The peripheral-type benzodiazepine receptors (PBR), also named the mitochondrial diazepam binding inhibitor receptor as well as mitochondrial benzodiazepine receptor or the \( \omega 3 \) 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 More recently, the anxiolytic drug alpidem (4), another PBR ligand [15], was withdrawn from the human pharmacopea as several cases of very severe hepatitis occurred in patients also receiving hepatotoxic drugs [16-18].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-arylquinoline system.

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.
Trials from the ethyl ester 9 using [1,1’-bis(diphenylphosphino)ferrocene] dichloro palladium (PdCl₂, 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.

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.

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-pyridineboronic 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.
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 (0.17 mmol) in dry DMF (50 mL, dried over 4 Å molecular sieves) was heated at 80 °C for 14 hours. As an 1H 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 1H 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 1H 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
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 77% yield, via a chromatography over silica gel eluting with dichloromethane. 
Mp = 138 °C (heptane). \( ^1H \) (CDCl\(_3\)): \( \delta = 4.04 \) (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), 8.14 (d, 1H, J = 8.4), 8.59 (s, 1H). \( ^13C \) (CDCl\(_3\)): \( \delta = 52.8, 123.7, 127.3, 128.0, 128.3, 128.5, 129.0, 129.6, 129.7, 130.1, 130.9, 134.5, 140.5, 140.8, 150.9, 156.6. \) Anal. (C\(_{17}\)H\(_{12}\)NO\(_2\)) : Calc: C: 72.72, H: 4.58, N: 10.6, found: C: 72.55, H: 4.57, N: 10.56.

Ethyl 1-bromoisooquinoline-3-carboxylate (9). 
This compound was prepared using our previously reported strategy [21] although from phthalide and diethyl acaciddomalonate 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 acacetidomalonate (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 diethyl ether (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 acetylaminoo-2-(3-oxo-1,3-dibromoisoquinolone-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 chloroform 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 phthalide). Mp = 117°C. \( ^1H \) (CDCl\(_3\)): \( \delta = 1.49 \) (t, 3H, J = 7.1), 1.45 (q, 2H, J = 7.1), 1.86 (m, 2H), 7.99 (m, 1H), 8.42 (m, 1H); 8.54 (s, 1H). \( ^13C \) (CDCl\(_3\)): \( \delta = 14.4, 62.1, 124.3, 128.6, 129.1, 130.4, 131.0, 131.9, 136.8, 141.3, 145.5, 164.5. \)

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 dioxyane (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 over 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. \( ^1H \) (CDCl\(_3\)): \( \delta = 1.47 \) (t, 3H, J = 7.2), 1.53 (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). \( ^13C \) (CDCl\(_3\)): \( \delta = 14.4, 63.8, 123.3, 127.3, 128.7, 129.3, 130.8, 131.5, 135.0, 135.6, 137.2, 141.0, 159.7, 165.7. \) HRMS m/z Calcd for C\(_{17}\)H\(_{17}\)ClNO\(_2\) (M+H\(^+\)) 313.0791. Found: 313.0823.

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. \( ^1H \) (CDCl\(_3\)): \( \delta = 1.48 \) (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). \( ^13C \) (CDCl\(_3\)): \( \delta = 14.4, 61.9, 124.0, 124.8, 126.8, 127.7, 128.7, 129.9, 131.1, 136.6, 141.4, 146.4, 150.0, 158.3, 165.6. \) HRMS m/z Calcd for C\(_{15}\)H\(_{15}\)N\(_2\)O\(_2\) (M+H\(^+\)) 279.1133. Found: 279.1146.

Ethyl 4-phenylisoquinoline-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.
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 4.4% yield respectively.

### 2-(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. **1H (CDCl3):** 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). **13C (CDCl3):** δ = 53.3, 121.2, 125.3, 127.5, 127.7, 128.9, 129.0, 129.5, 130.2, 130.3, 130.3, 131.1, 134.9, 147.4, 148.0, 148.3, 165.8. HRMS m/z Calcd for C_{17}H_{15}NO_{3} (M+H)^+ 295.1083. Found: 295.1092.

### Diethyl 1,1′-bis(isoquinolin-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. **1H (CDCl3):** 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). **13C (CDCl3):** δ = 14.4, 61.8, 124.6, 127.5, 128.4, 129.4, 130.9, 131.2, 136.7, 140.9, 157.6, 165.7. HRMS m/z Calcd for C_{23}H_{23}N_{6}O_{5} (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 (0.12 mmol) was 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.

### 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)isoquinolin-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). **1H (CDCl3 + DMSO-d_6):** δ = 4.75 (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). **13C (CDCl3 + DMSO-d_6):** δ = 122.0, 127.1, 127.5, 127.7, 127.9, 128.3, 129.0, 129.4, 130.3, 133.1, 136.6, 137.9, 139.7, 159.9, 166.0. **Anal.** (C_{17}H_{13}NO): 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). 1H (DMSO-d6): 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, 1H). 13C (DMSO-d6): δ = 123.2, 126.5, 127.0, 128.6, 128.8 (two signals), 129.5, 130.2 (two signals), 131.1, 132.2, 133.6, 140.5, 141.0, 158.3, 166.4. Anal. (C15H11N2O2, Cl2) Calc: 63.78, 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). 1H (DMSO-d6): 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). 13C (DMSO-d6): δ = 123.0, 126.7, 127.0, 128.4, 128.8, 130.2, 131.2, 131.8, 133.8, 136.3, 137.3, 141.1, 158.7, 166.5. Anal. (C16H12NO2Cl2) Calc: C: 67.36, H: 3.53, N: 4.97, Cl: 12.5, found: C: 67.49, H: 3.68, N: 4.93.

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 = 267 °C. 1H (DMSO-d6): 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). 13C (DMSO-d6): δ = 123.2, 123.4, 124.6, 126.5, 128.9, 130.3, 131.2, 134.2, 136.2, 137.4, 141.2, 149.8, 150.1, 157.2, 166.4. Anal. (C16H11N2O2, Cl2) 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. 1H (DMSO-d6): 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). 13C (DMSO-d6): δ = 123.6, 124.5, 126.3, 126.8, 128.8, 130.3, 131.2, 131.6, 145.8, 149.8, 157.5, 166.2. HRMS m/z Calcd for C15H11NO2 (M-H)+: 251.0863. 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 recrystallized in aqueous ethanol. Mp = 209 °C. 1H (DMSO-d6): 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). 13C (DMSO-d6): 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 C15H10NO2 (M-H)+: 251.0820. Found: 251.0853.

4-(4-Chlorophenyl)quinoline-2-carboxylic acid (18d). This compound was obtained in a 82% yield via the filtration of the precipitate obtained after acidification and was recrystallized in aqueous ethanol. Mp = 215 °C. 1H (DMSO-d6): 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). 13C (DMSO-d6): 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 C15H10ClNO2 (M-H)+: 251.0820. Found: 251.0853.

Methyl 4-oxo-1,4-dihydroquinoline-2-carboxylate (15). Under an inert atmosphere, a mixture of 2-aminoacetophenone (14) (8 g, 0.059 mol), dimethyl oxalate (28.0 g, 0.236 mol) and sodium methoxide (13.4 g, 0.236 mol) was dissolved in dry methanol (500 mL, dried over 3 Å molecular sieves). This solution 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 chromatography over silica gel (ethyl acetate) to yield compound 15 (5 g, 41%). Mp = 227 °C. 1H (DMSO-d6): 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). 13C (DMSO-d6): δ = 53.5, 110.2, 119.6, 124.0, 124.7, 125.9, 132.6, 137.7, 140.0, 162.7, 177.6. Anal. (C7H6NO2, 1/6 H2O): 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.
graphy over silica gel (dichloromethane-methanol 98/2) for characterization purposes. Mp = 139 °C lit, [60] 141-142 °C. 1H NMR: identical with the reported data. [60] 13C (CDCl3): 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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