Novel Substituted Aminoalkylguanidines as Potential Antihyperglycemic and Food Intake-Reducing Agents

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Abstract: We report the synthesis and evaluation of aminoalkylguanidine analogues and derivatives in C57BL/KsJ db/db diabetic mice, following identification by random screening of **1a** and **1b** as potential antihyperglycemics and/or modulators of food intake. These compounds are related to galegine, a γ,γ-dimethylallylguanidine. Between the newly identified compounds, **1h** *N*-(cyclopropylmethyl)-*N*′-(4-(aminomethyl)-cyclohexylmethyl)guanidine showed the most balanced activity as antihyperglycemic and food intake-reducing agent.

Type 2 diabetes is a growing major global public health problem, with a currently estimated worldwide incidence of about 194 million people and expected to increase to 330 million by 2025.[1] Type 2 diabetes is usually due to resistance to insulin,[2] arising as a consequence of obesity, sedentary lifestyle, and aging and resulting in hyperglycemia, blood pressure elevation, and dyslipidemia. Despite the relatively recent explosion of new classes of pharmacologic agents,[3] the medical need still remains very high.

During our research into new antidiabetic agents, we identified, by random in vivo screening of several molecules, two aminoalkylguanidine compounds, **1a** and **1b**, as antihyperglycemic agents and/or food intake modulators in C57BL/KsJ db/db diabetic mice after subcutaneous treatment. Compound **1b** had previously been investigated as an antihypertensive agent.[4]

These molecules are aminoalkyl derivatives of galegine (Figure 1), a γ,γ-dimethylallylguanidine active for the treatment of type 2 diabetes isolated from the goat's rue plant (*Galega officinalis*).[5] An investigation of its derivatives led to the discovery of metformin,[3i,j] a biguanidine introduced in the late 1950s and now a very widely used oral antidiabetic agent (Figure 1).

The activity of *Galega officinalis* on the reduction of food intake was also reported.[6] Compounds **1a** and **1b** are also structural analogues of agmatine (Figure 1), a polar metabolite extracted from the Venezuelan plant *verbesina caracasana*.

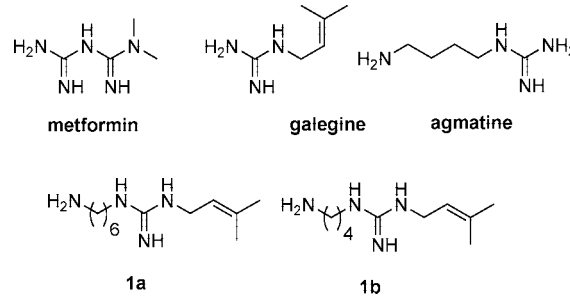
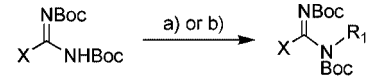


Figure 1

Scheme 1[a]



2a - b

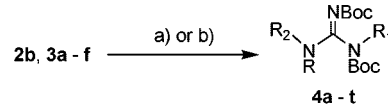
2a X = NHBoc
2b X = SMe

3a - f

3a R_1 = γ,γ - dimethylallyl, X = NHBoc
3b R_1 = γ,γ - dimethylallyl, X = SMe
3c R_1 = p-fluorobenzyl, X = SMe
3d R_1 = allyl, X = SMe
3e R_1 = cyclopropylmethyl, X = SMe
3f R_1 = 3-methylbutane, X = SMe

[a] Reagents and conditions: (a) KOH, Bu_4NBr, γ,γ-dimethylallyl bromide, 4-fluorobenzyl bromide or allyl bromide, DCM, MeCN, room temp, 12 h, 100%; (b) hydroxymethylcyclopropane or 3-methyl-1-butanol, PPh_3, DIAD, THF, reflux, 12 h, 95%.

Scheme 2[a]



4a - t

4a R = H, R_1 = γ,γ-dimethylallyl, R_2 = 6-aminohexyl
4b R = H, R_1 = γ,γ-dimethylallyl, R_2 = 4-Boc-aminobutyl
4c R = Boc, R_1 = γ,γ-dimethylallyl, R_2 = 2-Boc-aminoethyl
4d R = Boc, R_1 = γ,γ-dimethylallyl, R_2 = 3-Boc-aminopropyl
4e R = H, R_1 = cyclopropylmethyl, R_2 = 6-Boc-aminohexyl
4f R = H, R_1 = p-fluorobenzyl, R_2 = 4-aminobutyl
4g R = H, R_1 = allyl, R_2 = 4-aminobutyl
4h R = H, R_1 = cyclopropylmethyl, R_2 = 4-(aminomethyl)-cyclohexylmethyl
4i R = H, R_1 = γ,γ-dimethylallyl, R_2 = 4-(aminomethyl)-cyclohexylmethyl
4j R = H, R_1 = γ,γ-dimethylallyl, R_2 = trans-4-aminocyclohexyl
4k R = H, R_1 = γ,γ-dimethylallyl, R_2 = 7-aminoheptyl
4l R = H, R_1 = cyclopropylmethyl, R_2 = 4-(amino-methyl)-benzyl
4m R = H, R_1 = γ,γ-dimethylallyl, R_2 = 5-aminopentyl
4n R = H, R_1 = cyclopropyl-methyl, R_2 = 6-hydroxyhexyl
4o R = H, R_1 = cyclopropyl-methyl, R_2 = heptyl
4p R = H, R_1 = γ,γ-dimethylallyl, R_2 = 4-(aminomethyl)-benzyl
4q R = H, R_1 = 3-methyl-1-butyl, R_2 = 6-Boc-aminohexyl
4r R = H, R_1 = cyclopropyl-methyl, R_2 = trans-4-(Boc-aminomethyl)cyclohexylmethyl
4s R = H, R_1 = H, R_2 = 6-Boc-aminohexyl
4t R = H, R_1 = H, R_2 = 7-Boc-aminoheptyl

[a] Reagents and conditions: (a) suitable amine; (b) Boc-aminoalcohol, PPh_3, DIAD, THF, reflux, 12 h, 65−70%.

Agmatine and its derivatives have been studied as antihypertensive agents.[4]

In this paper we report the synthesis of compounds **1a** and **1b**, together with a series of new analogs, followed by their evaluation *in vivo* in diabetic mice as potential new antidiabetic and/or food intake modulators.

Compounds **1a**−**t** were synthesized starting either *N*,*N*′,*N*″-tris(*tert*-butoxycarbonyl)guanidine **2a** or commercially available thiourea **2b**, which were first alkylated with a suitable halide or alcohol to give **3a**−**f** (Scheme 1).

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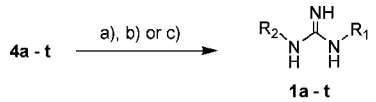
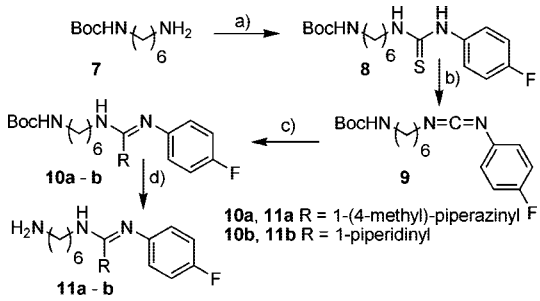
Scheme 3[a]



1a R_1 and R_2 as for **4a**
1b R_1 as for **4b**, R_2 = 4-aminobutyl
1c R_1 as for **4c**, R_2 = 2-aminoethyl
1d R_1 as for **4d**, R_2 = 3-aminopropyl
1e R_1 as for **4b**, R_2 = 6-aminohexyl
1f-1p R_1 and R_2 as for **4f-4p**
1q R_1 as for **4q**, R_2 = 6-aminohexyl
1r R_1 as for **4r**, R_2 = Trans-4(aminomethyl)cyclohexylmethyl
1s R_1 as for **4s**, R_2 = 6-aminohexyl
1t R_1 as for **4t**, R_2 = 7-aminoheptyl

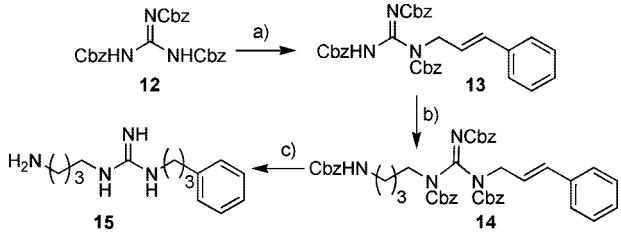
[a] Reagents and conditions: (a) TFA, DCM, room temp, 3−12 h, 98−100%; (b) methanesulfonic acid, dioxane, reflux, 2 h, 80−86%; (c) 12 N HCl, EtOH, 4 h at room temp, 6 h at 50 °C, 28−57%.

Scheme 4[a]



[a] Reagents and conditions: (a) *p*-fluorophenyl isothiocyanate, DCM, 12 h, 85%; (b) 2-chloro-*N*-methylpyridinium iodide, DIPEA, DCM, 12 h, 90%; (c) suitable amine, isocyanate resin, toluol, 50 °C, 4 h, 90−99%; (d) TFA, DCM, 3−12 h, 90−99%.

Scheme 5[a]



[a] Reagents and conditions: (a) Ph_3P, DIAD, cinnamic alcohol, THF, 0 °C to reflux, 12 h, 74%; (b) Ph_3P, DIAD, 4-(*N*-Boc)aminobutanol, THF, 0 °C to reflux, 12 h, 29%; (c) cyclohexene, 10% Pd/C, MeOH, reflux, 8 h, 88%.

Amines **4a**−**t** were obtained by alkylation of intermediate **3a** with suitable Boc[a]-aminoalcohols (intermediates **4c**,**d**) or by reaction of **2b** or **3b**−**f** with different amines (intermediates **4a**,**b**,**e**−**t**) (Scheme 2).

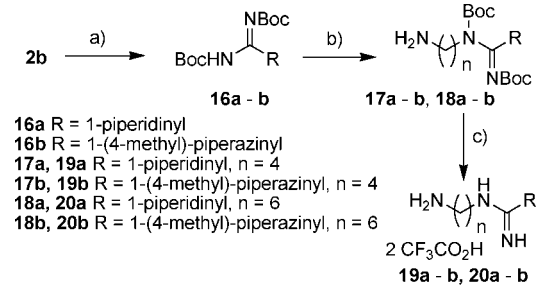
Deprotection of **4a**−**t** with TFA, HCl, or CH_3SO_3H gave the final compounds **1a**−**t** as corresponding salts (Scheme 3). Compounds **1s** and **1t** are two- and three-carbon superior homologues of agmatine.

Compound **6** (see Table 1) was synthesized starting from **4n** by standard bromination with CBr_4 in the presence of PPh_3, followed by deprotection with methanesulfonic acid.

Compounds **11a**,**b**, having three substituents on guanidine, were synthesized starting from Boc-protected 1,6-hexamethylenediamine **7** and *p*-fluorophenyl isothiocyanate to give thiourea **8**. Reaction of the thiourea with Mukaiyama's reagent readily gave carbodiimide **9**, which was in turn reacted with suitable amines to give **10a**,**b**, which after deprotection with trifluoroacetic acid furnished **11a**,**b** as trifluoroacetates (Scheme 4).

[a] Abbreviations: Boc, *tert*-butoxycarbonyl; TFA, trifluoroacetic acid; DIAD, diisopropyl azadicarboxylate; DCM, dichloromethane; DIPEA, diisopropylethylamine.

Scheme 6[a]



16a R = 1-piperidinyl
16b R = 1-(4-methyl)-piperazinyl
17a, 19a R = 1-piperidinyl, n = 4
17b, 19b R = 1-(4-methyl)-piperazinyl, n = 4
18a, 20a R = 1-piperidinyl, n = 6
18b, 20b R = 1-(4-methyl)-piperazinyl, n = 6

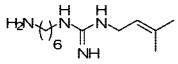
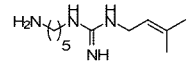
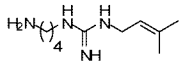
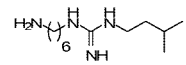
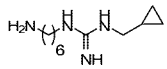
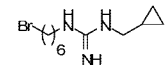
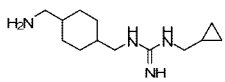
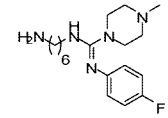
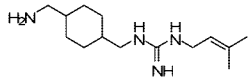
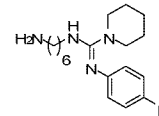
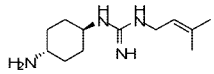
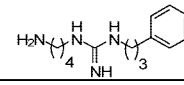
[a] Reagents and conditions: (a) $HgCl_2$, triethylamine, amine, DMF, 4 h, 80%; (b) 6-(*N*-Boc)amino-1-hexanol or 4-(*N*-Boc)amino-1-butanol, Ph_3P, DIAD, THF, 0 °C to room temp, 12 h, 95−96%; (c) TFA, DCM, 12 h, 99%.

Compound **15** was synthesized as reported in Scheme 5 from the wholly protected guanidine **12** by alkylation, first with cinnamic alcohol to give **13** and then with protected aminobutanol to give **14**, which after deprotection under standard conditions gave **15** as a free amine.

To obtain **19a**,**b** and **20a**,**b**, thiourea **2b** was first alkylated with piperidine and *N*-methylpiperazine to give **16a**,**b**, respectively (Scheme 6). Reaction of these intermediates with 4-*N*-(*tert*-butoxycarbonyl)amino-1-butanol and 6-*N*-(*tert*-butoxycarbonyl)amino-1-hexanol gave protected amines **17a**,**b** and **18a**,**b**, which were then deprotected with trifluoroacetic acid to give **19a**,**b** and **20a**,**b**.

All compounds were evaluated in vivo in the widely used diabetic db/db mice, characterized by a defect in the leptin receptor, inducing hyperphagia, obesity, hyperglycemia, hyperinsulinemia, and insulin resistance. Administration was performed in male mice twice a day for 4 days and once on day 5, by subcutaneous route, to overcome, in this first investigation, any possible interference in adsorption and gastrointestinal stability due to structural differences between the compounds. On day 5, 8 h after last administration and in postabsorptive conditions, improvements of glucose homeostasis, glucose tolerance, and insulin sensitivity were evaluated using the insulin suppression test (IST) of Greenfield et al.,[7] as modified for diabetic obese mice[8] and slightly further modified (somatostatin was substituted for propranolol and epinephrine,[9] and blood was withdrawn 60 min after the load injection, having verified that at this time nearly steady-state plasma glucose and insulin levels were reached). Values at time 0 can be viewed as postabsorptive glucose levels. All the investigated molecules were given at doses equivalent to 25 mg/kg **1a**, while the antidiabetic drugs metformin and rosiglitazone, used as reference compounds, were administered in the same way at the respective doses, as reported below. There was a significant reduction of glycemia with respect to control for **1a** (−31%), accompanied by a 53% reduction of water consumption and about a 20% reduction in food intake, while there was only a 13% reduction in glycemia with **1b**, together with a similar water consumption but a higher (−37% vs control) reduction of food intake with respect to **1a**. During the investigation of the effects of the alkyl chain length between amine and guanidine groups, the best antihyperglycemic effect was produced by the six-carbon chain while the five- and four-carbon chains (**1m** and **1b**, respectively) seemed to be endowed with the highest reduction in food intake. When the double bond of the unsaturated alkyl substituent was replaced by the corresponding saturated moiety, as in **1q**, the activity

Table 1. Reductions of Glycemia Levels at IST and of Cumulative Water and Food Intake, after 5 Days of Treatment in Male db/db Mice (4-6 per Group)[a,b]

No	Structure	Glucose Time 0 min/ 60 min	Water intake[a]	Food intake[a]	No	Structure	Glucose Time 0 min/ 60 min	Water intake[a]	Food intake[a]
1a		-31▲/ -13▲	- 53	- 19	**1m**		- 15▯/ -13	- 57	- 41
1b		-13/-11	- 53	- 37	**1q**		- 17/ - 24 ■	- 24	- 14
1e		-42▲/ -18	- 45	- 19	**6**		- 12/ -20 ■	- 30	- 22
1h		-29▲/ -43 △	- 59	- 40	**11a**		- 21▲/ -12	- 35	- 14
1i		-8/-29■	- 29	- 21	**11b**		- 15▲/-8	- 41	- 22
1j		-14/ -22■	- 44	- 27	**15**		+ 12/-8	- 44	- 33

[a] All compounds were administered subcutaneously twice a day at doses equivalent to 25 mg/kg **1a**. Values are expressed as % variation with respect to control. For clarity, the chemical structures are drawn without counterions, and only the data of active compounds are reported. Student's *t* test indicates (▲) $p < 0.05$, (□) $p < 0.02$, (■) $p < 0.01$, and (△) < 0.001 vs control diabetic mice. [b] For water and food intake, statistics were not applied, as the reported data are the result of cumulative measurements of 4−6 animals per cage. Animals were observed daily throughout the experiment, exhibiting no modifications in the general state of health or behavior.

was partially retained, but when a cyclopropylmethyl group was introduced, an even stronger activity was found, **1e** giving a 42% reduction in glucose blood levels, accompanied again by a lower water and food intake (−45% and −19%, respectively). The absence of substituents on the guanidine group led to inactive compounds (**1s** and **1t**). Introduction of a cyclohexyl moiety in place of the linear alkyl chain in **1h**, leaving the rest of the structure unaltered with respect to **1e**, resulted in good antihyperglycemic activity, −29% in blood glucose levels and a 40% reduction in food intake. We observed an even stronger reduction in glycemia with respect to controls (−43%) 60 min after IST, and water consumption (−59%) reflected the observed efficacy. The *trans*-cyclohexyl analogue **1r** had almost no effect, suggesting stereochemical implications in the interaction of these molecules with their unknown target(s). The activity was instead at least partially maintained with derivative **1j**, where the cyclohexyl moiety was directly linked to the amine and guanidine groups, and with **1i**, both carrying the dimethylallyl residue, as in **1a**. Substitution of the amino group of **1e** with a bromine, hydroxyl, or methyl group, as in **6**, **1n**, or **1o**, respectively, led to less active (**6**) or almost inactive compounds, indicating the importance of the original aminic functionality (only food intake appeared moderately reduced (−20%) in the methyl and bromine derivatives). Substitution of the dimethylallyl fragment with different moieties in **1f**, **15**, and **19a**,**b** (derivatives of aminobutylguanidine) and in **11a**,**b** and **20a**,**b** (derivatives of aminohexylguanidine) led to lower or no activity. It is worth noting that the effect of metformin, when administered twice a day in the same way, was modest and not statistically significant even at high doses (glycemic reduction of −11% at 13 mg/kg and −22% at 130 mg/kg), suggesting that besides the apparent first-view structural similarity, different mechanism(s) may actually be operating. Rosiglitazone, on the other hand, administered with the same modality at 5 mg/kg produced a glycemic reduction similar to that of our active compounds (−29% and −39%, $p < 0.05$, at 0 and 60 min after IST, respectively) with a corresponding reduction of water intake of about 52%.

In conclusion, several substituted aminoalkyguanidines were synthesized and tested, identifying a series of compounds with an interesting profile as potential antidiabetic and/or antiobesity drugs. The *N*-(cyclopropylmethyl)-*N*′-(4(aminomethyl)cyclohexylmethyl)guanidine **1h** appears to be the most balanced antihyperglycemic and food intake-modulating compound. The possibility of controlling glycemic levels and food intake appears particularly attractive, also considering that among the currently approved antidiabetic therapies only metformin and exenatide appear to have a moderate but positive impact on body weight while glitazones induce a further increment. Additional studies on the pharmacology of the described compounds for an evaluation of their mechanistic and pharmacokinetic properties and for a deeper investigation of their activity profile as antidiabetic and food intake-reducing agents are thus warranted.

Supporting Information Available: Experimental details and analytical data for listed compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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