# Synthesis and biological evaluation of sulfonylcyanoguanidines and sulfonamidonitroethylenes as bioisosteres of hypoglycemic sulfonylureas

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**Laboratory note**

# Synthesis and biological evaluation of sulfonylcyanoguanidines and sulfonamidonitroethylenes as bioisosteres of hypoglycemic sulfonylureas

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**Summary** — Sulfonylcyanoguanidines and sulfonamidonitroethylenes are bioisosteres of hypoglycemic sulfonylureas and were prepared and evaluated for their insulin release potency from rat pancreatic islets. At 25 μM, both bioisosteres of glibenclamide, sulfonylcyanoguanidine **22** and sulfonamidonitroethylene **23**, were as potent as their parent on insulin secretion.

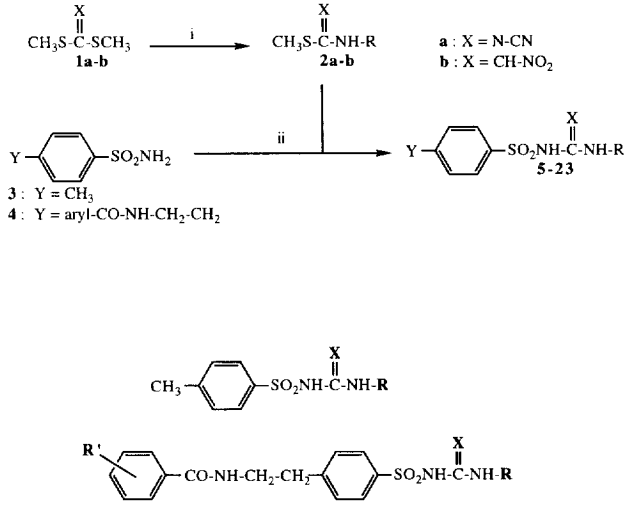
**sulfonylcyanoguanidine / sulfonamidonitroethylene / insulin secretion / diabetes**

## Introduction

The cyanoguanidine and the 1,1-diamino-2-nitroethylene functions are regarded as bioisosteres of the urea function [1]. This concept led to the discovery of powerful gastric antisecretory agents, such as cimetidine [2], a cyanoguanidine derivative, and ranitidine [3], a 1,1-diamino-2-nitroethylene compound. Recently, the cyanoguanidine bioisosteres of phenytoin [4], an antiepileptic acylurea, and torasemide [5], a diuretic sulfonylurea, were prepared and described as being less active than their leader. In this work, we applied a similar strategy to hypoglycemic sulfonylureas in order to obtain the corresponding sulfonylcyanoguanidines and sulfonamidonitroethylenes. As previously described [5], the presence of the electron-withdrawing groups (NC≡N and $CH{=}NO_2$) should preserve the required acidity of the sulfonamide moiety. Their potency as hypoglycemic drugs was evaluated by measuring insulin release from rat pancreatic islets.

## Chemistry

The bioisosteres of hypoglycemic sulfonylureas were synthesized by refluxing the sodium salt of the required sulfonamide **3** or **4** [6, 7] (scheme 1) with an excess of *N'*-substituted *N*-cyano-*S*-methylcarbamimidothioate **2a** or with 1-substituted amino-1-methylthio-2-nitroethylene **2b** to prepare sulfonylcyanoguanidines and 1-substituted amino-1-sulfonamido-2-nitroethylenes **5–23** (tables I and II). The carbamimidothioate derivatives and the nitro-




**Scheme 1.** (i) $RNH_2$, ethanol; (ii) NaOH, DMF, dioxane, reflux.

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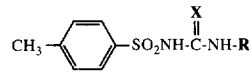
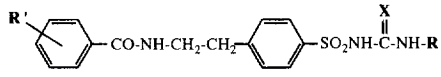
**Table I.** Effect of the first chemical generation bioisosteres on insulin release from rat pancreatic islets.



| *Compound* | *R* | *X* | *Drug concentration (μmol/L)* | *Percentage insulin release (mean ± SE)*[a] |
|---|---|---|---|---|
| **5** | $(CH_3)_2CH$ | NCN | 100 | NA |
| **6** | $CH_3(CH_2)_3$ | NCN | 100 | NA |
| | | | 25 | NA |
| **7** | Cyclohexyl | NCN | 100 | NA |
| **8** | Cycloheptyl | NCN | 100 | NA |
| **9** | $(CH_2)_5$=N | NCN | 100 | NA |
| **10** | $(CH_2)_6$=N | NCN | 25 | NA |
| **11** | 1-Azabicyclo[3.2.1]octane | NCN | 25 | NA |
| **12** | Cyclohexyl | $CHNO_2$ | 25 | 223.1 ± 15.3[b] |
| Tolbutamide | $CH_3(CH_2)_3$ | O | 100 | 429.5 ± 43.7[b] |
| | | | 25 | 363.5 ± 32.5[b] |
| Tolazamide | $(CH_2)_6$=N | O | 25 | 341.4 ± 55.3[b] |
| Gliclazide | 1-Azabicyclo[3.2.1]octane | O | 25 | 412.1 ± 35.0[b] |

[a]Percentage of insulin release from islets incubated in the presence of 8.3 mM glucose. Control (no added drug) was considered as 100%. NA = not active. [b]Different from control ($P < 0.05$).

**Table II.** Effect of the second chemical generation bioisosteres on insulin release from rat pancreatic islets.



| *Compound* | *R'* | *R* | *X* | *Percentage insulin release (mean ± SEM)*[a] |
|---|---|---|---|---|
| **13** | – | Cyclohexyl | NCN | 143.3 ± 9.5[b] |
| **14** | 2-Cl | Cyclohexyl | NCN | 325.3 ± 27.4[b] |
| **15** | 4-Cl | Cyclohexyl | NCN | 132.9 ± 10.9[b] |
| **16** | 3-$CH_3O$ | Cyclohexyl | NCN | 262.2 ± 23.7[b] |
| **17** | 4-$CH_3O$ | Cyclohexyl | NCN | 125.2 ± 10.5[b] |
| **18** | 3-F | Cyclohexyl | NCN | 303.8 ± 22.0[b] |
| **19** | 3-$CF_3$ | Cyclohexyl | NCN | 255.4 ± 19.6[b] |
| **20** | 2-$CH_3O$, 5-Cl | (±)-4-$CH_3$cyclohexyl | NCN | 273.9 ± 14.3[b] |
| **21** | 2-$CH_3O$, 5-Cl | Cyclopentyl | NCN | 452.5 ± 29.5[b] |
| **22** | 2-$CH_3O$, 5-Cl | Cyclohexyl | NCN | 552.8 ± 49.2[b] |
| **23** | 2-$CH_3O$, 5-Cl | Cyclohexyl | $CHNO_2$ | 492.2 ± 48.0[b] |
| Glibenclamide | 2-$CH_3O$, 5-Cl | Cyclohexyl | O | 485.6 ± 22.1[b] |

[a]Percentage of insulin release from islets incubated in the presence of 8.3 mM glucose and 25 μM of drug. Control (no added drug) was considered as 100%. [b]Different from control ($P < 0.05$).

ethylene intermediate were obtained by reaction of the appropriate primary amine with *N*-cyano-*S,S'*-dimethyldithioiminocarbonate **1a** [8] or with 1,1-bismethylthio-2-nitroethylene **1b** [9].

At pH 7.40, the lipophilicity of the sulfonylcyanoguanidines **6** (log $P$ = + 0.17 ± 0.01) and **22** (log $P$ = + 1.36 ± 0.02) was lower than that of their sulfonylurea counterparts, tolbutamide (log $P$ = + 0.41 ± 0.02) and glibenclamide (log $P$ = + 1.65 ± 0.04), respectively. The lipophilicity of the nitroethylene compound **23** was also lower (log $P$ = + 1.34 ± 0.02) than that of glibenclamide.

In contrast to the $^1$H-NMR spectrum of glibenclamide (δ = 10.27, br s, 1H; 6.25, 1H, br d), that of **22** showed that the two protons of the cyanoguanidine (δ = 4.7, br s, 2H) were indistinguishable and located with the residual water in the DMSO-$d_6$ solvent. For their nitroethylene bioisostere **23**, the nitroethylene proton (δ = 5.60, s, 1H) and the proton of the distal nitrogen (δ = 8.92, br d, 1H) were separated. These data suggest tautomeric forms of the sulfonylcyanoguanidine moiety only.

## Results and discussion

The compounds **5–12** (table I) are structurally related to the first chemical generation of hypoglycemic sulfonylureas (Y = $CH_3$). The sulfonylcyanoguanidines **6**, **10** and **11**, which are the bioisosteres of tolbutamide, tolazamide and gliclazide respectively, did not increase insulin secretion. At 25 μM, the nitroethylene **12** induced a twofold increase in insulin release (table I). It was more potent than its cyanoguanidine counterpart **7**, but was less active than tolbutamide ($P < 0.05$).

The compounds bearing a carboxamidoethyl side-chain **13–23** (table II) are chemically related to glibenclamide, one of the most powerful hypoglycemic sulfonylurea of the second chemical generation (Y = aryl-CONH$(CH_2)_2$). The presence of a cyclohexyl moiety reinforces the analogy with glibenclamide. A (±)-4-$CH_3$-cyclohexyl residue was placed on the distal nitrogen of the sulfonylcyanoguanidine function (**20**) to design a side-chain similar to that of glimepiride, a recently described hypoglycemic sulfonylurea [10]. As shown in table II, the substitution of the benzene ring strongly affected the biological response. Indeed, the absence of any substituent on the benzene ring (**13**) and the presence of a polar group in position 4 (**15** and **17**) strongly reduced the biological response. In contrast, *ortho* (**14**) or *meta* substitution (**16**, **18**, **19**) enhanced the capacity of these drugs to stimulate insulin secretion. The sulfonylcyanoguanidine **22** and the sulfonamidonitroethylene **23** were as active as glibenclamide ($P > 0.05$), their sulfonylurea counterpart (table II).

In conclusion, this work led to the preparation of sulfonylcyanoguanidines and to the synthesis of a new chemical function, the 1-amino-1-sulfonamido-2-nitroethylene group. At 25 μM, the bioisosteres of glibenclamide **22** (BM 208) and **23** (BM 225) were as potent as the leader glibenclamide at increasing insulin release from rat pancreatic islets. Further investigations are warranted to elucidate their mechanism of action and to confirm their usefulness in the treatment of type II diabetes.

## Experimental protocols

*Chemistry*

Elemental analyses for C, H, N, S were performed on a Carlo Erba EA 1108 analyzer and were within ± 0.4% of theoretical values. Melting points were determined in open capillary with a Büchi Tottoli apparatus and were uncorrected. $^1$H-NMR spectra were recorded on a Brucker 80 MHz using tetramethylsilane as internal standard and chemical shifts were expressed in part per million (δ). IR spectra were determined with a Perkin Elmer 1750 as KBr pellets. All reactions were routinely checked by TLC on silica gel 60F 254.

*General procedure for the synthesis of sulfonylcyanoguanidines **5–11** and **13–22***

The *N'*-substituted amino-*N*-cyano-*S*-methylcarbamimidothioates **2a** were prepared according to the previously described procedure [5]. In order to prepare the sulfonylcyanoguanidine **22**, the *N*-cyano-*N'*-cyclohexyl-*S*-methylcarbamimidothioate (0.80 g, 4.1 mmol) was added to the sodium salt of 4-(5-chloro-2-methoxybenzamidoethyl)benzene sulfonamide (1 g, 2.7 mmol) dissolved in 5 mL of *N,N'*-dimethylformamide/dioxane (3:2) and refluxed for 5 h. After evaporation of solvents under reduced pressure, the residue was dissolved in water (50 mL) and 2.5 N NaOH (5 mL). The solution was extracted three times with diethyl ether (50 mL) and adjusted to pH 1 with dilute hydrochloric acid. The precipitate was collected by filtration, washed with water, dried and recrystallized in ethanol to afford 0.71 g of **22** (yield: 51%). Mp = 92–95 °C; IR (KBr) 2188 cm$^{-1}$ (C≡N st). $^1$H-NMR (DMSO-$d_6$) δ 8.18 (t, 1H, CON*H*), 7.75 (d, 2H, aryl-$SO_2$), 7.58 (d, 1H, ClC=C*H*), 7.4 (dd, 3H, aryl), 7.05 (d, 1H, $CH_3$OC=C*H*), 4.70 (br s, 2H, $SO_2$N*H* and N*H*-cyclohexyl), 3.72 (s, 3H, OC$H_3$), 3.25–3.65 (m, 3H, NHC$H_2$ and NHC*H*<), 2.95 (m, 2H, C$H_2$-aryl), 1.80–0.95 (m, 10H, cyclohexyl). Anal $C_{24}H_{28}N_5O_4SCl$ (518.04).

*1-Cyclohexylamino-1-methylthio-2-nitroethylene **2b***

An excess of cyclohexylamine (2.1 mL, 18 mmol) was added to 1,1-bismethylthio-2-nitroethylene [9] (2.0 g, 12 mmol) and refluxed for 24 h. After cooling, the formed precipitate was filtered off, washed with ethanol and dried to give **2b** (yield: 75%). Mp = 101–103 °C; IR (KBr) 1563 cm$^{-1}$ (asym $NO_2$ st). $^1$H-NMR (80 MHz, DMSO-$d_6$) δ 10.37 (br s , 1H, N*H*), 6.68 (s, 1H, C*H*$NO_2$), 3.60 (m, 1H, NHC*H*<), 2.45 (s, 3H, SC$H_3$), 1.95–1.05 (m, 10H, cyclohexyl). Anal $C_9H_{16}N_2O_2S$ (216.30).

*General procedure for the synthesis of 1-cyclohexylamino-1-sulfonamido-2-nitroethylenes **12** and **23***

The nitroethylene **23** was obtained from reaction of an excess of 1-cyclohexylamino-1-methylthio-2-nitroethylene (0.90 g, 4.2 mmol) and 4-(5-chloro-2-methoxybenzamidoethyl) benzene sulfonamide (1 g, 2.7 mmol), following the procedure described above for **22**. The reaction gave 0.71 g of **23** (yield: 48%). Mp = 83–85 °C; IR (KBr) 1567 cm$^{-1}$ (asym $NO_2$ st). $^1$H-NMR (DMSO-$d_6$) δ 8.92 (br d, 1H, N*H*-cyclohexyl) 8.13 (t, 1H, CON*H*), 7.70 (d, 2H, aryl-$SO_2$), 7.60 (d, 1H, ClC=C*H*), 7.4 (dd, 3H, aryl), 7.07 (d, 1H, $CH_3$OC=C*H*), 5.60 (s, 1H, C*H*$NO_2$), 3.72 (s, 3H, OC$H_3$), 3.20–3.50 (m, 3H, NHC$H_2$ and NHC*H*<), 2.83 (m, 2H, C$H_2$-aryl), 1.95–0.90 (m, 10H, cyclohexyl). Anal $C_{24}H_{29}N_4O_6SCl$ (537.04).

*Lipophilicity*

The lipophilicity of **6**, **22**, **23**, tolbutamide and glibenclamide was expressed as the logarithm of the partition coefficient (log *P*) in *n*-octanol/phosphate buffer pH 7.40 by using the shake-flask technique [11].

*Insulin release from incubated pancreatic rat islets [12]*

Pancreatic islets were isolated from fed female rats. Groups of ten islets, each derived from the same batch of islets, were preincubated for 30 min at 37 °C in 1 mL of a buffered bicarbonate solution (in mM: NaCl 115, KCl 5, $CaCl_2$ 2.56, $MgCl_2$ 1.0, $NaHCO_3$ 24) supplemented with 2.8 mM D-glucose, 0.5% (w/v) dialysed albumin (fraction V) and bubbled with a mixture of $O_2/CO_2$ (95:5). The islets were then incubated at 37 °C for a further 90 min in 1 mL of the same buffered medium containing 8.3 mM D-glucose and, in addition, the required compound. Insulin release was measured radioimmunologically using rat insulin as standard.

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