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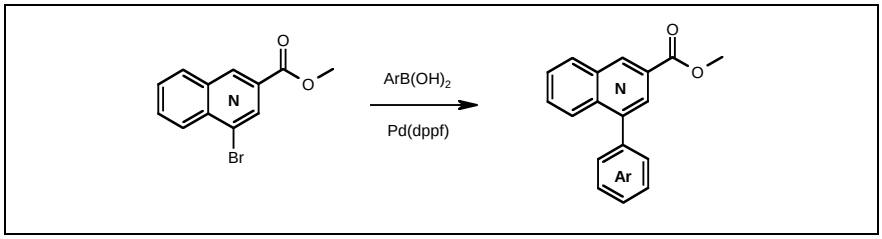

The peripheral-type benzodiazepine receptor ligands such as PK 11195 and Ro 5-4864 were found more than twenty years ago in the course of research on neurobiology. These ligands were instrumental in pointing out an involvement of the peripheral-type benzodiazepine receptor (PBR) in apoptosis processes. With in mind an improvement of the solubility of PK 11195 in biological media, we report here improved reaction conditions for the palladium-based arylation reaction of alkyl 1-bromoisoquinoline-3-carboxylates and its ethyl 4-bromoquinoline-2-carboxylate isomer. The use of [1,1'-bis(diphenylphosphino) ferrocene] dichloropalladium as a precatalyst enabled a much improved preparation of an array of the 1-arylisoquinoline-3-carboxylates as well as 4-arylquinoline-3-carboxylates. This work should pave the way for the design of chemical probes aiming at the elucidation of the PBR biological role(s).

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The peripheral benzodiazepine receptors (PBR), also named the mitochondrial diazepam binding inhibitor receptor as well as mitochondrial benzodiazepine receptor or the ω3 receptor [1], or more recently the translocator protein (18 kDa) [2], have been the subject of researches for more than 25 years. The many biological studies undertaken in this field have been very well reviewed [3-10]. Its discovery stemmed from central nervous system research programs that led to the preparation of PK 11195 (**1**) [11,12] and Ro 5-4864 (**2**), which turned out to bind PBR [13]. One the most remarkable aspect of this field of research is the fact that the anxiolytic drug diazepam (**3**) has a strong affinity for the PBR. This was the source of some concern in oncology, and led to a statistical survey in the 80's. This study showed that there was no promotion or acceleration of breast cancer progression in the case of diazepam use. On the contrary, a positive effect, especially for long-term consumers, was noted although an ascertainment bias could be involved [14]. More recently, the anxiolytic drug alpidem (**4**), another PBR ligand [15], was withdrawn from the human pharmacopea as several cases of very severe hepatitis occurred in patients also receiving hepatotoxic drugs [16-18]. On the other hand, the closely related zolpidem (**5**), does not bind PBR [19] and is still a successful sedative and hypnotic. The fact remains that a clear-cut picture, explaining the role(s) of PBR and the many-sided biological effects of PBR ligands is still lacking [3-10].

The limitation of the catalytic system used in the course of our preparation of 1-arylisoquinoline-3-carboxylates [20] leads us to report here much improved reaction conditions. Moreover, we used the optimized conditions in the construction of the isomeric 3-carboxyl-4-aryl-quinoline system.

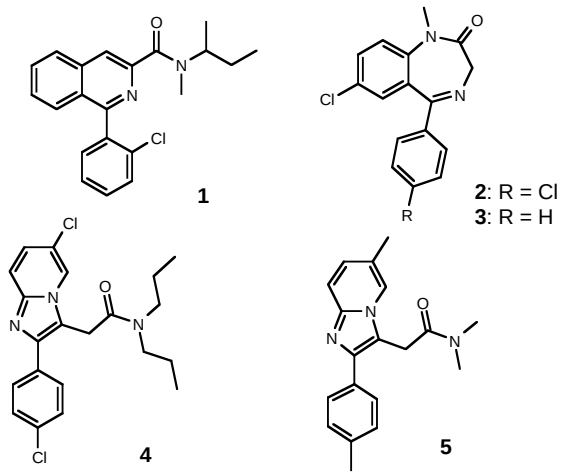
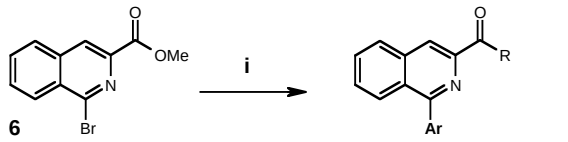


Figure 1

As depicted in scheme 1, from 1-bromoisoquinoline **6**, the reaction conditions previously used [20,21] led to the 3-carboxyl-1-aryl-isoquinolines **7a**-**e** which were readily hydrolysed to the corresponding acids **8a**-**e**. However, as described in the experimental part, the coupling reaction remained very slow and its completion much dependant on the boronate considered. For instance, a low 36 % yield was obtained from 4-chloroboronic acid and from 4-pyridylboronic acid very little of the corresponding coupling product **7f** could be detected by LC/MS.

Scheme 1

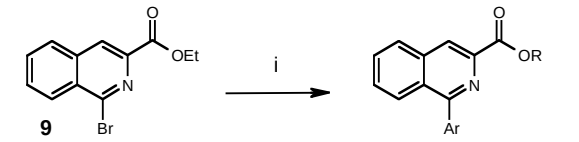


	Ar	% **7**	% **8**
a	C_6H_5	77%	65%
b	2-ClC_6H_4	90%	74%
c	3-ClC_6H_4	75%	75%
d	4-ClC_6H_4	36%	74%
e	3-pyridyl	77%	66%
f	4-pyridyl	traces	

i: $ArB(OH)_2$, $Pd(PPh_3)_4$, K_3PO_4, DMF 80°C, 2 days. ii: KOH, H_2O / EtOH reflux.

Trials from the ethyl ester **9** using [1,1'-bis(diphenylphosphino)ferrocene] dichloro palladium ($PdCl_2$, dppf) for catalyst, as previously reported [22], turned out to be rewarding. Indeed, a 72 % yield of the 4-chlorophenyl ester **10a** was obtained. Moreover, the reaction time turned out to be drastically shorter (one hour instead of days) and contrary to our previous trials the 4-pyridyl-bearing product **10b** could be prepared in a 58 % yield.

Scheme 2

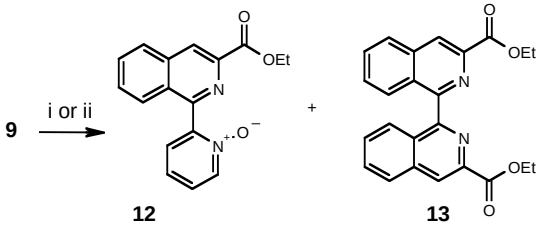


	Ar	% **10**	% **11**
a	4-ClC_6H_4	72%	-
b	4-pyridyl	58%	80%

i: $ArB(OH)_2$, $PdCl_2dppf$, Cs_2CO_3, dioxane / H_2O 85°C, 1 hour. ii: KOH, H_2O / EtOH reflux.

To further extend this study, we sought to prepare the 2-pyridyl derivatives and focused on the recently reported preparation of 2-pyridyl-*N*-oxide aryl derivatives from pyridinine-*N*-oxide using palladium acetate and tri-*tert*-butylphosphine as a catalyst [23,24]. From compound **9**, using dioxane as a solvent, a modest yield of the corresponding 2-pyridyl-*N*-oxide **12** was obtained only if quite strong reaction conditions were used. A microwave-based heating turned out to be very useful as it enabled to obtain pure compound **12** in 4.6 % yield using a one hour-long irradiation time at 150 °C. The LC/MS monitoring of the reaction explained this rather low yield as it pointed out the occurrence of a reductive debromination of compound **9** (peak with a m/z = 202) as well as the reductive dimerization product **13** (peak with m/z = 401) which was isolated in a 4 % yield. Further work led to an assay using di-*tert*-butylmethylphosphine as the palladium ligand and toluene for solvent which led to a much improved 39 % of compound **12** along with reduced material (m/z = 202) and as seen by LC/MS, traces of a biarylether (peak with a m/z = 417).

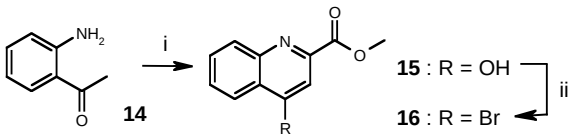
Scheme 3



i: pyridine-N-oxide, $Pd(OAc)_2$, $P(tBu)_3$, K_2CO_3, dioxane, 150 °C μν heating 1 hour. ii: pyridine-N-oxide, $Pd(OAc)_2$, $PMe(tBu)_2$, K_2CO_3, toluene, 170 °C μν heating 45 mn.

By improving a reported procedure using 2-amino-acetophenone (**14**) and dimethyloxalate [26] the isomeric 4-hydroxyquinoline **15** was obtained in a 41% yield. Treatment of this compound with phosphorus oxybromide gave the 4-bromoquinoline ester **16** in a 73 % yield.

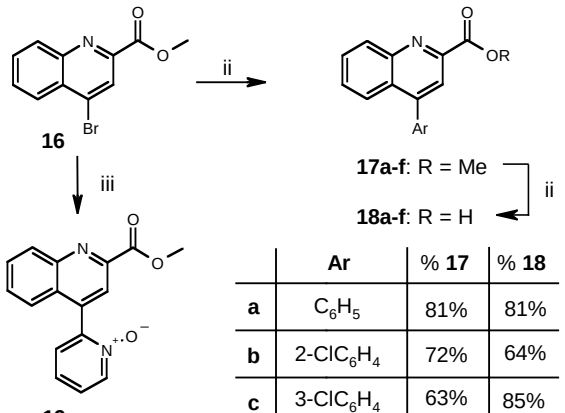
Scheme 4



i: $(COOMe)_2$, MeONa, MeOH reflux. ii: $POBr_3$, K_2CO_3, MeCN reflux.

As shown in scheme 5, we focused on the preparation of quinoline-bearing analogues **17a-f** which are structurally related to a family of strong PBR ligands [25]. The use of the optimized palladium-catalysed coupling method described above led to the quinolines **17a-f** in a 60-80% yield range. These esters were then readily hydrolized into acids **18a-f**. To prepare 2-pyridyl derivatives such as compound **19**, we investigated the reaction between the recently reported [27] 2-pyridine-boronic acid *N*-phenyldiethanolamine ester and compound **16**. The LC/MS monitoring of few trials pointed out the necessity of adding copper iodide in the reaction mixture to obtain any coupling reaction. However, side reactions, such as extensive transesterifications of the carboxyl moiety, were observed and rendered the purification of the reaction products quite difficult.

Scheme 5



	Ar	% 17	% 18
a	C_6H_5	81%	81%
b	2-ClC_6H_4	72%	64%
c	3-ClC_6H_4	63%	85%
d	4-ClC_6H_4	72%	78%
e	3-pyridyl	76%*	82%
f	4-pyridyl	61%	77%

*: using pyridine-3-boronic acid 1,3-propanediol ester

i: $ArB(OH)_2$, $PdCl_2dppf$, Cs_2CO_3, dioxane/H_2O 85°C. ii: KOH, H_2O/EtOH reflux. iii: pyridine N-oxide, $Pd(OAc)_2$, $PMe(tBu)_2$, K_2CO_3, toluene, 170 °C μv heating 45 mn.

Accordingly, we studied the palladium-catalysed coupling of compound **16** with pyridine-N-oxide. Using the microwave–based heating approach described above, the N-oxide derivative **19** was obtained in a 29 % yield. The LC/MS monitoring of this trial pointed out the occurrence of reduced material (peak with a *m/z = 188*), the presence of some starting material and many other substance including traces of an eventual dimerized material (*m/z = 373*) homologous to compound **13**.

In conclusion, from the isoquinoline or quinoline bromide derivatives **6, 9** or **16**, this work allowed the preparation of a diverse array of biaryl compounds featuring a core structure related to PK 11195 (**1**). The use [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium as a precatalyst instead of the tetrakis(triphenylphosphine) palladium we and others initially used [20,28] was rewarding in many instances. The few metal-catalysed coupling trials with pyridine-N-oxide pointed out some side reactions and the interest of using microwave heating. A future challenge would be to find better catalysts to further improve this reaction.

On the applications point of view, PBR ligands were described for their potential use in imagery techniques such as positron emission tomography [29,30]. Further results have actually been reported more recently [31-39]. On the biology point of view, PBR and their many known ligands [40,41] are the subject of a vast array of investigations. Some compounds are studied for their neuroprotective capacity [42], the treatment of neuropathic pain [43], the treatment of anxiety and depression [44], as well as the treatment of peripheral neuropathy or neurodegenerative diseases [45]. Moreover, some ligands were mentioned for their cosmetic enhancing effects [46,47] or their potential in anticancer chemotherapy [48-52]. Concerning the underlying biological mechanism(s) at work for these effects, recent investigations may herald a more complete unravelling of this challenging puzzle [53-57]. The inhibition of the mitochondrial F1F0-ATPase by PK 11195 (**1**) is noteworthy [58]. We thus hope that this synthetic work will be useful in the preparation of chemical tools designed for the elucidation of the many-faceted effects of PBR ligands.

EXPERIMENTAL

General Methods. A Biotage initiator 2 microwave oven was used for of the reactions requiring microwaves irradiations. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-300 or 400 spectrometers at 300 or 400 MHz and 75 or 100 MHz, respectively. Unless otherwise noted, $CDCl_3$ was the solvent used. Shifts (δ) are given in ppm with respect to the TMS signal and coupling constants (J) are given in Hertz. Column chromatography were performed over Merck silica gel 60 (0.035 - 0.070 mm), using a solvent pump operating at pressure between 2 and 7 bar (25-50 mL/mn) and an automated collecting system driven by a UV detector set to 254 nm unless stated otherwise (*i.e.* if ethylacetate was used then it would be set to 280 nm). Some of the low and high resolution mass spectra (HRMS) were obtained by Mrs Nicole Morin (ENS, 24 rue Lhomond, F-75231 Paris) on a MS 700 Jeol. Others were obtained on an Agilent 1100 serie LC/MSD system using an atmospheric electrospray ionisation system and the high resolution mass spectroscopy spectra (HRMS) were obtained using a water Micromass Q-Tof with an electrospray ion source.

General preparation of methyl 4-arylisoquinoline-3-carboxylates 7a-e. Under an inert atmosphere, a mixture of compound **6** (5.63 mmol), the arylboronic derivative considered (7.33 mmol), potassium phosphate (7.33 mmol) and tetrakis-(triphenylphosphine) palladium (0.17 mmol) in dry DMF (50 mL, dried over 4 Å molecular sieves) was heated at 80 °C for 14 hours. As an ^{1}H NMR monitoring of the reaction showed that the reaction had stopped, another portion of 2-chlorophenylboronic acid (2.23 mmol) and potassium phosphate (2.23 mmol) were added and the heating resumed for another 12 hours. Again, as an ^{1}H NMR monitoring of the reaction showed that the reaction had stopped, another portion of 2-chlorophenylboronic acid (0.56 mmol) and potassium phosphate (0.56 mmol) were added and the heating resumed for another 2 hours. The suspension was then concentrated to dryness and the residue purified by chromatography over silica gel as described below. *Note*: in the case of compound **7c** or **7d**, despite repeated addition of potassium phosphate and the corresponding arylboronic acid, the ^{1}H NMR monitoring of the reaction showed that we could not bring it to completion and thus work up was undertaken after 2 days.

Methyl 1-phenylisoquinoline-3-carboxylate (7a). This compound was obtained in a 77% yield, *via* a chromatography over silica gel eluting with dichloromethane. Mp = 155 °C

(cyclohexane). ^{1}H ($CDCl_3$): δ = 4.05 (s, 3H), 7.54 (m, 3H), 7.70 (m, 4H), 8.03 (d, 1H, J = 8.1), 8.14 (d, 1H, J = 8.4), 8.59 (s, 1H). ^{13}C ($CDCl_3$): δ = 52.8, 123.3, 127.8, 128.2, 128.4, 128.9, 129.4, 130.1, 130.7, 135.5, 138.9, 140.8, 161.2, 166.5. *Anal*. ($C_{17}H_{13}NO_2$): Calc: C: 77.55, H: 4.98, N: 5.32, found: C: 77.11, H: 4.98, N: 5.32.

Methyl 1-(2-chlorophenyl)isoquinoline-3-carboxylate (7b). Obtained in a 90% yield as described previously [20].

Methyl 1-(3-chlorophenyl)isoquinoline-3-carboxylate (7c). This compound was obtained in a 75% yield, *via* a chromatography over silica gel eluting with dichloromethane. Mp = 138 °C (heptane). ^{1}H ($CDCl_3$): δ = 4.04 (s, 3H), 7.46 (m, 2H), 7.55 (m, 1H), 7.71 (m, 2H), 7.79 (m, 1H), 8.03 (d, 1H, J = 8.1), 8.07 (d, 1H, J = 8.1), 8.6 (s, 1H). ^{13}C ($CDCl_3$): δ = 52.9, 123.7, 127.3, 128.0, 128.3, 128.5, 129.0, 129.6, 129.7, 130.1, 130.9, 134.5, 136.5, 140.5, 140.8, 159.6, 166.3. *Anal*. ($C_{17}H_{12}NO_2Cl$) : Calc: C: 68.58, H: 4.06, N: 4.7, Cl: 11.91, found: C: 68.35, H: 4.15, N: 4.70, Cl: 11.60.

Methyl 1-(4-chlorophenyl)isoquinoline-3-carboxylate (7d). This compound was obtained in a 36% yield, *via* a chromatography over silica gel eluting with dichloromethane. Mp = 188 °C (heptane-dichloromethane). ^{1}H ($CDCl_3$): δ = 4.03 (s, 3H), 7.50 (d, 2H, J = 7), 7.67 (m, 3H), 7.78 (m, 1H), 8.05 (m, 2H), 8.58 (s, 1H). ^{13}C ($CDCl_3$): δ = 52.9, 123.5, 127.4, 128.1, 128.6, 128.7, 129.6, 130.8, 135.2, 136.6, 137.3, 140.9, 159.9, 166.4. *Anal*. ($C_{17}H_{12}NClO_2$, 1/5 H_2O) : Calc: C: 67.76, H: 4.15, N: 4.65, Cl: 11.68, found: C: 67.78, H: 3.95, N: 4.71, Cl: 11.94.

Methyl 1-(3-pyridyl)isoquinoline-3-carboxylate (7e). This compound was obtained in a 77% yield, *via* a chromatography over silica gel (dichloromethane-methanol 98/2). Mp = 162 °C (toluene-cyclohexane). ^{1}H ($CDCl_3$): δ = 4.04 (s, 3H), 7.49 (dd, 1H, J = 5.2 and 8.1), 7.70 (m, 1H), 7.81 (m, 1H), 8.03 (m, 3H), 8.63 (s, 1H), 8.75 (d, 1H, J = 3.3), 8.96 (d, 1H, J = 1.5). ^{13}C ($CDCl_3$): δ = 52.9, 123.4, 123.9, 127.0, 128.2, 128.7, 130.0, 131.1, 134.7, 136.6, 137.5, 141.0, 150.0, 150.6, 158.0, 166.2. *Anal*. ($C_{16}H_{12}N_2O_2$) : Calc: C: 72.72, H: 4.58, N: 10.6, found: C: 72.55, H: 4.57, N: 10.56.

Ethyl 1-bromoisoquinoline-3-carboxylate (9). This compound was prepared using our previously reported strategy [21] although from phthalide and diethyl acetamidomalonate as described below. Phthalide (20 g, 0.149 mol) was dispersed in carbon tetrachloride (500 mL). To this was added *N*-bromosuccinimide (29.2 g, 0.16 mol) and benzoyl peroxide (0.36 g, 1.5 mmol). This was heated to reflux for 75 minutes and concentrated to dryness. The residue was dissolved in chloroform, filtered and concentrated to dryness again. The resulting syrup containing the bromophthalide and much less succinimide was then dissolved in DMF (250 mL, dried over 4 Å molecular sieves) and protected from air. In another flask protected from moisture by a calcium guard, dry diethyl acetamidomalonate (35.6 g, 0.164 mol) was dissolved in dry DMF (400 mL; dried over 4 Å molecular sieves) and cooled to 0°C using an ice bath. To this solution was added 60% sodium hydride (suspension in mineral oil) (6.56 g, 0.164 mol). The suspension was stirred until the end of the gas evolution (30-45 minutes) and then the bromophthalide solution described above was added. The resulting solution was stirred overnight at room temperature and then concentrated to dryness. The residue was dissolved in diethylether (800 mL), the organic phase was washed with a 1 *N* solution of sodium hydroxide (five times 70 mL), with water (five times 70 mL) and dried over magnesium sulfate before concentrating it to dryness. In the next step, the resulting 27 g of syrup containing the diethyl acetylamino-2-(3-oxo-1,3-dihydroisobenzofuran- 1-yl)-malonic acid was heated to reflux in acetic acid (300 mL) containing concentrated sulfuric acid (0.5 mL) for 30 hours. This was concentrated to dryness, the residue was dissolved in dichloromethane and the organic phase was washed with water, dried over magnesium sulfate before concentrating it to dryness. The residue was partially purified by chromatography over silica gel (dichloromethane/ethanol 98.5 – 1.5) to yield 12 g of a crude fraction containing the ethyl 1-hydroxyisoquinoline-3-carboxylate. This crude fraction was dissolved in acetonitrile (300 mL, dried over 4 Å molecular sieves) potassium carbonate was added (15.29 g, 0.11 mol) followed by phosphorus oxobromide (31 g, 0.11 mol.). This was heated to reflux for 90 minutes and the resulting suspension was concentrated to dryness. The residue was cautiously dispersed in cold water and extracted with dichloromethane. The organic phase was washed with water, dried over magnesium sulfate and concentrated to dryness. This was purified by a chromatography over silica gel (dichloromethane/cyclohexane 80-20). The corresponding fraction was concentrated to dryness, the resulting solid was dispersed in cold cyclohexane and filtered to yield pure compound **9** (6.94 g, 16 % from the starting phtalide). Mp = 117°C. ^{1}H ($CDCl_3$): δ = 1.49 (t, 3H, J = 7.1), 4.54 (q, 2H, J = 7.1), 7.86 (m, 2H), 7.99 (m, 1H), 8.42 (m, 1H); 8.54 (s, 1H). ^{13}C ($CDCl_3$): δ = 14.4, 62.1, 124.3, 128.6, 129.1, 130.4, 131.0, 131.9, 136.8, 141.3, 145.5, 164.5.

Improved synthetic procedure for the preparation of compounds 10a-b and 17a-f. In a 60 mL round-bottomed thick glass tube fitted with a PTFE-faced screw-cap, a mixture of compound **9** or **16** (1 mmol), the desired boronic acid (2.14 mmol), cesium carbonate (2.14 mmol) in dioxane (2 mL) and water (1 mL) was degassed with a slow stream of argon for ten minutes. Following this, [1,1'-bis(diphenylphosphino)ferrocene] dichloro palladium complexed with dichloromethane (0.053 mmol) was added, the tube was closed tightly and heated at 85 °C for 1 hour. After cooling to room temperature, the reaction mixture was diluted in water and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness. The residue was purified by chromatography on silica gel as described below.

Ethyl 1-(4-chlorophenyl)isoquinoline-3-carboxylate (10a). This compound was obtained in a 72 % yield, *via* a chromatography over silica gel (dichloromethane-ethanol 98/2). Mp = 119 °C. ^{1}H ($CDCl_3$): δ = 1.47 (t, 3H, J = 7.2), 4.53 (q, 2H, J = 7.2), 7.50 (m, 4H,), 7.66 (m, 1H), 7.77 (m, 1H), 8.02 (d, 1H, J = 8.1), 8.09 (d, 1H, J = 8.3), 8.56 (s, 1H). ^{13}C ($CDCl_3$): δ = 14.4, 61.8, 123.3, 127.3, 127.8, 128.5, 129.3, 129.6, 130.8, 131.5, 135.0, 136.5, 137.2, 141.0, 159.7, 165.7. HRMS *m/z* Calcd for $C_{18}H_{14}ClNO_2$ $(M+H)^+$ 312.0791. Found: 312.0823.

Ethyl 1-(4-pyridyl)isoquinoline-3-carboxylate (10b). This compound was obtained in a 58 % yield, *via* a chromatography over silica gel (dichloromethane-ethanol 98/2). Mp = 169 °C. ^{1}H ($CDCl_3$): δ = 1.48 (t, 3H, J = 7.2), 4.54 (q, 2H, J = 7.2), 7.49 (m, 2H), 7.64 (m, 1H), 7.82 (m, 1H), 8.14 (s, 1H), 8.40 (m, 1H), 8.82 (m, 2H). ^{13}C ($CDCl_3$): δ = 14.4, 61.9, 124.0, 124.8, 126.8, 127.7, 128.7, 129.9, 131.1, 136.6, 141.4, 146.4, 150.0, 158.3, 165.6. HRMS *m/z* Calcd for $C_{17}H_{14}N_2O_2$ $(M+H)^+$ 279.1133. Found: 279.1146.

Methyl 4-phenylquinoline-2-carboxylate (17a). This compound was obtained in a 81 % yield, *via* a chromatography over silica gel (cyclohexane-ethyl acetate 4/1). Mp = 103 °C lit.

[59] 101-102 °C. ^{1}H ($CDCl_3$): δ = 4.08 (s, 3H), 7.52-7.58 (m, 5H), 7.60 (m, 1H,), 7.76 (m, 1H), 7.97 (d, 1H), 8.15 (s, 1H), 8.38 (d, 1H). ^{13}C ($CDCl_3$): δ = 53.2, 121.2, 125.7, 127.8, 128.6, 128.7, 129.5, 130.1, 131.1, 137.4, 147.4, 148.1, 149.9, 166.0. HRMS *m/z* Calcd for $C_{17}H_{13}NO_2$ $(M+H)^+$ 264.1024. Found: 264.1026.

Methyl 4-(2-chlorophenyl)quinoline-2-carboxylate (17b). Obtained after a chromatography over silica gel eluting with a mixture of cyclohexane-ethyl acetate 4/1 in a 72 % yield. Mp = 153 °C (heptane). ^{1}H ($CDCl_3$): δ = 4.08 (s, 3H), 7.32-7.54 (m, 6H), 7.80 (m, 1H), 8.11 (s, 1H), 8.36 (d, 1H, J = 8.4), ^{13}C ($CDCl_3$): δ = 53.2, 121.7, 125.6, 126.8, 127.9, 128.8, 129.8, 130.1, 130.2, 131.0, 131.2, 133.1, 136.1, 147.2, 147.3, 147.7, 165.8. *Anal*. ($C_{17}H_{12}NClO_2$, 1/4 H_2O): Calc: C: 67.56, H: 4.17, N: 4.63, Cl: 11.73, found: C: 67.81, H: 3.99, N: 4.70, Cl: 11.75.

Methyl 4-(3-chlorophenyl)quinoline-2-carboxylate (17c). Obtained after a chromatography over silica gel eluting with dichloromethane in a 63 % yield. Mp = 163 °C. ^{1}H ($CDCl_3$): δ = 4.09 (s, 3H), 7.39-7.41 (m, 1H), 7.45-7.52 (m, 3H), 7.62 (m, 1H), 7.80 (m, 1H), 7.91 (m, 1H), 8.13 (s, 1H), 8.38 (d, 1H, J = 8.5) ^{13}C ($CDCl_3$): δ = 53.3, 121.2, 125.3, 127.5, 127.7, 128.9, 129.0, 129.5, 130.2, 130.3, 131.1, 134.6, 139.1, 147.4, 148.0, 148.3, 165.8. HRMS *m/z* Calcd for $C_{17}H_{13}ClNO_2$ $(M+H)^+$ 298.0635. Found: 298.0661.

Methyl 4-(4-chlorophenyl)quinoline-2-carboxylate (17d). Obtained after a chromatography over silica gel eluting with a mixture of cyclohexane-dichloromethane 70/30 in a 72 % yield. Mp = 127 °C. ^{1}H ($CDCl_3$): δ = 4.12 (s, 3H), 7.49 (m, 2H),7.52 (m, 2H), 7.61 (m, 1H), 7.83 (m, 1H), 7.95 (d, 1H, J = 8.5), 8.10 (s, 1H), 8.36 (d, 1H, J = 8.4). ^{13}C ($CDCl_3$): δ = 53.3, 121.2, 125.4, 127.6, 128.9, 129.0, 130.3, 130.8, 131.2, 135.1, 135.8, 147.5, 148.1, 148.5, 165.9. HRMS *m/z* Calcd for $C_{17}H_{13}ClNO_2$ $(M+H)^+$ 298.0635. Found: 298.0648.

Methyl 4-(3-pyridyl)quinoline-2-carboxylate (17e). Obtained after a chromatography over silica gel eluting with a mixture of dichloromethane-ethanol 99/1 in a 76 % yield. *Note*: in this case, the less expensive pyridine-3-boronic acid 1,3-propanediol ester was used. Mp = 159 °C. ^{1}H ($CDCl_3$): δ = 4.10 (s, 3H), 7.52 (m, 1H), 7.64 (m, 1H), 7.82 (m, 1H), 7.88 (m, 2H), 8.16 (s, 1H), 8.40 (d, 1H, J = 8.4), 8.80 (m, 2H). ^{13}C ($CDCl_3$): δ = 53.2, 121.5, 123.5, 124.9, 127.5, 129.2, 130.4, 131.3, 133.4, 136.9, 146.0, 147.5, 148.1, 149.7, 149.8, 165.7. HRMS *m/z* Calcd for $C_{16}H_{13}N_2O_2$ $(M+H)^+$ 265.0977. Found: 265.1014.

Methyl 4-(4-pyridyl)quinoline-2-carboxylate (17f). Obtained after a chromatography over silica gel eluting with a mixture of dichloromethane-ethanol 99/1 in a 61 % yield. Mp = 159 °C. ^{1}H ($CDCl_3$): δ = 4.10 (s, 3H), 7.48 (m, 2H), 7.63 (m, 1H), 7.82 (m, 2H), 8.14 (s, 1H), 8.40 (d, 1H, J = 8.4), 8.82 (m, 2H). ^{13}C ($CDCl_3$): δ = 53.3, 121.0, 124.3, 124.8, 126.8, 129.3, 130.5, 131.3, 145.4, 146.7, 147.5, 148.0, 149.9, 165.6. HRMS *m/z* Calcd for $C_{16}H_{13}N_2O_2$ $(M+H)^+$ 265.0977. Found: 265.0987.

Palladium-catalysed coupling of pyridine-N-oxide to compound **9**. In a 0.5 – 2 mL model tube fitting the Biotage microwave oven described above, a mixture of compound **9** (0.8 mmol), pyridine-N-oxide (3.3 mmol), potassium carbonate (1.7 mmol) and dioxane (1 mL) was degassed by a slow stream of argon for ten minutes. Following this, palladium acetate (0.042 mmol) and tri-*tert*-butylphosphine tetrafluoroborate (0.12 mmol) were added, the tube was quickly sealed and heated at 150 °C for 1 hour in the microwave oven. After cooling to room temperature, the reaction mixture was concentrated to dryness. The residue was purified by chromatography on silica gel (dichloromethane / ethanol 99-1 to 9-1) to yield compound **12** and **13** in 4.6 and 4% yield respectively.

2-(3-(Ethoxycarbonyl)isoquinolin-1-yl)pyridine 1-oxide (12). This compound was contained in the least migrating fraction of the chromatography and had to be further purified by a recrystallisation in cyclohexane to yield 4.6 % of compound **12**. Mp = 219 °C. ^{1}H ($CDCl_3$): δ = 1.39 (t, 3H, J = 7.1), 4.46 (q, 2H, J = 7.1), 7.39 (m, 2H), 7.64 (m, 4H), 7.97 (d, 1H, J = 8.1), 8.29 (m, 1H), 8.62 (s, 1H). ^{13}C ($CDCl_3$): δ = 14.4, 61.9, 125.5, 125.6, 126.4, 126.8, 128.4, 128.5, 128.9, 130.1, 131.2, 135.9, 139.9, 141.5, 148.0, 153.2, 165.4. HRMS *m/z* Calcd for $C_{17}H_{15}N_2O_3$ $(M+H)^+$ 295.1083. Found: 295.1092.

Diethyl 1,1'-biisoquinoline-3,3'-dicarboxylate (13). This compound was contained in the most migrating fraction of the chromatography and had to be further purified by a washing it in boiling cyclohexane to yield 4 % of compound **13**. Mp = 263 °C. ^{1}H ($CDCl_3$): δ = 1.47 (t, 3H, J = 7.1), 4.54 (q, 2H, J = 7.1), 7.62 (m, 1H), 7.81 (m, 2H), 8.10 (d, 1H, J = 8.2), 8.75 (s, 1H). ^{13}C ($CDCl_3$): δ = 14.4, 61.8, 124.6, 127.5, 128.4, 129.4, 129.8, 131.2, 136.7, 140.9, 157.6, 165.7. HRMS *m/z* Calcd for $C_{24}H_{21}N_2O_4$ $(M+H)^+$ 401.1501. Found: 401.1488.

Palladium-catalysed coupling of pyridine-N-oxide to compound **9** or **16**. In a 0.5 – 2 mL model tube fitting the Biotage microwave oven described above, a mixture of compound **9** or **16** (0.8 mmol), pyridine-N-oxide (3.3 mmol), potassium carbonate (1.7 mmol) and toluene (1 mL) was degassed by a slow stream of argon for ten minutes. Following this, palladium acetate (0.042 mmol) and di-*tert*-butylmethyl-phosphine tetrafluoroborate (0.12 mmol) were added, the tube was quickly sealed and heated at 170 °C for 45 minutes in the microwave oven. After cooling to room temperature, the reaction mixture was concentrated to dryness. From compound **9** using this procedure followed by the purification protocol described above compound **12** was obtained in a 39 % yield. From compound **16** a chromatography over silica gel of the resulting residues (dichloromethane-ethanol 95/5) led to compound **19** in 29 % yield.

2-(2-(Methoxycarbonyl)quinolin-4-yl)pyridine 1-oxide (19). Mp = 206 °C. ^{1}H ($CDCl_3$): δ = 4.11 (s, 3H), 7.46-7.49 (m, 3H), 7.64 (m, 2H), 7.82 (m, 1H), 8.26 (s, 1H), 8.40 (m, 1H), 8.45 (m, 1H). ^{13}C ($CDCl_3$): δ = 53.3, 122.0, 125.3, 125.5, 126.4, 126.9, 128.4, 129.4, 130.6, 131.4, 140.5, 140.8, 146.7, 147.7, 165.5. HRMS *m/z* Calcd for $C_{16}H_{13}N_2O_3$ $(M+H)^+$ 281.0926. Found: 281.0958.

General preparation of the corresponding acids 8a-e, 11b and 18a-f. The ester (3.96 mmol) and potassium hydroxide (1 g, 15.8 mmol) were refluxed in 60% aqueous ethanol (80 mL) for 90 minutes. The ethanol was removed under a reduced pressure and the residue made acid with diluted hydrochloric acid. This was sometime extracted with dichloromethane; the organic layer was washed with water and dried over magnesium sulfate as described below.

1-(Phenyl)isoquinoline-3-carboxylic acid (8a). This compound was obtained in a 65% yield *via* an extraction after acidification of the aqueous phase. Mp = 220 °C (ethanol-water). ^{1}H ($CDCl_3$ + DMSO-d_6): δ = 7.45 (m, 3H), 7.61 (m, 3H), 7.72 (m, 1H), 8.01 (d, 1H, J = 8.1), 8.07 (d, 1H, J = 8.4), 8.51 (s, 1H). ^{13}C ($CDCl_3$ + DMSO-d_6): δ = 122.0, 127.1, 127.5, 127.7, 127.9, 128.3, 129.0, 129.4, 130.3, 136.1, 137.9, 139.7, 159.9, 166.0. *Anal*. ($C_{16}H_{11}NO_2$): Calc: C: 77.1, H: 4.45, N: 5.62, found: C: 77.1, H: 4.44, N: 5.63.

1-(2-Chlorophenyl)isoquinoline-3-carboxylic acid (8b). Obtained in a 73 % yield as previously described [20].

1-(3-Chlorophenyl)isoquinoline-3-carboxylic acid (8c). This compound was obtained in a 75% yield *via* the filtration of the precipitate obtained after acidification. Mp = 238 °C (toluene-heptane). ^{1}H (DMSO-d_6): δ = 7.66 (m, 3H), 7.76 (m, 1H), 7.82 (m, 1H), 7.92 (m, 1H), 8.04 (d, 1H, J = 8.4), 8.30 (d, 1H, J = 8.0), 8.68 (s, 1H), 13.20 (s (br), 1H). ^{13}C: δ = 123.2, 126.5, 127.0, 128.6, 128.8 (two signals ?), 129.5, 130.2 (two signals ?), 131.1, 133.2, 136.3, 140.5, 141.0, 158.3, 166.4. *Anal*. ($C_{16}H_{10}NO_2Cl$): Calc: C: 67.74, H: 3.55, N: 4.97, Cl: 12.5, found: C: 67.49, H: 3.68, N: 4.93, Cl: 12.29.

1-(4-Chlorophenyl)isoquinoline-3-carboxylic acid (8d). This compound was obtained in a 74% yield *via* the filtration of the precipitate obtained after acidification. Mp = 242 °C (acetic acid-water). ^{1}H (DMSO-d_6): δ = 7.70 (m, 4H), 7.81 (m, 1H), 7.92 (m, 1H), 8.05 (m, 1H), 8.29 (d, 1H, J = 7.7), 8.58 (s, 1H), 13.15 (s, 1H). ^{13}C (DMSO-d_6): δ = 123.0, 126.7, 127.0, 128.4, 128.8, 130.2, 131.1, 131.8, 133.8, 136.3, 137.3, 141.1, 158.7, 166.5. *Anal*. ($C_{16}H_{10}NClO_2$): Calc: C: 67.74, H: 3.55, N: 4.97, Cl: 12.5, found: C: 67.36, H: 3.53, N: 4.97, Cl: 12.24.

1-(3-Pyridyl)isoquinoline-3-carboxylic acid (8e). This compound was obtained in a 66% yield, *via* the filtration of the precipitate obtained after acidification and a subsequent washing with hot ethylacetate. Mp = 269 °C. ^{1}H (DMSO-d_6): δ = 7.65 (dd, 1H, J = 5.0 and 8), 7.83 (m, 1H), 7.93 (m, 1H), 8.05 (d, 1H, J = 8), 8.15 (m, 1H), 8. 31 (d, 1H, J = 8.1), 8.70 (s, 1H), 8.78 (dd, 1H, J = 2.5 and 4.8), 8.90 (d, 1H, J = 2.5), 13.2 (s(br), 1H). ^{13}C (DMSO-d_6): δ = 123.2, 123.4, 126.5, 127.3, 128.9, 130.3, 131.2, 134.2, 136.2, 137.4, 141.2, 149.8, 150.1, 157.2, 166.4. *Anal*. ($C_{15}H_{10}N_2O_2$): Calc: C: 71.99, H: 4.03, N: 11.19, found: C: 71.84, H: 4.02, N: 10.98.

1-(4-Pyridyl)isoquinoline-3-carboxylic acid (11b). This compound was obtained in a 80% yield, *via* the filtration of the precipitate obtained after acidification. Mp = 267 °C. ^{1}H (DMSO-d_6): δ = 7.71 (m, 2H), 7.82 (m, 1H), 7.93 (m, 1H), 8.03 (m, 1H), 8.32 (m, 1H), 8.71 (s, 1H), 8.81 (m, 2H). ^{13}C (DMSO-d_6): δ = 123.6, 124.5, 126.3, 126.8, 128.8, 130.3, 131.2, 136.2, 141.2, 145.8, 149.8, 157.5, 166.2. HRMS *m/z* Calcd for $C_{15}H_{11}N_2O_2$ $(M+H)^+$ 251.0820. Found: 251.0860.

4-Phenylquinoline-2-carboxylic acid (18a). This compound was obtained in 81% yield *via* the filtration of the precipitate obtained after acidification and was recristallized in aqueous ethanol. Mp = 171 °C lit. [61] 170-173 °C. ^{1}H (DMSO-d_6): δ = 7.58-7.63 (m, 5H), 7.73 (m, 1H), 7.91 (m, 1H), 7.94 (s, 1H), 8.25 (m, 2H). ^{13}C (DMSO-d_6): δ = 120.6, 125.3, 126.7, 128.8, 129.4, 130.3, 136.9, 147.4, 148.6, 148.8, 166.3. HRMS *m/z* Calcd for $C_{16}H_{12}NO_2$ $(M+H)^+$ 250.0868. Found: 250.0894.

4-(2-Chlorophenyl)quinoline-2-carboxylic acid (18b). The residue obtained, after concentration to dryness, was recristallized in toluene to yield compound **18a** (0.74 g, 64 %). Mp = 201 °C. ^{1}H ($CDCl_3$): δ = 7.33 (dd, 1H, J = 2.2 and 7.6), 7.45 (m, 2H), 7.61 (m, 3H), 7.84 (m, 1H), 8.19 (s, 1H), 8.22 (d, 1H, J = 8.3). ^{13}C ($CDCl_3$): δ = 120.0, 126.1, 127.0, 128.6, 129.3, 129.8, 130.0, 130.4, 131.0, 131.1, 133.0, 135.7, 145.4, 146.0, 146.0, 164.2. *Anal*. ($C_{16}H_{10}NClO_2$): Calc: C: 67.74, H: 3.55, N: 4.94, Cl: 12.5, found: C: 67.33, H: 3.53, N: 4.93, Cl: 12.16.

4-(3-Chlorophenyl)quinoline-2-carboxylic acid (18c). This compound was obtained in a 81% yield *via* the filtration of the precipitate obtained after acidification and was recristallized in aqueous ethanol. Mp = 100 °C. ^{1}H ($CDCl_3$): δ = 7.45 (m, 1H), 7.55 (m, 2H), 7.72 (m, 1H), 7.90 (m, 1H), 8.01 (m, 1H), 8.26 (m, 3H). ^{13}C ($CDCl_3$): δ = 119.3, 125.8, 127.7, 128.1, 129.2, 129.5, 130.0, 130.1, 131.0, 134.8, 139.4, 143.3, 145.4, 146.4, 149.9, 166.3. HRMS *m/z* Calcd for $C_{16}H_{11}ClNO_2$ $(M+H)^+$ 284.0478. Found: 284.0479.

4-(4-Chlorophenyl)quinoline-2-carboxylic acid (18d). This compound was obtained in a 78% yield *via* the filtration of the precipitate obtained after acidification and was recristallized in aqueous ethanol. Mp = 149 °C lit. [62] 148-150 °C. ^{1}H (DMSO-d_6): δ = 7.62-7.68 (m, 4H), 7.74 (m, 1H), 7.92 (m, 2H), 7.99 (s, 1H), 8.26 (m, 1H). ^{13}C (DMSO-d_6): δ = 120.6, 125.2, 126.6, 128.8, 129.1, 130.2, 130.5, 131.3, 133.8, 135.6, 147.2, 147.8, 148.2, 166.0. HRMS *m/z* Calcd for $C_{16}H_{11}ClNO_2$ $(M+H)^+$ 284.0478. Found: 284.0513.

4-(3-Pyridyl)quinoline-2-carboxylic acid (18e). This compound was obtained in a 82% yield *via* the filtration of the precipitate obtained after acidification and was recristallized in aqueous ethanol. Mp = 209 °C lit. [63] 203 °C. ^{1}H (DMSO-d_6): δ = 7.64 (m, 1H), 7.76 (m, 1H), 7.87-7.95 (m, 2H), 8.04-8.09 (m, 2H), 8.27 (d, 1H), 8.80 (m, 2H). ^{13}C (DMSO-d_6): δ = 121.6, 124.2, 125.5, 127.2, 129.8, 130.9, 131.1, 133.2, 137.6, 146.0, 147.8, 148.8, 149.9, 150.4, 166.6. HRMS *m/z* Calcd for $C_{15}H_{11}N_2O_2$ $(M+H)^+$ 215.0820. Found: 251.0859.

4-(4-Pyridyl)quinoline-2-carboxylic acid (18f). This compound was obtained in a 77% yield *via* the filtration of the precipitate obtained after acidification and was recristallized in aqueous ethanol. Mp = 215 °C lit. [63] 225 °C. ^{1}H (DMSO-d_6): δ = 7.77-7.81 (m, 1H), 7.88 (m, 2H), 7.89 (m, 1H), 7.94-7.98 (m, 1H), 8.08 (s, 1H), 8.30 (d, 1H), 8.92 (m, 2H). ^{13}C (DMSO-d_6): δ = 121.1, 125.3, 125.9, 126.2, 130.1, 131.0, 131.3, 145.9, 147.7, 148.0, 148.8, 166.5. HRMS *m/z* Calcd for $C_{15}H_{11}N_2O_2$ $(M+H)^+$ 215.0820. Found: 251.0863.

Methyl 4-oxo-1,4-dihydroquinoline-2-carboxylate (15). Under an inert atmosphere, a mixture of 2-aminoacetophenone (**14**) (8 g, 0.059 mol), dimethyloxalate (28.0 g, 0.236 mol) and sodium methoxide (13.4 g, 0.236 mol) was dispersed in dry methanol (500 mL, dried over 3 Å molecular sieves). This was stirred at 25 °C for one hour and then refluxed for 40 hours. Most of the methanol was removed under reduced pressure and the residue dispersed in water (600 mL). This was extracted with dichloromethane six times and the organic layer was dried over magnesium sulfate. After concentration to dryness, the residue was purified by a chromatography over silica gel (ethyl acetate) to yield compound **15** (5 g, 41%). Mp = 227 °C. ^{1}H (DMSO-d_6): δ = 3.97 (s, 3H), 6.62 (d, 1H, J = 1.8), 7.37 (m, 1H), 7.71 (m, 1H), 7.94 (d, 1H, J = 8.4), 8.07 (d, 1H, J = 8.1), 12.1 (s(br), 1H). ^{13}C (DMSO-d_6): δ = 53.5, 110.2, 119.6, 124.0, 124.7, 125.9, 132.6, 137.7, 140.0, 162.7, 177.6. *Anal*. ($C_{11}H_9NO_3$, 1/6 H_2O): Calc: C: 64.07, H: 4.56, N: 6.79, O: 24.57, found: C: 64.36, H: 4.48, N: 6.90, O: 24.56.

Methyl 4-bromoquinoline-2-carboxylate (16). A mixture of compound **15** (5 g, 0.024 mol), phosphorus oxybromide (20 g, 0.073 mol) and potassium carbonate (10.5 g, 0.073 mol) was dispersed in dry acetonitrile (dried over 4 Å molecular sieves). The suspension was refluxed for 3 hours under a calcium chloride-protected atmosphere. After cooling, water (200 mL) was cautiously added and most of the acetonitrile removed under reduced pressure. This residue was extracted with dichloromethane and the organic layer was washed with water and dried over magnesium sulfate. After concentration to dryness, the residue was recristallized from heptane to give compound **16** (4.84 g, 73%). An analytical sample was further purified (from traces of the corresponding acid) by chromato-

graphy over silica gel (dichloromethane-methanol 98/2) for characterization purposes. Mp = 139 °C lit. [60] 141-142 °C. ^{1}H NMR: identical with the reported data. [60] ^{13}C ($CDCl_3$): δ = 53.5, 124.9, 126.6, 128.8, 129.8, 131.1, 131.6, 135.2, 147.3, 147.8, 164.7.

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REFERENCES

[1] Langer, S.Z.; Arbilla, S. *Pharmacol. Biochem. Behav*. **1988**, *29*, 763.

[2] Papadopoulos, V. *Trends Pharm. Sci*. **2006**, *27*, 402.

[3] Krueger, K.E. *Biochem. Biophys. Acta* **1995**, *1241*, 453.

[4] Zisterer, D.M.; Williams, D.C. *Gen. Pharmacol*. **1997**, *29*, 305.

[5] Gavish, M.; Bachman, I.; Shoukrun, R.; Katz, Y.; Veenman, L.; Weisinger, G.; Weizman, A. *Pharmacol. Rev*. **1999**, *51*, 629.

[6] Beurdeley-Thomas, A.; Miccoli, L.; Oudard, S.; Dutrillaux, B.; Poupon, M-F. *J. Neuro-Oncology* **2000**, *46*, 45.

[7] Veenman, L.; Gavish, M. *Drug. Dev. Res*. **2000**, *50*, 355.

[8] Casellas, P.; Galiegue, S.; Basile, A.S. *Neurochemistry Int*. **2002**, *40*, 475.

[9] Galiegue, S.; Tinel, N.; Casellas, P. *Curr. Med. Chem*. **2003**, *10*, 1563.

[10] Papadopoulos, V.; Baraldi, M.; Guilarte, T.R.; Knudsen, T.B.; Lacapere, J-J.; Lindemann, P.; Norenberg, M.D.; Nutt, D.; Weizman, A.; Zhang, M-R.; Gavish, M. *Trends Pharm. Sci*. **2006**, *27*, 402.

[11] Le Fur, G.; Guilloux, F.; Rufat, R.; Benavides, J.; Uzan, A.; Renault, C.; Dubroeucq, M.C.; Gueremy, C. *Life Sci*. **1983**, *32*, 1849.

[12] Le Fur, G.; Perrier, M.L.; Vaucher, N.; Imbault, C.; Dubroeucq, M.C.; Gueremy, C. *Life Sci*. **1983**, *32*, 1839.

[13] Wang, J.K.T.; Morgan, J.I.; Spector, S. *Mol. Pharmacol*. **1984**, *25*, 349.

[14] Kleinerman, R.A.; Brinton, L.A.; Hoover, R.; Fraumeni, J.F. Jr. *Cancer Res*. **1984**, *44*, 1223.

[15] Berson, A.; Descatoire, V.; Sutton, A.; Fau, D.; Maulny, B.; Vadrot, N.; Feldmann, G.; Berthon, B.; Tordjmann, T.; Pessayre, D. *J. Pharmacol. Exp. Ther*. **2001**, *299*, 793.

[16] Barki, J.; Larrey, D.; Pageaux, G.; Lamblin, G.; Gineston, J.L.; Michel, H. *Gastroenterol. Clin. Biol*. **1993**, *17*, 872.

[17] Baty, V.; Denis, B.; Goudot, C.; Bas, V.; Renkes, P.; Bigard, M.A.; Boissel, P.; Gaucher, P. *Gastroenterol. Clin. Biol*. **1994**, *18*, 1129.

[18] Ausset, P.; Malavialle, P.; Vallet, A.; Miremont, G.; Le Bail, B.; Dumas, F.; Saric, J.; Winnock, S. *Gastroenterol. Clin. Biol*. **1995**, *19*, 222.

[19] Romeo, E.; Auta, J.; Kosikowski, A.P.; Ma, D.; Papadopoulos, V.; Puia, G.; Costa, E.; Guidotti, A. *J. Pharmacol. Exp. Ther*. **1992**, *262*, 971.

[20] Janin, Y.L.; Roulland, E.; Beurdeley-Thomas, A.; Decaudin, D.; Monneret, C.; Poupon, M.-F. *J. Chem. Soc. Perkin Trans. 1* **2002**, 529.

[21] Janin, Y.L.; Decaudin, D.; Monneret, C.; Poupon, M.F. *Tetrahedron* **2004**, *60*, 5481.

[22] Jurcak, J.G.; Barrague, M.; Gillespy, T.A.; Edwards, M.L.; Musick, K.Y.; Weintraub, P.M.; Du, Y.; Dharanipragada, R.M.; Parkar, A.A. Patent WO 026175, 2005; *Chem. Abstr*. **2005**, *142*, 316835.

[23] Campeau, L.C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc*. **2005**, *127*, 18020.

[24] Leclerc, J-P.; Fagnou, K. *Angew. Chem., Int. Ed*. **2006**, *45*, 7781.

[25] Anzini, M.; Cappelli, A.; Vomero, S.; Seeber, M.; Menziani, M.C.; Langer, T.; Hagen, B.; Manzoni, C.; Bourguignon, J.J. *J. Med. Chem*. **2001**, *44*, 1134.

[26] Coltman, C.W.; Eyley, S.C.; Raphael, R.A. *Synthesis* **1984**, 150.

[27] Hodgson, P.B.; Salingue, F.H. *Tetrahedron Lett*. **2004**, *45*, 685.

[28] Stevenson, L.; Pimlott, S.L.; Sutherland, A. *Tetrahedron Lett*. **2007**, *48*, 7137.

[29] Camsonne, R.; Crouzel, C.; Comar, D.; Maziere, M.; Prenant, C.; Sastre, J.; Moulin, M.A.; Syrota, A. *J. Label. Comp. Radiopharm*. **1984**, *21*, 985.

[30] Hashimoto, K.; Inoue, O.; Suzuki, K.; Yamasaki, T.; Kojima, M. *Ann. Nucl. Med*. **1989**, *3*, 63.

[31] Næslund, C.; Koziorowski, J.; Batra, S.; Sjöberg, S. *J. Label. Comp. Radiopharm*. **1999**, *42 (S1)*, 806.

[32] Beinlich, A.; Strohmeier, R.; Kaufmann, M.; Kuhl, H. *Biochem. Pharmacol*. **2000**, *60*, 397.

[33] Rahman, O.; Kihlberg, T.; Långström, B. *J. Chem. Soc. Perkin Trans. 1* **2002**, 2699.

[34] Manning, H.C.; Goebel, T.; Marx, J.N.; Bornhop, D.J. *Org. Lett*. **2002**, *7*, 1075.

[35] Cappelli, A.; Pericot Mohr, G.; Gallelli, A.; Giuliani, G.; Anzini, M.; Vomero, S.; Fresta, M.; Porcu, P.; Maciocco, E.; Concas, A.; Biggio, G.; A., Donati *J. Med. Chem*. **2003**, *46*, 3568.

[36] Bennacef, I.; Haile, C.N.; Schmidt, A.; Koren, A.O.; Seibyl, J.P.; Staley, J.K.; Bois, F.; Baldwin, R.M.; Tamagnan, G. *Bioorg. Med. Chem*. **2006**, *14*, 7582.

[37] Suzuki, K.; Suhara, T.; Christar, H.; Zhang, M-R.; Nakazato, A. Patent WO 092902, 2006; *Chem. Abstr*. **2006**, *145*, 314672.

[38] Homes, T.P.; Mattner, F.; Keller, P.A.; Katsifis, A. *Bioorg. Med. Chem*. **2006**, *14*, 3838.

[39] Zhang, M-R.; Ogawa, M.; Maeda, J.; Ito, T.; Noguchi, J.; Kumata, K.; Okauchi, T.; Suhara, T.; Suzuki, K. *J. Med. Chem*. **2006**, *49*, 2735.

[40] Bourguignon, J.J. In *Peripheral Benzodiazepine Receptors*, Giesen-Crouse, E. Ed, Academic Press: London, 1993; pp 59-86.

[41] James, M.L.; Selleri, S.; Kassiou, M. *Curr. Med. Chem*. **2006**, *13*, 1991.

[42] Ferzaz, B.; Brault, E.; Bourliaud, G.; Robert, J.-P.; Poughon, G.; Claustre, Y.; Marguet, F.; Liere, P.; Schumacher, M.; Nowicki, J.P.; Fournier, J.; Marabout, B.; Sevrin, M.; George, P.; Soubrie, P.; Benavides, J.; Scatton, B. *J. Pharmcol. Exp. Ther*. **2002**, *301*, 1067.

[43] Tanabe, T. Patent WO 115302, 2006; *Chem. Abstr*. **2006**, *145*, 449245.

[44] Kondo, K.; Masumoto, K.; Kohayakawa, H. Patent WO 075619, 2006; *Chem. Abstr*. **2006**, *145*, 167074.

[45] Dubois, L.; Evanno, Y.; Maloizel, C.; Sevrin, M. Patent FR 2870239, 2005; *Chem. Abstr*. **2005**, *143*, 477962.

[47] Dalko M. Benzodiazepine Peripheral Receptor Antagonists for Treating Dry Skin. WO 2006 067327, 2006.

[46] Besne, I.; Dalko, M. Patent WO 067328, 2006; *Chem. Abstr*. **2006**, *145*, 89425.

[48] Maaser, K.; Hopfner, M.; Jansen, A.; Weisinger, G.; Gavish, M.; Kozikowski, A.P.; Weizman, A.; Carayon, P.; Riecken, E.O.; Zeitz, M.; Scherubl, H. *Br. J. Cancer* **2001**, *85*, 1771.

[49] Fisher, R.; Schmitt, M.; Bode, J.G.; Häussinger, D. *Gastroenterology* **2001**, *120*, 1212.

[50] Decaudin, D.; Castedo, M.; Nemati, F.; Beurdeley-Thomas, A.; De Pinieux, G.; Caron, A.; Pouillart, P.; Wijdenes, J.; Rouillard, D.; Kroemer, G.; Poupon, M.F. *Cancer Res*. **2002**, *62*, 1388.

[51] Sakai, M.; Fonseca, E.S.M.; Oloris, S.C.S.; Matsuzaki, P.; Otake, A.H.; Leite, K.R.M.; Massoco, C.O.; Dagli, M.L.Z.; Palermo-Neto, J. *Eur. J. Pharmacol*. **2006**, *550*, 1.

[52] Decaudin, D. *Anticancer Drugs* **2004**, *15*, 737.

[53] Glick, G.D. Patent US 241781, 2004; *Chem. Abstr*. **2004**,

142, 16792.

[54] Hans, G.; Wislet-Gendebien, S.; Lallemend, F.; Robe, P.; Rogister, B.; Belachew, S.; Nguyen, L.; Malgrange, B.; Moonen, G.; Rigo, J.M. *Biochem. Pharmacol.* **2005**, *69*, 819.

[55] Jiang, J.; Thomas, C.J.; Neumann, S.; Lu, X.; Rice, K.C.; Gershengorn, M.C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 733.

[56] Walter, R.B.; Pirga, J.L.; Cronk, M.R.; Mayer, S.; Appelbaum, F.R.; Banker, D.E. *Blood* **2005**, *106*, 2584.

[57] Gonzalez-Polo, R-A.; Carvalho, G.; Braun, T.; Decaudin, D.; Fabre, C.; Larochette, N.; Perfettini, J-L.; Djavaheri-Mergny, M.; Youlyouz-Marfak, I.; Codogno, P.; Raphael, M.; Feuillard, J.; Kroemer, G. *Oncogene* **2005**, *24*, 7503.

[58] Cleary, J.; Johnson, K.M.; Opipari, A.W.Jr; Glick, G.D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1667.

[59] Wu, Y-C.; Liu, L.; Li, H-J.; Wang, D.; Chen, Y-J. *J. Org. Chem.* **2006**, *71*, 6592.

[60] Salituro, F.G.; Harrison, B.L.; Baron, B.M.; Nyce, P.L.; Stewart, K.T.; Kehne, J.H.; White, H.S.; McDonald, I.A. *J. Med. Chem.* **1992**, *35*, 1791.

[61] Moreau, R.C.; Loiseau, P. *C. R. Hebd. Seances Acad. Sci.* **1976**, *283*, 589.

[62] Takahashi, K.; Mitsuhashi, K. *J. Heterocyclic. Chem.* **1977**, *14*, 881.

[63] Hey, D.H.; Williams, J.M. *J. Chem. Soc.* **1950**, 1678.