Chapter 4

Synthesis and Catalytic Applications of Derivatives of Tetrazole and Benzisothiazole

This Chapter is divided in two main parts. In the first part, the synthesis of a series of new tetrazolyl and benzisothiazolyl naphthylmethylic ethers and the development of experimental conditions for palladium-catalysed hydrogenolysis of these compounds, using a hydrogen donor or molecular hydrogen, is presented. Structural effects on the reactivity of the heteroaromatic ethers were investigated, and will also be discussed. The second part of this Chapter describes research inspired by the desire to find a route to the synthesis of a variety of novel molecules incorporating the tetrazole and benzisothiazole units, linked by a spacer-group. New benzisothiazole-tetrazolyl derivatives differing by the spacer-group used for linkage of the two heterocycles were produced, and tested as multidentate ligands in coordination reactions with manganese (II) and iron (II) complexes.

Part of the work described in this Chapter is included in the following international scientific journal: *Journal of Molecular Catalysis A: Chemical* **2005**, *242*, 241. Presently, a new publication is under preparation, where the results on the coordination ability of novel benzisothiazole-tetrazolyl derivatives with different transition metal complexes will be included. The contents of these publications are partly reproduced below.

PART I:
Palladium-catalysed Reduction of Heteroaromatic Naphthyl Ethers: Structural Effects on Reactivity

4.1.1. Introduction

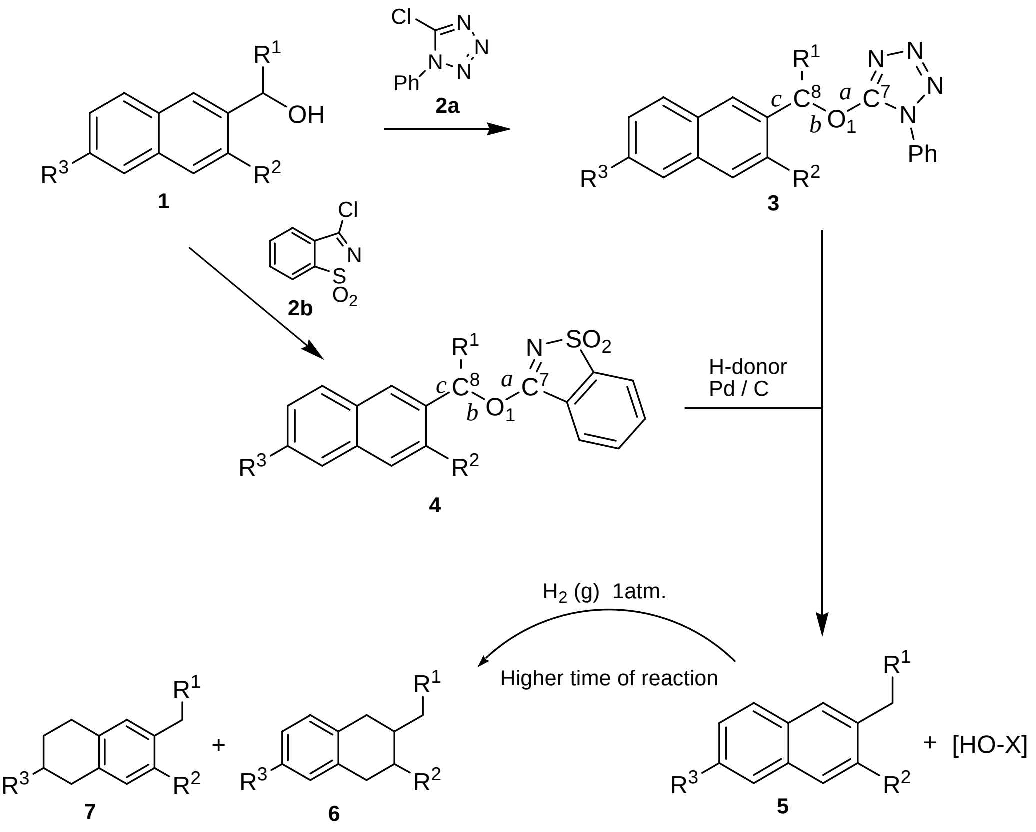
In previous Chapters of this thesis, a range of significant applications of different tetrazolyl and benzisothiazolyl derivatives in crucial fields such as medicide/health, agriculture or industry were already evidenced. Therefore, a description related with the practical applications of this type of compounds is omitted in this part in order to avoid repetitions.

Heterogeneous catalytic transfer hydrogenolysis of aryloxy and allyloxy-tetrazoles and -benzisothiazoles has been used in the hydrogenolysis of phenols and allylic alcohols, and presents a practical and selective synthetic alternative to other methods.[1-3] The hydrogenolysis of the C–OH bond is achieved after conversion of the hydroxyl group into an ether with the electron-withdrawing heteroaromatic tetrazole or benzisothiazole. Derivatization weakens the original C–O bond and increases the nucleophilic susceptibility of the carbon atom. The effect of the heterocyclic part of these ethers on the C–O bond strength has been clarified through X-ray studies.[4-6] The extent of cleavage and selectivity depends on the nature of the catalyst. We have also devised experimental conditions for easy to carry and selective conversion of benzyl alcohols to toluenes in good yields, over Pd/C, *via* transfer hydrogenolysis of the corresponding benzyl tetrazolyl and benzisothiazolyl ethers, using hydrogen donors. High yields, low reaction times and selectivity can be achieved for the reduction, and tetrazolyl and saccharyl ethers exhibit similar reactivity,[7] interpreted on the basis of structural data obtained by X-ray crystallography and molecular orbital calculations. Palladium is normally used, because it is known as a good catalyst for hydrogenolysis and, unlike rhodium or platinum catalysts, does not dearomatise the ring.[8]

Continuing the research program on the synthesis and reactivity of tetrazolyl[9-11] and benzisothiazolyl derivatives, we have now investigated the efficiency of tetrazole and benzisothiazole as leaving groups for heterogeneous catalytic reduction of the π–extended 2-naphthylic methanols, over 10% Pd/C, using a hydrogen donor or molecular hydrogen. Naphthyl derivatives are widely used in organic synthesis, as starting materials, protecting groups or synthetic intermediates.[12-16] A large variety of compounds containing the naphthalene unit show important applications in major areas, mainly in pharmaceutical and biotechnological industries.[17-18]

During this work, a series of 2-naphthylic methanols were derivatized with the heteroaromatic chlorides 5-chloro-1-phenyl-tetrazole **2a**[19] and 3-chloro-1,2-benzisothiazole 1,1-dioxide **2b**, affording good yields of the corresponding tetrazolyl or benzisothiazolyl ethers **3** and **4** (Scheme 1), which are stable crystalline compounds amenable to full characterization. A methodology for selective hydrogenolysis of naphthyl methanols **1**, *via* heteroaromatic ethers **3** and **4**, under mild conditions was developed (see Scheme 1). Toluene, THF, ethyl acetate and dichloromethane were tested as solvents. The effect of substituents on the naphthylic ring and on the benzylic carbon was also investigated. From the results obtained, it is clear that the heteroaromatics tetrazole and benzisothiazole behave differently as derivatizing agents in the hydrogenolysis of naphthyl methanol, in sharp contrast to what was observed with other hydroxylic compounds. The nature of solvent and the introduction of substituents close to the ether linkage were also found to affect reactivity. An interpretation of the reactivity of ethers **3** and **4** is based on their structural and electronic features, obtained through solid-state analysis and theoretically, and on comparative adsorption abilities onto the catalyst surface. Considering the observed structural similarities in ethers **3** and **4** around the reactive centre, in keeping with what had been observed previously with the corresponding benzylic derivatives,[7] the difference in reactivity presently observed cannot be ascribed to ground state structural features.

Scheme 1.



a : R^1=H; R^2=H; R^3=H
b : R^1=H; R^2=OMe; R^3=H
c : R^1=Me; R^2=H; R^3=H
d : R^1=Me; R^2=H; R^3=OMe
e : R^1=Ph; R^2=H; R^3=H

X = 1-phenyl-tetrazole or 1,2-benzisothiazole 1,1-dioxide

4.1.2. Results and Discussion

Ground state structural features are often used for predicting and interpreting reactivity.[20-22] The effect of converting naphthyl methanols in ethers **3** and **4** may be assessed through structural analysis obtained by X-ray crystallography. Crystal structures of 3-(2-naphthylmethoxy)-1,2-benzisothiazole 1,1-dioxide (**4a**, Figure 1) and of 5-(2-naphthylmethoxy)-1-phenyltetrazole (**3a**, Figure 2) were determined (Tables 1 and 2).

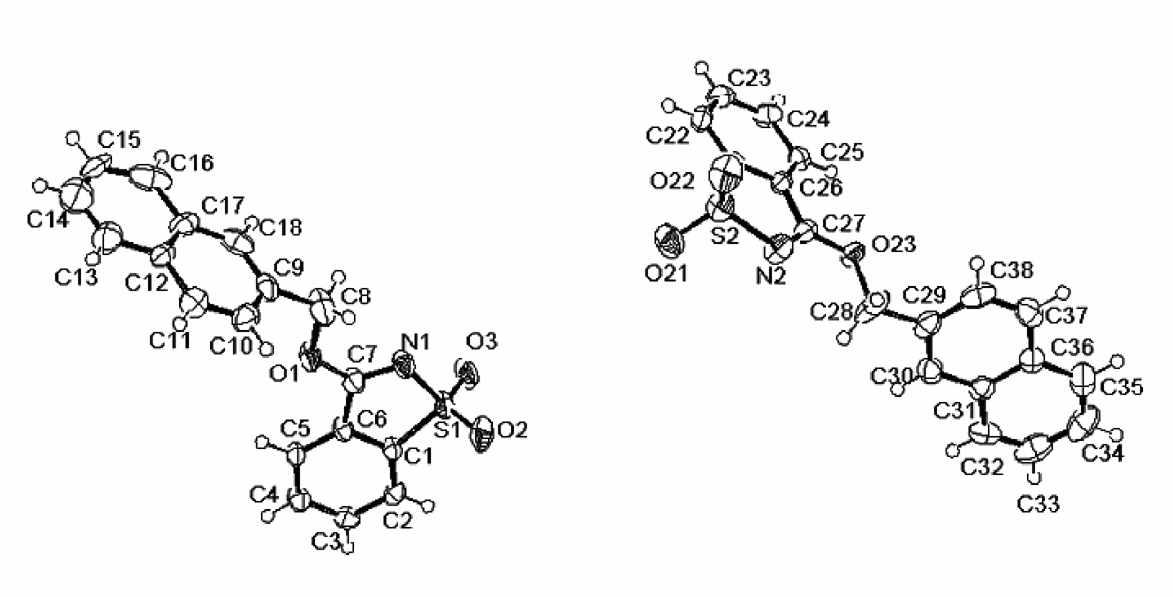


Figure 1. Crystal structure of 3-(2-naphthylmethoxy)-1,2-benzisothiazole 1,1-dioxide **4a**.

Solid-state analysis of compound **4a** shows that there are two molecules in the unit cell, but only one will be discussed because they are identical to within three times the error limits. Crystallographic analysis of **4a** reveals that the geometry of the naphthalene skeleton is very similar to that of naphthalene,[23] the same holding for that of the saccharyl skeleton compared with saccharin.[24] Analysis of the bond lengths around the central ether linkage (sequence of atoms $\mathrm{C}_{(7)}$–$\mathrm{O}_{(1)}$–$\mathrm{C}_{(8)}$–$\mathrm{C}_{(9)}$; Figure 1 and Table 1) shows that the heteroaromatic C–O bond ($\mathrm{C}_{(7)}$–$\mathrm{O}_{(1)}$) has a length of 131.4 pm and the "benzylic" C–O bond length ($\mathrm{C}_{(8)}$–$\mathrm{O}_{(3)}$) is 145.9 pm (mean 131.9 and 147.2 pm respectively for benzyloxy tetrazoles and benzisothiazoles). The bond angle $C_{(7)}$–$O_{(1)}$–$C_{(8)}$ is 116.2°, close to the value required for an sp^2 hybrid. The length for bond $C_{(8)}$–$C_{(9)}$ is 149.5 pm (mean 149.8 for benzylic derivatives) and is unexceptional for a CH_2 connected to an aryl ring.[25] Thus, the bond to be hydrogenolysed, $C_{(8)}$–$O_{(1)}$, is very long, whereas bond $C_{(7)}$–$O_{(1)}$ is very short.

Table 1. Selected structural data for 5-(2-naphthylmethoxy)-1-phenyltetrazole **(3a)** and 3-(2-naphthylmethoxy)-1,2-benzisothiazole 1,1-dioxide **(4a)** (Å, °) (crystallographic data).

(3a)				**(4a)**			
N(3)-N(4)	1.370(2)	N(3)-N(4)-C(1)	122.31(17)	C(1)-C(6)	1.380(4)	C(2)-C(1)-C(6)	122.6(3)
N(3)-N(2)	1.294(2)	C(7)-N(4)-C(1)	130.83(18)	C(1)-S(1)	1.768(3)	C(2)-C(1)-S(1)	130.1(2)
N(4)-C(7)	1.339(3)	N(2)-N(3)-N(4)	106.47(17)	C(6)-C(7)	1.469(4)	C(6)-C(1)-S(1)	107.3(2)
C(7)-N(1)	1.312(3)	N(1)-C(7)-O(1)	128.40(2)	C(7)-N(1)	1.293(4)	N(1)-C(7)-O(3)	123.7(3)
C(7)-O(1)	1.328(3)	N(1)-C(7)-N(4)	111.00(2)	C(7)-O(1)	1.314(4)	N(1)-C(7)-C(6)	118.4(3)
C(8)-O(1)	1.472(3)	O(1)-C(7)-N(4)	120.61(19)	C(8)-O(1)	1.459(4)	O(3)-C(7)-C(6)	117.8(3)
C(8)-C(9)	1.494(3)	O(1)-C(8)-C(9)	106.71(18)	C(8)-C(9)	1.495(5)	O(3)-C(8)-C(9)	107.8(3)
C(9)-C(10)	1.363(3)	C(7)-N(1)-N(2)	104.26(18)	C(9)-C(10)	1.406(5)	C(7)-N(1)-S(1)	108.9(2)
C(10)-C(11)	1.427(4)	C(7)-O(1)-C(8)	113.93(17)	C(9)-C(18)	1.359(5)	C(7)-O(1)-C(8)	116.2(2)
N(1)-N(2)	1.380(2)	N(3)-N(2)-N(1)	111.40(17)	N(1)-S(1)	1.663(3)	N(1)-S(1)-C(1)	95.88(14)

N(2)-N(3)-N(4)-C(1)	-179.8(2)	S(1)-C(1)-C(2)-C(3)	-177.4(3)
N(2)-N(3)-N(4)-C(7)	-0.3(2)	C(2)-C(1)-C(6)-C(7)	178.5(3)
N(3)-N(4)-C(7)-N(1)	-0.3(2)	S(1)-C(1)-C(6)-C(7)	-2.7(3)
N(3)-N(4)-C(7)-O(1)	179.6(2)	C(4)-C(5)-C(6)-C(7)	-179.7(3)
O(1)-C(8)-C(9)-C(10)	68.3(2)	C(1)-C(6)-C(7)-N(1)	1.9(5)
O(1)-C(7)-N(1)-N(2)	-179.4(2)	C(1)-C(6)-C(7)-O(1)	-178.4(3)
N(4)-C(7)-N(1)-N(2)	-0.1(2)	O(1)-C(8)-C(9)-C(10)	80.1(5)
N(1)-C(7)-O(1)-C(8)	3.2(2)	S(1)-N(1)-C(7)-O(1)	-179.6(3)
N(4)-C(7)-O(1)-C(8)	-175.9(2)	C(6)-C(7)-N(1)-S(1)	0.07(16)
C(9)-C(8)-O(1)-C(7)	-175.9(2)	N(1)-C(7)-O(1)-C(8)	-0.9(2)
C(7)-N(1)-N(2)-N(3)	0.0(2)	C(8)-O(1)-C(7)-C(6)	179.3(4)
N(4)-N(3)-N(2)-N(1)	0.2(2)	C(7)-O(1)-C(8)-C(9)	-175.5(3)

Crystallographic analysis of **3a** reveals general features similar to **4a**. Analysis of the bond lengths around the central ether linkage in **3a** (sequence of atoms $C_{(7)}$–$O_{(1)}$–$C_{(8)}$–$C_{(9)}$; Figure 2 and Table 1) shows that the heteroaromatic C–O bond ($C_{(7)}$–$O_{(1)}$) has a length of 132.8 pm and the “benzylic” C–O bond length ($C_{(8)}$–$O_{(1)}$) is 147.2 pm (mean 131.9 and 147.2 pm respectively for benzyloxy-tetrazoles and -benzisothiazoles).[7] The length for bond $C_{(8)}$–$C_{(9)}$ is 149.4 pm (mean 149.8 for benzylic derivatives) and is again unexceptional for a CH_2 connected to an aryl ring.[24] Thus, for the tetrazolyl derivative **3a** the bond to be hydrogenolysed, $C_{(8)}–O_{(1)}$, is also very long, whereas bond $C_{(7)}–O_{(1)}$ is considerably shortened.

Table 2. Experimental data for the X-ray diffraction studies on crystalline 5-(2-naphthylmethoxy)-1-phenyltetrazole (**3a**) and 3-(2-naphthylmethoxy)-1,2-benzisothiazole1,1-dioxide (**4a**).[a]

Formula	$C_{17}H_{12}N_4O$	$C_{18}H_{13}NO_3S$
Formula weight	288.31	323.35
Crystal system	Triclinic	Orthorhombic
Cell parameters at 213 K		
a/Å	6.4787(13)	14.504
b/Å	9.4652(19)	12.884
c/Å	12.824(3)	16.040
α/Degree	98.72(3)°	90°
β/Degree	100.03(3)°	90°
γ/Degree	97.28(3)°	90°
Volume/$Å^3$	755.9(3)	2997.3
Z	2	8
Calculated density/mg m^{-3}	1.267	1.433
Linear absorption coefficient/mm^{-1}	0.083	0.231
F(000)	300	1344
θ range/Degree	2.20 to 24.25	2.11 to 22.99
Reflections collected, unique	4164, 2259 [R(int) = 0.0392]	16226, 4087 [R(int) = 0.0537]
Completeness to	$2\theta = 26.06$, 92.6 %	$\theta = 22.99$, 100.0 %
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data, restraints, parameters	2259 / 0 / 208	4087 / 1 / 415
Goodness of fit on F^2	0.868	0.906
Final R indeces [$I > 2\sigma (I)$]	R1 = 0.0413, wR2 = 0.0907	R1 = 0.0345, wR2 = 0.0688
R indeces	R1 = 0.0783, wR2 = 0.1030	R1 = 0.0463, wR2 = 0.0715
Absolute structure parameter	-0.03(5)	0.08(7)
Largest diff. peak and hole (e. $Å^{-3}$)	0.179 and -0.206	0.330 and -0.257

[a] SHELXL 97: Program for the Refinement of Crystal Structures, University of Göttingen, 1997.

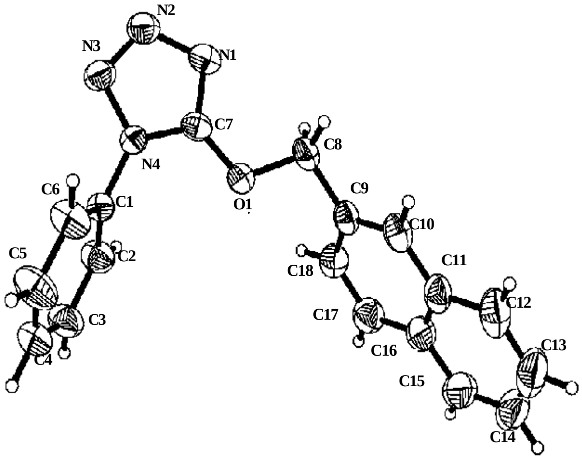


Figure 2. Crystal structure of 5-(2-naphthylmethoxy)-1-phenyltetrazole **3a**.

Table 3. Selected structural data obtained from X-ray crystallographic analysis and molecular orbital calculations of heteroaromatic naphthylmethylic ethers **3** and **4**(**a**-**e**).[a]

Structure	Bond distances/Å			Angles/º $C_{(7)}$-$O_{(1)}$-$C_{(8)}$	Method
	a	*b*	*c*		
3a	1.328	1.472	1.494	113.9	X-ray
3a	1.324	1.468	1.498	115.2	B3LYP/6-311G*
3b	1.345	1.453	1.508	115.1	B3LYP/6-311G*
3c	1.340	1.495	1.513	117.3	B3LYP/6-311G*
3d	1.344	1.503	1.524	116.3	B3LYP/6-311G*
3e	1.324	1.472	1.519	116.0	B3LYP/6-311G*
4a	1.314	1.459	1.495	116.2	X-ray
4a	1.324	1.454	1.506	119.2	B3LYP/6-311G*
4b	1.341	1.486	1.505	119.6	B3LYP/6-311G*
4c	1.343	1.494	1.514	120.2	B3LYP/6-311G*
4d	1.338	1.500	1.519	118.6	B3LYP/6-311G*
4e	1.335	1.493	1.508	119.7	B3LYP/6-311G*

[a] Atom numbering as in Scheme 1.

Theoretical calculations for the naphthylmethylic ethers **3** and **4** were performed with the Gaussian 98 program package as described in the experimental section. Selected results presented in Table 3 are in very good agreement with data obtained by X-ray crystallography for compounds **3a** and **4a**. Also, the values obtained for the bond lengths and angles ($C_{(7)}$–$O_{(1)}$–$C_{(8)}$) throughout the series of naphthyl ethers **3b-e** and **4b-e** (Table 3, bonds *a*, *b*, and *c* in Scheme 1), are very similar to those obtained by X-ray crystallography for derivatives **3a** and **4a**. Thus, all ethers appear to be structurally similar around the central ether linkage.

The favourable delocalisation of the ether oxygen lone pair on the heteroaromatic system by an effective p-conjugation in ethers **3a** and **4a** is the cause for the increase in the "benzylic" bond lengths. From these data, it is clear that structural features around the ether linkage are similar for naphthyl derivatives **3** and **4** and for the benzylic analogues.[7] These results have provided further evidence that both tetrazolyl and saccharyl rings (X in ethers **3** and **4**; Scheme 1) exert similar electron-withdrawing effects, resulting in an activation of the "benzylic" bond towards hydrogenolysis.

Experimental conditions were tuned for reduction of ethers **3** and **4** to naphthyl derivatives **5** over palladium on charcoal (10%), using an hydrogen donor or with molecular hydrogen (Scheme 1 and Table 4). The reaction times reported correspond to the maximum yields obtained for each set of reaction conditions. Sodium hypophosphite is known as an effective reducing agent for catalytic hydrogenolysis and hydrogenation of several functional groups and was also used in the present investigation.[7,26] Toluene, THF, ethyl acetate and dichloromethane were tested as solvents. The effect of substituents on the naphthylic ring and on the benzylic carbon was also investigated.

Table 4. Experimental conditions and yields for the transfer reduction of heteroaromatic naphthylmethylic ethers **3** and **4(a-e)** to give compounds **5**, **6** and **7(a-e)**.

Entry	Ether	Solvent	Temp. (ºC)	Hydrogen source	Reaction time	Yield [a] **5** (%)	Yield [a] **6**/**7** (%)
1	**3a**	THF	Reflux	NaH_2PO_2/H_2O	5 min	99	-
2	**3a**	THF	25ºC	NaH_2PO_2/H_2O	1 hour	83	-
3	**3a**	Toluene	25ºC	NaH_2PO_2/H_2O	1 hour	80	-
4	**3a**	THF	Reflux	H_2 (1atm)	2 hours	92	-
5	**3a**	THF	Reflux	H_2 (1atm)	18 hours	82	8
6	**3a**	THF	25ºC	H_2 (1atm)	2 hours	90	-
7	**3a**	THF	25ºC	H_2 (1atm)	18 hours	2	87
8	**3a**	DCM	Reflux	NaH_2PO_2/H_2O	30 min	96	-
9	**3a**	Ethyl acetate	Reflux	NaH_2PO_2/H_2O	10 min	91	-
10	**3b**	THF	25ºC	NaH_2PO_2/H_2O	5 hours	59	-
11	**3b**	Toluene	25ºC	NaH_2PO_2/H_2O	5 hours	35	-
12	**3c**	THF	25ºC	NaH_2PO_2/H_2O	6 hours	55	-
13	**3c**	Toluene	25ºC	NaH_2PO_2/H_2O	6 hours	47	-
14	**3d**	THF	25ºC	NaH_2PO_2/H_2O	6 hours	61	-
15	**3d**	Toluene	25ºC	NaH_2PO_2/H_2O	6 hours	44	-
16	**3e**	THF	25ºC	NaH_2PO_2/H_2O	5 hours	52	-
17	**3e**	Toluene	25ºC	NaH_2PO_2/H_2O	5 hours	33	-
18	**4a**	THF	Reflux	NaH_2PO_2/H_2O	15 hours	70	-
19	**4a**	THF	25ºC	NaH_2PO_2/H_2O	19 hours	57	-
20	**4a**	Toluene	25º C	NaH_2PO_2/H_2O	24 hours	40	-
21	**4a**	THF	Reflux	H_2 (1atm)	2 hours	84	-
22	**4a**	THF	Reflux	H_2 (1atm)	18 hours	81	3
23	**4a**	THF	25ºC	H_2 (1atm)	2 hours	23	-
24	**4a**	THF	25ºC	H_2 (1atm)	18 hours	5	16
25	**4a**	DCM	Reflux	NaH_2PO_2/H_2O	3 hours	43	-
26	**4a**	Ethyl acetate	Reflux	NaH_2PO_2/H_2O	4 hours	35	-
27	**4b**	THF	25ºC	NaH_2PO_2/H_2O	15 hours	42	-
28	**4b**	Toluene	25ºC	NaH_2PO_2/H_2O	15 hours	20	-
29	**4c**	THF	25ºC	NaH_2PO_2/H_2O	19 hours	46	-
30	**4c**	Toluene	25ºC	NaH_2PO_2/H_2O	19 hours	15	-
31	**4d**	THF	25ºC	NaH_2PO_2/H_2O	19 hours	37	-
32	**4d**	Toluene	25ºC	NaH_2PO_2/H_2O	19 hours	17	-
33	**4e**	THF	25ºC	NaH_2PO_2/H_2O	23 hours	37	-
34	**4e**	Toluene	25ºC	NaH_2PO_2/H_2O	23 hours	31	-

[a] Obtained by gas chromatography with reference to durene as internal standard.

For the unsubstituted 2-naphthyl tetrazolyl ether **3a**, transfer hydrogenolysis is achieved quantitatively after 5 minutes in THF, 10 minutes in ethyl acetate and 30 minutes in DCM, under reflux. At room temperature, hydrogenolysis still occurs selectively in THF but is slower (1 hour; entries 1, 2). Using molecular hydrogen, hydrogenolysis of this ether also occurs selectively, in over 90% yield, in refluxing THF or at room temperature (2 hours; entries 4, 6). On extended reaction times (18 hours), hydrogenation of 2-methyl naphthalene **5a** is observed in high yield, at room temperature, but much less in refluxing THF (87% *versus* 8%; entries 5, 7). Thus, hydrogenolysis of **3a** can be achieved in excellent yields in refluxing THF, with sodium phosphinate or molecular hydrogen. With this source of hydrogen, further reduction of **5a** can be obtained in very high yields by extending the reaction time, at room temperature.

The introduction of a methoxy group on position 3 of the naphthyl ring (compound **3b**) appears to alter substantially the reactivity. Maximum yields of **5b** obtained are 59 and 35%, in THF and toluene respectively (5 hours; entries 10, 11). In order to clarify the reasons for this difference in reactivity, comparative adsorption experiments for compounds **3a** and **3b** were carried out. From these experiments, it was observed that, in the same experimental conditions, the percentage of 5-(2-naphthylmethoxy)-1-phenyltetrazole adsorbed onto the catalyst surface was about 3 times greater than that of 5-((2-naphthylmethoxy)-3-methoxy)-1-phenyltetrazole (8.5 *versus* 2.8%). Thus, the methoxy group appears to hinder adsorption of ether **3b** onto the catalyst surface, resulting in a decrease in yield of hydrogenolysis. This effect is more pronounced in toluene than in THF, because the former competes more for active sites than the later.

The introduction of a methyl group on the benzylic carbon (compound **3c**) also results in a decrease in the yield of hydrogenolysis and an increase in time of reaction. Maxima of 55 and 47 % yields of **5c** are obtained after 6 hours, in THF and toluene respectively (entries 12, 13). If the methyl group attached to the benzylic carbon is replaced by a phenyl (**3e**) the yields of hydrogenolysis are similar to those obtained for **3c** (entries 12, 13 and 16, 17). Comparing results obtained for compound **3c** with those obtained for compound **3d** indicates that the introduction of a methoxy group on the naphthylic ring in position 7 does not appear to further affect the reactivity (entries 12, 13 and 14, 15).

In all equivalent sets of experimental conditions, the hydrogenolysis of benzisothiazolyl ethers **4** is slower and lower yielding than that of the corresponding tetrazolyl ethers. This behaviour contrasts with what was observed for benzyloxy-tetrazoles and -benzisothiazoles,[7] since these exhibited similar reactivity. For the unsubstituted benzisothiazolyl derivative **4a**, hydrogenolysis using sodium hypophosphite is also selective, but much slower and low yielding than for the tetrazolyl derivative **3a.** Maximum yields obtained are 70, 43 and 35%, in refluxing THF, DCM and ethyl acetate respectively (entries 18, 25 and 26). At room temperature, the product yield lowers to 57 and 40%, in THF and toluene respectively (entries 19, 20). For ether **4a**, the best product yield (84%) and lower reaction time (2 hours) are obtained when using molecular hydrogen in refluxing THF. On extended heating to 18 hours, dearomatisation of **5a** occurs in only 3% yield (entries 21, 22). However, at room temperature the maximum product yield decreases to 23%, and on extending the time of reaction dearomatization of **5a** is favoured (entries 23, 24).

It appears from these results that the best set of conditions for selective hydrogenolysis of ether **4a** requires molecular hydrogen in refluxing THF.

As was observed for ethers **3**, the introduction of a methoxy group on the naphthylic ring, adjacent to the ether linkage (**4b**), or substitution at the benzylic carbon by methyl or phenyl (**4c** and **4e**) results in a decrease in reactivity (entries 27, 28; 29, 30 and 33, 34 respectively). In keeping with what had been observed for the corresponding tetrazolyl derivatives, substituents in positions close to the reaction centre hinder the adsorption of the substrate onto the catalyst, inhibiting H-transfer. Again, the effect is more pronounced in toluene, because less active sites are available, for substrate adsorption.

Dearomatization of **5** only occurs when using molecular hydrogen, and is only of some meaning in terms of yields if the system is kept at room temperature. Under reflux, the percentage of conversion of **5** in tetrahydronaphthalene (**6**/**7**) is very low (entries 5, 22). Yields of tetrahydronaphthalene are much higher from ether **3a** than from ether **4a**. For hydrogenation to occur, methylnaphthalene has to be adsorbed onto the catalyst surface. If the by-product tetrazolone is more easily desorbed from the catalyst surface than benzisothiazole, more active sites will be available for methylnaphthalene, leading to a higher rate of hydrogenation.

▪ Conclusions

In keeping with what was observed for benzylic derivatives,[7] THF is a better solvent for hydrogenolysis than toluene. In contrast to what was observed for benzyl alcohols, it is clear from the present investigation that the heteroaromatics tetrazole and benzisothiazole behave differently as derivatizing agents in the hydrogenolysis of naphthyl methanols. For derivatives **3** and **4**, reductive C–O cleavage over Pd/C can be achieved using sodium hypophosphite or molecular hydrogen as source of hydrogen. Under the reaction conditions tested, hydrogenolysis is generally faster and higher yielding for tetrazolyl than for benzisothiazolyl derivatives. For ether **3a**, hydrogenolysis is considerably faster than for benzyloxy-tetrazole, but for ether **4a** it is much slower and lower yielding. When using sodium hypophosphite as source of hydrogen, only hydrogenolysis is observed. However, when using molecular hydrogen, dearomatization of methylnaphthalene is observed after extended periods of time, at room temperature. Again, this behaviour is different from what is known to occur with benzyl derivatives. This difference in reactivity is ascribed to the higher affinity of the flat extended π–surface in 2-methylnaphthalene for the metal catalyst.

4.1.3. Experimental Section

Equipment and experimental conditions. All chemicals were used as purchased from Aldrich. Solvents for extraction and chromatography were of technical grade. When required, the solvents used in reactions were freshly distilled from appropriate drying agents before use. Analytical TLC was performed with Merck silica gel 60 F_{254} plates and visualization was accomplished with UV light. Flash chromatography was carried out using Merck silica gel 60 (230-400 mesh ASTM). Melting points were recorded on a Stuart Scientific SMP3 Melting Point Apparatus and are uncorrected. Proton NMR (300, 400 MHz) spectra were obtained on a Varian Gemini 300 FT or a Bruker AM-400 spectrometers using $CDCl_3$, with TMS as an internal reference (δ = 0.0 ppm). Mass spectra were obtained on a VG 7070E mass spectrometer by electron ionization (EI, 70 eV) or chemical ionization (CI, NH_3). Data are reported in the form m/z (intensity relative to base = 100). Infrared spectra (IR) were obtained on a Mattson 1000 FTIR spectrometer, over KBr. Elemental analyses were performed in an EA1108-Elemental Analyser (Carlo Erba Instruments). Gas chromatography was carried out on a Chrompack CP9001 instrument fitted with a flame ionisation detector and a CP-SIL 5CB capillary column (25 m × 0.35 mm), using 1,2,4,5-tetramethylbenzene (durene) as internal standard for measurement of relative retention times and for quantification of product yields. GC-MS analyses were performed using a Hewlett Packard 5890 Series II gas chromatograph with a 5971 series mass selective detector (E.I. 70 eV). A CP-WAX 58CB capillary column (25 m × 0.25 mm) (Chrompack) was used. The initial temperature of 70°C was maintained during 3 min and then a heating rate of 5°C/min was used until a final temperature of 250°C was reached. Adsorption experiments were determined by analysis of HPLC chromatograms, obtained on an Agilent 1100 Series chromatograph with a 655A-22 UV-detector and Shimadzu SPD-M6A photodiode array. A Merck LiChroCART 125 column (RP-18, 5 μm) was used and the runs were performed using a mixture of water and acetonitrile (40:60) as the eluent.

Preparation of alcohols 1b and 1e.

2-Hydroxymethyl-(3-methoxy)-naphthalene (1b): a solution of $NaBH_4$ (0.96 g; 30.00 mmol) in dry ethanol (25 mL) was added slowly (during 20 min) to a solution of 2-methoxy-1-naphthaldehyde (2,81 g; 15.00 mmol) in dry ethanol (25 mL) under anhydrous conditions. The mixture was stirred at room temperature until TLC analysis (DCM as eluent) indicated the absence of starting material (1 h). DCM (100 mL) was added to the reaction mixture and the whole was washed with brine (3 × 50 mL) and the organic extract was dried over sodium sulphate. The filtrate was evaporated to dryness at room temperature to give a brown solid. Recristallization from toluene gave compound **1b** as pale yellow crystals (2.54 g; 90% yield), mp 110-111°C. IR ν_{max}: 3280 (O–H), 2966, 1625, 1513, 1471, 1251, 1085, 983, 804 cm^{-1}; MS (EI), *m/z* 188 ($[M]^+$, 100).

*Similarly, alcohol **1e** was prepared.*

2-Naphthyl phenylmethanol (1e): obtained from 2-naphthyl-phenyl-ketone (3.00 g; 12.90 mmol). Recristallization of the resulting pale yellow solid from toluene gave compound **1e** as yellow crystals (2.52 g; 84% yield), mp 92-94°C. IR ν_{max}: 3370 (O–H), 3058, 3027, 2871, 1600, 1492, 1452, 1270, 1120, 1022, 813 cm^{-1}; MS (EI), *m/z* 234 ($[M]^+$, 100).

Preparation of 3-chloro-1,2-benzisothiazole 1,1-dioxide (2b): from saccharin (10.20 g; 56.00 mmol) and phosphorus pentachloride (14.00 g; 66.00 mmol) heated at 180°C for 2 h. Colourless needles from trichloromethane (7.00 g; 63% yield), mp 143-145°C. IR $_{\nu max}$: 1724, 1654, 1603 (C=C), 1346 (SO_2), 775 (Ar–H), 692 (C–Cl) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.85 (4H, m, Ar–H); Anal. Calcd for $C_7H_4NO_2SCl$: C, 41.7; H, 2.0; N, 7.0%; Found: C, 41.5; H, 2.0; N, 6.9%; MS (EI), *m/z* 201 ($[M]^+$, 100).

General procedure for the preparation of ethers 3.

The required naphthylmethylic alcohol **1** (7.00 mmol) in dry THF (10 mL) was added to a suspension of sodium hydride (55-60%; 0.50 g; 12.50 mmol) in dry THF (20 mL), at room temperature, under an inert atmosphere. When effervescence had ceased (30 min), a solution of 5-chloro-1-phenyltetrazole (1.50 g; 8.30 mmol) in dry THF (10 mL) was added slowly. The mixture was refluxed with stirring until TLC analysis (toluene/acetone 5:1) indicated the absence of starting material. The crude was extracted with dichloromethane (3 × 30 mL) and the organic layer was dried over anhydrous sodium sulfate. Evaporation of solvent to dryness under reduced pressure and recrystallization from toluene afforded ethers **3**.

5-(2-Naphthylmethoxy)-1-phenyltetrazole (3a): obtained from 2-(hydroxymethyl) naphthalene (1.11 g; 7.00 mmol). The reaction mixture was refluxed for 2h. Recrystallization from toluene gave compound **3a** as colourless crystals (1.70 g; 80% yield), mp 139-140°C. IR ν_{max}: 2964 (C–H, CH_2), 1593 (C=N), 1566, 1099, 1070 (C–O–C), 1024, 764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.80 (2H, s), 7.40-7.60 (6H, m), 7.69-7.72 (2H, d), 7.85-7.91 (3H, m), 7.98 (1H, s) ppm; MS (EI), *m/z* 302 ($[M]^+$, 100).

5-[(2-Naphthyl-(3-methoxy))methoxy]-1-phenyltetrazole (3b): obtained from (2-hydroxymethyl-3-methoxy)-naphthalene (1.32 g; 7.00 mmol). The reaction mixture was refluxed for 6 h. Recrystallization gave compound **3b** as pale yellow crystals (1.54 g; 66% yield), mp 93-95°C. IR ν_{max}: 2966 (C–H, CH_2), 1590 (C=N), 1556, 1504, 1456, 1251, 1095 (C–O–C), 921, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.95 (3H, s), 6.20 (2H, s), 7.20 (1H, s), 7.25-7.45 (4H, m), 7.55-7.58 (1H, t), 7.65-7.67 (2H, d), 7.80-7.83 (1H, d), 7.85-7.95 (2H, m) ppm; Anal. Calcd for $C_{19}H_{16}N_4O_2$: C, 68.66; H, 4.85; N, 16.86%; Found: C, 68.38; H, 4.87; N, 16.81%; MS (EI), *m/z* 332 ($[M + H]^+$, 100).

5-[1-(2-Naphthyl)ethoxy]-1-phenyltetrazole (3c): obtained from 1-(2-naphthyl)- ethanol (1.21 g; 7.00 mmol). The reaction mixture was refluxed for 20 h. Recrystallization from toluene gave compound **3c** as yellow crystals (1.75 g; 79% yield), mp 147-149°C. IR ν_{max}: 2981 (C–H, CH_3), 1594 (C=N), 1554, 1498, 1382, 1351, 1126, 1055 (C–O–C), 901, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.95-1.98 (3H, d), 6.30-6.35 (1H, q), 7.30-7.55 (5H, m), 7.58-7.68, (2H, d), 7.73-8.93 (5H, m) ppm; MS (EI), *m/z* 317 ($[M + H]^+$, 66).

5-{1-[2-Naphthyl-(6-methoxy)]ethoxy}-1-phenyltetrazole (3d): obtained from 1-(2-methoxynaphthalen-6-yl)ethanol (1.42 g; 7.00 mmol). The reaction mixture was refluxed for 20 h. Recrystallization from toluene gave compound **3d** as pale yellow crystals (1.60 g; 66% yield); mp 135-136°C. IR ν_{max} 2967 (C–H, CH_3), 1610 (C=N), 1492, 1378, 1265, 1164, 1027 (C–O–C), 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.00-2.05 (3H, d), 3.95 (3H, s), 5.70-5.75 (1H, q), 7.05-7.25 (3H, m), 7.35-7.38 (2H, t), 7.42-7.45 (1H, d), 7.70-7.73 (2H, d), 7.80 (1H, s), 7.85-7.88 (2H, d) ppm; Anal. Calcd for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.34; N, 16.17%; Found: C, 69.25; H, 5.30; N, 15.93%; MS (CI, NH_3), *m/z* 347 ($[M + NH_4]^+$, 17).

5-(2-Naphthylbenzyloxy)-1-phenyltetrazole (3e): obtained from (naphthalene)-(phenyl)methanol (1.64 g; 7.00 mmol). The mixture was refluxed for 36 h. Recrystallization from toluene gave compound **3e** as pale yellow crystals (1.44 g; 54% yield), mp 125-127°C. IR ν_{max}: 2956, 1621 (C=N), 1565, 1498, 1393, 1354, 1156, 1067 (C–O–C), 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.90 (1H, s), 7.16-7.20 (1H, d), 7.24-7.26 (2H, t), 7.38-7.44 (3H, m), 7.45-7.65 (5H, m), 7.80-7.87 (2H, m), 7.88-8.05 (4H, m) ppm; MS (CI, NH_3), *m/z* 395 ($[M + NH_4]^+$, 10).

General procedure for the preparation of ethers 4.

A mixture of the required naphthylmethylic alcohol **1** (6.00 mmol), 3-chloro-1,2-benzisothiazole 1,1-dioxide (1.21 g; 6.00 mmol) and anhydrous sodium carbonate (3.82 g; 35.90 mmol) in toluene (60 mL), was refluxed with stirring until TLC analysis (DCM as eluent) indicated the absence of starting material. The excess of base was filtered off and then dichloromethane (100 mL) was added to the reaction mixture. The crude was washed with diluted hydrochloric acid (1M, 3 × 50 mL), then with brine

(3 × 50 mL) and finally dried over anhydrous sodium sulphate. Evaporation of solvent to dryness under reduced pressure and recrystallization from a mixture of toluene/dichloromethane (3:2) afforded compounds **4**.

3-(2-Naphthylmethoxy)-1,2-benzisothiazole 1,1-dioxide (4a): obtained from 2-(hydroxymethyl)-naphthalene (0.95 g; 6.00 mmol). The reaction mixture was refluxed for 4 h. Recrystallization gave compound **4a** as colourless crystals (1.10 g; 56% yield), mp 150-152°C. IR ν_{max}: 3029 (C–H, CH_2), 1427, 1311, 1184, 1043, 748, 582 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.10 (2H, s), 7.12 (1H, s), 7.45-7.50 (2H, d), 7.58-7.63 (1H, d), 7.80-7.90 (4H, m), 7.92-7.97 (2H, m), 8.05-8.10 (1H, d) ppm; Anal. Calcd for $C_{18}H_{13}NO_3S$: C, 66.86; H, 4.05; N, 4.49%; Found: C, 66.70; H, 4.17; N, 4.51%; MS (EI), *m/z* 323 ($[M]^+$, 100).

3-[(2-Naphthyl-(3-methoxy))methoxy]-1,2-benzisothiazole 1,1-dioxide (4b): obtained from (2-hydroxymethyl-3-methoxy)-naphthalene (1.13 g; 6.00 mmol). The reaction mixture was refluxed for 4 h. Recrystallization gave compound **4b** as pale yellow crystals (1.16 g; 47% yield), mp 100-102°C. IR ν_{max}: 2952 (C–H, CH_2), 1594, 1450, 1336, 1247, 1182, 1095, 817, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.13 (3H, s), 5.66 (2H, s), 7.32-7.40 (2H, t), 7.52-7.56 (1H, d), 7.72-7.85 (4H, m), 7.85 (1H, s), 8.02-8.05 (1H, d), 8.29-8.32 (1H, d) ppm; MS (CI, NH_3), *m/z* 323 ($[M + NH_4]^+$, 38).

3-[1-(2-Naphthyl)ethoxy]-1,2-benzisothiazole 1,1-dioxide (4c): obtained from 1-(2-naphthyl)ethanol (1.03 g; 6.00 mmol). The reaction mixture was refluxed for 6 h. Recrystallization from toluene/dichloromethane (3:2) gave compound **4c** as pale yellow crystals (1.05 g; 45% yield), mp 75-77°C. IR ν_{max}: 2926 (C–H, CH_2), 1658, 1599, 1450, 1277, 1276, 1116, 819, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.45-1.55 (3H, d), 4.20-4.26 (1H, q), 7.26 (1H, s), 7.45-7.63 (4H, m), 7.75-7.80 (2H, d), 7.83-8.10 (4H, m) ppm; MS (CI, NH_3), *m/z* 354 ($[M + NH_4]^+$, 34).

3-{1-[2-Naphthyl-(6-methoxy)]ethoxy}-1,2-benzisothiazole 1,1-dioxide (4d): obtained from 1-(2-methoxynaphthalen-6-yl)ethanol (1.21 g; 6.00 mmol). The reaction mixture was refluxed for 6 h. Recrystallization gave compound **4d** as pale yellow crystals (1.12 g, 3.05 mmol, 44% yield), mp 104-107°C. IR ν_{max}: 2962, 1606, 1460, 1261, 1162, 1074, 1030, 893, 843, 815 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.55-1.58 (3H, d), 3.91 (3H, s), 5.05-5.11 (1H, q), 7.10-7.12 (1H, d), 7.14 (1H, s), 7.45-7.54 (2H, d), 7.73-7.82 (3H, m), 7.90-8.05 (4H, m) ppm; Anal. Calcd for $C_{20}H_{17}NO_4S$: C, 65.38; H, 4.66; N, 3.81%; Found: C, 65.43; H, 4.65; N, 3.74%; MS (CI, NH_3), *m/z* 384 ($[M + NH_4]^+$, 43).

3-(2-Naphthylbenzyloxy)-1,2-benzisothiazole 1,1-dioxide (4e): obtained from (naphthalene)(phenyl)methanol (1,41 g; 6.00 mmol). The reaction mixture was refluxed for 24 h. Recrystallization gave compound **4e** as pale yellow crystals (0,95 g; 34% yield), mp 89-92°C. IR ν_{max}: 3059, 1334, 1290, 1249, 1184, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.62 (1H, s), 7.41 (1H, d), 7.50-7.62 (5H, m), 7.65-7.67 (1H, d), 7.70-7.82 (5H, m), 7.94-8.12 (4H, m) ppm; MS (CI, NH_3), *m/z* 417 ($[M + NH_4]^+$, 21).

Typical procedure for transfer hydrogenolysis of ethers 3 and 4 using sodium hypophosphite. Palladium-on-charcoal (10%; 0.10 g) was added to a stirred solution of 3-(2-naphthylmethoxy)-1,2-benzisothiazole 1,1-dioxide (**3a**) (0.10 g; 0.31 mmol) and an internal standard (1,2,4,5-tetramethylbenzene (durene); 0.10 g) in THF (25 mL) and the mixture was heated to reflux. Sodium hypophosphite (0.20 g; 1.89 mmol) in distilled water (5 mL) was added, and the progress of the reaction was monitored for formation of 2-methyl-naphthalene by gas chromatography, and for the disappearance of the starting material by thin layer chromatography. Other ethers were treated similarly. Yields for transfer hydrogenolysis of ethers **3** and **4** are presented in Table 4.

Typical procedure for reduction of ethers 3 and 4 using molecular hydrogen. Palladium-on-charcoal (10%; 0.02 g) was added to a stirred solution of 3-(2-naphthylmethoxy)-1,2-benzisothiazole 1,1-dioxide (**3a**) (0.05 g; 0.16 mmol) and an internal standard (1,2,4,5-tetramethylbenzene (durene); 0.07 g) in THF (25 mL). The final mixture was transferred to a pressure reactor and kept under molecular hydrogen (1 atm). The reaction was monitored by gas chromatography. Reduction products were identified by GC/MS and by comparison with standard samples. Other ethers were exposed to similar reaction conditions. Yields for reduction of ethers **3** and **4** are presented in Table 4.

Comparative adsorption experiment. A solution of 5-(2-naphthylmethoxy)-1-phenyltetrazole **3a** (20 mL, 1.0×10^{-4} M in THF) was vigorously stirred with palladium-on-charcoal (15 mg) in a round bottom flask for 10 min. The catalyst was filtered off and the remaining solution analysed by HPLC. The percentage of adsorption was calculated by the decrease in the peak area for the compound. This experiment was repeated with a solution of 5-((2-naphthylmethoxy)-3-methoxy)-1-phenyltetrazole **3b** (20 mL, 1.0×10^{-4} M in THF) and palladium-on-charcoal (15 mg). The percentage of adsorption was 3 times greater for 5-(2-naphthylmethoxy)-1-phenyltetrazole (8.5%) than for 5-((2-naphthylmethoxy)-3-methoxy)-1-phenyltetrazole (2.8%).

Computational methodology. The equilibrium geometries for naphthylmethylic ethers **3-4**(**a-e**) were fully optimized at the DFT level of theory with the standard 6-311G(d) basis set, using the Gaussian 98 program.[27] DFT calculations were carried out with the three-parameter density functional abbreviated as B3LYP, which includes Becke's gradient exchange correction[28] and the Lee, Yang and Parr correlation functional.[29] No symmetry restrictions were imposed on the initial structures. Selected results obtained for compounds **3-4**(**a-e**) are presented in Table 3.

X-ray crystallographic studies. Experimental data for the X-ray diffraction studies of crystalline 5-(2-naphthylmethoxy)-1-phenyltetrazole (**3a**) and 3-(2-naphthylmethoxy)-1,2-benzisothiazole 1,1-dioxide (**4a**) are presented in Tables 1 and 2.

4.1.4. References

1. Boutros, A.; Legros, J.-Y.; Fiaud, J.-C. *Tetrahedron* **2000**, *56*, 2239.
2. Hussey, B.J.; Johnstone, R.A.W.; Entwistle, I.D. *Tetrahedron* **1982**, *38*, 3775.
3. Cristiano, M.L.S.; Johnstone, R.A.W.; Price, P.J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1453.
4. Alves, J.A.C.; Barkley, J.V.; Brigas, A.F.; Johnstone, R.A.W. *J. Chem. Soc., Perkin Trans. 2*, **1997**, 669.
5. Araújo, N.C.P.; Barroca, P.M.M.; Brigas, A.F.; Cristiano, M.L.S.; Jonhstone, R.A.W.; Loureiro, R.M.S.; Pena, P.C.A. *J. Chem. Soc., Perkin 1* **2002**, *9*, 1213.
6. Barkley, J.V.; Cristiano, M.L.S.; Johnstone, R.A.W.; Loureiro, R.M.S. *Acta Cryst., C53* **1997**, 383.
7. Araújo, N.C.P.; Brigas, A.F.; Cristiano, M.L.S.; Frija, L.M.T.; Guimarães, E.M.O.; Loureiro, R.M.S. *J. Mol. Catal. A: Chem.* **2004**, *215*, 113.
8. Rylander, P. *Catalytic Hydrogenation in Organic Synthesis*, Academic Press, New York, 1979.

9. Frija, L.M.T.; Khmelinskii, I.V.; Cristiano, M.L.S. *Tetrahedron Lett.* **2005**, *46*, 6757.
10. Cristiano, M.L.S.; Johnstone, R.A.W. *J. Chem. Soc., Perkin Trans. 2* **1997**, 489.
11. Cristiano, M.L.S.; Johnstone, R.A.W. *J. Chem. Res.* **1997**, 164.
12. Larock, R.C. *in Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, 2nd ed., John Wiley & Sons, 1999.
13. Hayashy, M.; Yamada, K.; Nakayama, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1501.
14. Green, T.W.; Wutts, P.G.M. *in Protecting Groups in Organic Synthesis*, 3rd ed., John Wiley & Sons, New York, 1999.
15. McCombie, S.W. *in Comprehensive Organic Synthesis*, eds. Trost, B.M.; Fleming, I., Pergamon Press, Oxford, (1991) Vol. 8, Chap. 4.2, 811-825.
16. Entwistle, I.D.; Wood, W.W. *in Comprehensive Organic Synthesis*, eds. Trost, B.M.; Fleming, I., Pergamon Press, Oxford, (1991), Vol. 8, Chap. 4.7, 895-981.
17. Matsunaga, N.; Kaku, T.; Ojida, A.; Tanaka, T.; Hara, T.; Yamaoka, M.; Kusakab, M.; Tasakaa, A. *Bioorg. Med. Chem.* **2004**, *12*, 4313.
18. Routier, S.; Peixoto, P.; Mérour, J-Y.; Coudert, G.; Dias, N.; Bailly, C.; Pierré, A.; Léonce, S.; Caignard, D-H. *J. Med. Chem.* **2005**, *48*, 1401.
19. Bugalho, S.C.S.; Lapinski, L.; Cristiano, M.L.S.; Frija, L.M.T.; Fausto, R. *Vib. Spectrosc.* **2002**, *30*, 213.
20. Jones, G.P.; Kirby, A.J. *J. Chem. Soc., Chem. Commun.* **1997**, 288.
21. Kirby, A.J.; Jones, P.G. *J. Amer. Chem. Soc.* **1984**, *106*, 6207.
22. Pauling, L. *The Nature of the Chemical Bond*, Cornell University Press, Ithaca, 1960.
23. Mitchel, A.D.; Cross, L.C. *Tables of Interatomic Distances and Configurations in Molecules and Ions*, M223-M224, London: The Chemical Society, 1958.
24. Dart, J.C.J. *J. Chem. Soc. B* **1968**, 376.
25. Allen, F.H.; Kennard, O.; Watson, D.G.; Brammer, L.; Orpen A.G.; Taylor, R. *J. Chem. Soc. Perkin Trans.2* **1987**, S1-S19.
26. Boyer, S.K.; Bach, J.; McKenna, J.; Jagdmann, E. *J. Org. Chem.* **1985**, *50*, 3408.
27. Frisch, M.; Trucks, G.; Schlegel, H.; Scuseria, G.; Robb, M.; Cheeseman, J.; Zakrzewski, V.; Montgomery, J.; Stratmann, R.; Burant, K.; Dapprich, S.; Millam, J.; Daniels, A.; Kudin, K.; Strain, M.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G.; Ayala, P.; Cui, Q.; Morokuma, K.; Malick, D.; Rabuck, A.; Raghavachari, K.; Foresman, J.; Cioslowski, J.; Ortiz, J.; Baboul, A.; Stefanov, B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R.; Fox, D.; Keith, T.; Al-Laham, M.; Peng, C.; Nanayakkara, A.; Challacombe, M.; Gill, P.; Johnson, B.; Chen, W.; Wong, M.; Andres, J.; Gonzalez, C.; Head-Gordon, M.; Replogle, S.; Pople, J., Gaussian 98, Revision A.9, Gaussian Inc. Pittsburgh, PA 1998.
28. Becke, A.D. *Phys. Rev. B: Condens. Matter* **1988**, *38*, 3098.
29. Lee, C.; Yang, W.; Parr, R.G. *Phys. Rev. B: Condens. Matter* **1988**, *37*, 785.

PART II:
Synthesis of new benzisothiazole-tetrazolyl derivatives for potential application as nitrogen ligands

4.2.1. Introduction

In the last decade, a significant part of the research carried out in the research group of Synthesis and Organic Reactivity at the University of Algarve, has been directed towards the investigation of the structure and reactivity of tetrazole- and benzisothiazole-based compounds, aiming at the development of synthetic methodologies. Special attention was devoted to ethers derived from tetrazole and benzisothiazole, with important synthetic uses as intermediate compounds in the transformation of alcohols.[1,2] Lately, a research program aimed at studying of the photochemistry of tetrazolyl derivatives was undertaken.[3-13] An important part of the results obtained during these years, related to studies of the structure and reactivity of tetrazole- and benzisothiazole-based compounds was described in the previous Chapters of this thesis. Further investigation is now being carried out, aiming at the application of both heteroaromatics in coordination chemistry. Some of the results obtained are described in this part.

In recent years, the design of new bridging ligands for controlling the molecular architectures required for defining specific physical properties in resulting coordination compounds has been a topic for many research groups, in major fields such as supramolecular chemistry[14,15] and molecular magnetism.[16,17]

The 5-substituted tetrazolate group has been scarcely explored in building coordination frameworks, mainly because no effective method for synthesizing

5-substituted tetrazoles in good yields was known. However, in the past few years, new effective synthetic routes to these heterocycles were developed. For instance, Sharpless and Demko have devised a convenient route to 5-substituted tetrazoles by addition of azide to organic nitriles, catalyzed by zinc salts, in water.[18,19] Since then, studies on 5-substituted tetrazolate-bridged coordination frameworks have been slowly emerging.[20-23]

In the same way, the diversity of bonding modes adopted by the saccharin anion and the fortuitous crystalline nature of the resulting complexes are also excellent reasons to scrutinize this system. Over sixty structures of metal saccharinates have been reported up to date. As a polyfunctional ligand, deprotonated saccharin can exist as an ion or it can be included into a complex as a ligand, and it can also exist simultaneously as ionic and coordinated species in the same structure.

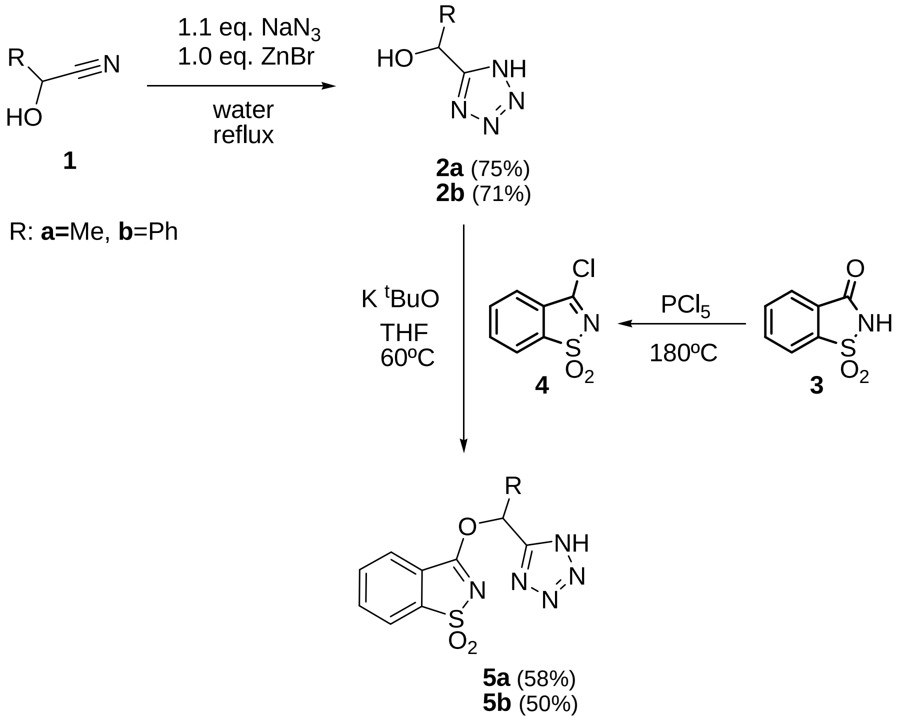
Sustained in our experience concerning the synthesis and reactivity of tetrazolyl and benzisothiazolyl derivatives, and using as advantage the great versatility of these compounds in terms of the diversity of chemical processes in which they can participate, we have formulated the possibility of formation of a variety of novel molecules, incorporating the tetrazole and benzisothiazole units linked by a spacer-group, and their application as nitrogen ligands for coordination with transition metals.

To date, three new benzisothiazole-tetrazolyl derivatives differing on the spacer-group used for linkage of the two heterocycles were produced. Preliminary tests involving these molecules as multidentate ligands in coordination reactions with manganese(II) and iron(II) complexes were performed.

4.2.2. Results and Discussion

The synthetic processes adopted to produce the benzisothiazole-tetrazolyl derivatives are easy-to-carry, and are presented in Schemes 1 and 2. The synthesis of the hydroxyl-tetrazoles **2a** and **2b** was performed in water, following the methodology developed by Sharpless and Demko.[18]

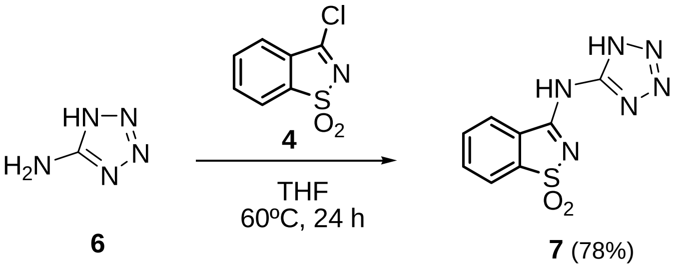
Scheme 1.



Compounds **5a** and **5b** were prepared by reaction of the corresponding hydroxyl-tetrazole (**2a** and **2b**) with *pseudo*-saccharyl chloride, in the presence of base. The reaction yields achieved for the synthesis of these two derivatives are reasonable, compared with the yields obtained for a large range of nucleophilic substitution reactions with *pseudo*-saccharyl chloride, involving different alcohols.[1-2] The nucleophilic substitution is believed to occur through initial addition of the nucleophile to the sp^2 carbon of *pseudo*-saccharyl chloride. The proposed associative mechanism may involve a short-lived tetrahedral zwitterionic intermediate in the rate-determining step, or simply an asynchronous S_N2-type TS from which the halide departs. The reaction is catalysed by base, and sensitive to steric hindrance on the attacking nucleophile.[24]

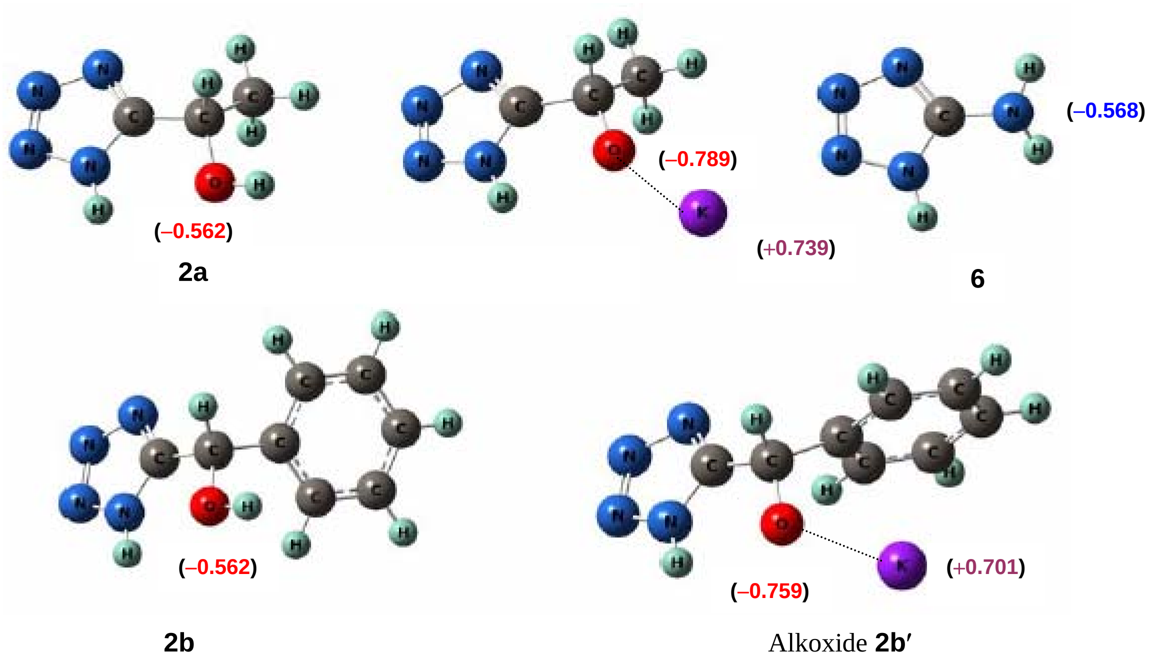
The procedure adopted for the synthesis of derivative **7** involved reaction of 5-aminotetrazole with *pseudo*-saccharyl chloride in dry THF. The required 5-saccharylamino-1*H*-tetrazole **7** was obtained in a good yield (78%).

Scheme 2.



Steric effects in alcohols **2a** and **2b** play a major role, hindering an ideal approximation of the nucleophile to the reactive centre on *pseudo*-saccharyl chloride. In contrast, the amino group of 5-aminotetrazole is much more accessible for nucleophilic attack on the sp^2 carbon of the imine moiety (see Figure 1 for minimized structures and atomic charges of oxygen of alcohols **2a-b** and alkoxides **2a′-b′** and amino nitrogen of 5-aminotetrazole).

In order to obtain some relevant structural data on the synthesized molecules (**5a-b**, and **7**), so as to support the assumption of their applicability as potential nitrogen ligands in reactions with different transition metals, DFT(B3LYP)/6-31G(d,p) calculations were carried out for derivatives **5a** and **7**.



2a

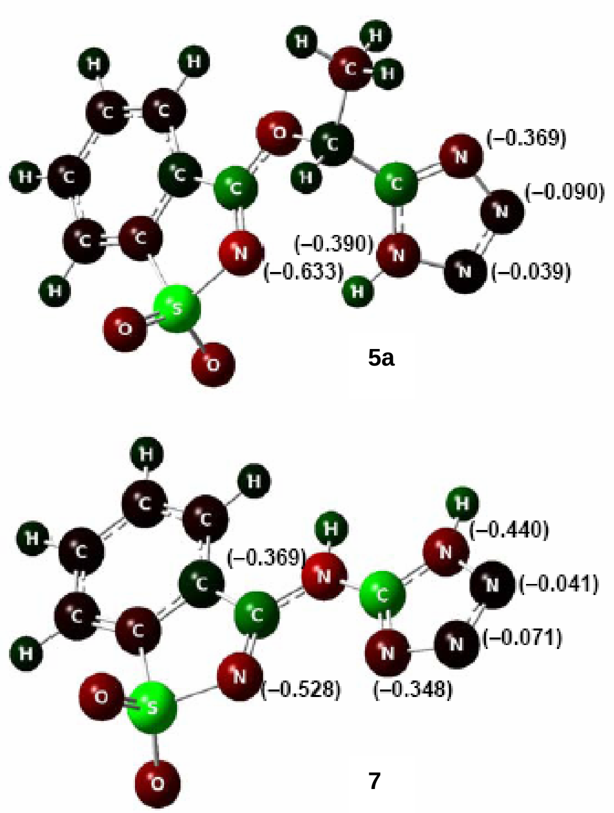
6

2b

Alkoxide **2b′**

Figure 1. B3LYP/6-31G(d,p) optimized structures of tetrazoles **2a-b**, alkoxides **2a′-b′** and 5-aminotetrazole (**6**). Selected Mulliken atomic charges (a.u.) of atoms O and K of tetrazoles **2a-b** and alkoxides **2a′-b′** and amino nitrogen atom of 5-aminotetrazole (**6**) are showed in parenthesis. The bond lengths O–K for alkoxides **2a′-b′** are 2.31 Å and 2.41 Å respectively, calculated at the same level of theory.

Derivatives **5a** and **7** have three and two internal rotational degrees of freedom respectively, which may result in the existence of different conformers. However, a complete conformational study of these derivatives was not carried out during this work. The two conformers selected, presented in Figure 2, are those that possess the best geometry predicted for coordination of both tetrazole and benzisothiazole nitrogen atoms with transition metals.[23] In both optimized structures of derivatives **5a** and **7**, the two heterocyclic systems (tetrazole and benzisothiazole) have approximately planar geometries. However, only for derivative **7** these two moieties share the same plane. The angle between the tetrazole ring and the benzisothiazolyl system in derivative **5a** was predicted by the calculations to be ca. 110°. Certainly, structural differences on the benzisothiazole-tetrazolyl derivatives, bearing an ether or an amino linkage, will play a major role in determining their coordination behaviour with transition metals. However, the rotational freedom of the tetrazolic moiety in relation to the benzisothiazolyl system allows us to believe that compounds **5a-b** and **7** can adopt a conformation with the required orientation of the two ring units for formation of metal complexes. Partial negative charges on nitrogen atoms are also shown in Figure 2. The relatively high values of partial negative charges in two of the nitrogen atoms of the tetrazolyl ring and in the nitrogen atom of benzisothiazolyl system (see Figure 2) suggest that these atoms will have the capacity for charge donation and, therefore, the ability to form coordination bonds with transition metals.



5a

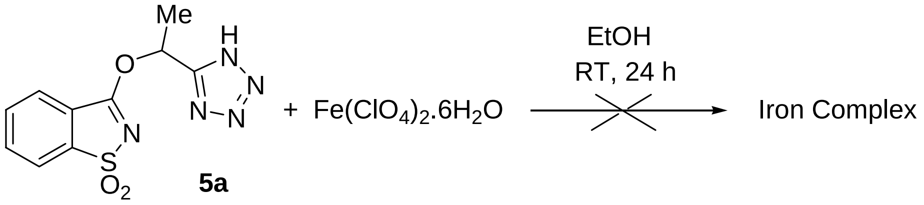
7

Figure 2. B3LYP/6-31G(d,p) optimized structures of derivatives **5a** and **7**. Selected Mulliken atomic charges (a.u.) of nitrogen atoms are showed in parenthesis. Colour atoms by charge with force symmetric charge range (red: atoms with positive partial charge; green: atoms with negative partial charge).

Thus, until now, the synthesis of three new benzisothiazole-tetrazolyl derivatives, **5a-b** and **7**, from *pseudo*-saccharyl chloride **4** and tetrazoles **2a-b** and **5** was achieved successfully. The experimental investigation on the ability of these compounds to bind cations of transition metals is currently ongoing. Preliminary complexation reactions involving derivative **5a** as a potential multidentate nitrogen ligand, with manganese(II) and iron(II) complexes, were already carried out. Results of these reactions will be presented and discussed below.

Accordingly, derivative **5a** was first tested as a potential nitrogen ligand in a reaction with an iron(II) complex. The procedure adopted in the synthesis involved reaction of **5a** with the iron(II) perchlorate complex, $Fe(ClO_4)_2.6H_2O$, (in equimolar amounts) in ethanol. The reaction was processed with vigorous stirring, at room temperature, for a period of 24 h. Evaporation of the solvent at room temperature gave a dark-yellow powder which was analysed and shown not to correspond to any complex associating iron and derivative **5a** (Scheme 3). Mass spectrum of the obtained product confirmed the occurrence of some degradation of **5a** during reaction, inferred by the presence of molecular ion peaks corresponding to isolated saccharin. In fact, in this particular case, degradation of the potential ligand **5a** can explain the failure on the coordination of iron(II) perchlorate complex with the benzisothiazole-tetrazolyl derivative. In any case, the reaction procedure needs to be optimized in order to really understand which are the significant factors for the success of the coordination process. Diverse solvents, as well as different temperatures of reaction will be tested soon for this system.

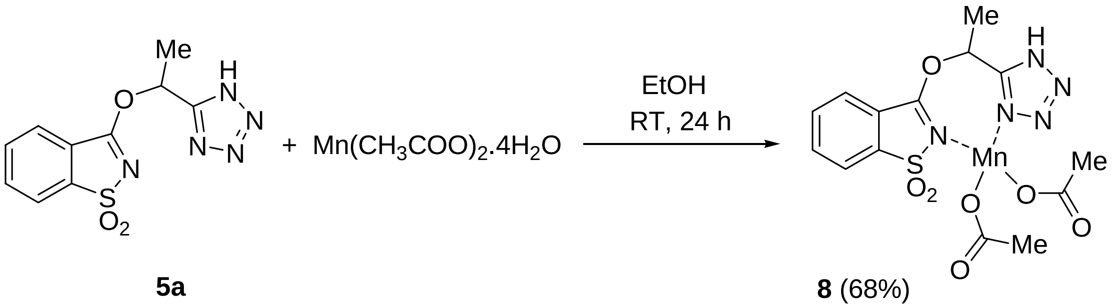
Scheme 3.



Derivative **5a** was then reacted with the manganese(II) acetate tetrahydrate complex, $Mn(CH_3COO)_2.4H_2O$. The procedure adopted in this reaction was identical to that described before for the complex of iron(II) (see Scheme 4). In this case, after solvent evaporation, a pale-yellow powder was obtained. Product analysis attested the presence of a coordination complex between manganese and derivative **5a**. Structure **8**, represented in Scheme 4, was proposed for the final product.

Having in mind that similar conditions were used during the two reactions represented in Schemes 3 and 4, we can infer that, probably, the failure on the reaction involving the iron(II) complex with derivative **5a** can be attributed to the chemical nature of the iron(II) perchlorate complex itself. Perhaps, the presence of the perchlorate ligand, a powerful oxidant, in the reaction medium, can be in the origin of the decomposition of benzisothiazole-tetrazolyl derivative.

Scheme 4.



At this stage, new strategies aiming at the coordination of transition-metals (for instance: Fe, Mn, Ni, Co, Cu, Pd), with the three potential benzisothiazole-tetrazolyl nitrogen ligands synthesized, **5a-b** and **7**, are in progress. A subsequent study of catalytic applications of the resulting complexes (such as compound **8**), was already devised and could be the next step for this research.

4.2.3. Experimental Section

Equipment and experimental conditions. All chemicals were used as purchased from Aldrich. Solvents for extraction and chromatography were of technical grade. When required, the solvents used in reactions were freshly distilled from appropriate drying agents before use. Analytical TLC was performed with Merck silica gel 60 F_{254} plates and visualization was accomplished with UV light. Melting points were recorded on a Stuart Scientific SMP3 Melting Point Apparatus and are uncorrected. Proton NMR (400 MHz) spectra were obtained on a Bruker AM-400 spectrometer using $CDCl_3$ or d6-DMSO, with TMS as an internal reference ($\delta = 0.0$ ppm). Mass spectra were obtained on a VG 7070E mass spectrometer by electron ionization (EI, 70 eV), chemical ionization (CI, NH_3) or electrospray positive ionization (ES+). Data are reported in the form m/z (intensity relative to base = 100). Infrared spectra (IR) were obtained on a Mattson 1000 FTIR spectrometer, over KBr.

3-Chloro-1,2-benzisothiazole 1,1-dioxide (4) was prepared as described in Part I (Experimental Section) of this Chapter.

Preparation of hydroxy-tetrazoles 2a-b.

1-(*1H*-Tetrazol-5-yl)ethanol (2a): to a 250 mL round-bottomed flask was added sodium azide (1.43 g; 22.00 mmol), zinc bromide (4.50 g; 20.00 mmol), 2-hydroxy-propanenitrile (1.45 mL; 20.00 mmol) and water (50 mL). The reaction mixture was refluxed for 20 h with vigorous stirring. HCl (3 N, 30 mL) and ethyl acetate (100 mL) were added, and vigorous stirring was continued until no solid was present and the aqueous layer had a pH of 1. The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 × 50 mL). The combined organic layers were evaporated, 200 mL of 0.25 N NaOH was added to the residue, and the mixture was stirred for 30 min, until the original precipitate was dissolved and a suspension of zinc hydroxide was formed. The suspension was filtered, and the solid washed with 20 mL of 1 N NaOH. 3 N HCl (40 mL) was added to the filtrate with vigorous stirring, causing the separation of the product as an oil. After addition of NaCl, the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to afford the final product as a white solid (1.70 g; 75% yield), mp > 320°C (sodium salt). IR $_{\nu max}$: 3390 (OH), 1696, 1624, 1243, 1123 cm^{-1}; ^1H NMR (400 MHz,$CDCl_3$): δ 7.35 (3H, d), 7.22-7.35 (1H, q), 7.55 (1H, br); MS (CI, NH_3), *m/z* 115 ($[M+H]^+$, 33), *m/z* 132 ($[M+NH_4]^+$, 100); Acc. Mass (CI): Found = 115.1145, Calcd for $C_3H_7N_4O$: 115.1134.

Phenyl(1*H*-tetrazol-5-yl)methanol (2b): Preparation of this compound was described before.[18] Based on the previous reported procedure, the synthesis of **2b** is now described, with some modifications. To a 250 mL round-bottomed flask was added sodium azide (1.43 g; 22.00 mmol), zinc bromide (4.50 g; 20.00 mmol), 2-hydroxy-2-phenylacetonitrile (2.66 g; 20.00 mmol) and water (60 mL). The reaction mixture was refluxed for 18 h with vigorous stirring. Extraction as described above for derivative **2a**, afforded the required product as a colourless solid (2.5 g; 71% yield), mp 176-177°C (lit.[18] 178-179°C). IR $_{\nu max}$: 3445 (OH), 2589, 1699, 1434, 1251, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.15 (1H, s), 6.81 (1H, br), 7.30 (1H, m), 7.35 (2H, m), 7.47 (2H, m); MS (CI, NH_3), *m/z* 178 ($[M+2H]^+$, 91), *m/z* 194 ($[M+NH_4]^+$, 100).

Preparation of ligands 5a-b and 7.

3-[1-(2-*1H*-Tetrazol-5-yl)ethoxy]-1,2-benzisothiazole 1,1-dioxide (5a): a mixture of 1-(*1H*-tetrazol-5-yl)ethanol (0.20 g; 1.75 mmol), 3-chloro-1,2-benzisothiazole 1,1-dioxide (0.35 g; 1.75 mmol) and a suspension of potassium tert-butoxide (0.65 g; 5.25 mmol) in dry THF (50 mL), was stirred at 60°C under a nitrogen atmosphere, until TLC analysis (DCM/toluene (3:1)) indicated the absence of starting material (48 h). The excess of base was filtered off and then ethyl acetate (100 mL) was added to the reaction mixture. The crude was washed with diluted hydrochloric acid (1M, 3 × 50 mL), then with brine (3 × 50 mL) and finally dried over anhydrous sodium sulphate. Evaporation of the solvent under reduced pressure and recrystallization from a mixture of toluene/dichloromethane (3:2) afforded compound **5a** as a pale-yellow solid (0.28 g; 58% yield), mp 210-211°C. IR $_{\nu max}$: 3091, 2974, 1721, 1593, 1463, 1336 (SO_2), 1177 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.39-1.41 (3H, d), 5.26 (1H, d), 7.86-7.90 (1H, d), 7.91-7.95 (2H, m), 8.05-8.08 (1H, d); MS (EI), *m/z* 279 $[M]^+$; Acc. Mass (CI): Found = 280.1089, Calcd for $C_{10}H_{10}N_5O_3S$: 280.1022.

3-[(2-*1H*-Tetrazol-5-yl)benzyloxy]-1,2-benzisothiazole 1,1-dioxide (5b): a mixture of phenyl(*1H*-tetrazol-5-yl)methanol (0.28 g; 1.50 mmol), 3-chloro-1,2-benzisothiazole 1,1-dioxide (0.30 g; 1.50 mmol) and a suspension of potassium tert-butoxide (0.55 g; 4.50 mmol) in dry THF (50 mL), was stirred at 60°C under nitrogen atmosphere, until TLC analysis (DCM / toluene (3:1)) indicated the absence of starting material (72 h). The excess of base was filtered off and then ethyl acetate (100 mL) was added to the reaction mixture. The crude was washed with diluted hydrochloric acid (1M, 3 × 50 mL), then with brine (3 × 50 mL) and finally dried over anhydrous sodium sulphate. Evaporation of the solvent under reduced pressure and recrystallization from a mixture of toluene / dichloromethane / ethyl acetate (1:1:1) afforded compound **5b** as a light yellow solid (0.26 g; 50% yield), mp171-173°C. IR $_{\nu max}$: 3091/2974, 1722/1686, 1453, 1336 (SO_2), 1177, 920, 758, 708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.13(1H, s), 7.46-7.51 (1H, t), 7.55-7.63 (2H, m), 7.89-7.93 (2H, m), 8.05-8.08 (1H, d), 8.08-8.13 (2H, m), 8.67-8.70 (1H, d); MS (EI), *m/z* 342 $[M+H]^+$; Acc. Mass (CI): Found = 342.2019, Calcd for $C_{15}H_{11}N_5O_3S$: 342.2131.

N-(1,1-Dioxo-1,2-benzisothiazol-3-yl)-amine-1H-tetrazole (7): a mixture of anhydrous 5-aminotetrazole (0.22 g; 2.56 mmol) and 3-chloro-1,2-benzisothiazole 1,1-dioxide (0.53 g; 2.56 mmol) in dry THF (20 mL) was stirred at 60°C for 24 h under a nitrogen atmosphere. The solvent was then evaporated under reduced pressure and the remaining solid was washed with acetone, dried under vacuum at room temperature and recrystallised from a mixture of acetone/ethanol (1:1) to give the required product as a white powder (0.5 g; 78% yield), mp 270-271°C. IR $_{\nu max}$: 3221 (NH), 3091, 1608, 1542, 1430, 1323 (SO_2), 1172, 1037, 951 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ 2.51 (1H, s), 7.91-7.96 (2H, m), 8.10-8.13 (1H, m), 8.49-8.54 (1H, m); MS (EI), *m/z* 251 ($[M+H]^+$, 17); Acc. Mass (CI): Found = 251.2010, Calcd for $C_8H_6N_6O_2S$: 251.2028.

Preparation of benzisothiazole-tetrazolyl manganese complex (8): a mixture of ligand **5a** (0.10 g; 0.36 mmol) and manganese(II) acetate tetrahydrate (0.09 g; 0.36 mmol) in ethanol (10 mL) was stirred at room temperature for 24 h. After solvent evaporation under reduced pressure, at room temperature, the required product was obtained as a pale-yellow solid (0.11 g; 68% yield). Acc. Mass (ES+): Found = 475.0053, Calcd for $C_{14}H_{15}N_5O_7SNaMn$: 474.9970.

Computational methodology. Quantum chemical calculations for the derivatives **5a** and **7**, alcohols **2a-b**, alkoxides **2a′-b′** and 5-aminotetrazole (**6**) were performed with the Gaussian 03 program package,[25] at the DFT level of theory, using the 6-31G(d,p) basis set and the three-parameter density functional, abbreviated as B3LYP, which includes Becke's gradient exchange correction[26] and the Lee, Yang, Parr correlation functional.[27] No symmetry restrictions were imposed on the initial structures.

4.2.4. References

1. Frija, L.M.T.; Cristiano, M.L.S.; Guimarães, E.M.O.; Martins, N.C.; Loureiro, R.M.S.; Bikley, J. *J. Mol. Catalysis A: Chem.* **2005**, *242*, 241.
2. Araújo, N.C.P.; Brigas, A.F.; Cristiano, M.L.S.; Frija, L.M.T.; Guimarães, E.M.O.; Loureiro, R.M.S. *J. Mol. Catalysis A: Chem.* **2004**, *215*, 113.
3. Gómez-Zavaglia, A.; Reva, I.D.; Frija, L.; Cristiano, M.L.; Fausto, R. *J. Phys. Chem. A* **2005**, *109*, 7967.
4. Gómez-Zavaglia, A.; Reva, I.D.; Frija, L.; Cristiano, M.L.; Fausto, R. *J. Photochem. Photobiol., A: Chem.* **2006**, *179*, 243.
5. Frija, L.M.T.; Khmelinskii, I.V.; Cristiano, M.L.S. *Tetrahedron Lett.* **2005**, *46*, 6757.
6. Frija, L.M.T.; Khmelinskii, I.V.; Cristiano, M.L.S. *J. Org. Chem.* **2006**, *71*, 3583.
7. Frija, L.M.T.; Gómez-Zavaglia, A.; Reva, I.D.; Cristiano, M.L.S.; Fausto, R. *J. Phys. Chem. A* **2007**, *111*, 2879.
8. Gómez-Zavaglia, A.; Reva, I.D.; Frija, L.; Cristiano, M.L.; Fausto, R. *J. Mol. Struct.* **2006**, *786*, 182.
9. Gómez-Zavaglia, A.; Reva, I.D.; Frija, L.; Cristiano, M.L.; Fausto, R. *J. Photochem. Photobiol. A* **2006**, *180*, 175.
10. Frija, L.M.T.; Reva, I.D.; Gómez-Zavaglia, A.; Cristiano, M.L.S.; Fausto, R. *Photochem. Photobiol. Sci.* **2007**, *6*, 1170.
11. Frija, L.M.T.; Khmelinskii, I.V.; Cristiano, M.L.S *J. Org. Chem.* **2006**, 71, 3583.
12. Frija, L.M.T.; Khmelinskii, I.V.; Serpa, C.; Reva, I.D.; Fausto, R.; Cristiano, M.L.S. *Org. Biomol. Chem.* **2008**, *6*, 1046.
13. Gómez-Zavaglia, A.; Reva, I.D.; Frija, L.; Cristiano, M.L.; Fausto, R. C*hemical Physics Research Journal* **2008**, vol.1, issue 4 .
14. Balzani, V.; Scandola, F. *Supramolecular Photochemistry* Horwood, Chichester, UK, 1991.
15. Lehn, J.-M. *Supramolecular Chemistry* VCH, Weinheim, 1995.
16. Kahn, O. (Ed.) *Magnetism: A Supramolecular Function*; Kluwer Academic Publishers: Dordrecht, the Netherlands, 1996.
17. Kahn, O. *Molecular Magnetism* VCH, New York, 1993.
18. Demko, Z.P.; Sharpless, K. B. *J. Org. Chem.* **2001**, *66*, 7945.

19. Demko, Z.P.; Sharpless, K. B. *Org. Lett.* **2001**, *3*, 4091.
20. Xue, X.; Wang, X.-S.; Wang, L.-Z.; Xiong, R.-G.; Abrahams, B.F.; You, X.-Z.; Xue, Z.-L.; Che, C.-M. *Inorg. Chem.* **2002**, *41*, 6544.
21. Xiong, R.-G.; Xue, X.; Zhao, H.; You, X.-Z.; Abrahams, B.F.; Xue, Z.-L. *Angew. Chem., Int. Ed.* **2002**, *41*, 3800.
22. Wang, L.-Z.; Qu, Z.-R.; Zhao, H.; Wang, X.-S.; Xiong, R.-G.; Xue, Z.-L. *Inorg. Chem.* **2003**, *42*, 3969.
23. Qu, Z.-R.; Zhao, H.; Wang, X.-S.; Li, Y.-H.; Song, Y.-M.; Liu, Y.-J.; Ye, Q.; Xiong, R.-G.; Abrahams, B.F.; Xue, Z.-L.; You, X.-Z. *Inorg. Chem.* **2003**, *42*, 7710.
24. Gago, D.J.P.; Correia, S.M.A.; Gueifão, C.L.F.; Cristiano, M.L.S. *manuscript in preparation for J. Org. Chem.*.
25. Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Montgomery, J.A.; Vreven, T.; Kudin, K.N.; Burant, J.C.; Millam, J.M.; Iyengar, S.S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G.A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J.E.; Hratchian, H.P.; Cross, J.B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R.E.; Yazyev, O.; Austin, A.J.; Cammi, R.; Pomelli, C.; Ochterski, J.W.; Ayala, P.Y.; Morokuma, K.; Voth, G.A.; Salvador, P.; Dannenberg, J.J.; Zakrzewski, V.G.; Dapprich, S.; Daniels, A.D.; Strain, M.C.; Farkas, O.; Malick, D.K.; Rabuck, A.D.; Raghavachari, K.; Foresman, J.B.; Ortiz, J.V.; Cui, Q.; Baboul, A.G.; Clifford, S.; Cioslowski, J.; Stefanov, B.B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R.L.; Fox, D.J.; Keith, T.; Al-Laham, M.A.; Peng, C.Y.; Nanayakkara, A.; Challacombe, M.; Gill, P.M.W.; Johnson, B.; Chen, W.; Wong, M.W.; Gonzalez, C.; Pople, J. A. Gaussian 03, Revision C.02 ed.; Gaussian, Inc.: Wallingford CT, 2004.
26. Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098.
27. Lee, C. T.; Yang, W. T.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.