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Imidazolines as efficacious glucose-dependent stimulators of insulin secretion

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Abstract

Synthesis of a series of imidazolines with glucose dependent effects on insulin exocytosis from pancreatic β-cells is reported. Regioisomers and enantiomers were found to exhibit marked differences in exocytotic effects as well as different activities on the K_{ATP}-channel; the (*R* (+)) isomer of 2-[2-(4,5-dihydro-1*H*-imidazol-2-yl)-1-thiophene-2-ylethyl]pyridine (**4a**) and the (+) isomer of 2-[2-(4,5-dihydro-1*H*-imidazol-2-yl)-1-thiophene-3-ylethyl]pyridine (**4d**) were found to give a significant increase in insulin release—in contrast to findings for their enantiomers—without influence on the K_{ATP}-channel. The (+) isomer (**4a**) showed glucose dependent insulin release from β-cells at concentrations above 2.5 mM and a marked glucose lowering effect in *ob/ob* mice as well as in fed but not in fasted rats.

Keywords: Glucose dependent insulin release; Imidazolines; K_{ATP} current

1. Introduction

2-Substituted imidazolines have for years been targets for the search for compounds that can modulate e.g. blood pressure, heart rate, and CNS diseases, and drugs like clonidine and phentolamine have been marketed for the treatment of hypertension [1–3]. Several imidazolines have been reported to modulate insulin release from pancreatic β-cells through activity on the adrenergic α_1-, α_2-, imidazoline I_1-, or I_2-receptors and/or the K_{ATP} channel [4,5]. This is, however, not an ideal mechanism of action as severe cardiovascular side effects as well as hypoglycaemic events can arise [6]. The actual target for the imidazolines in the β-cell is far from fully explored but it seems to be accepted that besides activity on the above mentioned receptors and on the K_{ATP}-channel, there might be a third imidazoline receptor, or other mechanisms involved in the increase of insulin release for compounds which do not exhibit their activity through a blocking of the K_{ATP}-channel [7–12]. The aim of the present investigation was to discover imidazoline containing compounds that could increase insulin release from the β-cell at elevated glucose concentrations only, without or with very little effect on the pancreatic K_{ATP}-channel as well as on peripheral or central imidazoline- and α-receptors.

A Japanese patent [13] claimed racemic **4a** to be able to increase insulin release, but no details regarding the mechanism of action were given. We have found that this compound as the racemic mixture—in addition to its insulin releasing property—also exhibited a pronounced inhibitory activity at the K_{ATP}-channel, while one of the enantiomers was without this effect. This prompted us to investigate a series of close analogues in more detail.

2. Chemistry

Several methods for the preparation of 2-substituted imidazolines are described in the literature, mainly using nitriles or esters as starting material via condensation with ethylenediamine or salts thereof [14–16]. Also methods utilising ketones and imidazoline derivatives are described [17]. In order to prepare different 2-

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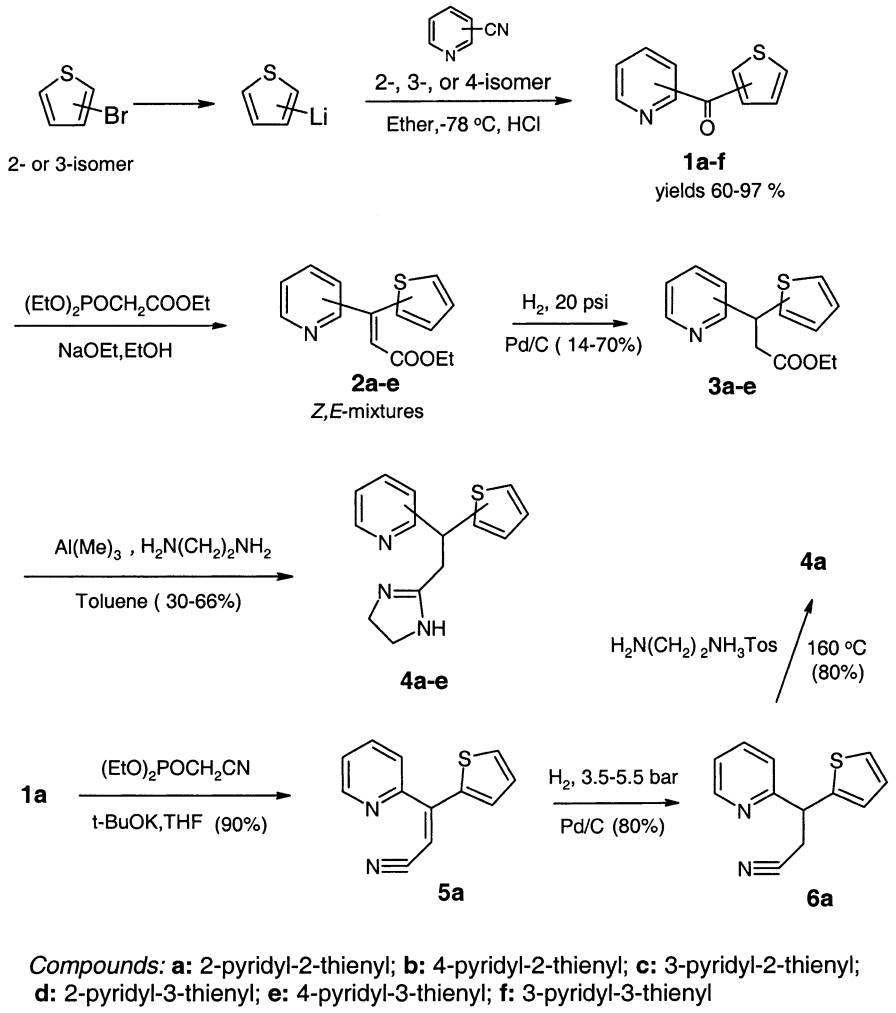

Fig. 1. Synthetic route for the preparation of compounds **4a–e**.

(pyridyl-thienylethyl)imidazolines we have used three approaches as depicted in Figs. 1 and 2.

Pyridyl-thienyl ketone starting materials (**1a-f**) were conveniently prepared from pyridine carbonitriles and 2- or 3-thienyl lithium in Et_2O or THF at −78 °C. Acid hydrolysis during work-up afforded ketones (**1a–f**) in fair to good yields. Subsequent reaction with triethyl phosphonoacetate or diethyl cyanomethylphosphonate

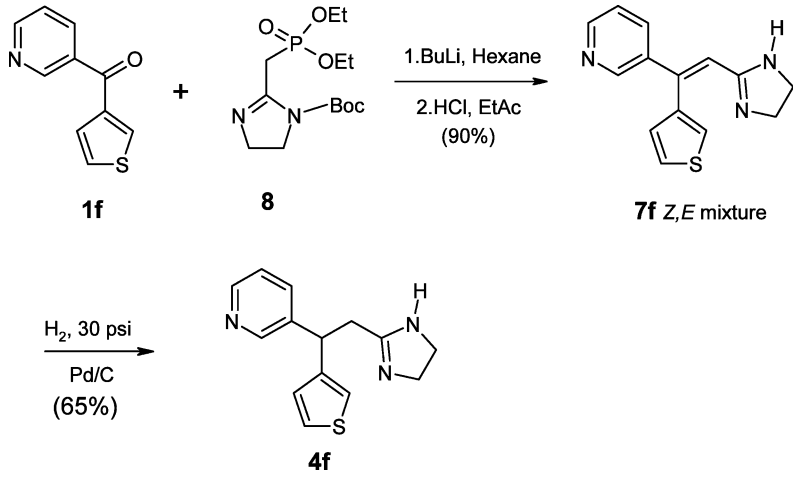

Fig. 2. Synthetic route for the preparation of compound **4f**.

gave the unsaturated esters or nitrile **2a–e** and **5a**, respectively, in good yields. These unsaturated intermediates were hydrogenated at atmospheric pressure or up to 5.5 bar using Pd/C as catalyst. This reduction gave low to good yields and often required long reaction times and renewal of the catalyst. The saturated esters **3a–e** were conveniently reacted with ethylenediamine in the presence of $AlMe_3$ [5] to give **4a–e**, and the cyano compound **6a** was melted with dry ethylenediamine–monotosylate affording imidazoline **4a** in good yield Fig. 1.

The 3-thienyl-3-pyridyl compound **4f** was not prepared by these routes since the reduction of the cyano or the ester-intermediates **2f** or **5f** gave very low yields. Compound **4f** was therefore prepared using the synthetic pathway described in Fig. 2. Ketone **1f** was reacted with the Li-salt of Boc-protected 2-diethoxyphosphorylmethylimidazoline **8**. Work up with HCl gave in good yield the unsaturated compound **7f** as a *Z,E*-mixture. This was reduced to **4f** without further purification as attempts to isolate the pure diastereomers resulted in decomposition. The yield was good (65%) in contrast to previous findings [17].

Imidazolines that showed promising effects on insulin exocytosis as racemic mixtures were separated into pure enantiomers by HPLC using chiral OD columns. Resolution by fractional crystallisation in the presence of chiral acids was unsuccessful. The exact configuration of the enantiomers of compound **4a** was determined by X-ray crystallography on the corresponding hydrochloride salts, showing the configuration of the (+) isomer to be *R* and the (−) isomer to be *S*.

3. Results and discussion

Compounds **4a–e** were tested in a patch clamp exocytosis assay (mouse pancreatic β-cells) measuring their ability to release insulin. Imidazolines that increased the exocytotic rate were further tested for their effect on the K_{ATP}-channel as well as in assays for insulin release, activity on α-, and imidazoline-receptors. Table 1 shows the in vitro data for selected compounds.

The in vitro results clearly indicates that there is a difference in the degree to which the compounds could increase the rate of the insulin exocytosis, both for stereoisomers like in **4a**, **4d** and **4e** and between regioisomers, whereas compound **4c** gave no increase in the exocytotic rate.

Also activity on the K_{ATP}-channel differed considerably between the stereoisomers as well as between the regioisomers. (*R*)-(+) **4a** was further investigated for insulin release from isolated mouse β-cells as well as in in vivo experiments in rats and *ob/ob* mice. The results from these investigations showed that (*R*)-(+) **4a** increased insulin release dose dependently only at blood glucose concentrations above 2.5 mM (Fig. 3). In rats, the plasma insulin level was increased significantly after 2 min in fed but not in fasted animals (20 mg/kg i.v.), and the blood glucose levels were significantly decreased in the fed compared to the fasted animals after 30 min. In *ob/ob* mice (*R*)-(+) **4a** (100 mg/kg p.o.) decreased the blood glucose level significantly, (data not shown). Although compound (*R*)-(+) **4a** showed significant in vivo effect on blood glucose levels in different animal models of type 2 diabetes it also exhibited strong

Table 1
In vitro data for selected imidazolines

Compound	K_{ATP} channel [a] (ratio)	Insulin exocytosis [b] *(fF/s)*	IC_{50} (μM)				
			α_{2a}	α_{2b}	α_{2ns} [c]	I_{2c} [d]	I_{2p} [e]
4a +,−	0.20	12.3	1.98	1.94	0.66	0.43	3.51
4a −	nd	4.0	6.94	7.9	3.06	3.15	>10
4a +	1.03	11.5	0.76	1.42	0.6	0.5	0.9
4b +,−*	0.67	9.1					
4c +,−	nd	4.8					
4d +,−	nd	9.2					
4d +	0.93	9.3	8.03	3.6	4.8	3.97	3.59
4d −	0.56	5.8	5.02	2.4	2.56	0.92	0.89
4e +,−	0.59	10.9	7.34	5.85	3.14	1.89	0.72
4e +	nd	5.9					
4e −	0.23	8.9					

The data from the α- and I-receptors were obtained from a standard Panlab-screen. Test concentration for the patch clamp measurements was 100 μM.

[a] The ratio of whole-cell K_{ATP} current with or without test compound is given.

[b] Change in cell capacitance by application of test compound is given as a measure of exocytosis.

[c] Non-selective α_2-receptor.

[d] I_2-central.

[e] I_2-peripheral.

* The (+) and the (−) -isomers showed <30% inhibition of the K_{ATP}-channel in INS-1 cells.

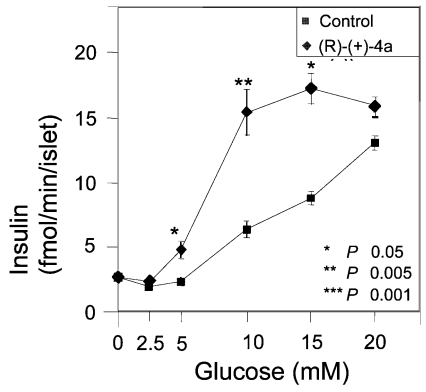

Fig. 3. Insulin release from mouse islets (fmol insulin/min/islet) as a function of glucose concentration (mM) for compound (*R*)-(+) **4a** at 100 μM.

affinities for both the α_2- and the I_2-receptors thus not being ideal for further exploration. Compound (+)**-4d**, however, showed a more promising profile. In conclusion, we have shown that it was possible to find imidazolines that could increase insulin release without having activity at the K_{ATP}-channel and with low affinities for the α- and imidazoline-receptors. The exocytotic effect was found to be strongly dependent on the structure with great variance between the individual enantiomers.

4. Experimental

4.1. General procedures

The general synthetic methods described previously [18] were used. Combustion analyses were within ±0.4% of the theoretical value.

4.2. Pharmacological methods

The assays used have been described previously [19,20].

4.3. General procedure for the preparation of compounds (*1a–f*)

4.3.1. Pyridine-3-yl-thiophene-2-yl-methanone (*1c*)

n-Butyl lithium (10.0 mL, 1.6 M in hexane, 16 mmol) was added to dry diethyl ether (30 mL) under a nitrogen atmosphere below −78 °C. 2-Bromothiophene (2.44 g, 15 mmol) in dry diethyl ether (25 mL) was added dropwise at a temperature below −72 °C. The mixture was subsequently stirred at −30 °C for 20 min. Further cooling to −78 °C followed by addition of 3-cyanopyridine (1.56 g, 15 mmol) in dry diethyl ether (30 mL) over 10 min. The mixture was kept at −78 °C for 20 min followed by heating to 0 °C for 10 min. HCl (6 N) was added to pH 1, followed by stirring for 30 min. KOH was then added to pH 10. Ethyl acetate (50 mL) and water (10 mL) were added and the organic phase was separated, dried with $MgSO_4$ and evaporated to dryness resulting in yellow oil.

The crude product was treated with HCl (6 N, 50 mL) for 1 h and the pH was then adjusted to 10 by addition of solid KOH. Extraction, drying, and evaporation as described above resulted in yellow crystals 2.4 g (85%) of pyridine-3-yl-thiophene-2-yl-methanone **1c**, Mp: 90-91.5 °C. EI/MS: *m/z* 189 $(M)^+$. ^{1}H-NMR ($CDCl_3$): δ 9.10 (d, 1H); 8.80 (dd, 1H); 8.18 (dd, 1H); 7.80 (d, 1H); 7.65 (dd, 1H); 7.48 (dd, 1H); 7.20 (t, 1H). ^{13}C NMR ($CDCl_3$): δ 186.6; 153.2; 150.3; 143.4; 136.9; 135.6; 135.5; 134.1; 128.7; 123.9. Anal. $C_{10}H_7NOS$ (C,H,N).

The following intermediates were prepared from the appropriate starting materials using the same procedure as described for the preparation of **1c**.

4.3.2. Pyridine-2-ylthiophene-2-ylmethanone (*1a*)

Oil, ^{1}H-NMR ($CDCl_3$): δ 8.75 (d, 1H); 8.37 (d, 1H); 8.12 (d, 1H); 7.85 (t, 1H); 7.75 (d, 1H); 7.45 (dd, 1H); 7.14 (dd, 1H).

4.3.3. Pyridine-4-ylthiophene-2-ylmethanone (*1b*)

M.p.: 101 °C, EI/MS: *m/z* 189 $(M)^+$.

4.3.4. Pyridine-2-ylthiophene-3-ylmethanone (*1d*)

Oil. LC/MS: *m/z* 190 $(M+1)^+$.

4.3.5. Pyridine-4-ylthiophene-3-ylmethanone (*1e*)

M.p.: 105–106 °C, EI/MS: *m/z* 189 $(M)^+$.

4.3.6. Pyridine-3-ylthiophene-3-ylmethanone (*1f*)

M.p.: 71.5–72 °C, EI/MS: *m/z* 189 $(M)^+$.

4.4. General procedure for the preparation of compounds (*4a–e*)

4.4.1. [2-(4,5-Dihydro-1H-imidazol-2-yl)-1-thiophene-2-ylethyl]pyridine (*4c*)

Sodium (0.12 g, 5 mmol) was dissolved in dry ethanol (10 mL), the solution was cooled to −5 °C and triethyl phosphonoacetate (1.13 g, 5 mmol) in ethanol (1 mL) was added and the mixture stirred for 30 min. Pyridine-3-ylthiophene-2-ylmethanone **1c** (0.76 g, 4 mmol) dissolved in ethanol (1 mL) was added and the mixture was heated at 55 °C for 3 days. The reaction mixture was then evaporated to dryness to give crude *Z–E* mixture of 3-pyridine-3-yl-3-thiophene-2-ylacrylic acid ethyl esters **2c** as an oil (1.2 g). The crude product was dissolved in dry ethanol (40 mL) and hydrogenated over Pd/C (10%, 0.25 g) at 20 psi overnight. The reaction mixture was filtered through celite and evaporated to dryness. The crude product was purified on silica gel using dichloromethane/MeOH (19:1) as eluent, which af-

forded 265 mg of 3-pyridin-3-yl-3-thiophen-2-yl-propionic acid ethyl ester **3c**. LC/MS: *m/z* 262 $(M+1)^+$.

To trimethyl aluminium (2 M in toluene, 0.75 mL, 1.5 mmol) cooled to −10 °C was slowly added ethylenediamine (0.1 mL, 1.5 mmol) and the mixture was stirred for 30 min. **3c** (260 mg, 1 mmol) in dry toluene (10 mL) was added dropwise over 30 min. The mixture was heated at reflux for 1 h and cooled to 0 °C. Water (1 mL), MeOH (2 mL) and dichloromethane (2 mL) were added and the mixture heated to 40 °C for 20 min. The organic phase was separated and the aqueous phase was extracted with dichloromethane (3 × 3 mL). The combined organic phases were dried (Na_2SO_4) and evaporated to dryness. Purification on silica gel using dichloromethane/MeOH/triethylamine (45:5:3) as eluent afforded 70 mg (27%) of 3-[2-(4,5-dihydro-1*H*-imidazol-2-yl)-1-thiophene-2-ylethyl]pyridine **4c** as an oil. LC/MS: *m/z* 258 $(M+1)^+$, ELS purity: 99%.

*4.4.2. [2-(4,5-Dihydro-1H-imidazol-2-yl)-1-thiophene-2-ylethyl]pyridine (**4a**)*

The title compound was prepared from pyridine-2-ylthiophene-2-ylmethanone **1a** using the method described for **4c**. ^{1}H-NMR ($CDCl_3$): δ 8.55 (d, 1H); 7.65 (dt, 1H); 7.41 (d, 1H); 7.21 (dd, 1H); 7.15 (dd, 1H); 6.99 (t, 1H); 6.91 (dd, 1H); 6.2–5.7 (broad, 1H); 5.02 (dd, 1H); 3.60 (s, 4H); 3.58 (dd, 1H); 3.19 (dd, 1H). ^{13}C NMR ($CDCl_3$): δ 168.5; 161.2; 149.4; 145.3; 137.3; 127.1; 125.7; 125.1; 123.9; 122.6; 47.5; 45.7; 34.8. Anal. $C_{14}H_{15}N_3S$ (C,H,N).

*4.4.2.1. [2-(4,5-Dihydro-1H-imidazol-2-yl)-1-thiophene-2-ylethyl]pyridine (**4a**).* To a cooled (10 °C) mixture of diethyl cyanomethylphosphonate (19.5 g, 0.11 mol) in THF (400 mL) was added *t*-BuOK (14 g, 0.125 mol). After stirring for 5 min **1a** (18.9 g, 0.1 mol) was added and the mixture was stirred at RT for 4 h. The mixture was then poured on ice (300 mL), toluene (100 mL) was added, the organic layer separated, dried with Na_2SO_4 and concentrated to give crude 19.11 g (90%) of **5a** as a *Z*/*E*-mixture. **5a** (41 g, 0.19 mol) was hydrogenated over Pd/C (10%, 3 g) in EtOH (300 mL) at 50 °C and 3.5–5.5 bar for 1 day, the mixture was filtered and more Pd/C (10%, 3 g) was added and the hydrogenation continued. This procedure was repeated 2 times more resulting in 95% conversion to the saturated compound **6a**. The crude product was purified by silicagel chromatography using toluene as eluent giving 32.57 g (80%) of pure **6a**. This was reacted neat with dry ethylenediamine mono-tosylate (2 equiv.) at 160 °C for 8 h. Subsequent cooling and addition of $CHCl_3$ (300 mL), followed by extraction with KOH solution (5%), separation of the organic phase, drying with Na_2SO_4, and evaporation to dryness gave 31.3 g (80%) of **4a**.

*4.4.2.2. Resolution of (**4a**).* Racemic **4a** was separated into pure enantiomers using a Chiralcel OD column (250–20 mm, Daicel, Japan) eluted with a mixture of *n*-heptane/2-propanol/diethylamine (90:10:0.1). The two enantiomers eluted at Rt. 46–64 min $[\alpha]_D^{20} = -67.7°$ ($c = 0.52$, MeOH) and Rt. 74–98 min $[\alpha]_D^{20} = +65.6°$ ($c = 0.51$, MeOH). The configuration of the first eluting isomer was found to be (*S*) by X-ray crystallography.

*4.4.3. [2-(4,5-Dihydro-1H-imidazol-2-yl)-1-thiophene-2-ylethyl]pyridine (**4b**)*

The title compound was prepared from pyridine-4-ylthiophene-2-ylmethanone using the method described for **4c**. The resulting product was purified twice on a silica gel column. In the second purification EtOAc/MeOH/ NH_3 (25%) (4:1:1) was used as the eluent. **4b** was isolated as an oil. MS: *m/z* 257 $(M)^+$.

*4.4.3.1. Resolution of (**4b**).* Racemic **4b** was separated on Chiralcel OD using a mixture of 2-propanol/heptane/diethylamine (50:50:0.1) as eluent. (+)-**4b**. Rt.: 10.4 min. Purity: > 98.9% ee. $[\alpha]_D^{20} = +28.7°$ (2-propanol/heptan/diethylamine (50:50:0.1)). (−)-**4b**. Rt.: 13.0 min, purity: > 98.2% ee. $[\alpha]_D^{20} = -26.3°$ (2-propanol/heptane/diethylamine) (50:50:0.1)).

*4.4.4. [2-(4,5-Dihydro-1H-imidazol-2-yl)-1-thiophene-3-ylethyl]pyridine (**4d**)*

The compound was prepared using the methodology described for compound **4c**. LC/MS: *m/z* 258 $(M+1)^+$, ELS purity 99%.

*4.4.4.1. Resolution of (**4d**).* Separation as described for **4b**. (+) Rt.: 10.2 min; purity: 80.1% ee. (−) Rt.: 14.4 min.; purity: 99.5% ee. The assignment to (+) and (−) was arbitrarily set in analogy to the findings for compounds **4b** and **4e**.

*4.4.5. [2-(4,5-Dihydro-1H-imidazol-2-yl)-1-thiophene-3-ylethyl]pyridine (**4e**)*

Compound **4e** was prepared from pyridine-4-ylthiophene-3-ylmethanone **1e** as described for **4c**. Yield 30%. EI/MS: *m/z* 257 $(M)^+$. ^{13} C NMR ($CDCl_3$): δ 165.8, 152.7, 150.3, 143.0, 127.5, 126.8, 123.4, 121.7, 49.9, 44.0, 35.7.

*4.4.5.1. Resolution of (**4e**).* Separation as described for **4b**. Rt.: 13.9 min, purity: > 99.3% ee, $[\alpha]_D^{20} = +42.0°$ (2-propanol/heptan/diethylamine (50:50:0.1)). Rt.: 17.6 min, purity: > 93.0% ee, $[\alpha]_D^{20} = -41.0°$ (2-propanol/heptan/di-ethylamine (50:50:0.1)).

*4.4.6. [2-(4,5-Dihydro-1H-imidazol-2-yl)-1-thiophene-3-ylethyl]pyridine (**4f**)*

Z/*E*-3-[2-(4,5-Dihydro-1*H*-imidazol-2-yl)-1-thiophen-3-ylvinyl]pyridine **7f** (0.52 g) was hydrogenated over Pd/

C (10%, 50 mg) in ethanol (10 mL) at 30 psi for 4 h. The reaction mixture was filtered through celite and evaporated to dryness to give 360 mg (65%) **4f**. LC/MS: *m/z*: 258 $(M+1)^+$, ELS purity: 97%. ^{13}C NMR ($CDCl_3$): δ 167.4, 149.5, 148.4, 143.0, 138.8, 135.7, 127.6, 126.8, 124.0, 121.7, 57.7, 48.1, 41.8, 35.1.

4.5. *Z/E-3-[2-(4,5-Dihydro-1H-imidazol-2-yl)-1-thiophen-3-yl-vinyl]pyridine (**7f**)*

Preparation from 3-thienyl-3-pyridyl ketone **1f** (5 g) and 2-(diethoxyphosphorylmethyl)-4,5-dihydro-imidazole-1-carboxylic acid *tert*-butyl ester **8** (8.45 g) by means of *n*-BuLi (20 mL, 1.6 N in hexane) in THF at −78 °C. Subsequent stirring at −20 °C for 20 min and then at RT overnight followed by quenching by addition of saturated aqueous NH_4Cl (25 mL) and extraction with EtOAc afforded 9.2 g (98%) of BOC-protected **7f**. **7f** (2 g, 5.63 mmol) was de-protected in a mixture of 3N HCl (4 mL) and EtOAc (4 mL) by stirring overnight. Evaporation of the solvent afforded 1.2 g (90%) of **7f**. LC/MS *m/z*: 256 $(M+1)^+$.

4.6. *(Diethoxyphosphorylmethyl)-4,5-dihydro-1H-imidazole-1-carboxylic acid tert-butyl ester (**8**)*

Diethyl cyanomethylphosphonate (50 g) was converted to the imidate hydrochloride by addition of ethanol (22 mL) and Et_2O (300 mL), cooling to 0 °C followed by saturation with HCl (g).

The mixture was kept in a closed bottle for 48 h, and subsequently evaporated to dryness.

The resulting imidate hydrochloride was added portionwise to a mixture of ethylene diamine (16.6 g) in ethanol (140 mL) and heated to 40 °C for 1h. Ethanol (350 mL) was added and the mixture concentrated yielding 90% of 2-imidazolinylmethyl diethyl phosphonate hydrochloride. This crude product was dissolved in dichloromethane (150 mL) and triethylamine (140 mL) and reacted with BOC-anhydride (65 g) added in 3 portions over 30 min. The mixture was stirred at room temperature for 20 h. Water was added and the organic phase was isolated and evaporated to dryness. The crude product was purified on a silicagel column using 95:5 dichloromethane/methanol as eluent. Yield: 23.5 g light red oil. LC/MS: *m/z* 321 $(M+1)^+$; ^1H-NMR ($CDCl_3$): δ 4.14 (dq, 4H); 3.75 (m, 4H); 3.50 (d, 2H); 1.48 (s, 9H); 1.30 (t, 6H).

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References

[1] D.J. Reis, P. Bousquet, A. Parini (Eds.), The Imidazoline Receptor, Ann. NY Acad. Sci. 763 (1995).
[2] M. Gothert, G.J. Molderings, D.J. Reis (Eds.), Imidazoline Receptors and their Endogenous Ligands, Ann. NY Acad. Sci. 881 (1999).
[3] G.J. Molderings, Drug Future 22 (7) (1997) 757–772.
[4] S.V. Zaitsev, et al., Ann. NY Acad. Sci. 881 (1999) 241–252.
[5] F. Rondu, et al., J. Med. Chem. 40 (1997) 3793–3803.
[6] E.F. Pfeiffer, et al., Horm. Metab. Res. 6 (Suppl.) (1976) 112–126.
[7] N.G. Morgan, Exp. Opin. Invest. Drugs 8 (5) (1999) 575–584.
[8] S.V. Zaitsev, et al., Diabetes 45 (1996) 1610–1618.
[9] U. Hari, U. Roettig, M. Paal, Tetrahedron Lett. 42 (2001) 5187–5189.
[10] M.A. Efanov, S.V. Zaitsev, H.-J. Mest, A. Raap, I.B. Appelkog, O. Larsson, P.-O. Berggren, S. Efendic, Diabetes 50 (2001) 797–802.
[11] G. Morgan, S.L.F. Chan, C.A. Brown, E. Tsoli, Ann. NY Acad. Sci. 763 (1995) 361–373.
[12] S.L.F. Chan, C.A. Brown, K.E. Scarpello, N.G. Morgan, Ann. NY Acad. Sci. 763 (1995) 153–156.
[13] S. One et al., JP 04069385.
[14] P. Oxley, W.F. Short, J. Chem. Soc. (1947) 497–505.
[15] N. Sperber, R. Fricano, J. Am. Chem. Soc. 75 (1953) 2986–2988.
[16] W. Kuzmerkiewicz, F. Saczewski, H. Foks, Arch. Pharm. 319 (1986) 830–834.
[17] F. Ishikawa, Chem. Pharm. Bull. 28 (5) (1980) 1394–1402.
[18] P. Jakobsen, B.R. Pedersen, E. Persson, Bioorg. Med. Chem. 8 (2000) 2095–2103.
[19] J. Gromada, et al., J. Physiol. 518 (3) (1999) 745–759.
[20] H.S. Andersen, P. Jakobsen, P. Madsen, WO 200238559.