# Structure−Activity Relationships in Carboxamide Derivatives Based on the Targeted Delivery of Radionuclides and Boron Atoms by Means of Peripheral Benzodiazepine Receptor Ligands

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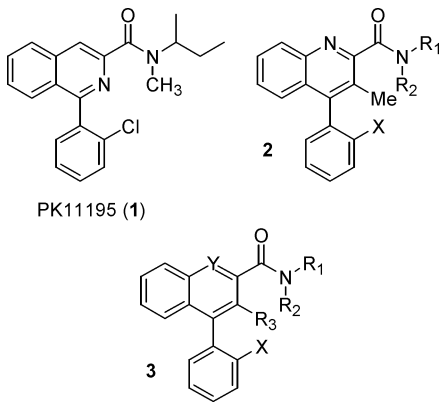
*Received March 24, 2003*

**Abstract:** The structure−activity relationship studies on 2-quinolinecarboxamide peripheral benzodiazepine receptor (PBR) ligands have been refined with the aim of using these ligands as carriers of radionuclides and boron atoms. Some new ligands show enhanced affinity and steroidogenic activity with respect to reference compound **1** and are interesting candidates for radiolabeling and PET studies. Moreover, carborane derivative **3q**, representing the first example of PBR ligand bearing a carborane cage, can be useful to explore an alternative mechanism in BNCT.

**Introduction.** The peripheral benzodiazepine receptor (PBR) was found to be overexpressed in a variety of tumors (e.g., certain brain tumors, ovarian cancer, liver tumors, breast carcinoma, colorectal cancer, etc.), and the PBR expression appears to be related to the tumor malignancy degree.[1] Furthermore, increased concentrations of PBR were observed in lesioned brain areas in a variety of neuropathologies such as multiple sclerosis, Alzheimer's disease, and Huntington's disease.[2]

The isoquinolinecarboxamide PK11195 (**1**, Chart 1) was the first non-benzodiazepine ligand which was found both to bind the PBR with nanomolar affinity and to facilitate the transport of cholesterol from the outer to the inner mitochondrial membrane, increasing the rate of pregnenolone synthesis. Compound **1** is nowadays the most widely used pharmacological tool for the study of the expression and the function of PBR (e.g., steroidogenesis and apoptosis). For example, compound **1** labeled with positron emitter carbon-11 was used in the imaging of brain tumors, multiple sclerosis, cerebral infarction, and abnormalities of calcium channels in heart diseases by positron emission tomography (PET).[3] Moreover, compound **1** was conjugated with the antineoplastic drug gemcitabine to selectively increase the anticancer drug delivery to the tumor cells.[4] In this interesting drug-targeting approach both the selective interaction of **1** with PBR and the overexpression of this receptor in the tumor cells were used to increase the uptake of the antitumoral agent on the part of the tumoral cells.

**Chart 1**




Our research in the field led to the design and synthesis of potent ligands in the class of PK11195 derivatives.[5] Moreover, the results of a synthetic−computational approach based on conformationally constrained ligands afforded the development of theoretical models for the interaction of PBR with the best known ligands.[6] Again, the quinoline carboxamide derivatives **2a**−**c** (**2a**: X = H, $R_1$ = $CH(CH_3)CH_2CH_3$, $R_2$ = $CH_3$; **2b**: X = F, $R_1$ = $CH(CH_3)CH_2CH_3$, $R_2$ = $CH_3$; **2c**: X = H, $R_1$ = $CH_2C_6H_5$, $R_2$ = $CH_3$) were [$^{11}$C]-labeled, and the biodistribution studies suggested that these compounds are promising PET tracers for the in vivo imaging of PBR.[7] A preliminary evaluation of [$^{11}$C]-labeled **2a**−**c** in an excitotoxic model of Huntington's disease in rats indicated that benzyl derivative **2c** is an interesting candidate for the in vivo PET monitoring of neurodegenerative processes.[8]

These results stimulated the extension of the structure−affinity relationship studies to compounds **3** with the aim of optimizing the interaction of the quinolinecarboxamide derivatives with PBR and once again developing better candidates for PET studies. Furthermore, the benzylic substituent of compound **2c** was replaced with a 1,2-dicarba-*closo*-dodecaboran-1-ylmethyl moiety in order to obtain a PBR ligand liable to be labeled with different radionuclides and potentially useful in boron neutron capture therapy (BNCT).[9] By means of this drug-targeting approach, we expected to obtain a BNCT agent which accumulated in the tumor cells and, when radiolabeled, could reveal the tumor area (e.g., by means of PET) to be subjected to thermal neutron irradiation. Moreover, the carborane cage could be used as a small organometallic ligand for radionuclides useful in diagnostic imaging and radiotherapy.

In the present paper we describe the synthesis and the preliminary pharmacological characterization of new

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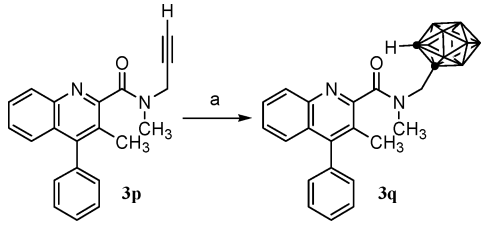
10.1021/jm034068b CCC: $25.00 
Published on Web 07/18/2003

**Scheme 1**[a,b]




[a] In icosahedral cage structure, closed circles represent carbon atoms, and the vertexes represent BH units. [b]Reagents: (a) $B_{10}H_{14}$, $CH_3CN$, $CH_3C_6H_5$.

PBR ligands **3**. Some of the most potent compounds in inhibiting the specific binding of [$^3$H]CB 34[10] at PBR were tested for their potential stimulant activity of steroid biosynthesis as a measure of their capability of reaching the PBR in vivo.

**Results and Discussion. Chemistry.** The already known quinolinecarboxamide derivatives **3g** and **3h** (**2c** in the Introduction) were resynthesized following the procedure previously described,[5] while new target carboxamide derivatives **3a**−**f**,**i**−**p** were prepared by means of the chemistry already developed (Supporting Information).[5,6] Finally, 1,2-dicarba-*closo*-dodecaboran-1-ylmethyl derivative **3q** was obtained by reaction of propargyl derivative **3p** with a bis(acetonitrile)decaborane complex in toluene under reflux conditions (Scheme 1).

**Binding Studies.** Compounds **3** were tested for their activity in inhibiting the specific binding of [$^3$H]CB 34[10] to rat cortical membrane in comparison with reference compound **1**. The results of the binding studies (Table 1) revealed that all the tertiary amide derivatives **3b**,**d**,**f**,**h**,**j**−**q** show nanomolar affinity for PBR ($IC_{50}$ values ranging from 0.45 to 73 nM). In particular, the most potent 3-chloromethyl derivative **3m** showed subnanomolar PBR affinity and was 20 times more potent than reference compound **1**, while 2-fluorophenyl derivative **3j** showing nanomolar affinity was, however, significantly more potent than **1**. Thus, these two PBR ligands (**3m**,**j**) represent interesting candidates for radiolabeling and PET studies.

The carborane derivative **3q** shows a very good affinity for PBR so that this compound is the first PBR ligand showing a carborane cage in its structure. The result could have intriguing aspects because PBR is localized mainly on the outer mitochondrial membrane, and it has been suggested that mitochondrial events play a fundamental role in the control of cell death.[11] Thus, the irradiation with thermal neutrons could produce severe damages to the mitochondria bearing compound **3q** bound to PBR. This could lead to cytochrome *c* release in the cytosol with the formation of a complex with Apaf-1 and the activation of caspase cascades up to apoptosis. Therefore, carborane derivative **3q** constitutes an interesting tool to explore an alternative mechanism in BNCT. Finally, the carborane moiety of **3q** can be used as an organometallic ligand for radionuclides useful in diagnostic imaging (e.g., Tc-99m) or radiotherapy (e.g., Re-188)[12] in order to develop new diagnostic agents, radiotherapeutics, or agents which can be used in both diagnosis and BNCT.

**Structure−Affinity Relationships.** The introduction of substituents in position 3 of the quinoline nucleus of compound **3d** increased the PBR affinity in variable degree depending on the stereoelectronic properties of the substituent involved. The introduction of a methyl group produced an affinity enhancement of about an order of magnitude (compare **3h** with **3d**), while an affinity increase of about 2 orders of magnitude was observed when a chloromethyl substituent was involved (compare **3m** with **3d**). The introduction of a hydroxymethyl (compound **3l**) or differently substituted aminomethyl groups (compounds **3n**,**o**) had less dramatic effects on PBR affinity, and the comparison of the affinities shown by **3d**,**h**,**l**−**o** suggests that the presence in 3-position of substituents showing a wide range of stereoelectronic properties is compatible with a productive binding to PBR. This represents valuable information for the design of new PBR ligands possessing the desired properties. Other information concerns (a) the favorable effect of the introduction of a fluorine atom in position 2 of the pendent phenyl group (compare **3j** vs **3h**), (b) the incomplete bioisosterism of both the 1,2-dicarba-*closo*-dodecaboran-1-ylmethyl (**3q**) and the propargyl (**3p**) moieties with respect to the benzyl one of compound **3h**, (c) the tolerance showed by the receptor in accommodating the second benzyl group on the amide

**Table 1.** PBR Binding Affinities of Compounds **3a**−**q**

| compd | X | Y | $R_1$ | $R_2$ | $R_3$ | $IC_{50}$ (nM) ± SEM[a] |
|---|---|---|---|---|---|---|
| **3a** | H | CH | $CH_2C_6H_5$ | H | H | 2700 ± 198 |
| **3b** | H | CH | $CH_2C_6H_5$ | $CH_3$ | H | 64 ± 5.3 |
| **3c** | H | N | $CH_2C_6H_5$ | H | H | 11500 ± 629 |
| **3d** | H | N | $CH_2C_6H_5$ | $CH_3$ | H | 38 ± 2.6 |
| **3e** | H | CH | $CH_2C_6H_5$ | H | $CH_3$ | 6600 ± 501 |
| **3f** | H | CH | $CH_2C_6H_5$ | $CH_3$ | $CH_3$ | 9.8 ± 1.1 |
| **3g** | H | N | $CH_2C_6H_5$ | H | $CH_3$ | 10270 ± 920 |
| **3h**[b] | H | N | $CH_2C_6H_5$ | $CH_3$ | $CH_3$ | 4.6 ± 0.7 |
| **3i** | F | N | $CH_2C_6H_5$ | H | $CH_3$ | 1490 ± 152 |
| **3j** | F | N | $CH_2C_6H_5$ | $CH_3$ | $CH_3$ | 2.2 ± 0.8 |
| **3k** | H | N | $CH_2C_6H_5$ | $CH_2C_6H_5$ | $CH_3$ | 11 ± 7 |
| **3l** | H | N | $CH_2C_6H_5$ | $CH_3$ | $CH_2OH$ | 8.7 ± 1.1 |
| **3m** | H | N | $CH_2C_6H_5$ | $CH_3$ | $CH_2Cl$ | 0.45 ± 0.2 |
| **3n** | H | N | $CH_2C_6H_5$ | $CH_3$ | $CH_2N(C_2H_5)_2$ | 12 ± 1.5 |
| **3o** | H | N | $CH_2C_6H_5$ | $CH_3$ | $CH_2N(C_2H_5)$-$CH_2C_6H_5$ | 13 ± 0.9 |
| **3p** | H | N | $CH_2C{\equiv}CH$ | $CH_3$ | $CH_3$ | 32 ± 5.2 |
| **3q** | H | N | $CH_2C(B_{10}H_{10})CH$ | $CH_3$ | $CH_3$ | 73 ± 6.1 |
| **1** | | | | | | 8.4 ± 0.9 |

[a] Each value is the mean ± SEM of three determinations and represents the concentration given half the maximum inhibition of [$^3$H]CB 34 (final concentration 1 nM) specific binding to rat cortical membranes. [b] Compound **3h** is referred to the introduction as **2c**.

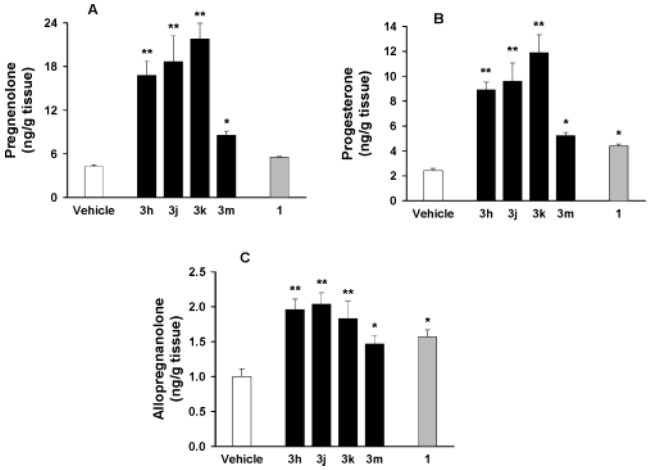



**Figure 1.** Effects of compounds **3h**,**j**,**k**,**m** and **1** on the concentrations of pregnenolone (A), progesterone (B), and allopregnanolone (C) in rat cerebral cortex. Rats were killed 30 min after intraperitoneal administration of 25 mg/kg of compounds **3h**,**j**,**k**,**m**, or **1**. Control animals received the same amount of vehicle. Data are means ± SEM of six rats. *$P$ < 0.05; **$P$ < 0.001 vs vehicle-treated rats.

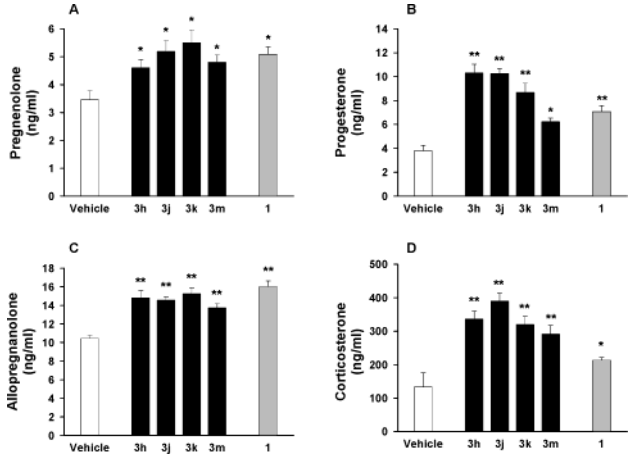



**Figure 2.** Effects of compounds **3h**,**j**,**k**,**m** and **1** on the plasma concentrations of pregnenolone (A), progesterone (B), allopregnanolone (C), and corticosterone (D). Rats were killed 30 min after intraperitoneal administration of 25 mg/kg of compounds **3h**,**j**,**k**,**m**, or **1**. Control animals received the same amount of vehicle. Data are means ± SEM of six rats. *$P$ < 0.05; **$P$ < 0.001 vs vehicle-treated rats.

nitrogen (compare **3k** vs **3h**), and (d) the slight superiority of the quinoline bicyclic system with respect to naphthalene (**3d** vs **3b** and **3h** vs **3f**). The rationalization of these data is now under study as an effort aimed at both the validation of the theoretical receptor model previously developped[6] and the design of new PBR ligands furnished with the desired properties.

**Effects of Compounds 3j,h,k,m on Steroidogenesis.** Intraperitoneal administration of **3h**,**j**,**k**,**m** and **1** (25 mg/kg) in rats resulted in a marked increase in the brain concentration of pregnenolone [$F(5,29) = 17.79$; $p < 0.0001$], progesterone [$F(5,29) = 18.38$; $p < 0.0001$], and allopregnanolone [$F(5,29) = 6.07$; $p < 0.001$] measured 30 min after injection (Figure 1). The effects of compounds **3h**,**j**,**k** were more marked than those produced by reference compound **1**. For example, **3j** increased the pregnenolone, progesterone, and allopregnanolone brain concentrations by 340, 295, and 104%, respectively (as compared with the control), while compounds **3m** and **1** showed relatively lower increases.

Compounds **3h**,**j**,**k**,**m** also significantly increased the amounts of the neuroactive steroids pregnenolone [$F(5,29) = 3.94$; $p < 0.01$], progesterone [$F(5,29) = 19.21$; $p < 0.0001$], and allopregnanolone [$F(5,29) = 10.72$; $p < 0.001$] in plasma (Figure 2) showing effects comparable with those shown by reference compound **1**. Finally, compounds **3h**,**j**,**k**,**m** and **1** increased the plasma concentration of corticosterone [$F(5,29) = 12.78$; $p < 0.0001$], the major adrenal corticosteroid in rat, with **3j** being the most effective (Figure 2).

These results demonstrated that quinolinecarboxamide derivatives **3h**,**j**,**k**,**m** are capable of reaching and interacting with the PBR in vivo and of stimulating the cholesterol transport into the mitochondria both in the brain and in peripheral tissues.

**Conclusions.** The structure−activity relationship studies on 2-quinolinecarboxamide PBR ligands have been refined with the aim of using these ligands as carriers of radionuclides and boron atoms. Among the newly synthesized compounds, the tertiary amide bearing a chloromethyl group **3m** showed subnanomolar PBR affinity and was found to be 20-times more potent than reference compound **1**. Moreover, 2-fluorophenyl derivative **3j** showing nanomolar affinity was, however, significantly more potent than **1**. Thus, these two PBR ligands (**3m**,**j**) represent interesting candidates for radiolabeling and PET studies. The powerful activity of **3h**,**j**,**k** in stimulating steroid biosynthesis demonstrated that these quinolinecarboxamide derivatives are capable of reaching and interacting with the PBR in vivo and of stimulating the transport of cholesterol both in the brain and in peripheral tissue mitochondria.

Furthermore, 1,2-dicarba-*closo*-dodecaboran-1-ylmethyl derivative **3q** represents the first example of PBR ligand bearing a carborane cage potentially useful in BNCT and as an organometallic ligand for radionuclides useful in diagnostic imaging (e.g., Tc-99m) or radiotherapy (e.g., Re-188).[12] Intriguingly, the targeting of a boron-rich moiety to the mitochondrial receptor of tumoral cells could represent a new approach to the anticancer therapy, which could benefit from the key role of mitochondrial signaling in apoptosis.

**Acknowledgment.** The authors are grateful to Prof. Stefania D'Agata D'Ottavi for the careful reading of the manuscript. This work was financially supported by Italian MIUR.

**Supporting Information Available:** Experimental details for the synthesis and the characterization of compounds **3** (chemistry, NMR, MS). This material is available free of charge via Internet at http://pubs.acs.org.

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