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Synthesis and biological activity of '3 + 1' mixed ligand (3-thiapentane-1,5-dithiolato)oxorhenium(V) complexes bearing 1,2,3,4-tetrahydro(iso)quinoline and quinoline†

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'3 + 1' mixed ligand oxorhenium(V) complexes of the type $ReO(SSS)S(CH_2)_nHet_N$ have been synthesized by the reaction of the preliminary prepared tetrahydro(iso)quinolyl containing monodentate ligands with chloro(3-thiapentane-1,5-dithiolato)oxorhenium(V). The newly synthesized ligands and complexes were characterized by elemental analysis, IR, ^1H, and ^{13}C NMR spectroscopy. Metal complexes were screened for psychotropic and antitumour activities and receptor-binding properties and were found to be active in this respect. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: oxorhenium complexes; tetrahydroquinoline; tetrahydroisoquinoline; quinoline; 3-thiapentane-1,5-dithiolate; psychotropic activity; antitumour activity; receptor-binding properties; NMR spectra; toxicity

INTRODUCTION

Substantial efforts have been directed towards developing radioligands as tracers for single-photon emission computed tomography (SPECT).[1,2] Many research groups[3–7] are involved in the search for new technetium-based compounds, called the third generation of radiopharmaceuticals, which employ the principles of modern pharmacology to achieve biochemical specificity. A number of attempts to synthesize technetium-99m-labelled ligands for various targets, e.g. for dopamine receptor,[8] muscarinic receptor,[9,10] 5-HT_{1A} receptor,[11–13] cholinergic neurons,[14] and steroid hormone receptor[15,16] have been reported. Investigations with β-emitters rhenium-188 have been done to design therapeutic radiopharmaceuticals.[17]

As transition metals, technetium and rhenium offer many opportunities for designing molecules by modifying the environment around the core and allowing certain biological properties to be imposed upon the molecule. Recently, mixed-ligand coordination spheres have gained increasing interest,[18] as they extend the opportunities of mimicking biological substrates and enable application of simpler ligand pathways. Whereas research in the past was mainly concerned with biological properties that allow relatively unspecific functional imaging, as in brain or miocardium perfusion studies, nuclear medicine is now requiring more and more biochemical information on low-capacity, high-specificity targets. According to the literature, some tetrahydro(iso)quinoline-containing ligands display affinity to serotonin (5-HT_{1A}),[19,20] dopamine,[21] and *N*-methyl-D-aspartate (NMDA)[22] receptors. So, prompted by the fact that some alkaloids with opiate activity contain hydrogenated moieties of quinoline or isoquinoline, we have designed some receptor-affine (receptor binding) rhenium complexes, using quinolyl moieties as anchor groups. To bind the metal we make use of the '3 + 1' principle,[23,24] which consists in binding of the oxometal(V) group at a mercaptide sulfur of the 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline, and quinoline molecules and blocking of the remaining free coordination sites by a tridentate 3-thiapentane-1,5-dithiolate.

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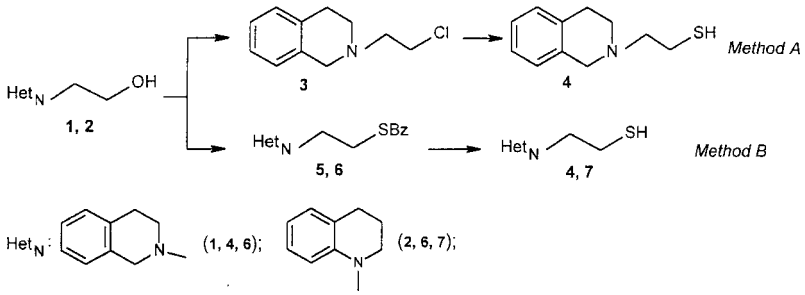
EXPERIMENTAL

General

^1H and ^{13}C NMR spectra were obtained on a Varian Inova-



Scheme 1.

400 (400 MHz for ^{1}H, 100 MHz for ^{13}C) instrument with $CDCl_3$ and dimethylsulfoxide-d_6 (DMSO-d_6) as solvent and internal standard. Infrared spectra (IR) were recorded on a Perkin Elmer FTIR Specord 2000 spectrometer in the phase indicated. Elemental analyses were performed on a LECO CHNS 932 elemental analyser. Melting points were determined on a Boetius melting point apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on Macherey–Nagel silica gel plastic plates, with visualization under UV (254 mm) and/or by 3,5-dinitrobenzoic acid. Column chromatography was performed using Merck silica gel (0.040–0.063 mm). Solvents and reagents were purchased from the following commercial sources: Fluka, Lancaster, and Aldrich. Tetrahydrofuran (THF) was distilled from sodium–benzophenone ketyl prior use. The syntheses involving air-sensitive compounds were carried out under argon. The following compounds were synthesized according to the literature procedures: *N*-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (**1**),[25] *N*-(2-hydroxyethyl)-1,2,3,4-tetrahydroquinoline (**2**),[25] chloro-(3-thiapentane-1,5-dithiolato)oxorhenium(V) (**8**).[26] 'SSS' = $-SCH_2CH_2SCH_2CH_2S-$.

Synthesis of ligands: method A

An outline is given in Scheme 1.

N-(2-Chloroethyl)-1,2,3,4-tetrahydroisoquinoline (**3**)[27]

1.78 ml (0.024 mol) of thionyl chloride was dropped into the solution of 3.54 g (0.02 mol) of *N*-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (**1**) in chloroform under stirring and cooling. The reaction mixture was refluxed for 4 h and neutralized by sodium hydrogencarbonate. The organic layer was separated, dried, and evaporated. The product was isolated by column chromatography using chloroform/methanol (100:5) as eluent. Yield 59%. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.00–7.18 (4H, m, Ar), 3.73 (2H, s, $ArCH_2$), 3.65 (2H, t, CH_2Cl), 2.93 (4H, m, $NCH_2 + 3\text{-}CH_2$), 2.82 (2H, t, 4-CH_2). ^{13}C NMR ($CDCl_3$), δ (ppm): 134.64, 134.42, 128.61, 126.54, 126.23, 125.04 (Ar), 60.45, 55.88, 53.46, 50.72, 28.66. Anal. Found: C, 67.31; H, 7.19; Cl, 18.20; N, 7.13. Calc. for $C_{11}H_{14}ClN$: C, 67.52; H, 7.16; Cl, 18.16; N, 7.16%.

N-(2-Mercaptoethyl)-1,2,3,4-tetrahydroisoquinoline (**4**)[28]

To 1.5 g (7.67 mmol) of alkyl halide **3** in 15 ml dimethylformamide (DMF) was added two equivalents of sodium thiophosphate dodecahydrate in water. The mixture was stirred for 1 h and the pH was lowered to neutral with hydrochloric acid (HCL). The reaction mixture was extracted with dichloromethane and dried. The filtered organic solution was dried under vacuum to obtain pure product **4**. Yield 49%. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.00–7.18 (4H, m, Ar), 3.65 (2H, s, $ArCH_2N$), 2.95 (2H, t, SCH_2, J = 5.9 Hz), 2.79 (2H, t, NCH_2, J = 5.9 Hz), 2.75 (4H, m, 3-CH_2 + 4-CH_2), 1.88 (1H, s, SH). ^{13}C NMR ($CDCl_3$), δ (ppm): 134.42, 134.14, 128.60, 126.54, 126.49, 125.58 (Ar), 60.68, 55.58, 50.55, 28.98, 22.27 (C—S).

Synthesis of ligands: method B

See outline in Scheme 1.

N-(2-Benzoylthioethyl)-1,2,3,4-tetrahydroisoquinoline (**5**)

2.2 ml (10.25 mmol) of 90% diisopropylazodicarboxylate was added to an efficiently stirred solution of 2.7 g (10.25 mmol) triphenylphosphine (PPh_3) in 20 ml of THF. The mixture was stirred for 30 min. 0.91 ml of **1** and 1.33 ml (10.25 mmol) of 95% thiobenzoic acid in 10 ml of THF were added and stirring of the mixture was continued for 1 h at room temperature. To the resulting yellow solution 100 ml of chloroform was added and the mixture was washed with H_2O. After drying over magnesium sulfate ($MgSO_4$) and evaporation of the solvent, a pale yellow residue was obtained; this was purified by flash chromatography. Compound **5** was isolated as a yellow oil. Yield 78%. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.99 (2H, m, 2′,6′-H), 7.55 (1H, t, 4′-H), 7.46 (2H, m, 3′,5′-H), 7.03–7.15 (4H, m, Ar), 3.77 (2H, s, $ArCH_2N$), 3.34 (2H, t, SCH_2), 2.82–2.95 (6H, m, $NCH_2 + 3\text{-}CH_2 + 4\text{-}CH_2$). ^{13}C NMR ($CDCl_3$), δ (ppm): 191.88 (C=O), 136.95, 133.30, 128.53, 127.17 (Bz), 134.42, 134.12, 128.63, 126.55, 126.11, 125.58 (Ar), 57.14, 55.74, 50.59, 28.92 (aliphatic), 26.52 (C—S). Anal. Found: C, 72.41; H, 6.38; N, 4.67; S,

10.47. Calc. for $C_{18}H_{19}NOS$: C, 72.72; H, 6.40; N, 4.71; S, 10.77%.

*N-(2-Benzoylthioethyl)-1,2,3,4-tetrahydroquinoline (**6**)*
Compound **6** was obtained by the method described above for **5** as a yellow oil. Yield 82%. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.80–8.00 (5H, m, Ar), 6.82–7.22 (4H, m, Ar), 3.60 (2H, t, SCH_2), 3.31–3.50 (4H, m, $2NCH_2$), 2.90 (2H, t, 4-CH_2), 2.07 (2H, qui, 3-CH_2). Anal. Found: C, 72.50; H, 6.32; N, 4.63; S, 10.65. Calc. for $C_{18}H_{19}NOS$: C, 72.72; H, 6.40; N, 4.71; S, 10.77%.

*N-(2-Mercaptoethyl)-1,2,3,4-tetrahydroisoquinoline (**4**)*
1.2 g (4.04 mmol) of thiobenzoate **5** was dissolved in 3.3 ml of 5 M sodium methoxide in methanol. After 1 h of stirring the pH was adjusted to pH 8 by 1 M HCl. Afterwards, 100 ml of water was added and the solution was extracted with chloroform. Drying over $MgSO_4$ and evaporation of the solvent yielded a yellow liquid residue, which was purified by flash chromatography (9/1, EtOAc/*n*-hexane). Yield 95%. The physico-chemical parameters were the same as for compound **4** obtained by method A.

*N-(2-Mercaptoethyl)-1,2,3,4-tetrahydroquinoline (**7**)*[29]
Compound **7** was obtained by the method described above for **4** as a yellow liquid. Yield 93%. ^{1}H NMR ($CDCl_3$), δ (ppm): 6.61–7.05 (4H, m, Ar), 3.35–3.42 (4H, m, $2NCH_2$), 2.87 (4H, m, 4-CH_2 + SCH_2), 2.00 (2H, qui, 3-CH_2), 1.58 (1H, s, SH).

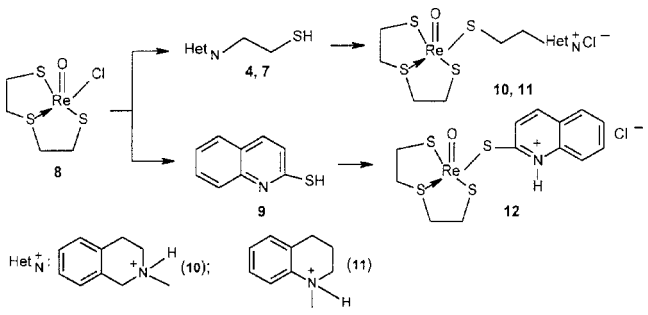
SYNTHESIS OF COMPLEXES

An outline is given in Scheme 2.

*[2-(N-Tetrahydroisoquinolyl)ethanethiolato](3-thiapentane-1,5-dithiolato)oxorhenium(V) hydrochloride (**10**)*
222 mg (1.14 mmol) of chloro(3-thiapentane-1,5-dithiolato)oxorhenium(V) (**8**) was dissolved in 12 ml of hot acetonitrile while stirring. At 80 °C, 220 mg (1.14 mmol) of *N*-(2-mercaptoethyl)-1,2,3,4-tetrahydroisoquinoline (**4**) dissolved in 4 ml of acetonitrile was added slowly. The mixture was stirred at 80 °C for 2 h. Afterwards, it was evaporated to dryness. The residue was purified by passing through a silica gel column with chloroform/methanol (10:1) as eluent. After slow evaporation of the solvents, a brown powder was obtained. Yield 94%. Melting point 190–192 °C. IR (KBr): ν = 964 cm^{-1} (s, Re=O). Anal. Found: C, 31.00; H, 4.01; Cl, 6.12; N, 2.53; S, 21.54. Calc. for $C_{15}H_{23}ClNOReS_4$: C, 30.90; H, 3.95; Cl, 6.09; N, 2.57; S, 21.97%. ^{1}H NMR (DMSO-d_6), δ (ppm): 7.21 (4H, m, Ar), 4.35 (2H, dd, D-part of ABCD system/'SSS'), 4.12 (2H, dd, C-part of ABCD system/'SSS'), 4.08 (2H, t, SCH_2), 3.43 (6H, m, CH_2Ar + 3-CH_2 + 4-CH_2), 3.10 (4H, m, α-NCH_2 + B-part of ABCD system/'SSS'), 2.31 (2H, m, A-part of ABCD system/'SSS'). ^{13}C NMR (DMSO-d_6), δ (ppm): 131.46, 128.61, 127.71, 126.73 (Ar), 57.26, 52.10, 48.98 (C—N), 45.82, 43.13 (S—C—C—S), 29.00 (C—S), 25.12 (4-C).

*[2-(N-Tetrahydroquinolyl)ethanethiolato](3-thiapentane-1,5-dithiolato)oxorhenium(V) hydrochloride (**11**)*
Complex **11** was obtained by the method described above for **10** as a brown powder. Yield 84%. Melting point 120–122 °C. IR (KBr): ν = 965 cm^{-1} (s, Re=O). Anal. Found: C, 31.01; H, 3.98; Cl, 6.10; N, 2.38; S, 21.94. Calc. for $C_{15}H_{23}ClNOReS_4$: C, 30.90; H, 3.95; Cl, 6.09; N, 2.40; S, 21.97%. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.61 (1H, bs, N^+H), 7.21 (4H, m, Ar), 4.31 (2H, dd, D-part of ABCD system/'SSS'), 4.25 (2H, t, SCH_2), 4.02 (2H, dd, C-part of ABCD system/'SSS'), 3.79 (2H, m, NCH_2 cycl.), 3.60 (2H, bs, NCH_2), 3.10 (2H, m, B-part of ABCD system/'SSS'), 2.87 (2H, t, 4-CH_2), 2.22 (2H, bs, 3-CH_2), 2.05 (2H, m, A-part of ABCD system/'SSS'). ^{13}C NMR ($CDCl_3$), δ (ppm): 130.17, 127.71, 115.22, 110.35 (Ar), 48.50, 58.92 (C—N), 46.87, 43.71 (S—C—C—S), 29.94 (C—S), 25.57 (4-C), 19.00 (3-C).

*2-Quinolylthiolato(3-thiapentane-1,5-dithiolato)oxorhenium(V) hydrochloride (**12**)*
Complex **12** was obtained by the method described above for **10** as brown powder in 83% yield. Melting point 209–210 °C. IR (KBr): ν = 964 cm^{-1} (s, Re=O). Anal. Found: C, 28.36; H, 2.70; Cl, 6.50; N, 2.59; S, 23.29. Calc. for $C_{13}H_{15}ClNOReS_4$: C, 28.34; H, 2.72; Cl 6.45; N, 2.54; S, 23.25%. ^{1}H NMR (DMSO-d_6), δ (ppm): 7.54–8.26 (6H, m, Ar), 3.97 (2H, m, D-part of ABCD system/'SSS'), 3.84 (2H, t, C-part of ABCD system/'SSS'), 2.96 (4H, m, A + B parts of ABCD system/'SSS'). ^{13}C NMR (DMSO-d_6), δ (ppm): 148.20, 135.01, 129.72, 129.00, 127.34, 126.75, 126.00 (Ar), 46.10, 43.22 (S—C—C—S).



Scheme 2.

Biological tests

Psychotropic activity
The complexes synthesized were studied for neurotropic activity on BALB/c mice of both sexes weighing 18–23 g in the autumn season.[30] The room temperature was maintained within the limits 22 ± 1.5 °C. The trials were performed on groups of animals, consisting of six individuals. The substances investigated were administered at dosages of

5 mg kg^{-1} in the form of DMSO solutions and were injected intraperitoneally 45 min before the test was set up. The control animals were injected in the abdominal cavity with the same volume of the solvent. A comparative assessment was made of the action of the complexes:

- on the body temperature, by measuring the rectal temperature with an electric thermometer;
- from the antispasmodic activity, estimated by the maximal electric shock test (alternating current with an intensity of 50 mA and a pulse frequency of 50 Hz, duration of stimulation 0.2 s);
- from corazol spasms caused by the intravenous titration with 1% corazol solution at a rate of 0.01 ml s^{-1};
- from the influence on the duration of hexenal anaesthesia (70 mg kg^{-1}, i.v.) and ethanol anaesthesia (25% solution of ethanol i.p., dose of 5 g kg^{-1});
- from the life time of animals under hypoxic hypoxia, created by placing the mouse in a separate chamber with a volume of 220 cm^3 without absorption of CO_2;
- from the change in the locomotor activity, enforced by phenamine (10 mg kg^{-1}, s.c.).

Acute toxicity was determined by intraperitoneal introduction of the substances investigated and by establishing the lethal dose (LD_{50}).

The experimental data were treated statistically. The mean values of LD_{50} and ED_{50} were determined by a rapid method given in Ref. 31. The arithmetical means and their standard deviations ($M \pm m$) were calculated to assess the average duration of the anaesthetic effect of the hexenal and phenamine stereotypy, the protective properties in the corazol spasms and hypoxia, and the degree of hypothermia. The significance of differences between mean values was assessed by Student's criterion: differences were considered as significant at a probability level $p < 0.05$.

Cytotoxicity

Monolayer tumour cell lines MG-22A (mouse hepatoma), HT-1080 (human fibrosarcoma), Neuro 2A (mouse neuroblastoma) and B16 (mouse melanoma) were cultivated for 72 h in standard Dulbecco's modified Eagle's medium (Sigma) without an indicator and antibiotics.[32] After the ampoule was defrosted, not more than four passages were performed. The control cells and cells with substances tested in the range of $(2–5)\times10^4$ cell ml^{-1} concentration (depending on line nature) were placed on separate 96-well plates. Solutions containing test compounds were diluted and added in wells to give the final concentrations of 50, 25, 12.5 and 6.25 μg ml^{-1}. Control cells were treated in the same manner, only in the absence of test compounds. Plates were cultivated for 72 h. The quantity of surviving cells was determined using crystal violet (CV) or 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolinium bromide (MTT) coloration, which was assayed by a multiscan spectrophotometer. The quantity of living cells on the control plate was taken in calculations for 100%.[32,33] The concentration of NO was determined according to Ref.[33]

RESULTS AND DISCUSSION

N-(2-Hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (**1**) and *N*-(2-hydroxyethyl)-1,2,3,4-tetrahydroquinoline (**2**) have been converted into *N*-(2-mercaptoethyl)-1,2,3,4-tetrahydro(iso)quinolines (**4, 7**) suitable for complexation.

N-(2-Mercaptoethyl)-1,2,3,4-tetrahydroisoquinoline (**4**) was synthesized from the corresponding aminoalcohol by its conversion to chloroethyl derivative **3** in reaction with $SOCl_2$ and subsequent treatment with two equivalents of sodium thiophosphate dodecahydrate in dimethylformamide, followed by acid hydrolysis[34] (method A) and by the Mitsunobu procedure,[35,36] by treatment of the alcohols with a previously prepared PPh_3–diisopropylazodicarboxylate–benzoic acid system and subsequent hydrolysis (method B) (Scheme 1). The introduction of a thiol group into the tetrahydroquinoline molecule via thiobenzoate **6** was the method of choice, due to the hydroxy–mercapto function conversion under mild conditions and high yield.

Thus obtained tetrahydro(iso)quinolyl thiols **4** and **7** as well as 2-mercaptoquinoline (**9**) were transformed into the corresponding '3 + 1' mixed-ligand complexes **10–12** by their interaction with chloro(3-thiapentane-1,5-dithiolato)oxorhenium(V) (**8**; Scheme 2).

With regard to examination of the structure–biological activity correlation, we investigated the acute toxicity, the antitumour, and the receptor-binding properties of [2-(*N*-tetrahydroisoquinolyl)ethanethiolato]- (**10**), [2-(*N*-tetrahydroquinolyl)ethanethiolato]- (**11**), and 2-quinolylthiolato(3-thiapentene-1,5-dithiolato)oxorhenium(V) (**12**) hydrochlorides.

The complexes were tested for psychotropic activity and acute toxicity *in vivo* on mice under intraperitoneal administration in doses of 5 mg kg^{-1}. The action on the central nervous system was evaluated using indicators of hypoxia, hexenal- and ethanol-induced narcosis, phenamine hyperactivity, corazol-induced convulsions, electroshock, and retrograde amnesia. The results of the biological investigation are presented in Table 1.

The compounds investigated possess strongly marked sedative action. Compounds **10** and **12** show an antihypoxic action, prolonging the mice life under hypoxia.

With respect to hexenal-induced narcosis, 2-quinolylthiolato(3-thiapentane-1,5-dithiolato)oxorhenium(V) (**12**) was the most active compound, prolonging hexenal anaesthesia by more than a factor of two. In contrast to **11** and **12**, [2-(*N*-tetrahydroisoquinolyl)ethanethiolato](3-thiapentane-1,5-dithiolato)oxorhenium (**10**) was the only complex that exhibited antagonistic action to ethanol in the test of ethanol-induced narcosis.

The antagonistic action to phenamine is mostly marked for [2-(*N*-tetrahydroquinolyl)ethanethiolato]- (**11**) and 2-quino-

Table 1. Neurotropic activity of oxorhenium(V) complexes **10, 11**, and **12** *in vivo* (on mice)

Test	**10**	**11**	**12**
LD_{50} (mg kg^{-1})	>500	>500	>500
Hypoxic hypoxia (%)[a]	120	103	131
Phenamine hyperthermia (°C, 30 min)	−0.8	−1.4	−0.4
Phenamine-induced hyperactivity (%)[a]	96	43	21
Hexenal-induced narcosis (%)[a]	113	106	206
Ethanol-induced narcosis (%)[a]	82	114	100
Corazol-induced convulsions (clonic/tonic) (%)[a]	128/212	125/141	106/115
Retrograde amnesia (%)[a]	40	80	80

[a] With respect to control (100%).

Table 2. *In vitro* binding data of oxorhenium(V) complexes **10, 11**, and **12** to serotonin receptors (5-HT_{1A}, 5-HT_{2A})

Compound	IC_{50} (nM)	
	5-HT_{1A} competitor [^{3}H]8-OH-DPAT[a]	5-HT_{2A} competitor [^{3}H]ketanserin
10	389.5 ± 4.9	1259 ± 15
11	2015 ± 50	3622 ± 21
12	17989 ± 691	6408 ± 75

[a] 8-OH-DPAT: 8-hydroxy-(2-di-N-propylamino)tetraline.

lylthiolato(3-thiapentane-1,5-dithiolato)oxorhenium(V) (**12**). The latter almost fully depresses the phenamine action (by 80%).

Contrary to the test of maximal electroshock, where no protective properties were found, all the compounds synthesized demonstrated anticonvulsive activity in the test of corazol-induced convulsions (clonic and tonic). The most active compound in this test was [2-(*N*-tetrahydroquinolyl)ethanethiolato](3-thiapentane-1,5-dithiolato)oxorhenium(V) (**11**), increasing the threshold of corazol convulsions up to 112% (tonic phase) and 28% (clonic phase).

It should be mentioned that the neurotropic action of the complexes is strongly dependent on the nature of the heterocyclic moiety in the monodentate ligand. Tetrahydroisoquinoline containing **10** is the most active in the tests of hypoxia and corazol-induced convulsions, but in the tetrahydroquinoline containing compound **11**, action is mostly expressed in the interaction with phenamine and in the influence on memory process. The result of their interaction with ethanol in the test of ethanol-induced anaesthesia is quite opposite.

[2-(*N*-Tetrahydroisoquinolyl)- (**10**), [2-(*N*-tetrahydroquinolyl)ethanethiolato]- (**11**), and 2-quinolylthiolato(3-thiapentane-1,5-dithiolato)oxorhenium (**12**) were used in receptor binding assays[37] to determine the affinity and selectivity of these ligands for serotonin 5-HT_{1A} and 5-HT_{2A} receptors *in vitro* (Table 2). The affinity (IC_{50} values) to receptor subtypes is relatively low, but complexes **10** and **11**, contrary to

Table 3. *In vitro* cell cytotoxicity against various cell lines and the ability of intracellular NO generation caused by oxorhenium(V) complexes **10, 11**, and **12**

Compound	HT-1080			MG-22A			Neuro2A			B16		
	IC_{50} (mg ml^{-1})[a]		[NO][b] (%)	IC_{50} (mg ml^{-1})[a]		[NO][b] (%)	IC_{50} (mg ml^{-1})[a]		[NO][b] (%)	IC_{50} (mg ml^{-1})[a]		[NO][b] (%)
	CV	MTT		CV	MTT		CV	MTT		CV	MTT	
10	5	6	150	0.5	0.9	200	7.7	9	250	3	4.5	500
11	–[c]	–[c]	21	–[c]	–[c]	20	–	–	–	–	–	–
12	47	72	950	50	30	950	–	–	–	–	–	–

[a] Concentration providing 50% cell killing effect determined by coloration (CV and MT)
[b] NO concentration determined by coloration (CV).
[c] No cytotoxic effect.

complex **12**, reveal a higher selectivity to serotonin 5-HT_{1A} subtype than to 5-HT_{2A}.

The antitumour activity was tested *in vitro* on four monolayer tumour cell lines: MG-22A (mouse hepatoma), HT-1080 (human fibrosarcoma), Neuro 2A (mouse neuroblastoma) and B16 (mouse melanoma). The experimental evaluation of cytotoxicity properties is presented in Table 3.

The complex [2-(*N*-tetrahydroisoquinolyl)ethanethiolato](3-thiapentane-1,5-dithiolato)oxorhenium(V) (**10**) possesses good antitumour activity and NO-induction ability. It has the highest cytotoxic effect on MG-22A (mouse hepatoma) and B16 (mouse melanoma) cell lines and high NO-generation activity, being most active (500%) in the test B16 (Table 3).

The mixed-ligand approach offers easy and rational access to neutral rhenium complexes in which one site can be easily modified by a large variety of pharmacologically relevent groups. We think that this class of '3 + 1' compounds has considerable potential in the design of new functionalized technetium and rhenium complexes.

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