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Masereel, Bernard; Lebrun, Philippe; Dogné, Jean-Michel; de Tullio, Pascal; Pirotte, Bernard; Pochet, Lionel; Diouf, Ousmane; Delarge, Jacques

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First Synthesis of 4-Substituted Benzenesulfonylcyanoguanidines

Bernard Masereel*, Philippe Lebrun†, Jean Michel Dogné, Pascal de Tullio, Bernard Pirotte,
 Lionel Pochet, Ousman Diouf and Jacques Delarge

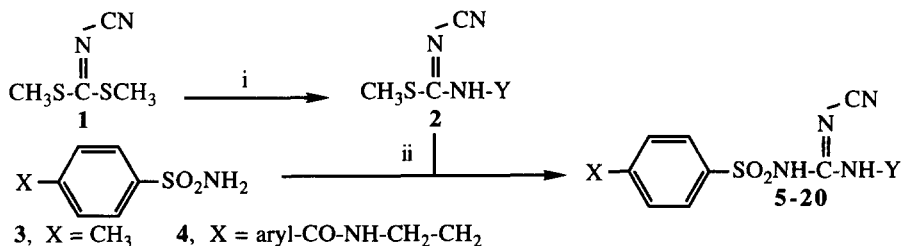
*Department of Medicinal Chemistry, University of Liège, 3, rue Fusch, 4000 Liège, Belgium

†Department of Pharmacology, University of Brussel, 808, route de Lennik, 1070 Brussels, Belgium

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

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The cyanoguanidine group is regarded as a non-classical bioisostere of the urea and thiourea function¹. This concept has been developed for the gastric antisecretory N'-alkyl-N-imidazolylalkylthioureas to give cimetidine². Conversely, 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-NH₂ (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 carbamidithioates **2** were synthesized by stirring a mixture of N-cyano-S,S'-dimethylimino carbonate **17** in ethanol with the required amine (Y-NH₂, 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 = CH₃)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 drug⁸. The electron-withdrawing groups (SO₂ and =N-CN) should maintain the acidity of the moiety as compared to the sulfonylurea function. The ¹H-NMR spectra⁹ 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-d₆. 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 sulfonylurea bioisosteres. The chemical shift values lead to the proposal that **7** is probably more acidic than **16**, as it is

reported for tolbutamide ($pK_a = 5.3$)¹⁰ compared to glibenclamide ($pK_a = 6.8$)¹¹. All compounds were characterized by analytical and spectral methods⁹.

Table I : Synthesis of 4-substitutedbenzenesulfonylcyanoguanidines

N°	X	Y	Yield (%)	Mp (°C) ^a
5	CH ₃	C ₂ H ₅	17	131-133
6	CH ₃	(CH ₃) ₂ CH	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 ₃ cyclohexyl	52	163-165
11	CH ₃	(CH ₂) ₅ N	14	210-212
12	CH ₃	(CH ₂) ₆ N	22	193-195
13	CH ₃	1-azabicyclo[3,2,1]octane	19	186-188
14	C ₆ H ₅ CONHCH ₂ CH ₂	cyclohexyl	76	174-176
15	4-CH ₃ OC ₆ H ₄ CONHCH ₂ CH ₂	cyclohexyl	26	176-178
16	2-CH ₃ O,5-ClC ₆ H ₃ CONHCH ₂ CH ₂	cyclohexyl	50	92-95
17	2-CH ₃ O,5-ClC ₆ H ₃ CONHCH ₂ CH ₂	(±)4-CH ₃ cyclohexyl	64	85-87
18	2-furfurylCONHCH ₂ CH ₂	cyclohexyl	55	146-148
19	C ₆ H ₅ NHCONHCH ₂ CH ₂	cyclohexyl	37	108-110
20	4-ClC ₆ H ₄ NHCONHCH ₂ CH ₂	cyclohexyl	82	128-130

^a All compounds were crystallized from ethanol.

REFERENCES AND NOTES

- 1 Thornber, C.W. *Chem. Soc. Rev.* **1979**, *8*, 563-580
- 2 Durant, G.J.; Emmett, J.C.; Gannellin C.R.; Miles, P.D.; Pearsons, M.E.; Prain, H.D.; White G.R. *J. Med. Chem.* **1977**, *20*, 901-906
- 3 Manley, Q.W.; Quast, U. *J. Med. Chem.* **1992**, *35*, 2327-2340
- 4 Takemoto, T.; Eda, M.; Okada, T.; Sakashita, H.; Matzno, S.; Gohda, M.; Ebisu, H.; Nakamura, M.; Fukaya, C.; Hihara, M.; Eikaku, M.; Yamanoushi, K.; Yokoyama, K. *J. Med. Chem.* **1994**, *37*, 18-25
- 5 Arndt, F.; Martius, C. *Justus Liebigs Ann. Chem.* **1932**, *499*, 228-287
- 6 Weber, H.; Aumüller, W.; Muth, K.; Weyer, R.; Heerdt, R.; Fauland, E.; Bänder, A.; Pfaff, W.; Schmidt, F.H.; Stork, H. *Drug Research / Arz. Forschung* **1969**, *19*, 1326-1346
- 7 Hantzsch, A.; Wolvekamp, M. *Justus Liebigs Ann. Chem.* **1904**, *331*, 264-297
- 8 Marchetti P.; Navalesi, R. *Clinical Pharmacokinetics* **1989**, *16*, 100-128
- 9 The elemental analyses for C,H,N,S are within 0.4% of the theoretical values and were performed on a Carlo Erba 1108 analyzer. All new compounds gave IR and ¹H-NMR spectra in accordance with their proposed structure. 7: ¹H-NMR (80 MHz, d₆-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: ¹H-NMR (80 MHz, d₆-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).
- 10 Häussler, A.; Hajdù, P. *Arch. Pharm.* **1958**, *291*, 531-535
- 11 Hajdù, P.; Kohler, K.F.; Schmidt, F.M.; Spingler, H. *Drug Research / Arz. Forschung* **1969**, *19*, 1381-1386

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