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First Synthesis of 4-Substituted Benzenesulfonylcyanoguanidines

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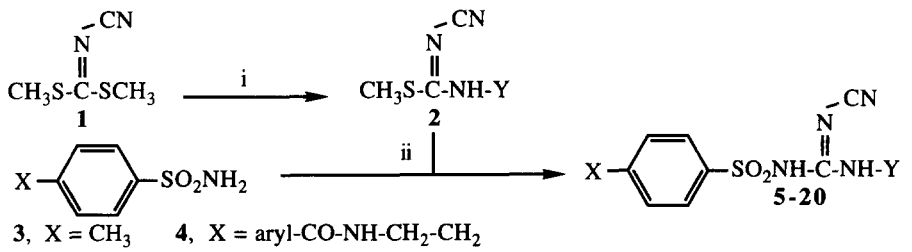
Abstract: N'-substituted-N-cyano-S-methylcarbamimidothioates react with 4-substitutedbenzene sulfonamides to give the corresponding sulfonylcyanoguanidines.

The cyanoguanidine group is regarded as a non-classical bioisostere of the urea and thiourea function[1]. This concept has been developed for the gastric antisecretory N'-alkyl-N-imidazolylalkylthioureas to give cimetidine[2]. Conversly, N'-alkyl-N-substituted pyridyl-thioureas and -ureas were found to be as active as pinacidil, an antihypertensive cyanoguanidine[3,4]. In the present study, we have applied this strategy to hypoglycemic sulfonylureas to obtain original drugs bearing a new moiety: the sulfonylcyanoguanidine function.



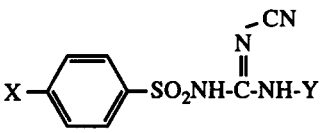
Scheme 1 *Reagents :* i, Y-NH_2 (1.5 equiv), ethanol, 25°C; ii, NaOH (1 equiv), DMF, dioxane, reflux.

The N"[4-(substitutedphenyl)sulfonyl]-N'-substituted-N"cyanoguanidines **5-20** (table 1) were prepared by refluxing an excess (1.2 equiv) of N'-substituted-N-cyano-S-methylcarbamimidothioate **2** with the sodium salt of 4-methylbenzenesulfonamide **3**[5] or the 4-substitutedcarboxamidoethylbenzenesulfonamide **4**[6] (scheme 1). The carbamimidothioates **2** were synthesized by stirring a mixture of N-cyano-S,S'-dimethylimino carbonate **1**[7] in ethanol with the required amine (Y-NH_2, 1.5 equiv).

The compounds **7**, **8**, **12** and **13** are the bioisosteres of tolbutamide, tolcyclamide, tolazamide and gliclazide, the main representatives of the hypoglycemic drugs of first chemical generation (X = CH_3)[8]. The antidiabetic sulfonylureas bearing a substituted carboxamidoethyl side-chain belong to the second chemical generation. Compound **16** is the bioisostere of glibenclamide, one of the most potent hypoglycemic drug[8]. The electron-withdrawing groups (SO_2 and =N-CN) should maintain the acidity of the moiety as compared to the sulfonylurea function. The ^{1}H-NMR spectra[9] of **7** (δ = 5.6, 2H, br s) and **16** (δ = 4.7, 2H, br s) revealed that both protons of the cyanoguanidine moiety were not distinguishable and located with the residual water contained in DMSO-d_6. On the contrary, tolbutamide (δ = 10.41, 1H, br s; 6.30, 1H, br t) and glibenclamide (δ = 10.27, 1H, br s; 6.25 1H, br d), their sulfonylurea counterparts, clearly exhibited three different signals corresponding to the two urea protons and residual water. These data suggest tautomeric forms of the sulfonylcyanoguanidine moiety and a higher lability of their acidic proton as compared to their sufonylurea bioisosteres. The chemical shift values lead to the proposal that **7** is probably more acidic than **16**, as it is

reported for tolbutamide (pKa = 5.3)[10] compared to glibenclamide (pKa = 6.8)[11]. All compounds were characterized by analytical and spectral methods[9].

Table I : Synthesis of 4-substitutedbenzenesulfonylcyanoguanidines



N°	X	Y	Yield (%)	Mp (°C)[a]
5	CH_3	C_2H_5	17	131-133
6	CH_3	$(CH_3)_2CH$	72	132-134
7	CH_3	$CH_3(CH_2)_3$	28	108-110
8	CH_3	cyclohexyl	79	156-158
9	CH_3	cycloheptyl	78	144-146
10	CH_3	(±)4-CH_3cyclohexyl	52	163-165
11	CH_3	$(CH_2)_5N$	14	210-212
12	CH_3	$(CH_2)_6N$	22	193-195
13	CH_3	1-azabicyclo[3,2,1]octane	19	186-188
14	$C_6H_5CONHCH_2CH_2$	cyclohexyl	76	174-176
15	4-$CH_3OC_6H_4CONHCH_2CH_2$	cyclohexyl	26	176-178
16	2-CH_3O,5-$ClC_6H_3CONHCH_2CH_2$	cyclohexyl	50	92-95
17	2-CH_3O,5-$ClC_6H_3CONHCH_2CH_2$	(±)4-CH_3cyclohexyl	64	85-87
18	2-furfurylCONHCH$_2$CH$_2$	cyclohexyl	55	146-148
19	$C_6H_5NHCONHCH_2CH_2$	cyclohexyl	37	108-110
20	4-$ClC_6H_4NHCONHCH_2CH_2$	cyclohexyl	82	128-130

[a] All compounds were crystallized from ethanol.

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9 The elemental analyses for C,H,N,S are within 0.4% of the theorical values and were performed on a Carlo Erba 1108 analyzer. All new compounds gave IR and ^{1}H-NMR spectra in accordance with their proposed structure. **7**: ^{1}H-NMR (80 MHz, d$_6$-DMSO) δ 7.65 (2H, d, *J*=8Hz), 7.30 (2H, d, *J*=8Hz), 5.60 (2H, m), 3.15 (2H, br s), 2.30 (3H, s), 1.65-1.25 (4H, m), 0.8 (3H, t). IR (KBr) 2199 cm^{-1} (C≡N st). **16**: ^{1}H-NMR (80 MHz, d$_6$-DMSO) δ 8.18 (1H, m), 7.75 (2H, d), 7.58 (1H, d), 7.4 (3H, dd), 7.05 (1H, d), 4.70 (2H, br s), 3.72 (3H, s), 3.25-3.65 (3H, m), 2.95 (2H, m), 1.80-0.95 (10H, m). IR (KBr) 2188 cm^{-1} (C≡N st).

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