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Synthesis and Dopamine Receptor Selectivity of the Benzyltetrahydroisoquinoline, (*R*)-(+)-*nor*-Roefractine

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Abstract: (*R*)-(+)-*nor*-Roefractine (**1**) was synthesized by the Bischler–Napieralski route, using asymmetric reduction of the 1,2-didehydro precursor imine with sodium (*S*)-*N*-CBZ-prolinylxyborohydride. Compound **1** was able to displace [³H]-raclopride (a D₂ dopamine receptor-selective ligand) from its specific binding sites in rat striatum with selectivity vs [³H]-SCH23390 (D₁ dopamine receptor-selective ligand).

Among the isoquinoline alkaloids and related synthetic compounds, the conformationally restricted aporphines have been the subject of extensive structure–activity studies with regard to their interactions with dopamine receptors.¹ As a consequence, it is commonly accepted that the D ring of the aporphine skeleton, together with atoms C-7, C-6a, and N-6, mimic an “extended” pharmacophoric conformation of dopamine and that a hydroxyl group at C-11 (corresponding to the meta hydroxyl of dopamine) is necessary for high dopamine receptor affinity, while a hydroxyl group or

a fluorine atom at C-2 (meta to a “folded” aminoethyl chain) only enhances this behavior (Figure 1). Nevertheless, recent work from our laboratories has shown that four tetrahydroprotoberberine (THPB) alkaloids that possess two O-methylated dopamine moieties locked in “folded” conformations displace [³H]raclopride (a D₂ dopamine receptor-selective ligand) from its specific binding sites in rat striatum with IC₅₀ 0.028–0.075 μM and [³H]-SCH 23390 (a D₁ dopamine receptor-selective ligand) with IC₅₀ 1.14–7.13 μM. These results indicate that such alkaloids, and particularly coreximine, have rather high affinity and selectivity for the striatal D₂ receptor despite the lack of an “extended” dopamine moiety. Although the two hydroxyl groups of coreximine occupy positions corresponding to the para hydroxyl of dopamine, no clear structure–activity relationships can be delineated from the measured affinities of these few compounds. It is noteworthy, however, that even (*S*)-tetrahydropalmatine, which is completely O-methylated, retains quite strong affinity for the D₂ site.²

The conformationally labile 1-benzyl-1,2,3,4-tetrahydroisoquinolines (BTHIQ) are able to exist as either syn or anti rotamers (named on the basis of the spatial relationship of the benzene rings) approximating the geometries of aporphines or protoberberines, respectively. ¹H NMR studies have suggested that the “protoberberine-like” conformation is preferred in solution when the nitrogen atom is unsubstituted, while for *N*-methylated or more highly substituted compounds the “aporphinoid-like” conformation predominates.³ Racemic tetrahydropapaveroline and some of its O-methylated derivatives, including reticuline and norreticuline, were tested 15 years ago as dopamine receptor ligands. In general, they were found to displace [³H]spiroperidol from dopamine binding sites with IC₅₀ values in the 4–20 μM range, with only 4'-*O*-methyltetrahydropapaveroline showing much lower affinity.⁴ More recently, we have found that (*S*)-reticuline and (*R*)-coclaurine bind with low micromolar or submicromolar affinities to both D₁ and D₂ rat striatal receptors, possibly with some marginal selectivity for the latter.⁵ In these

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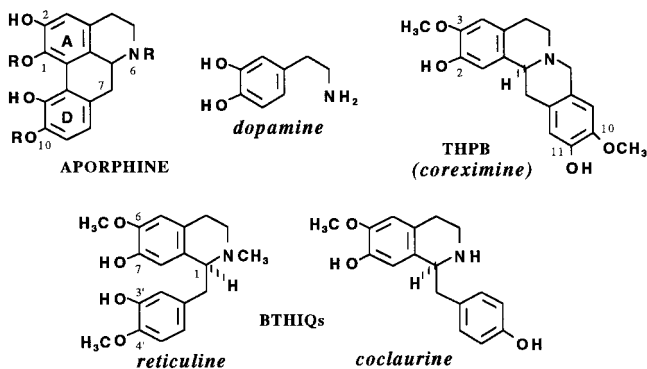


Figure 1. Aporphine, dopamine, THPB, and BTHIQs.

alkaloids, one (O-methylated) dopamine moiety is held in a “folded” conformation, and the free hydroxyl group of this substructure is para to the amine side chain, as is the case for both dopamine moieties of coreximine. The pendant 1-benzyl substituent affords a second dopamine-like fragment in reticuline, but this does not seem to enhance dopamine receptor affinity, as the simple *p*-hydroxybenzyl group of coclaurine is associated with several times greater potency: the IC₅₀ values for the displacement of tritiated raclopride or SCH23390 by (*R*)-(+)-coclaurine are 0.13 and 0.24 μ M, respectively. In coclaurine, but not reticuline, the lack of an *N*-methyl group suggests that a “protoberberine-like” conformation should be preferred in the absence of specific ligand–receptor interactions. Contrary to what may be the rule in aporphines, *N*-demethylation appears to be associated with greater rather than lesser potency in these BTHIQ's, although obviously more extensive series must be studied in this regard.

As an initial target, we considered (*R*)-*nor*-roefractine [**1**, 1-(4'-methoxybenzyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline], a hitherto unknown (*R*)-coclaurine analogue with the apparently unimportant 4'-hydroxy group O-methylated to enhance lipophilicity and the C-6 and C-7 substituents exchanged to leave a hydroxyl meta to the amine side chain. We accomplished the synthesis of this analogue of natural roefractine⁶ in a seven-step stereoselective sequence.

Compound **1**⁷ was prepared starting from isovanillin (**2**) via *O*-benzylisovanillin (**3**, yield 90%), (4-methoxy-3-benzyloxy)- β -nitrostyrene (**4**, 77%), and β -(3-benzyloxy-4-methoxyphenyl)ethylamine (**5**, 68%) by standard methods.^{8,9} This amine and 4-methoxyphenylacetyl chloride (**6**) were condensed under Schotten–Baumann conditions,^{10,11} and the resulting *N*-(4-methoxy-3-benzyloxy)phenylethyl-4'-methoxyphenacetamide (**7**, 44%) was cyclized by a Bischler–Napieralski approach to afford 1-(4'-methoxybenzyl)-6-benzyloxy-7-methoxy-3,4-dihydroisoquinoline (**8**, 89%).^{9,11} This product was reduced without purification using sodium (*S*)-*N*-CBZ-prolinylxyborohydride prepared in situ from NaBH₄ (1 equiv) and (*S*)-*N*-CBZ-proline (3 equiv).^{13,14} The reaction gave (+)-1-(4'-methoxybenzyl)-6-(benzyloxy)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (**10**, 49%). The reducing agent provided an effective asymmetric reduction of the prochiral cyclic imine. Selective hydrolysis of the benzyloxy protective group in this compound was achieved in 72% yield by refluxing (3 h) with equal volumes of ethanol and concentrated HCl, while the

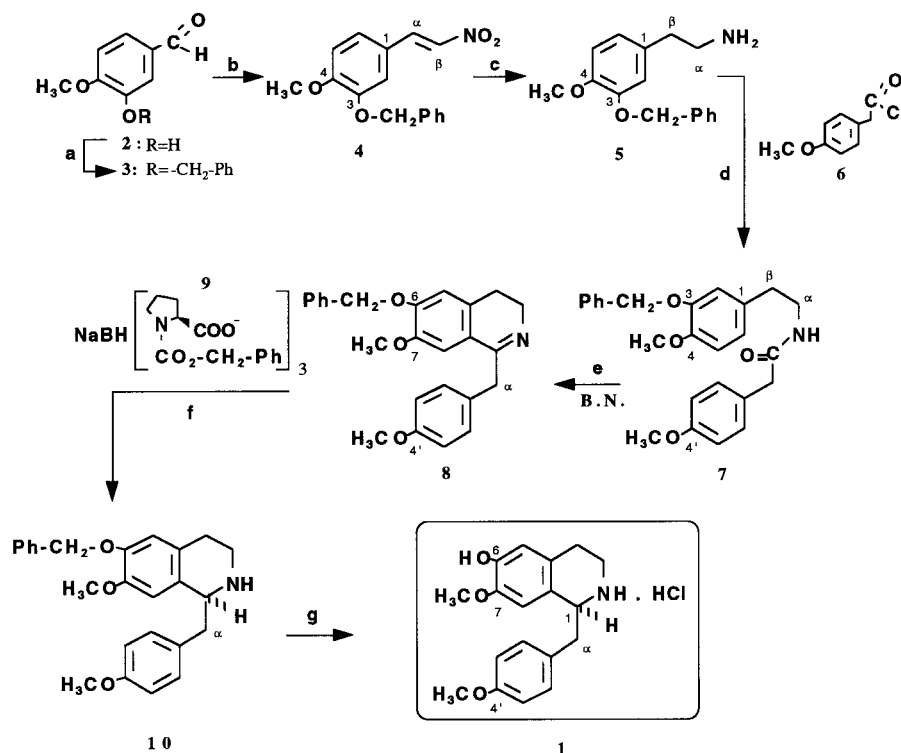
methyl ether linkage remained intact. This final de-blocking stage afforded **1** (92%) as its hydrochloride salt, whose structure was confirmed by spectroscopic methods and assigned as (*R*)-(+)-1-(4'-methoxybenzyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (**1**). HPLC analysis with UV detection at 282.5 nm established the purity of **1** (Scheme 1).

The *1R* configuration of our (+)-*nor*-roefractine (**1**) is indicated by the positive optical rotation of the free base and the negative optical rotation of the salt. This result is in line with those for analogous *N*-unsubstituted compounds in the BTHIQ series.^{3,12–15}

(*R*)-(+)-*nor*-Roefractine (**1**) was able to displace both [³H]-SCH 23390 (a D₁ dopamine receptor-selective ligand) and [³H]raclopride (a D₂ dopamine receptor-selective ligand) from their specific binding sites in rat striatum (Figure 2).^{16,17}

Compared to the other BTHIQs previously tested by us, coclaurine and reticuline,⁵ **1** appears to be less potent at both the D₁ and D₂ dopamine receptors. Nevertheless, although our results are not strictly comparable with those of Nimit et al.,⁴ the dopamine receptor affinity of **1** seems to be in the same range as that of most of the assayed tetrahydropaveroline analogues. More interestingly, **1** exhibits 6-fold selectivity for D₂ receptors, while the other similar ligands for which affinity measurements have been made with both major dopamine receptor subtypes are practically unselective. The decreased affinity of **1** with regard to coclaurine and reticuline could be attributed to the fact that in the “folded” O-methylated dopamine moiety in coclaurine and reticuline the free hydroxyl group lies para to the amine side chain, whereas it is meta to the amine side chain in **1**. However, we have observed that the THPBs coreximine, containing two meta O-methylated dopamine moieties in “folded” conformations, and 10-demethylidiscetretine, containing two para O-methylated dopamine moieties in “folded” conformations, display similar micromolar affinities for D₁ dopamine receptors and nanomolar affinities for D₂ dopamine receptors.² Comparison of data obtained for THPB and aporphine alkaloids¹⁸ leads to another suggestion: since the *nor*-roefractine structure is present both in 10-demethylidiscetretine (THPB) and in lauroilsine (aporphine), and the affinities of **1** for D₁ and D₂ dopamine receptors resemble those of lauroilsine much more closely than those of 10-demethylidiscetretine, it would seem possible that the “aporphine-like” conformation of **1** is preferred when this BTHIQ is bound to the active site of dopamine receptors. NMR studies consistently suggest that in *N*-unsubstituted BTHIQs the “protoberberine-like” conformation predominates in solution. Experimental and theoretical studies on the rotational behavior of BTHIQ's are lacking, however, and it seems possible that any one conformer may undergo rotation through a large angle around the C-1/C- α bond upon binding to a receptor macromolecule.

Molecular biology studies on seven transmembrane segment G-protein-coupled receptors¹⁹ indicate that the binding of catecholamines involves specific interactions between certain critical amino acid residues and complementary groups on the neurotransmitter molecule: the positively charged, protonated amino group with an aspartate residue and the phenolic hydroxyl groups with

Scheme 1. Synthesis of 1^a

^a Reagents and conditions: (a) benzyl chloride, K₂CO₃/EtOH, reflux, 5 h; (b) H₃CNO₂, NH₄OAc/AcOH, reflux, 3 h; (c) LiH₄Al, ether/THF (1:1), reflux, 2 h; (d) CH₂Cl₂/NaOH 5%, rt, 2 h; (e) POCl₃, CH₂Cl₂, reflux, 3 h; (f) CH₂Cl₂, -30 °C, 7 h; (g) HCl-EtOH (1:1), reflux, 3 h.

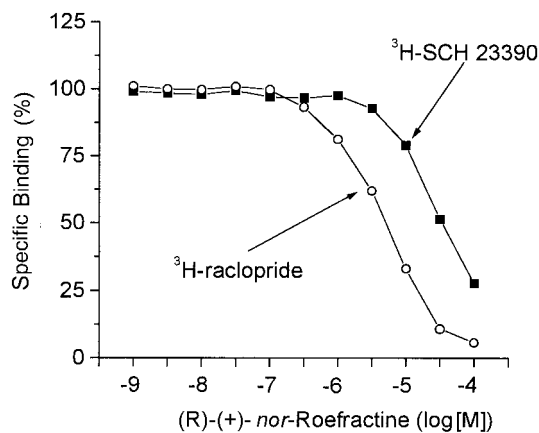


Figure 2. Displacement curves of [³H]-SCH 23390 and [³H]raclopride binding by (*R*)-(+)-nor-roefractine. Displacement curves correspond to four determinations at each concentration. IC₅₀ (μM) values are 32.9 (11.9–80.4) and 5.0 (2.0–12.6) for [³H]-SCH 23390 and [³H]raclopride binding, respectively.

two serine residues are apparently similar but with different global environments in different receptors. In addition, some amino acid residues (especially phenylalanine and tryptophan) appear to be involved in conformational changes of the receptors and, for conformationally labile ligands, in conformational changes of dopamine or of nonphysiological ligands. It seems reasonable to assume that a protonated BTHIQ, even if lacking an *N*-substituent, may tend to assume an "aporphine-like" conformation when interacting with the key aspartate residue of the receptor. Comparison of our data obtained with coclaurine and **1** seems to indicate that a hydroxyl group meta to the amine side

chain, as opposed to a para hydroxyl, only increases selectivity for D₂ receptors by selective reduction of D₁ receptor affinity. If hydrogen bonding to only one of the active-site serine residues were important for high affinity binding, this interaction with a para (C-7) hydroxyl might allow the BTHIQ molecule to adopt a less energetic conformation and thus obtain a lower IC₅₀ value. These hypotheses will be tested using data obtained from a rational series of BTHIQs that are now being synthesized.

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- (7) All compounds were purified by chromatography on SiO₂ (60 H, Merck) and characterized by full spectroscopic (¹H and ¹³C NMR, IR, and low-resolution MS) data. Yields refer to spectroscopically and chromatographically homogeneous (HPLC, TLC) materials. Selected data for key intermediates and products are summarized below. Compound **4**: 3-(benzyloxy)-4-methoxy-β-nitrostyrene, C₁₆H₁₅NO₄; mp 126–128 °C; IR (film) ν_{max} 1621 (NO₂), 1334 (NO₂) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 3.92 (3H, s, OCH₃-4), 5.17 (2H, s, OCH₂-3), 6.91 (1H, d, *J* = 8.4 Hz, H-5),

- 7.04 (1H, d, $J = 2.0$ Hz, H-2), 7.15 (1H, dd, $J = 8.4$ Hz, $J = 2.0$ Hz, H-6), 7.33–7.44 (5H, m, Ph), 7.44 (1H, d, $J = 13.5$ Hz, α -CHAr), 7.89 (1H, d, $J = 13.5$ Hz, β -CHNO₂); EIMS m/z 285 [M]⁺ (62), 91 (100). Compound 5: β -(3-(benzyloxy)-4-methoxyphenylethylamine), C₁₆H₁₉NO₂; IR (film) ν_{\max} 3326 (NH₂) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 2.60 (2H, t, $J = 6.8$ Hz, α -CH₂-NH₂), 2.83 (2H, t, $J = 6.8$ Hz, β -CH₂Ar), 3.85 (3H, s, OCH₃-4), 5.13 (2H, s, OCH₂-3), 6.73 (1H, d, $J = 1.8$ Hz, H-2), 6.74 (1H, dd, $J = 8.8$ Hz, $J = 1.8$ Hz, H-6), 6.83 (1H, d, $J = 8.8$ Hz, H-5), 7.30 (1H, d, $J = 7.4$ Hz, H-4'), 7.35 (2H, t, $J = 7.4$ Hz, H-3', 5'), 7.43 (2H, d, $J = 7.4$ Hz, H-2', 6'); EIMS m/z 257 [M]⁺ (45), 228 (76), 137 (34), 91 (100). Compound 7: *N*-(3-(benzyloxy)-4-methoxyphenylethyl)-4'-methoxyphenacetamide, C₂₅H₂₇NO₄; IR (film) ν_{\max} 3250 (NH), 2950, 1700 (amide I), 1600, 1510 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 2.61 (2H, t, $J = 6.6$ Hz, β -CH₂Ar), 3.38 (2H, t, $J = 6.6$ Hz, α -CH₂NHCO), 3.42 (2H, s, CH₂CO), 3.78 (3H, s, OCH₃-4'), 3.86 (3H, s, OCH₃-4), 5.08 (2H, s, OCH₂-3), 6.56 (1H, dd, $J = 8.1$ Hz, $J = 1.9$ Hz, H-6), 6.64 (1H, d, $J = 1.9$ Hz, H-2), 6.75 (1H, d, $J = 8.1$ Hz, H-5), 6.82 (2H, d, $J = 6.7$ Hz, H-3', 5'), 7.05 (2H, d, $J = 6.7$ Hz, H-2', 6'), 7.27–7.45 (5H, m, Ph); ¹³C NMR (CDCl₃, 62.5 MHz) δ 171.4 (CO), 158.6 (C-4'), 148.0 (C-3), 147.8 (C-4), 137.3, 128.4, 127.8 and 127.3 (Ph), 131.0 (C-1), 130.4 (C-2', 6'), 126.8 (C-1), 121.3 (C-6), 114.7 (C-2), 114.3 (C-3', 5'), 112.0 (C-5), 71.0 (OCH₂Ph), 56.0 (OCH₃-4), 55.2 (OCH₃-4'), 42.8 (β -CH₂Ar), 40.5 (CH₂CO), 34.8 (α -CH₂NH₂); EIMS m/z 405 [M]⁺ (30), 240 (100), 91 (98). Compound 8: 1-(4'-methoxybenzyl)-6-(benzyloxy)-7-methoxy-3,4-dihydroisoquinoline, C₂₅H₂₅NO₃; IR (film) ν_{\max} 1657 (C=N) cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 2.79 (2H, t, $J = 7.6$ Hz, CH₂-4), 3.71 (3H, s, OCH₃-4'), 3.78 (3H, s, OCH₃-7), 3.83 (2H, t, $J = 7.6$ Hz, CH₂-3), 4.36 (2H, s, CH₂- α), 5.16 (2H, s, OCH₂-6), 6.72 (1H, s, H-8), 6.83 (2H, d, $J = 8.5$ Hz, H-3', 5'), 7.17 (1H, s, H-5), 7.27 (2H, d, $J = 8.5$ Hz, H-2', 6'), 7.30–7.42 (5H, m, Ph); ¹³C NMR (CDCl₃, 62.5 MHz) δ 165.6 (C-1), 158.1 (C-4'), 149.9 (C-6), 147.7 (C-7), 136.5, 128.4, 127.8, and 127.3 (Ph), 131.6 (C-4a), 130.0 (C-2', 6'), 129.5 (C-8a), 126.6 (C-1'), 114.0 (C-3', 5'), 112.3 (C-5), 110.2 (C-8), 70.7 (OCH₂-6), 56.1 (OCH₃-7), 55.1 (OCH₃-4'), 47.0 (CH₂- α), 42.4 (CH₂-3), 25.6 (CH₂-4); EIMS m/z 387 [M]⁺ (89), 296 (71), 267 (5), 121 (30), 91 (100). (**R**)-(+)-*nor*-Roefractine (1): (1-(4'-methoxybenzyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline), C₁₈H₂₁NO₃; [α]_D²⁵ +5° (c 1.2, EtOH) base form; [α]_D²⁵ -12° (c 1.0, H₂O) salt form; IR (film) ν_{\max} 3363, 2922, 1594, 1509, 1458, 1246, 1175, 1109, 1031 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 2.71 (2H, m, H-4), 2.90 (2H, m, H-3), 2.90 (1H, m, α_1), 3.16 (1H, m, α_2), 3.80 (3H, s, OCH₃-4), 3.81 (3H, s, OCH₃-7), 4.13 (1H, m, H-1), 6.57 (1H, s, H-8), 6.65 (1H, s, H-5), 6.87 (2H, d, $J = 8.4$ Hz, H-3', 5'), 7.16 (2H, d, $J = 8.4$ Hz, H-2', 6'); ¹³C NMR (CDCl₃, 100 MHz) δ 158.3 (C-4'), 144.7 (C-6), 144.0 (C-7), 130.8 (C-8a), 130.4 (C-2', 5'), 129.5 (C-1), 127.8 (C-4a), 114.7 (C-5), 114.0 (C-3', 5'), 108.7 (C-8), 56.9 (C-1), 56.0 (OCH₃-7), 55.3 (OCH₃-4'), 41.7 (C-3), 40.5 (CH₂- α), 29.0 (C-4); EIMS m/z 178 (100), 163 (31), 121 (16), 91 (22); CIMS m/z 300 [M]⁺. Inspection of the 2D homonuclear correlation (¹H-¹H COSY 45) and carbon-multiplicity spectra (DEPT) allowed resonance assignments and complete characterization of compound 1.
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 (17) Binding experiments were performed on striatal membranes. Each striatum was homogenized in 2 mL of ice-cold Tris–HCl buffer (50 mM, pH = 7.4 at 22 °C) with a Polytron (4 s, maximal scale) and immediately diluted with Tris buffer. The homogenate was centrifuged either twice ([³H]-SCH 23390 binding experiments) or four times ([³H]raclopride binding experiments) at 20 000g for 10 min at 4 °C with resuspension in the same volume of Tris buffer between centrifugations. For [³H]-SCH 23390 binding experiments, the final pellet was resuspended in Tris buffer containing 5 mM MgSO₄, 0.5 mM EDTA, and 0.02% ascorbic acid (Tris–Mg buffer), and the suspension was briefly sonicated and diluted to a protein concentration of 1 mg/mL. A 100 μ L aliquot of freshly prepared membrane suspension (100 μ g of striatal protein) was incubated for 1 h at 25 °C with 100 μ L of Tris buffer containing [³H]-SCH 23390 (0.25 nM final concentration) and 800 μ L of Tris–Mg buffer containing the required drugs. Nonspecific binding was determined in the presence of 30 μ M SK&F 38393 and represented around 2–3% of total binding. For [³H]raclopride binding experiments, the final pellet was resuspended in Tris buffer containing 120 mM NaCl, 5 mM KCl, 1 mM CaCl₂, 1 mM MgCl₂, and 0.1% ascorbic acid (Tris–ions buffer), and the suspension was treated as described above. A 200 μ L aliquot of freshly prepared membrane suspension (200 μ g of striatal protein) was incubated for 1 h at 25 °C with 200 μ L of Tris–ion buffer containing [³H]raclopride (0.5 nM final concentration) and 400 μ L of Tris–ion buffer containing the drug being investigated. Nonspecific binding was determined in the presence of 50 μ M apomorphine and represented ~5–7% of total binding. In both cases, incubations were stopped by addition of 3 mL of ice-cold buffer (Tris–Mg buffer or Tris–ion buffer, as appropriate) followed by rapid filtration through Whatman GF/B filters. Tubes were rinsed with 3 mL of ice-cold buffer, and filters were washed with 3 \times 3 mL of ice-cold buffer. After the filters had been dried, radioactivity was counted in 4 mL BCS scintillation liquid at an efficiency of 45%. Filter blanks corresponded to approximately 0.5% of total binding and were not modified by drugs.
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