APPLIED ORGANOMETALLIC CHEMISTRY
Appl. Organometal. Chem. 2007; **21**: 288–293
Published online in Wiley InterScience
(www.interscience.wiley.com) DOI:10.1002/aoc.1201

Tetrahydroquinoline and tetrahydroisoquinoline mixed ligand rhenium complexes with the SNS/S donor atom set

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Received 6 November 2006; Revised 6 November 2006; Accepted 6 November 2006

New oxorhenium complexes with 3-methylazapentane-1,5-dithiolate (SNMeS) and thiol functionalized monodentate tetrahydroquinolyl and tetrahydroisoquinolyl derivatives have been synthesized by simultaneous reaction of $[PPh_3]_2[Re(O)Cl_3]$ with tridentate HSNMeSH and the corresponding N-heterocycle containing thiol. The characterization of complexes involved elemental analysis, IR, ^1H and ^{13}C NMR spectroscopy and X-ray crystallographic analysis. The nature of the heterocycle in monodentate ligand, even situated at the distance of two methylene group length, has been found to have a significant influence on the molecular conformation. Metal complexes were found to be active in psychotropic *in vivo* and cytotoxicity *in vitro* screening. Copyright © 2007 John Wiley & Sons, Ltd.

KEYWORDS: rhenium; mixed-ligand oxorhenium complexes; tetrahydroquinoline; tetrahydroisoquinoline; molecular structure; psychotropic activity; cytotoxicity; metal-based drugs

INTRODUCTION

Studies on the synthesis and biological properties of metal-based anticancer compounds different from *cis*-platin are a field of growing interest. The increase in the number of chemical publications over the years reflects the progress made in transition metal coordinated chemistry. This progress, however, does not yet seem to have been adequately transferred into medical use. Current research is largely motivated by the needs of modern medicine for more sensitive and specific molecular probes for targetting diseased organs or physiological functions in medicine, both in the diagnostic and therapeutic fields.

To extend the research focused on rhenium-based pharmaceuticals and rhenium complexes as non-radioactive models for the radiopharmaceutically relevant technetium compounds,[1–4] we have been evaluating the possibility of using quinoline derivative containing ligands for preparing oxorhenium(V) complexes with biological interest.

The chemical design of metal complexes of the type $[Het_NSReO(SNMeS)]$, where Het_N is hydrogenated quinoline or isoquinoline residue, has been carried out in an approach to better understanding how the nature of their components affects their biological activity. The choice of tetrahydro(iso)quinoline derivatives for pharmacological investigation was stipulated by their potential biological properties. Tetrahydro(iso)quinoline derivatives have been discussed as affine ligands for CNS receptors[5–8] and possess sedative[9–11] and antitumour properties.[12–16] In addition, hydrogenated quinoline moieties are present as structural fragments in Amsacrine, Bruneomycinum, Vincristine and Vinblastinum, which are widely used in oncology.[17,18]

Prompted by these facts, we have designed some receptor–affine rhenium complexes using tetrahydro(iso)quinolyl moieties as anchor groups. In this paper we report on the synthesis and structural and biological characterization of new oxorhenium(V) adducts where the ligands coordinate to the metal centre in [3 + 1]-dentate fasion.[4,19]

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Contract/grant sponsor: Latvian Council of Sciences; Contract/grant number: 1792.

EXPERIMENTAL SECTION

Chemicals and instrumentation

^{1}H and ^{13}C NMR spectra were determined on a Varian Inova-400 (400 MHz for ^{1}H, 100 MHz for ^{13}C) instrument at 303 K with $CDCl_3$ as a solvent and internal standard ($\delta = 7.25$ ppm for $CHCl_3$). Infrared spectra (IR) were recorded on a Perkin Elmer FTIR Specord 2000 spectrometer in the indicated phase. 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 Machery–Nagel silica gel plastic plates, with visualization under UV (254 nm) and/or by 5,5′-dithionitrobenzoic acid. Column chromatography was performed using Merck silica gel (0.040–0.063 nm). Solvents and reagents were purchased from the following commercial sources: Fluka, Lancaster and Aldrich. 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-mercaptoethyl)-1,2,3,4-tetrahydroisoquinoline **1**,[16] *N*-(2-mercaptoethyl)-1,2,3,4-tetrahydroquinoline **2**,[16] *trans*-monooxotrichlorobis(triphenylphosphine)rhenium(V),[20] bis(2-mercaptoethyl)-*N*-methylamine.[3] THQ = 1, 2, 3, 4-tetrahydroquinoline, THiQ = 1, 2, 3, 4-tetrahydroisoquinoline, SNMeS = $-SCH_2CH_2N(CH_3)CH_2CH_2S-$, THiQ$(CH_2)_2$ SReO(SNMeS) = [2-(*N*-tetrahydroisoquinolyl)ethanethiolato][3-(*N*-methyl)azapentane-1,5-dithiolato]oxorhenium(V), THQ$(CH_2)_2$SReO(SNMeS) = [2-(*N*-tetrahydroquinolyl) ethanethiolato][3-(*N*-methyl)azapentane-1,5-dithiolato]oxorhenium(V).

[2-(*N*-tetrahydroisoquinolyl)ethanethiolato][3-(*N*-methyl)azapentane-1,5-dithiolato]oxorhenium(V) (3)

A mixture of *N*-(2-mercaptoethyl)-1,2,3,4-tetrahydroisoquinoline (**1**) (26.6 mg, 138 μmol), *N*-methyl-3-azapentane-1,5-dithiol (18.9 mg, 125 μmol), *trans*-monooxotrichlorobis (triphenylphosphine)rhenium(V) (104 mg, 125 μmol) and 1 M methanolic NaOAc (1 ml) in 5 ml of methanol were refluxed for 2 h, during which time the reaction mixture became dark green-brown colored. Afterwards, it was evaporated to dryness. The residue was purified by passing through a silica gel column with chloroform–methanol (100 : 1) as eluent. After slow evaporation of the solvents, a product was obtained as green powder. Yield: 68%; m.p. (MeOH): 135–136 °C. IR (KBr): $\nu = 949$ cm^{-1} (s, Re = O). Anal. found: C, 35.35; H, 4.64; N, 5.13; S, 17.64; calcd. for $C_{16}H_{25}N_2OReS_3$: C, 35.34; H, 4.63; N, 5.15; S, 17.69%. ^{1}H NMR ($CDCl_3$), δ (ppm): 2.63 (m, 2H, A-part of ABCD-system/'SNS'), 2.88 (t, 2H, NCH_2, $J = 5.5$ Hz), 2.95 (m, 4H, 3,4-CH_2), 3.16 (m, 4H, B- and C-part of ABCD-system/'SNS'), 3.34 (s, 3H, NCH_3), 3.55 (m, 2H, D-part of ABCD-system/'SNS'), 3.77 (s, 2H, 1-CH_2), 3.97 (bs, 2H, $-CH_2-$SReO'SNS'), 7.02–7.12 (m, 4H, Ar). ^{13}C NMR ($CDCl_3$), δ (ppm): 29.08 (C-4), 41.11 (C–S), 41.42 (C–S 'SNS'), 50.96 (C-3), 52.78 (N–CH_3 'SNS'), 55.99 (C-1), 60.48 (N–CH_2), 68.55 (C–N 'SNS'), 125.5, 126.0, 126.6, 128.6, 134.3, 134.9 (Ar).

[2-(*N*-tetrahydroquinolyl)ethanethiolato][3-(*N*-methyl)azapentane-1,5-dithiolato]oxorhenium(V) (4)

Complex **4** was obtained by the method described above for **3** as green powder. Yield: 77%; m.p. (MeOH): 188–189 °C. IR (KBr): $\nu = 960$ cm^{-1} (s, Re=O). Anal. found: C, 35.29; H, 4.64; N, 5.16; S 17.62; calcd for $C_{16}H_{25}N_2OReS_3$: C, 35.34; H, 4.63; N, 5.15; S, 17.69%. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.96 (m, 2H, 3-CH_2), 2.63 (m, 2H, A-part of ABCD-system/'SNS'), 2.76 (t, 2H, 4-CH_2, $J = 6.3$ Hz), 3.16 (m, 4H, B- and C-part of ABCD-system/'SNS'), 3.35 (s, 3H, NCH_3), 3.42 (t, 2H, 2-CH_2, $J = 5.4$ Hz), 3.56 (m, 2H, D-part of ABCD-system/'SNS'), 3.64 (t, 2H, NCH_2, $J = 7.5$), 3.94 (bs, 2H, $-CH_2-$SReO'SNS'), 6.55–7.06 (m, 4H. Ar). ^{13}C NMR ($CDCl_3$), δ (ppm): 22.22 (C-3), 28.16 (C-4), 39.29 (C–S), 41.44 (C–S 'SNS'), 49.55 (C-2), 52.81 (N–CH_3 'SNS'), 53.74 (N–CH_2), 68.65 (C–N 'SNS'), 110.78, 115.35, 127.12, 129.09 (Ar).

Crystal structure determination

The structures of the compounds **3** and **4** were established by X-ray structure analysis. A single crystal diffractometer 'Nonius KappaCCD' [MoK_α-radiation, $\lambda = 0.71073$ Å, $T = 293(2)$ K] was used for data collection. All calculations were carried out with the help of *SIR97* and *maXus* programs.[21,22]

CCDC-602 458 (**3**) and -602 457 (**4**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk).

Biological tests

In vivo psychotropic activity

The compounds **3** and **4** were studied for neurotropic activity on ICR mice of both sexes according to the procedure described.[3]

In vitro cytotoxicity

Monolayer tumour cell lines MG-22A (mouse hepatoma), HT-1080 (human fibrosarcoma), SHSY5Y (human neuroblastoma) and B16 (mouse melanoma) were cultivated for 72 h in DMEM standard medium (Sigma) without an indicator and antibiotics.[23] Tumour cell lines were taken from European Collection of Cell Culture (EAACC).

After the ampoule was thawed not more than four passages were performed. The control cells and cells with tested substances in the range of $2–5 \times 10^4$ cell/ml concentration (depending on line nature) were placed on a 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. Control cells were treated in the same manner in the absence of test compounds. Plates were cultivated for 72 h at 37 °C in 5% CO_2. A quantity of survived cells was

DOI: 10.1002/aoc

determined using crystal violet (CV), 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolinium bromide (MTT) and neutral red (NR) coloration which was assayed by multiscan spectrophotometer. The quantity of living cells on the control plate was taken in calculations for 100%.[23,24] Concentration of NO was determined according to the procedure.[24]

RESULTS AND DISCUSSION

Synthesis

The introduction of a thiol group into the tetrahydro(iso)quinoline molecule succeeded via thiobenzoate by the Mitsunobu procedure[25,26] starting from the corresponding aminoalcohols. Treatment of *N*-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline and *N*-(2-hydroxyethyl)-1,2,3,4-tetrahydroquinoline with the preliminary prepared PPh_3–diisopropylazodicarboxylate–thiobenzoic acid system and subsequent saponification of the corresponding thiobenzoates by sodium methoxide in MeOH resulted in the desired *N*-(2-mercaptoethyl)-1,2,3,4-tetrahydroisoquinoline (**1**) and *N*-(2-mercaptoethyl)-1,2,3,4-tetrahydroquinoline (**2**).[16]

Coordination of the tetrahydro(iso)quinolyl ligands **1** and **2** to the rhenium precursor according to the '3 + 1' approach offers access to the oxorhenium(V) complexes [2-(*N*-tetrahydroisoquinolyl)ethanethiolato][3-(*N*-methyl)azapentane-1,5-dithiolato]oxorhenium(V) (**3**) and [2-(*N*-tetrahydroquinolyl)ethanethiolato][3-(*N*-methyl)azapentane-1,5-dithiolato]oxorhenium(V) (**4**), respectively. Preparation of complexes was accomplished in moderate yields by a one-pot synthesis of the preliminarily prepared *trans*-monooxotrichlorobis(triphenylphosphine)rhenium(V), the protected tridentate 3-(*N*-methyl)azapentane-1,5-dithiol and the corresponding monodentate ligand under basic conditions (Scheme 1).

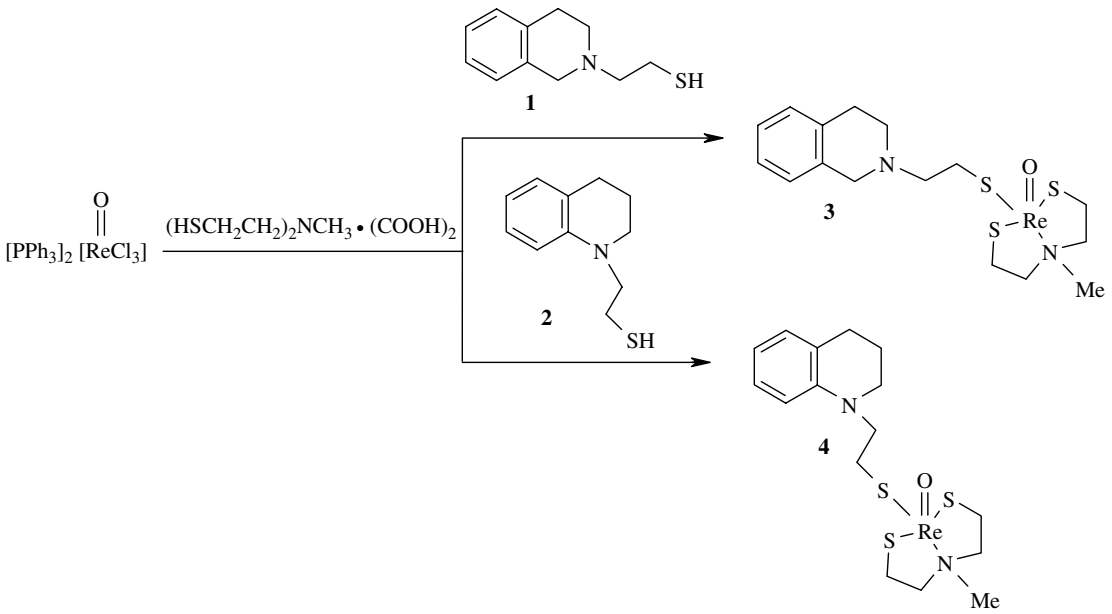
The complexes synthesized were characterized by the data of elemental analysis, ^1H and ^{13}C NMR and IR spectroscopy. The infrared spectra of both complexes display the characteristic strong absorption band in the region of 949 cm^{-1} for **3** and 960 cm^{-1} for **4**, which is distinctive of the central $Re{=}O^{3+}$ moiety. In the ^1H NMR spectra of compounds **3** and **4** the protons of the tridentate chelator give representative coupling patterns at $\delta_H = 2.63$, 3.16 and 3.55.

Crystal structure

Dark green crystals of **3** and **4** suitable for an X-ray crystal structure determination were obtained by slow evaporation of chloroform–methanol solution. Compound **3** crystallizes in the triclinic space group $P\,\bar{1}$ with 2 independent molecules per unit cell. Compound **4** crystallizes in the monoclinic space group $P\,2_1/n$ with four independent molecules per unit cell.

The molecular structures of [2-(*N*-tetrahydroisoquinolyl) ethanethiolato][3-(*N*-methyl)azapentane-1,5-dithiolato]oxorhenium(V) (**3**) and [2-(*N*-tetrahydroquinolyl)ethanethiolato][3-(*N*-methyl)azapentane-1,5-dithiolato]oxorhenium(V) (**4**) with atomic numbering scheme are presented in Figs 1 and 2.

According to X-ray data the ligands are coordinated around the central metal core, forming a distorted trigonal bipyramidal geometry, where the axial position is occupied by the nitrogen donor of the tridentate ligand and the sulfur atom of the monodentate ligand. The corner sites of the triangular plane are taken up by the oxygen atom of the $Re{=}O^{3+}$ unit and the two sulfanyl groups of the 'SNMeS' ligand. The rhenium atom deviates from the bipyramid equatorial plane



Scheme 1. Synthesis of complexes **3** and **4**.

DOI: 10.1002/aoc

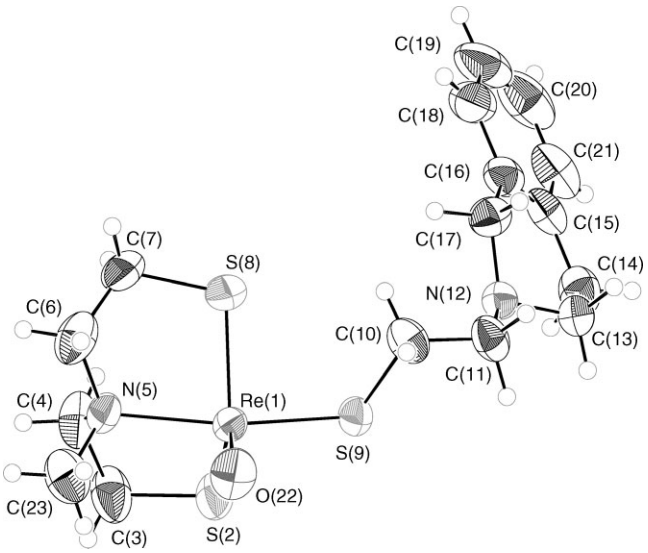


Figure 1. Molecular structure of [2-(*N*-tetrahydroisoquinolyl) ethanethiolato][3-(*N*-methyl)azapentane-1,5-dithiolato]oxo-rhenium(V) (**3**).

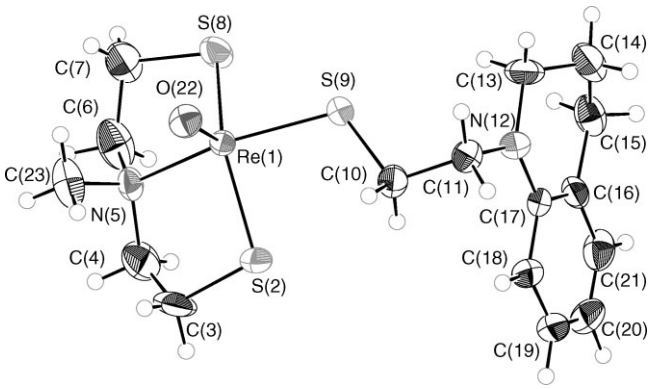


Figure 2. Molecular structure of [2-(*N*-tetrahydroquinolyl) ethanethiolato][3-(*N*-methyl)azapentane1,5-dithiolato]oxo-rhenium(V) (**4**).

with the atoms S(2), S(8), O(22) on 0.0804(1) and 0.0747(2) Å to the side of S(9) in the molecules **3** and **4** respectively.

The conformation of the six-membered heterocycle in **3** is semi-chair. The deviations of the atoms N(12) and C(13) from the plane of C(14), C(15), C(16), C(17), C(18), C(19), C(20), C(21) are 0.497(4) and −0.299(5) Å respectively. In the molecule **4** the conformation of this heterocycle is envelope. The deviation of the atom C(14) from the plane of N(12), C(13), C(15), C(16), C(17), C(18), C(19), C(20), C(21) is 0.589(7) Å.

For N(12) of the molecule **3**, there is the pyramidal coordination [sum of the valence angles is 330.2(4)°] and N(12)–C bonds are ordinary. In the molecule **4**, the planar coordination occurs for the nitrogen atom N(12) [sum of the valence angles is 358.8(2)°]. Thus, the lone electron pair of N(12) is delocalized and the lengths of N(12)–C bonds are shortened. The conformation of the molecule **3** relatively the C(10)–C(11) bond is + synclynal, while one for molecule **4** is − synclynal [the S(9)–C(10)–C(11)–N(12) torsion angles are 76.5(3) and −70.3(5)° for **3** and **4** respectively].

Figures 3 and 4 illustrate the packing diagrams with coordination polyhedra of rhenium atoms in the crystals **3** and **4**. In structures **3** and **4** bond lengths and angles within the polyhedra are of the order of magnitude expected for these types of rhenium coordination compounds.[3] However, there is a different environment of the polyhedra in the crystal structures **3** and **4**.

Probably, the better donor characteristic of the conjugated tetrahydroquinoline moiety influences the rhenium

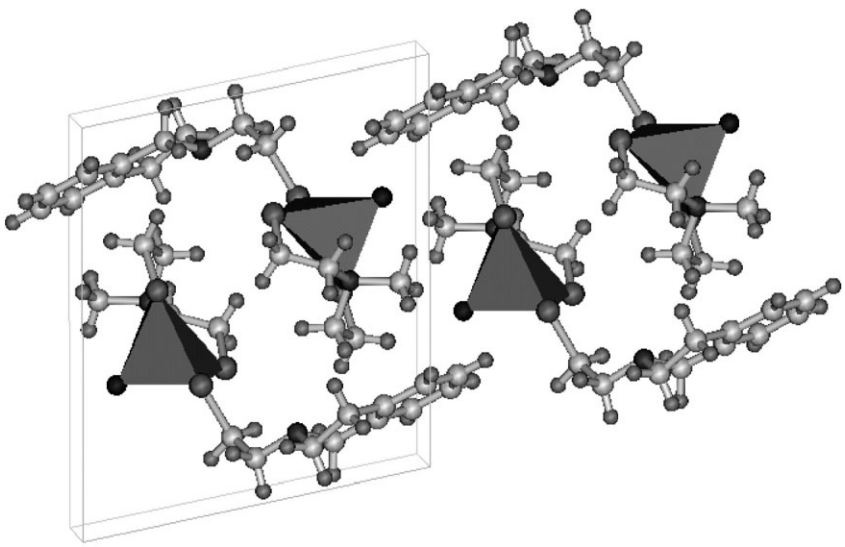


Figure 3. Crystal structure of [2-(*N*-tetrahydroisoquinolyl)ethanethiolato][3-(*N*-methyl)azapentane-1,5-dithiolato]oxorhenium(V) with rhenium polyhedra (**3**).

DOI: 10.1002/aoc

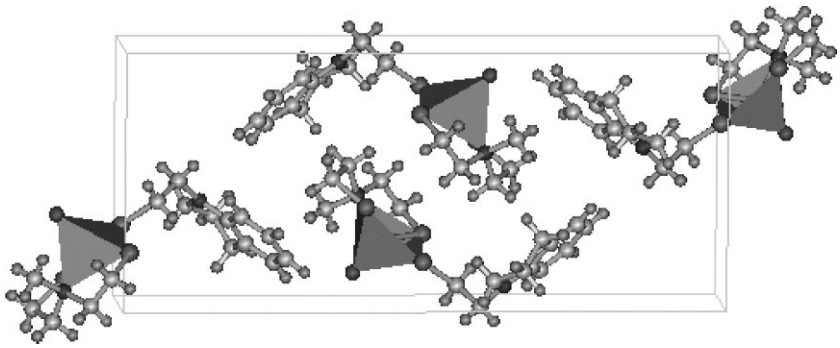


Figure 4. Crystal structure of [2-(*N*-tetrahydroquinolyl)ethanethiolato][3-(*N*-methyl)azapentane-1,5-dithiolato]oxorhenium(V) with rhenium polyhedra (**4**).

polyhedra by elongation of either basal Re–S (tridentate ligand), Re-O, or axial Re-N bonds within polyhedra of tetrahydroquinoline monodentate containing compound **4** in comparison with tetrahydroisoquinoline containing one **3**. All other bond lengths and angles are near to the standard values.

Biological evaluation

Neurotropic properties and cytotoxicity of [2-(*N*-tetrahydroisoquinolyl)ethanethiolato][3-(*N*-methyl)azapentane-1,5-dithiolato]oxorhenium(V) (**3**) and [2-(*N*-tetrahydroquinolyl) ethanethiolato][3-(*N*-methyl)azapentane-1,5-dithiolato]oxorhenium(V) (**4**) were investigated.

The compounds were tested for psychotropic activity *in vivo* on mice under intraperitoneal administration in doses 5 mg kg^{-1}. The action on the CNS was evaluated on indicators of hexenal-induced narcosis, phenamine hyperthermia, phenamine hyperactivity and corazol-induced convulsions. The results of investigation of psychotropic activity are presented in Table 1.

The investigated compounds possess sedative action. With respect to hexenal-induced narcosis [2-(*N*-tetrahydroisoquinolyl)ethanethiolato][3-(*N*-methyl)azapentane-1,5-dithiolato]oxorhenium(V) (**3**) was the more active compound, prolongating the hexenal anaesthesia by 27%. Both compounds are phenamine antagonists and have demonstrated an anticonvulsive activity in the test of corazol-induced convulsions (clonic and tonic). The most active compound in the latter test is [2-(*N*-tetrahydroquinolyl)ethanethiolato]-[3-(*N*-methyl)azapentane-1,5-dithiolato]oxorhenium(V) (**4**), increasing the threshold of corazol convulsions by up to 33% (tonic phase) and 52% (a clonic one).

Thus tetrahydroisoquinoline containing compound **3** is more active in the test of hexenal-induced narcosis, but

Table 1. *In vivo* neurotropic activity of oxorhenium(V) complexes **3** and **4** (on mice)

Test	3	4
Phenamine hyperthermia (%)[a]	98.5 (30 min)	100.5 (30 min)
	97.5 (60 min)	99.8 (60 min)
Phenamine-induced hyperactivity (%)[a]	92 (30 min)	98 (30 min)
	94 (60 min)	92 (60 min)
Hexenal-induced narcosis (%)[a]	127	100
Corazol-induced convulsions (clonic/tonic) (%)[a]	110/139	133/152

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

Table 2. *In vitro* cell cytotoxicity and the ability of intracellular NO generation caused by oxorhenium(V) complexes **3** and **4**

	HT-1080			MG-22A			SHSY5Y			B16			NIH 3T3	
	LC_{50}		NO	LC_{50}		NO	LC_{50}		NO	LC_{50}		NO	LC_{50}	
Test/compound	CV[a]	MTT[b]	CV[c]	CV	MTT	CV	CV	MTT	CV	CV	MTT	CV	NR[d]	LD_{50}, mg/kg
3	4	3	140	8.6	5.5	78	4	5	122	21	15	200	23	597
4	66	52	41	NE	NE	20	NE	NE	8	78	62	18	119	1195

[a] Concentration (μg/*ml*) providing 50% cell killing effect (CV : coloration).
[b] Concentration (μg/*ml*) providing 50% cell killing effect (MTT : coloration).
[c] NO concentration (CV : coloration), determined according to reference.[24]
[d] Concentration (μg/*ml*) providing 50% cell killing effect (NR : coloration).
NE, No cytotoxic effect.

DOI: 10.1002/aoc

tetrahydroquinoline containing compound **4** action is mostly expressed in the test of corazol-induced convulsions.

The cytotoxicity of [2-(*N*-tetrahydroisoquinolyl)ethanethiolato]- (**3**) and [2-(*N*-tetrahydroquinolyl)ethanethiolato][3-(*N*-methyl)azapentane-1,5-dithiolato]oxorhenium(V) (**4**) was tested *in vitro* on four monolayer tumour cell lines: HT-1080 (human fibrosarcoma), MG-22A (mouse hepatoma), SHSY5Y (human neuroblastoma), B16 (mouse melanoma) and normal 3T3 cell lines. The experimental evaluation of cytotoxicity properties is presented in Table 2.

Compounds **3** and **4** have selective cytotoxic effects on different tumour cell lines. [2-(*N*-Tetrahydroquinolyl)ethanethiolato][3-(*N*-methyl)azapentane-1,5-dithiolato]oxorhenium(V) (**4**) is non-toxic for hepatoma MG-22A and neuroblastoma SHSY5Y and possesses low toxic effect on fibrosarcoma HT-1080 and melanoma B16. [2-(*N*-tetrahydroisoquinolyl)ethanethiolato][3-(*N*-methyl)azapentane-1,5-dithiolato]oxorhenium(V) **3** possesses good cytotoxic effects and NO-induction ability. It has high cytotoxic effect on HT-1080 (human fibrosarcoma), SHSY5Y (human neuroblastoma) and MG-22A (mouse hepatoma) cell lines and high NO-generation activity, being most active in the test B16 (mouse melanoma).

Both complexes are moderately cytotoxic compounds against normal cell lines NIH 3T3 and have relatively high LD_{50} values.

CONCLUSION

Oxorhenium(V) complexes of the 1,2,3,4-tetrahydroquinoline and 1,2,3,4-tetrahydroisoquinoline correspondingly containing ligands, namely THiQ$(CH_2)_2$SReO(SNMeS) (**3**) and THQ$(CH_2)_2$SReO(SNMeS) (**4**) have been synthesized and characterized by various physico-chemical and biological methods.

The nature of the heterocycle in monodentate ligand even situated at the distance of two methylene group length has been found to have a significant influence on the molecular conformation.

The investigated compounds are non-toxic compounds concerning normal cell lines, possess moderate sedative action *in vivo* on mice and exhibit good *in vitro* cytotoxic effects on some tumour cell lines. The complex [2-(*N*-tetrahydroisoquinolyl)ethanethiolato][3-(*N*-methyl)azapentane-1,5-dithiolato]oxorhenium(V) (**3**) has been found to have good NO-induction ability and to be highly cytotoxic against HT-1080 (human fibrosarcoma) and SHSY5Y (human neuroblastoma).

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

Acknowledgements

This work was supported by Latvian Council of Sciences (grant no.1792). Additionally we are grateful to Mrs L. Zvejniece for the experiments concerning psychotropic activity tests and to Dr I. Shestakova for cytotoxicity tests.

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