiophosgene (0.11 ml, 1.43 mmoles) in water (5 ml) and the reaction was allowed to proceed at 25° for 18 hours with stirring. The reaction mixture was filtered and the two layers were allowed to separate. The aqueous layer was extracted with chloroform (2 x 10 ml), and the combined organic layers were dried (magnesium sulfate). Removal of the solvent *in vacuo* gave an oil which was dissolved in methanol (10 ml) prior to cooling to 0°. Ammonia gas was bubbled slowly into this solution for 10 minutes, and then the reaction was allowed to proceed for three hours at 0° with stirring. Removal of the solvent *in vacuo* yielded a residue which was purified by silica gel column chromatography using ethyl acetate-ethanol (95:5, v/v) as eluent to afford **10** (98 mg, 20%), mp 100° after recrystallization from ethyl acetate-hexane; ir (potassium bromide): ν 3385 (NH), 1671 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.08 and 1.26 (two d, J = 6 Hz, 3H each,

CH*Me*$_2$), 2.34 (s, 6H, C-2 and C-6 *Me's*), 3.60-3.90 (br s, 2H, N*H*$_2$), 4.10-4.30 (m, 4H, C*H*$_2$C*H*$_2$), 5.0 (sept, J = 6 Hz, 1H, C*H*Me$_2$), 5.41 (s, 1H, H-4), 5.87 (br s, 1H, N*H*), 6.60 (br s, 1H, N*H*), 7.12 (t, J = 8 Hz, 1H, aryl H-5), 7.26-7.36 (m, 2H, aryl H-4 and H-6); uv (98% ethanol): λ (log ε) 206 (3.16), 241 (3.05), 363 (2.41) nm.

Anal. Calcd. for $C_{21}H_{25}Cl_2N_3O_4.1/4H_2O$: C, 51.37; H, 5.24; N, 8.55. Found: C, 51.44; H, 5.36; N, 8.15.

3-[2-(*S*-Methylisothioureidoethyl)] 5-Isopropyl 2,6-Dimethyl-1,4-dihydro-4-(2,3-dichlorophenyl)pyridine-3,5-dicarboxylate Hydroiodide (**11**).

A mixture of **10** (100 mg, 0.205 mmole) and iodomethane (0.1 ml, 1.68 mmoles) in acetonitrile (3 ml) was stirred at 25° for 16 hours. Removal of the solvent *in vacuo* and recrystallization of the residue obtained from ethyl acetate-hexane afforded **11** (110 mg, 85%), mp 125°; ir (potassium bromide): ν 3394 (NH), 1685 and 1635 (C=O) cm^{-1}; uv (98% ethanol): λ (log ε) 205 (4.59), 219 (4.56), 363 (3.78) nm; ^{1}H nmr (DMSO-d$_6$): δ 1.20 and 1.42 (two d, J = 6 Hz, 3H each, CH*Me*$_2$), 2.77 and 2.78 (two s, 3H each, C-2 and C-6 *Me's*), 2.84 (s, 3H, S*Me*), 3.76-3.90 (m, 2H, C*H*$_2$NH), 4.20-4.30 (m, 1H, CO$_2$CH*H'*), 4.42-4.52 (m, 1H, CO$_2$CH*H'*), 5.08 (sept, J = 6 Hz, 1H, C*H*Me$_2$), 5.53 (s, 1H, H-4), 7.46-7.58 (m, 2H, aryl H-5 and H-6), 7.68 (dd, J = 8, J = 2 Hz, 1H, aryl H-4), 9.22 (br s, 1H, N*H*), 9.42 (br s, 2H, N*H*$_2$), 9.72 (br s,1 H, N*H*).

Anal. Calcd. for $C_{22}H_{28}Cl_2IN_3O_4S$: C, 42.05; H, 4.49; N, 6.69. Found: C, 42.33; H, 4.53; N, 6.50.

3-[2-(*S*-Methylisothioureidoethyl)] 5-Isopropyl 2,6-Dimethyl-1,4-dihydro-4-(2,3-dichlorophenyl)pyridine-3,5-dicarboxylate Hydrochloride (**12**).

A saturated aqueous solution of sodium bicarbonate (1 ml) was added to a solution of **11** (60 mg, 0.95 mmole) in dioxane (1 ml) and the mixture was stirred at 25° for five minutes. Extraction with ethyl acetate (3 x 10 ml), drying the combined organic extracts (sodium sulfate), removal of the solvent *in vacuo,* dissolution of the residue obtained in dioxane (1 ml), addition of a 4*N* hydrogen chloride solution in dioxane (1 ml), stirring the reaction mixture at 25° for one hour, and then addition of diethyl ether (10 ml) precipitated the organic product. This solid product was removed by filtration prior to recrystallization from ethyl acetate-hexane to afford **12** (45 mg, 88%), mp 125°; ir (potassium bromide): ν 3398 (NH), 1687 and 1638 (C=O) cm^{-1}; uv (98% ethanol): λ (log ε) 205 (4.53), 364 (3.70) nm; ^{1}H nmr (DMSO-d$_6$): δ 1.20 and 1.44 (two d, J = 6 Hz each, 3H each, CH*Me*$_2$), 2.76 and 2.77 (two s, 3H each, C-2 and C-6 *Me's*), 2.86 (s, 3H, S*Me*), 3.56-3.76 (m, 2H, C*H*$_2$NH), 4.22-4.32 (m, 1H, CO$_2$CH*H'*), 4.42-4.52 (m, 1H, CO$_2$CH*H'*), 5.08 (sept, J = 6 Hz, 1H, C*H*Me$_2$), 5.54 (s, 1H, H-4), 7.46-7.56 (m, 2H, aryl H-5 and H-6), 7.66 (dd, $J_{4,5}$ = 8, $J_{4,6}$ = 2 Hz, 1H, aryl H-4), 9.3 (br s, 1H, N*H*), 9.52 (br s, 2H, N*H*$_2$), 9.78 (br s,1H, N*H*).

Anal. Calcd. for $C_{22}H_{28}Cl_3N_3O_4S$: C, 49.22; H, 5.26; N, 7.83. Found: C, 49.20; H, 5.10; N, 7.69.

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