Synthesis of 2-Aminoquinazoline-4(3*H*)-one Derivatives as Potential Potassium Channel Openers

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Starting from 2-thioxoquinazolin-4-one, the synthesis of 2-amino-4(3*H*)-one derivatives, structurally related to potassium channels openers pinacidil and diazoxide, is described.

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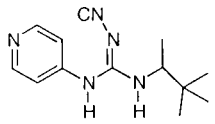
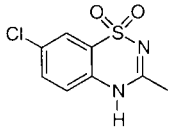
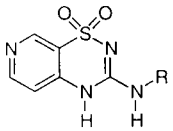
Potassium channels represent a very diversified group of ionic channels [1]. Compounds acting by the opening of potassium channels might be of particular usefulness in the treatment of seizures, angina pectoris, hypertension, urinary incontinence or asthma [2]. A subtype of potassium channels, called adenosine triphosphate (ATP)-sensitive potassium channels or K_{ATP} channels, represents a class of channels regulated by changes in the intracellular concentration of adenosine triphosphate. Many hypotensive or myorelaxant agents such as cromakalim, aprikalim, nicorandil, minoxidil sulfate, pinacidil (**1**) or diazoxide (**2**) have the properties to open this type of potassium channel [2]. Using the bioisosterism concept [3], Pirotte and de Tullio mixed structural elements of compounds **1** and **2**; products **3** and **4** resulting from this concept were found to be powerful inhibitors of insulin secretion [4]. Moreover, some examples of compounds of general formula **3**, being more potent on the pancreatic than on the vascular smooth muscle tissue, were identified as tissue selective K_{ATP} channel openers [4]. (Figure 1).



1 Pinacidil



2 Diazoxide



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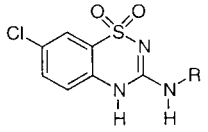

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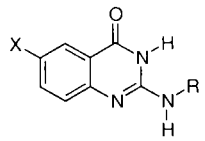
Figure 1

In the chemical structure of these compounds (Scheme 1), like in that of other potassium channel openers, it is possible to observe the presence of an electron poor aromatic ring (pyridine or chlorobenzene), the presence of a lipophilic substituent (in the 3 position of benzo- and pyridothiadiazine dioxides or in the *N*-position of *N*-alkyl-*N'*-aryl-*N''*-cyanoguanidines) and the presence of an electronegative site (iminonitrile or sulfonamide group). Therefore, we decided to apply the bioisosteric exchange of the sulfonamide moiety by the chemically related amide group, and to utilize a bromobenzene ring as an electron poor aromatic ring with an improved lipophilicity, in the hope to obtain a compound with a better activity and/or a better tissue selectivity. In this paper we describe the synthesis of 2-amino-6-bromo-4(3*H*)-one derivatives **5** as well as the preparation of compounds **6** and **7** made for comparison (Figure 2).



5 X = Br
6 X = H

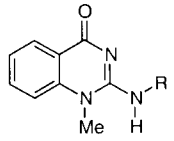


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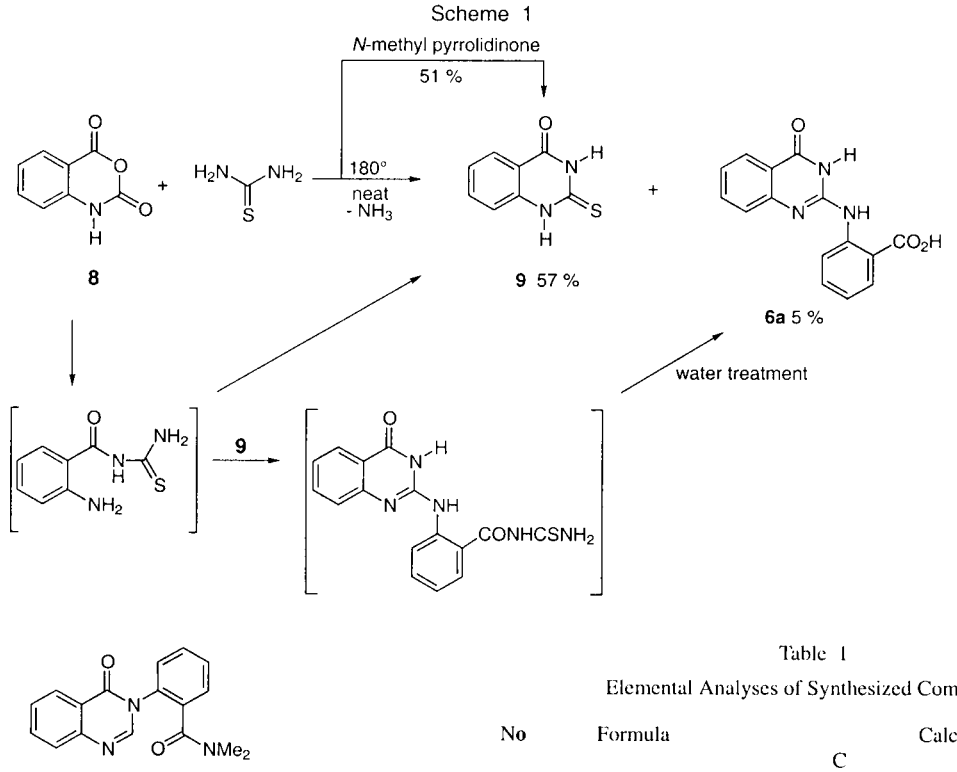
Figure 2

Many synthetic pathways to 2-aminoquinazolin-4(3*H*)-ones are described in the literature. It is possible to start from a benzoxazinone [5], a carbodiimide [6], a 2-ethoxyquinazoline [7] or from a 2-thioxoquinazolin-4-one **9** [8]. Isatoic acid **8** [9] is a good starting block for having access to this last compound, and its reaction with neat thiourea has been described [10a]. In our hands, this method yields a mixture of 2-thioxoquinazolin-4-one **9** in 57% yield and of the 2-aminobenzoic acid derivative **6a** (5%); by performing the condensation in *N*-methyl pyrrolidinone, only traces of **6a** were observed, and compound **9** was obtained in 51% yield (Scheme 1). It has to be noted

that the reaction of isatoic anhydride **8** with the Vilsmeier reagent leads to another dimeric compound **8a** [10b] (Figure 3). A possible mechanism for the formation of by-product **6a** is given in Scheme 1.

Scheme 1



8a

Figure 3. Product of the reaction between isatoic anhydride and the Vilsmeier reagent [10b].

The structure of product **6a** was deduced from its solubility in basic media and from its nmr spectra (^{1}H nmr: 8 aromatic protons; ^{13}C nmr: 15 carbons and 2 carbonyl functions; DEPT: 8 C-H groups; HETCOR correlations); the HETCOR 7 Hz correlations are shown in Figure 4.

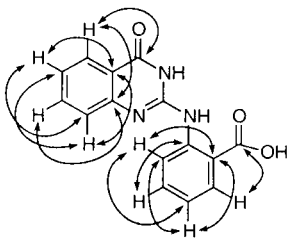


Figure 4. HETCOR 7 Hz Correlations for Acid **6a**.

The last proof of the structure of product **6a** comes from an alternative synthesis. Reaction of neat anthranilic acid with the thiomethyl-substituted compound **10** gives a 36% yield of **6a**. When the condensation was performed in refluxing dimethylformamide, a mixture of **6a** and of the dimethylamino-substituted product **6b** was formed (it was checked by nmr that dimethylformamide did not contain

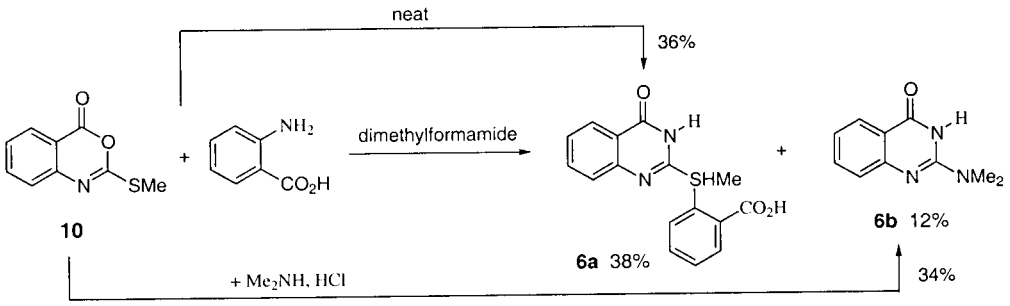
Table 1

Elemental Analyses of Synthesized Compounds

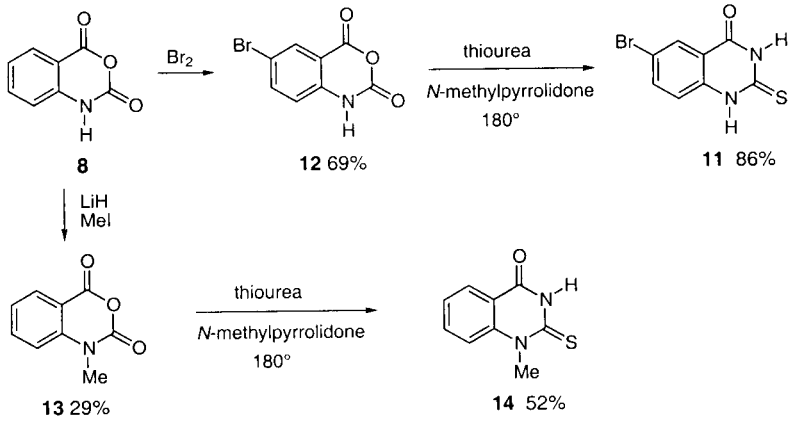
No	Formula	Calcd./Found C	H	N
5c	$C_{12}H_{14}N_3OBr$	48.67	4.76	14.19
		48.60	4.69	14.02
5d	$C_{13}H_{15}N_4OBr, H_2O$	45.76	5.02	16.42
		45.53	4.95	16.05
5e	$C_{14}H_{10}N_3OBr$	53.19	3.19	13.29
		51.83 [a]	3.22	12.87
5f	$C_{18}H_{18}N_3O_3Br$	53.48	4.49	10.39
		53.42	4.41	10.49
5h	$C_{15}H_{12}N_3OBr$	54.56	3.66	12.73
		54.26	3.60	12.60
6a	$C_{15}H_{11}N_3O_3$	64.05	3.94	14.94
		64.01	3.89	14.85
6b	$C_{10}H_{11}N_3O$	63.48	5.86	22.21
		63.26	5.94	21.93
6f	$C_{18}H_{19}N_3O$	66.45	5.89	12.91
		66.21	5.99	13.03
6g	$C_{14}H_{19}N_3O$	68.54	7.81	17.13
		67.58 [a]	7.72	16.84
9	$C_8H_6N_2OS$	53.92	3.39	15.72
		53.89	3.46	15.62
10	$C_9H_8N_2OS$	56.23	4.19	14.57
		56.05	4.21	14.36
12	$C_8H_4NO_3Br$	39.70	1.67	5.79
		39.79	1.64	5.84
13	$C_9H_7NO_3$	61.02	3.98	7.91
		61.09	3.84	7.87
15	$C_9H_7N_2OSBr$	39.87	2.60	10.33
		40.45 [a]	2.66	10.03

[a] We were not able to obtain a better carbon analysis.

Scheme 2



Scheme 3

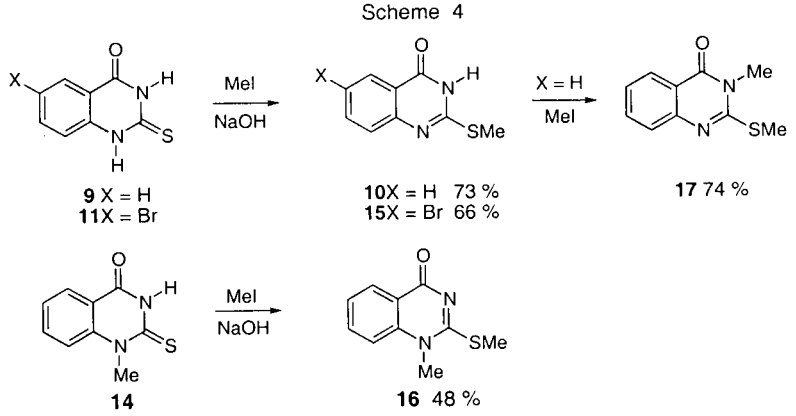


dimethylamine). The structure of **6b** was deduced from its nmr spectra and from its synthesis by reaction of compound **10** with dimethylamine hydrochloride (Scheme 2). Dimethylamino-substituted by-products coming from the interaction between dimethylformamide and a leaving group have already been reported in the literature [11].

The 6-bromo-substituted analog **11** of the 2-thioxo-quinoxalin-4-one **9** was obtained as described in Scheme 3, after bromination [12] of isatoic anhydride **8** followed by the reaction of **12** with thiourea. If this last reaction is performed neat or in dimethylformamide a mixture of at least four products was obtained. But by working at 180° in *N*-methylpyrrolidinone, compound **11** was obtained in 86% yield, with a sufficient purity to be used without further purification. Based on the same procedure, the reaction of thiourea in *N*-methylpyrrolidone with *N*-methylisatoic anhydride **13**, obtained by methylation of the lithium salt of **8**, gives a 52% yield in product **14** (Scheme 3).

Methylsulfanyl-substituted **10**, **15** and **16** were then obtained from their thioxo precursors and methyl iodide in a sodium hydroxide solution. When two equimolar amounts of methyl iodide were used, the dimethyl-substituted product **17** was formed; the position of the *N*-methyl

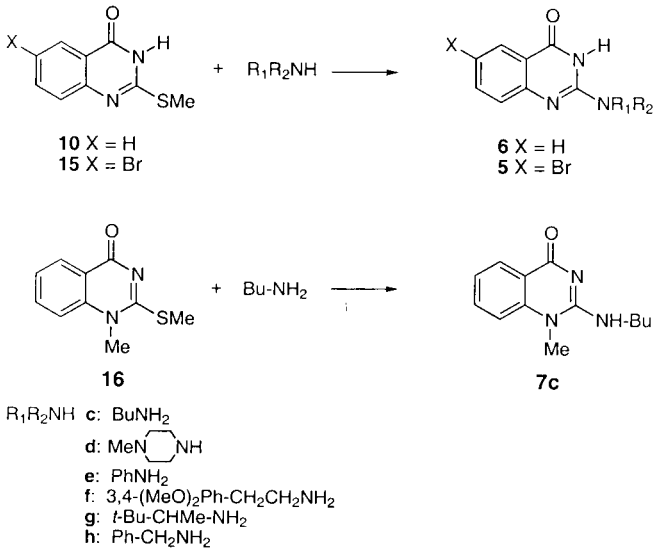
Scheme 4



group of **17** was deduced from comparison with product **16** (Scheme 4).

Heating a neat mixture of methylsulfanyl-substituted compounds **10**, **15** or **16** with amines gives products **5**, **6** and **7**. Even though the 6-bromo-substituted compound **15** was less reactive than the thiomethyl ether **10** (Table 2), good yields were generally obtained (the 25% yield obtained for **5f** came from purification difficulties) (Scheme 5).

Scheme 5



As an alternate way to bromo derivatives **5** and **15**, we have submitted compounds **6** and **10** to the action of bromine in water. Ring bromination occurred with the amines **6**, giving compounds **5** in good yields. In the same conditions, the thiomethyl ether **10** was oxidized [13], then hydrolyzed, to give the quinazoline-2,4-dione **18**. Oxidation of **10** to sulfoxide **10a** by using *m*-chloroperbenzoic acid has already been described [8c] (Scheme 6).

Scheme 6

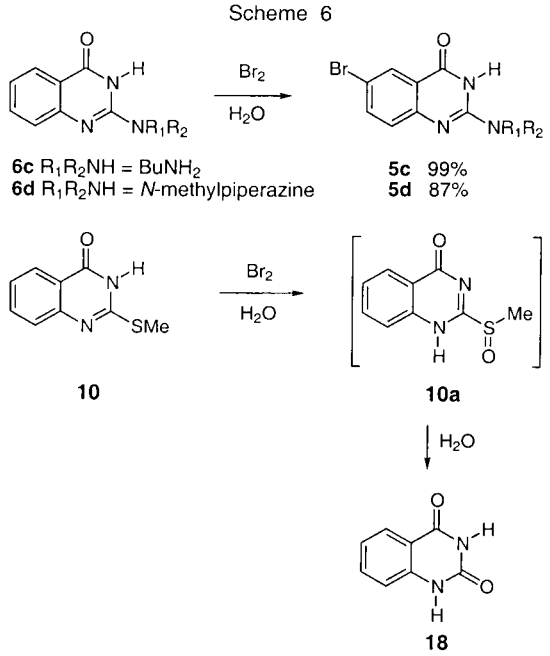
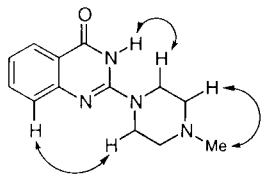


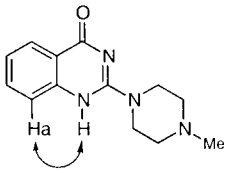
Table 2

Yields and Physical Properties of 2-Amino-quinazolin-4(3*H*)-ones

No	R_2N	temperature, °C (time, hours)	Yield %	MP°C	IR (KBr) υ cm^{-1}
5c	NHBu	75 (62)	62	306 (dimethylformamide)	3250 (NH), 1715, 1680 (C=O), 1630 (C=N), 1540, 1480, 1460 (C=C)
6a	$NHC_6H_4CO_2H$	150 (4)	36	292 (acetic acid)	3475, 3380 (OH, NH), 1700 (C=O), 1620 (C=N), 1490, 1470 (C=C)
6b	NMe_2	150 (96)	34	230 (methyl alcohol)	3150 (NH), 1680 (C=O), 1595 (C=N), 1475, 1435 (C=C)
5d	1-methylpiperazinyl	135 (4)	58	299 (dimethylformamide)	3100 (NH), 1685 (C=O), 1600 (C=N, C=C), 1500, 1470 (C=C)
6d	1-methylpiperazinyl	135 (2)	82	219 (acetone)	3150 (NH), 1680 (C=O), 1600 (C=N), 1480, 1450 (C=C)
5e	NHPh	170 (5)	58	315 (ethyl acetate)	3395 (NH), 1690 (C=O), 1620 (C=N), 1590, 1570, 1495, 1465, 1445 (C=C)
6e	NHPh	170 (2)	68	252 (acetone)	3400 (NH), 1680 (C=O), 1620 (C=N), 1590, 1500, 1470 (C=C)
5f	$NHCH_2CH_2Ph(OMe)_2$	170 (5)	25	228 (ethyl acetate)	3330 (NH), 1670 (C=0), 1625 (C=N), 1590, 1575, 1520, 1460 (C=C)
6f	$NHCH_2CH_2Ph(OMe)_2$	170 (2)	70	160 (acetone)	3325 (NH), 1680 (C=O), 1625 (C=N), 1610, 1590, 1515, 1470 (C=C)
5h	$NHCH_2Ph$	170 (2)	67	264 (ethyl acetate)	3425 (NH), 1690 (C=O), 1630 (C=N), 1605, 1565, 1530, 1470 (C=C)
6h	$NHCH_2Ph$	170 (1)	76	206 (acetone)	3250 (NH), 1680 (C=O), 1630, 1610 (C=N, C=C), 1500, 1450 (C=C)
6g	NH-CHMe-*t*-Bu	150 (12)	61	271 (acetone)	3350 (NH), 1650 (C=O), 1625 (C=N), 1570, 1530, 1500, 1470 (C=C)



Stucture I
ROESY correlation observed for **6d**



Stucture II
Non observed correlation for **6d**

Figure 5

correlation between N-H and an aromatic proton H_a was present, thus excluding alternate structure II.

Amine **19** used in the synthesis of compound **5g** was obtained in medium yield by reduction of oxime **20** with lithium aluminum hydride. This method was found to be easier than the reduction of **20** with sodium in ethanol [18], while in our hands, reduction of acetate **21** with sodium borohydride [19] did not yield **19** (Scheme 7).

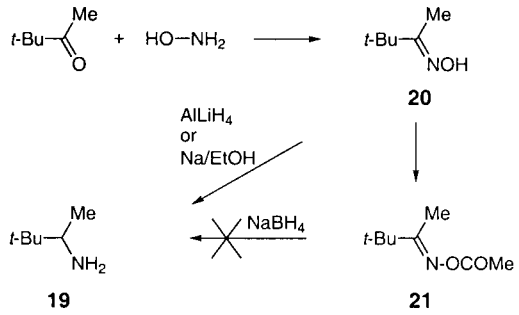
Table 3
NMR Spectra of 2-Amino-quinazolin-4(3*H*)-ones

No	^{1}H NMR δ ppm (deuteriochloroform and trifluoroacetic acid)	^{13}C NMR δ ppm (deuteriochloroform and trifluoroacetic acid)
5d	3.11 (d, J = 3.7 Hz, 3H), 3.36-3.63 (m, 2H), 3.95 (d, J = 14.7 Hz, 2H), 4.10 (d, J = 12.6, 2H), 4.56 (d, J = 14.7 Hz, 2H), 7.46 (d, J = 8.7 Hz, 1H, H_8), 8.05 (dd, J = 8.7, 2.2 Hz, 1H, H_7), 8.40 (d, J = 2.2 Hz, 1H, H_5), 9.27 (bs,1H, NH)	44.1 (CH_3), 44.3 (CH_2), 52.6 (CH_2-NMe), 115.4 (C_{4a}), 119.8 (C_8), 122.1 (C_6), 130.9 (C_5), 137.1 (C_{8a}), 142.2 (C_7), 149.3 (C_2), 162.0 (C_4)
5e	2.33 (NH), 7.30-7.39 (m, 2H), 7.43 (d, J = 8.9 Hz, 1H, H_8), 7.53-7.63 (m, 3H), 7.99 (dd, J = 8.9, 2 Hz, 1H, H_7), 8.32 (d, J = 2 Hz, 1H, H_5)	116.1 (C_{4a}), 119.6 (C_8), 120.9 (C_6), 126.8 (Ar), 130.4 (C_5), 131.1, 131.4, 131.6 (Ar), 137.3 (C_{8a}), 141.7 (C_7), 149.7 (C_2), 162.7 (C_4)
5f	3.0 (t, J = 6.9 Hz, 2H), 3.79 (t, J = 6.9 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 6.84 (d, J = 5.5 Hz, 2H), 6.86 (s, 1H), 7.32 (d, J = 8.8 Hz, 1H, H_8), 7.97 (dd, J = 8.8, 2.1 Hz, 1H, H_7), 8.31 (d, J = 2.1 Hz, 1H, H_5), 8.90 (bs, 1H, NH)	34.5 ($ArCH_2$), 44.3 (N-CH_2), 56.3 (OCH_3)$_2$), 112.8, 113.1 (Ar), 115.1 (C_{4a}), 119.3 (C_8), 120.6 (C_6), 122.3 (Ar), 129.9 (C_5), 131.1 (Ar), 137.6 (C_{8a}), 142.1 (C_7), 148.1, 149.0 (Ar), 149.5 (C_2), 162.4 (C_4)
5h	4.76 (d, J = 5.3 Hz, 2H), 7.2-7.46 (m, 6H, ArH, H_8), 7.98 (dd, J = 8.8, 2.1 Hz, 1H, H_7), 8.33 (d, J = 2.1 Hz, 1 H, H_5), 9.37 (bs, 1H, NH)	46.1 (CH_2), 115.3 (C_{4a}), 119.4 (C_8), 120.6 (C_6), 127.5, 129.8, 129.9 (ArH), 131.0 (C_5), 137.7 (C_{8a}), 142.0 (C_7), 149.4 (C_2), 162.1 (C_4)
6a	(D_2O and NaOD) 7.05 (t, J = 7.6 Hz, 1H), 7.25 (t, J = 7.9 Hz, 1H, H_6), 7.47 (d, J = 7.9 Hz, 1H, H_8), 7.50 (td, J = 7.6, 1.5 Hz, 1H), 7.66 (td, J = 7.8, 1.5 Hz, 1H, H_7), 7.86 (dd, J = 7.8, 1.5 Hz), 8.01 (d, J = 7.9 Hz, 1H, H_5), 8.50 (d, J = 7.8 Hz, 1H)	(D_2O and NaOD) 120.7 (C_{4a}), 122.5, 123.3 (Ar), 125.1 (C_6), 126.1 (Ar), 126.3 (C_8), 128.2 (C_5), 133.4, 134.3 (Ar), 135.9 (C_7), 143.7 (Ar), 154.2 (C_{8a}), 161.3 (C_2), 177.4 (C_4), 178.6 (CO_2H)
6b	(methanol-d_4) 3.21 (s, 6H, NMe_2), 7.23 (dt, J = 7.5, 1.1 Hz, 1H, H_6), 7.42 (dd, J = 8.4, 1.1 Hz, 1H, H_8), 7.60 (dt, J = 7.5, 1.5 Hz, 1H, H_7), 8.0 (ddd, J = 8.0, 1.5, 0.6 Hz, 1H, H_5)	
6c	0.98 (t, J = 7.3 Hz, 3H, Me), 1.34-1.57 (m, 2H), 1.63-1.82 (m, 2H), 3.52 (t, J = 6.0 Hz, 2H, N-CH_2), 7.42 (d, J = 8.0 Hz, 1H, H_8), 7.54 (t, J = 8.0 Hz, 1H, H_6), 7.90 (dt, J = 8.0, 1.3 Hz, 1H, H_7), 8.24 (dd, J = 8.0, 1.3 Hz, 1H, H_5), 8.47 (bs, 1H, NH)	13.2 (CH_3), 19.9, 30.8 (CH_2), 43.2 (N-CH_2), 114.0 (C_{4a}), 117.7 (C_8), 127.6 (C_6), 128.9 (C_5), 139.0 (C_{8a}), 139.4 (C_7), 149.7 (C_2), 163.9 (C_4)
6d	3.10 (d, J = 4.3 Hz, 3H), 3.94 (d, J = 14.7 Hz, 2H), 4.09 (d, J = 12.1 Hz, 4H), 4.56 (d, J = 14.7 Hz, 2H), 7.54 (d, J = 8.3 Hz, 1H, H_8), 7.65 (t, J = 7.7 Hz, 1H, H_6), 7.97 (dt, J = 8.1, 1.3 Hz, 1H, H_7), 8.28 (dd, J = 8.0, 1.3 Hz, 1H, H_5), 9.25 (bs, 1H, NH)	44.5 (CH_3), 49.7 (CH_2), 53.2 (CH_2-NMe), 114.6 (C_{4a}), 118.5 (C_8), 129.0 (C_6), 129.2 (C_5), 138.5 (C_{8a}), 139.8 (C_7), 149.8 (C_2), 163.7 (C_4)
6e	7.31-7.41 (m, 2H), 7.48-7.62 (m, 5H), 7.91 (dt, J = 7.9, 1.5 Hz, 1H, H_7), 8.20 (dd, J = 8.4, 1.5 Hz, 1H, H_5)	114.5 (C_{4a}), 177.8 (C_8), 126.7 (Ar), 127.4 (C_6), 128.5 (C_5), 130.5, 131.0, 131.4 (Ar), 138.4 (C_{8a}), 138.6 (C_7), 149.6 (C_2), 161.8 (C_4)
6f	3.0 (t, J = 6.8 Hz, 2H), 3.80 (t, J = 6.8 Hz, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 6.84 (d, J = 4.4 Hz, 2H), 6.85 (s, 1H), 7.41 (d, J = 8.3 Hz, 1H, H_8), 7.51 (dt, J = 7.7, 0.7 Hz, 1H, H_6), 7.88 (dt, J = 7.9, 1.3 Hz, 1H, H_7), 8.18 (dd, J = 7.9, 1.3 Hz, 1H, H_5), 8.82 (bs, 1H, NH)	34.5 (Ar-CH_2), 44.1 (N-CH_2), 56.1 (OMe), 56.2 (OMe) 112.6, 112.9 (ArH), 113.6 (C_{4a}), 117.5 (C_8), 122.2 (ArH), 127.3 (C_6), 128.6 (C_5), 129.9 (ArH), 138.7 (C_{8a}), 139.1 (C_7), 148.0, 148.9 (ArH), 149.5 (C_2), 163.6 (C_4)
6g	1.02 (s, 9H), 1.33 (d, J = 6.6 Hz, 3H), 3.65-3.84 (m, 1H), 7.43 (d, J = 8.2 Hz, 1H, H_8), 7.52 (t, J = 7.7 Hz, 1H, H_6), 7.89 (dt, J = 7.9, 1.5 Hz, 1H, H_7), 8.11 (bd, J = 9.6 Hz, 1H, NH), 8.21 (dd, J = 7.9, 1.5 Hz, 1H, H_5)	15.5 (CH_3), 25.5 (tB_u), 35.4 (C-tB_u), 59.0 (N-CH), 113.6 (C_{4a}), 117.6 (C_8), 127.3 (C_6), 128.6 (C_5), 138.8 (C_{8a}), 139.1 (C_7), 149.0 (C_2), 163.7 (C_4)
6h	4.77 (d, J = 5.7 Hz, 2H), 7.30-7.46 (m, 5H, ArH), 7.46 (d, J = 8.3 Hz, 1H, H_8), 7.53 (t, J = 7.7 Hz, 1H, H_6), 7.90 (t, J = 8.3 Hz, 1H, H_7), 8.21 (d, J = 7.7 Hz, 1H, H_5), 9.54 (bs, 1H, NH)	46.1 (CH_2), 113.9 (C_{4a}), 117.7 (C_8), 127.5 (C_6), 128.7 (C_5), 129.7 (ArH), 129.9 (ArH), 132.9 (Ar), 138.7 (C_{8a}), 139.1 (C_7), 149.5 (C_2), 163.3 (C_4)
7c	0.91 (t, J = 7.3 Hz, 3H, CH_3), 1.30-1.50 (m, 2H), 1.55-1.75 (m, 2H), 3.48-3.64 (m, 2H), 3.64 (s, 3H, NMe), 6.22 (bs, 1H, NH), 7.21 (d, J = 8.9 Hz, 1H, H_8), 7.28 (t, J = 7.8 Hz, 1H, H_6), 7.64 (t, J = 7.5 Hz, 1H, H_7), 8.17 (d, J = 8.1 Hz, 1H, H_5)	

In a first approach, the carbon-nitrogen double bond of compounds **5** and **6** was assigned as in the structure I (Figure 5), as drawn in the different Schemes. Indeed, when a ROESY spectrum [14] was recorded on **6d**, only the correlations indicated in Figure 5 were observed; no

The structures of new compounds were established by elemental analysis and spectral data. Preliminary biological results indicate that some synthesized compounds act on pancreatic as well as on the vascular smooth muscle tissue and appear to adopt, at least in part, the pharmacological

Scheme 7



profile of potassium channel openers (data not shown). However, the exact mechanism of action remains to be elucidated.

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were recorded on a 'Perkin-Elmer' 700 spectrometer and the nmr spectra on a Varian 'Gemini 2000' at 200 MHz for ^1H and 50 MHz for ^{13}C, using tetramethylsilane as an internal reference. Elemental analyses were performed by the «Service Central de Microanalyses» (CNRS, Vernaison, France).

2-(Butylamino)-6-bromo-quinazolin-4(3*H*)-one (**5c**).

By bromination of **6c**:

Compound **6c** (2 g, 9 mmol) in water (20 ml) was stirred while bromine (1.5 g, 0.5 ml, 9 mmol) was added dropwise (10 min). The mixture was stirred at room temperature for 30 minutes then at 80° for 1 hour. The solid formed was collected by filtration then washed with water, giving 99% in compound **5c**. Following the same method, compound **5d** was obtained in 87% yield.

Starting from thioether **15**:

A stirred mixture of thioether **15** (16.3 g, 60 mmol) and butylamine (22.2 g, 30 ml, 304 mmol) was heated at 75° for 62 hours. Water (100 ml) was added and the mixture was stirred at room temperature for 2 hours. The solid obtained was recristallized from dimethylformamide.

2-(Phenylamino)-6-bromo-quinazoline-4(3*H*)-one (**5e**).

A stirred mixture of thioether **15** (3.3 g, 12 mmol) and aniline (9.3 g, 9 ml, 99 mmol) was heated at 170° for 5 hours. After cooling, the mixture was refluxed in ether. The solid obtained was recristallized from ethyl acetate. Except for **5c**, **7c** and **6g**, the amines described in the Tables were obtained according the same method.

2-[*N*-(4-Oxo-3,4-dihydro-3*H*-quinazolin-2-yl)amino]benzoic acid (**6a**).

Reaction in dimethylformamide:

A stirred mixture of thioether **10** (5 g, 26 mmol) and anthranilic acid (11 g, 80 mmol) in dimethylformamide (30 ml) was refluxed for 18 hours. After cooling at 0° for 12 hours, the solid was collected by filtration (**6b**, 12%). The filtrate was evaporated and the residue was washed with water, giving compound **6a**, yield 38%, mp 292° (acetic acid).

Reaction without solvent:

A stirred mixture of thioether **10** (5 g, 26 mmol) and anthranilic acid (7.5 g, 55 mmol) was heated at 150° for 4 hours. After cooling, methanol (200 ml) was added and this mixture was refluxed for 2 hours. The solid obtained was washed with methanol, then recristallized from acetic acid, giving compound **6a**, yield 36%.

2-(Dimethylamino)-quinazolin-4(3*H*)-one (**6b**) .

A stirred mixture of thioether **10** (3.9 g, 20 mmol) and dimethylamine hydrochloride (1.6 g, 20 mmol) in dimethylformamide (10 ml) was refluxed for 4 days. The precipitate obtained after cooling and filtration was washed with ether then refluxed in acetone (20 ml), giving compound **6b**.

2-(3,3-Dimethyl-2-butylamino)-quinazolin-4(3*H*)-one (**6g**).

A mixture of thioether **10** (1.9 g, 9.5 mmol) and amine **19** (2 g, 20 mmol) was placed in a 100 ml round-bottomed flask. After cooling (liquid nitrogen), the flask was sealed under vacuum then heated at 150° for 12 hours. After cooling, the mixture was refluxed with ether and the solid was recristallized from acetone.

1-Methyl-2-(butylamino)-quinazolin-4(1*H*)-one (**7c**).

This compound was obtained, starting from **16,** following the same method used for **5c**.

2,3-Dihydro-2-thioxo-quinazolin-4(3*H*)-one (**9**).

A mixture of thiourea (70 g, 920 mmol) and isatoic anhydride (50 g, 307 mmol) in *N*-methylpyrrolidone (200 ml) was refluxed for 12 hours. After cooling, water (800 ml) was added and the mixture was refluxed for 1 hour. The solid was washed with water. After drying it was recristallized from acetic acid, yield 51%, mp 281° (281-282° [10 a]); ir (potassium bromide) ν cm^{-1}: 3100 (NH), 1695 (C=O), 1620, 1490 (C=C); ^1H nmr (deuteriochloroform and trifluoroacetic acid) δ ppm: 7.41 (d, J = 8.3Hz, 1H, H_8), 7.53 (t, J = 7.7 Hz, 1H, H_6), 7,89 (dt, J = 8.0, 1.2 Hz, 1H, H_7), 8.22 (dd, J = 8.0, 1.2 Hz, 1H, H_5); ^{13}C nmr (deuteriochloroform and trifluoroacetic acid) δ ppm: 116.1 (C_{4a}), 117.2 (C_8), 127.6 (C_6), 128.5 (C_5), 138.2 (C_{8a}), 140.8 (C_7), 163.1 (C_4), 177.0 (C_2). When the reaction was performed in the absence of solvent, at 180° for 3 hours, a mixture of **9** (57%) and **6a** (5%) was obtained.

2-(Methylsulfanyl)-quinazolin-4(3*H*)-one (**10**).

A stirred solution of compound **9** (1.8 g, 10 mmol) in sodium hydroxide solution (1*N*, 10 ml) and methyl iodide (1.6 g, 0.7 ml, 11 mmol) was heated at 40° for 1 hour. After cooling, the solid was collected by filtration, washed with water, then recrystallized from acetone, yield 73%;mp 210° (acetone); ir (potassium bromide) ν cm^{-1}: 3180 (NH), 1680 (C=O), 1580 (C=N), 1600, 1500, 1460 (C=C); ^1H nmr (deuteriochloroform and trifluoroacetic acid) δ ppm: 2.99 (s, 3H, Me), 7.73 (d, J = 8.2 Hz, 1H, H_8), 7.76 (t, J = 7.8 Hz, 1H, H_6), 8.04 (dt, J = 8.0, 1.4 Hz, 1H, H_7), 8.34 (d, J = 8.0 Hz, 1H, H_5); ^{13}C nmr (deuteriochloroform and trifluoroacetic acid) δ ppm 13.8 (Me), 116.8 (C_{4a}), 119.1 (C_8), 128.5(C_6), 130.3 (C_5), 138.7 (C_{8a}), 139.2 (C_7), 161.1 (C_4), 165.4 (C_2).

6-Bromo-2,3-dihydro-2-thioxo-quinazolin-4(3*H*)-one (**11**).

A stirred mixture of thiourea (15 g, 197 mmol) and isatoic anhydride (15 g, 62 mmol) in *N*-methylpyrrolidone (80 ml) was refluxed for 12 hours. After cooling, water (250 ml) was added

and the mixture was refluxed for 1 hour. The solid was washed with water. After drying, product **11** was used without further purification, yield 86%; mp > 340°; ^{1}H nmr (deuteriochloroform and trifluoroacetic acid) δ ppm: 7.38 (d, J = 8.7 Hz, 1H, H_8), 7.98 (dd, J = 8.7, 2.3Hz, 1H, H_7), 8.36 (d, J = 2.3Hz, 1H, H_5); ^{13}C (deuteriochloroform and trifluoroacetic acid) δ ppm:115.8 (C_{4a}), 119.4 (C_8), 120.7 (C_6), 131.0 (C_5),, 137.1 (C_{8a}), 141.4 (C_7), 150.6 (C_4), 175.9 (C_2).

6-Bromo-1,4-dihydro-2*H*-3,1-benzoxazine-2,4-dione (**12**).

Bromine (49.9 g, 16 ml, 312 mmol) was added dropwise (3 hours) at 50° to a suspension of isatoic anhydride (50 g, 307 mmol) in water (800 ml). The mixture was stirred for 1 hour then cooled. The solid was washed with water then with acetone, giving compound **12**, 69%; mp 270° (270-275° [12]); ir (potassium bromide) ν cm^{-1}: 3175 (NH), 1800, 1750, 1700 (C=O), 1620, 1600, 1500, 1430 (C=C); ^{1}H nmr (dimethyl-d_6-sulfoxide) δ ppm: 7.11 (d, J = 8.6 Hz, 1H, H_8), 7.86 (dd, J = 8.6, 2.4 Hz, 1H, H_7), 7.99 (d, J = 2.4 Hz, 1H, H_5); ^{13}C nmr dimethyl-d_6-sulfoxide) δ ppm: 112.4 (C_{4a}), 114.7 (C_6), 117.8 (C_8), 130.7 (C_5), 139.4 (C_7), 140.7 (C_{8a}), 146.9 (C_2), 158.9 (C_7).

1-Methyl-1,4-dihydro-2*H*-3,1-benzoxazine-2,4-dione (**13**).

A mixture of lithium hydride (1.2 g, 150 mmol) and isatoic anhydride (16.3 g, 100 mmol) in tetrahydrofuran (100 ml) was stirred at 40° for 4 hours. Methyl iodide (20.5 g, 9 ml, 144 mmol) was added and the mixture was stirred at 40° for 3 hours, then at room temperature for 12 hours. The solid was collected by filtration, then washed with ether. After drying, product **13** was used without further purification, yield 29%; ^{1}H nmr (deuteriochloroform) δ ppm: 3.60 (s, 3H, Me), 7.22 (d, J = 8.5 Hz, 1H, H_8), 7.33 (dt, J = 8.1, 0.9 Hz, 1H, H_6), 7.81 (dt, 8.1, 1.7 Hz, 1H, H_7), 8.15 (ddd, J = 2.4, 1.7, 0.4 Hz, 1H, H_5).

1-Methyl-2,3-dihydro-2-thioxo-quinazolin-4(1*H*)-one (**14**).

A stirred mixture of compound **13** (5.1 g, 29 mmol) and thiourea (7 g, 92 mmol) in *N*-methylpyrrolidone (50 ml) was heated at 180° for 12 hours. After cooling, water (100 ml) was added. The solid obtained was washed with water. After drying, product **14** was used without further purification, yield 52%, ^{1}H nmr (dimethyl-d_6-sulfoxide) δ ppm: 4.01 (s, 3H, Me), 7.41 (t, J = 8.3Hz, 1H, H_6), 7.61 (d, J = 7.7 Hz, 1H, H_8), 7.85 (t, J = 8.3Hz, 1H, H_7), 8.05 (d, J = 8.0 Hz, 1H, H_5).

2-(Methylsulfanyl)-6-bromo-quinazolin-4(3*H*)-one (**15**).

A stirred mixture of methyl iodide (8 g, 3.5 ml, 56 mmol) and compound **11** (12 g, 47 mmol) in sodium hydroxide solution (0.5 *N*, 100 ml) was heated at 40° for 2 hours. After cooling the solid was collected by filtration then washed with water and recristallized from ethyl acetate, yield 66%; mp 212°; ir (potassium bromide) ν cm^{-1}: 3325, 3225 (NH), 1680 (C=O), 1625 (C=N), 1610, 1590, 1515, 1475 (C=C); ^{1}H nmr (deuteriochloroform and trifluoroacetic acid) δ ppm: 2.99 (s, 3H, Me), 7.63 (d, J = 8.8 Hz, 1H, H_8), 8.12 (dd, J = 8.8, 2.2 Hz, 1H, H_7), 8.46 (d, J = 2.2 Hz, 1H, H_5); ^{13}C (deuteriochloroform and trifluoroacetic acid) δ ppm: 13.9 (Me), 118.9 (C_{4a}), 122.6 (C_8), 123.2 (C_6), 130.2 (C_5),140.9 (C_7), 141.0 (C_{8a}), 160.7 (C_2), 162.7 (C_4).

1-Methyl-2-(methylsulfanyl)-quinazolin-4(1*H*)-one (**16**).

A stirred mixture of compound **14** (2.7 g, 15 mmol) and methyl iodide (2.3 g, 1 ml, 16 mmol) in a sodium hydroxide solution (1*N*, 20 ml) was heated at 40° for one day. After cooling, methylene dichloride (20 ml) was added. The organic phase was washed with water, dried and evaporated. Compound **16**, 48% was used without further purification; ^{1}H nmr (deuteriochloroform) δ ppm: 2.68 (s, 3H, S-Me), 3.78 (s, 3H, N-Me), 7.33 (d, J = 8.2 Hz, 1H, H_8), 7.43 (t, J = 7.8 Hz, 1H, H_6), 7.72 (dt, J = 8.0, 1.4 Hz, 1H, H_7), 8.33 (dd, J = 8.0, 1.4 Hz, 1H, H_5).

2-(Methylsulfanyl)-3-methyl-quinazolin-4(3*H*)-one (**17**).

A mixture of compound **9** (5 g, 28 mmol) and methyl iodide (8 g, 3.5 ml, 56 mmol) in a sodium hydroxide solution (1*N*, 30 ml) was heated at 40° for 2 hours then stirred at room temperature for 12 hours. Methylene dichloride (30 ml) was added and the organic layer was washed with water, dried and evaporated, giving compound **17** (74%). This product was used without further purification; ^{1}H nmr (deuteriochloroform) δ ppm: 2.63 (s, 3H, S-Me), 3.58 (s, 3H, N-Me), 7.34 (dt, J = 7.5, 1.3Hz, 1H, H_6), 7.52 (ddd, J = 8.2, 1.3, 0.6 Hz, 1H, H_8), 7.66 (dt, J = 7.6, 1.6 Hz, 1H, H_7), 8.19 (ddd, J = 8.3, 1.6, 0.6 Hz, 1H, H_5); ^{13}C nmr (deuteriochloroform) δ ppm: 15.1 (S-Me), 30.2 (N-Me), 119.0 (C_{4a}), 125.7 (C_6), 126.0 (C_8), 127.0 (C_5), 134.3 (C_7), 147.4 (C_{8a}), 157.8 (C_2), 161.9 (C_4).

1,2,3,4-Tetrahydro-quinazoline-2,4-dione (**18**).

Bromine (1.6 g, 0.5 ml, 10 mmol) was added dropwise (10 min) to a suspension of compound **10** (1.9 g, 10 mmol) in water (25 ml). The mixture was heated at 80° for 2 hours and the solid was collected by filtration then washed with water, giving compound **18** in a yield of 100%; mp > 320° (359° [17]).

3,3-Dimethyl-2-butylamine (**19**).

A solution of oxime **20** (76 g, 661 mmol) in ether (200 ml) was added dropwise (30 min) to a suspension of lithium aluminum hydride (25 g, 0.66 mmol) in ether (300 ml). The mixture was refluxed for 30 hours, then the flask was cooled in a water bath at 0°. Methanol (150 ml) was added at this temperature, followed by water (23 ml), sodium hydroxide solution (2*N*, 23 ml) then water (55 ml). Solids were filtered (filter paper) and were washed with ether. The organic phases were extracted by using hydrochloric acid (1*N*, 3 × 150 ml). The water phases were evaporated, then dissolved in the minimum amount of water. Solid sodium hydroxide was added to the solution and the organic phase was separated, giving amine **19** in a yield of 64%, bp 85° (85° [18]); ^{1}H nmr (deuteriochloroform) δ ppm: 0.88 (s, 9H), 1.00 (d, J = 6.6 Hz, 3H), 1.60 (s, 1H, NH), 2.61 (q, J = 6.6 Hz, 1H).

3,3-Dimethyl-2-butanone Oxime (**20**).

2,2-Dimethyl butanone (100.2 g, 125 ml, 1 mole) was added dropwise (20 min) to a solution of hydroxylamine hydrochloride (69.5 g, 1 mol) in water (150 ml). Sodium carbonate (69.1 g, 0.65 mol) in water (200 ml) was added dropwise (10 min), and the mixture was stirred for 4 hours. The solid was filtered and washed with water, giving oxime **20** (88%); mp 74° (73-75° [18]); ^{1}H nmr (dimethyl-d_6-sulfoxide) δ ppm: 1.06 (s, 9H), 1.72 (s, 3H), 10.29 (s, 1H, OH).

O-Acetyl-3,3-dimethyl-2-butanone Oxime (**21**).

A stirred mixture of oxime **20** (5.8 g, 50 mmol), acetic anhydride (60 ml, 640 mmol) and pyridine (60 ml) was cooled at 0° for 1 day. Methylene dichloride (60 ml) and water (100 ml) were added and the organic layer was washed with a sodium hydrogenocarbonate solution. The organic layer was dried then

evaporated and the residue was distilled, giving 61% of compound **21** which was directly used for the reduction reactions, bp 85° (12 mm Hg); ^{1}H nmr (deuteriochloroform) δ ppm: 1.19 (s, 9H), 1.94 (s, 3H), 2.19 (s, 3H).

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