Synthesis and Characterization of Rhenium(V) Complexes Having 3-(4-*m*-Chlorophenylpiperazin-1-yl)butane-1-thiol as Coligand toward $5HT_{2A}$ Specific Radiopharmaceuticals

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The development of technetium-99m-labeled imaging agent for brain receptors is still a formidable challenge in radiopharmaceutical research.[1] The specific serotonin receptor-binding imaging agent, particularly the 5-HT_2 receptor antagonist, attracts great attention because it is known to be involved in many neurological and psychological diseases including Alzhemier's disease and depression.[2] Many imaging agents suitable for positron emission tomography bearing ^{11}C and ^{18}F as a radiotracer were developed on the basis of known $5HT_{2A}$ receptor antagonist.[3] Imaging agents for single photon emission computed tomography (SPECT) labeled with ^{123}I or ^{125}I were also developed.[4] Preparation of technetium-99m-labeled imaging agent for the $5HT_{2A}$ receptor stems from mimicking the receptor binding compounds as biologically active molecules (BAMs) which bind to the metals to form proper metal complex with other ligands to accommodate all coordination sites. A novel "3+1" mixed ligand rhenium oxo complex can be generated from the combination of tridentate ligand and monodentate BAM.[5]

A few reports describe the synthesis and evaluation of technetium(V) and rhenium(V) complex for $5HT_{2A}$ serotonin receptor binding based on the ketanserin (**1**) and its derivatives.[6] A ligand used for BAM based on ketanserin can be designed on the basis of two structural units *i.e.* quinazoline as part A and phenyl piperidinyl ketone as part B. Either part A or B can be used for BAM while the other part goes as metal binding site. Among two approaches, part B, phenyl piperidinyl ketone site is more favorable for biologically active ligand because it is longer and adjustable. The size and structural similarity to replace part A quinazoline ring is more acceptable and its metal complex with technetium-99m showed better imaging agent. Recently ketanserin surrogate **2** showed very selective and potent binding activity toward $5HT_{2A}$ that may serve as a template to design a new technetium-99m-labelled imaging agent.[7] Triazolopyridin-3-one can be replaced by the relatively small metal complex while the pendent 1-alkyl-4-phenylpyrazine is served as a biologically recognizable site.

In this study, we synthesized and characterized a novel "3+1" mixed ligand rhenium oxo complex with 2-mercapto-ethyl sulfide as a ligand and 3-(4-*m*-chlorophenyl piperazin-1-yl) butane-1-thiol as a biologically active co-ligand.

3-(4-*m*-Chlorophenyl piperazin-1-yl)butane-1-thiol **4** as a BAM was designed on the basis of prototype $5HT_{2A}$ serotonin specific antagonist **2** that was originated from ketanserin **1** as its analog. The synthesis of monodentate thiol ligand **4** was planned to achieve by the reductive coupling reaction between 4-mercaptobutane-2-one and 1-*m*-phenylpiperazine.

At first, ethyl acetoacetate was protected with ethyleneglycol followed by sequential reactions of ester reduction and tosylation to afford 2-[2-methyl-[1,3]-dioxolane-2-yl]ethyl *p*-toluenesulfonate (**5**). Tosyl group was replaced by potassium thiolacetate to introduce sulfur that will be ended as binding site to metal.[8] Removal of acetyl group from thiolacetate **6** by carbonate in MeOH did not give the expected free thiol but its dimerized disulfide was formed **7**. Then diketone **8** was yielded by treatment of hydrochloric acid in acetone. Reductive cleavage of disulfide at this stage was not quite successful. Instead of reductive amination with two mole equivalents of 1-*m*-chlorophenylpiperazine coupling

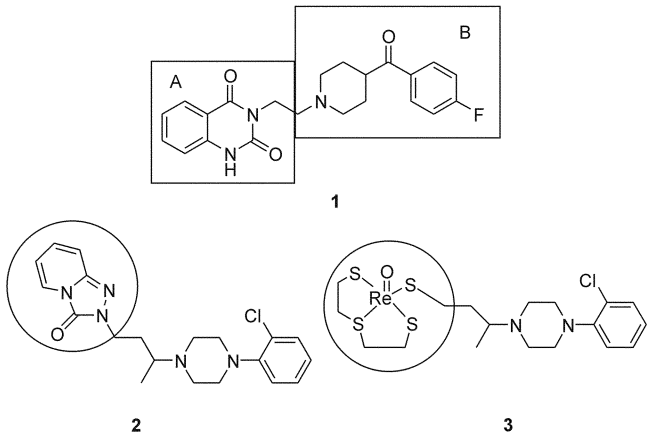

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Figure 1.

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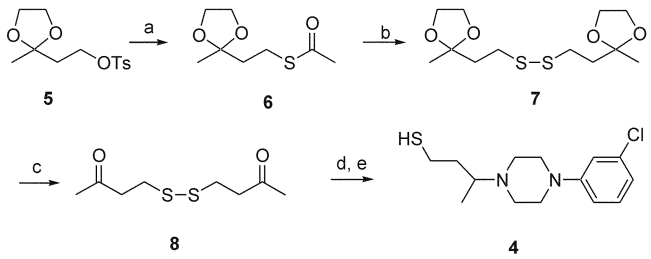

Scheme 1. Reagents and conditions: (a) $KSCOCH_3$, CH_3CN; (b) Na_2CO_3, MeOH; (c) H_3O^+, acetone; (d) 4-*m*-chlorophenylpiperazine, $NaBH(OAc)_3$, AcOH; (e) Zn dust, AcOH and water (4:1, V/V).

reaction between diketone **8** and 1-*m*-chlorophenylpiperazine was conducted with various reducing agents under different conditions. The best result was obtained from the reaction with $NaBH(OAc)_3$ and 3 N NaOH solution in 1,2-dichloroethane at room temperature to afford the coupled dimeric compound **9** in 65% yield.[9] The target molecule, 3-(4-*m*-chlorophenylpiperazin-1-yl)-butane-1-thiol (**3**) was obtained from the coupled dimeric compound **9** by reduction with Zn powder in mixed solvent AcOH and water (4 : 1, V/V) in 47% yield.[10]

Once the ligand **4** was ready, complexation with metal was followed. Mixing $ReO(SCH_2CH_2SCH_2CH_2S)Cl$ (**10**) and monodentate thiol **4** as BAM would form "3+1" mixed ligand rhenium oxo complex with removal of HCl. The best result was obtained by mixing two with 1 : 5.5 ratio to maximize the formation of complex with monodentate thiol in CH_3CN at 0 ºC for 1 h. Once all thiol ligands were used and the pure product **3** was obtained by crystallization from the crude solid product after evaporation of solvent under reduced pressure. This complex was characterized spectroscopically including ^1H NMR and IR. IR spectrum showed a distinctive Re = O peak at 909 cm^{-1}. The similar ^1H NMR peaks corresponding to the ligand 3-(4-*m*-chlorophenyl piperazin-1-yl) butane-1-thiol (**4**) was observed at almost the same region in DMSO-d_6 that corresponds to the free ligand.

Successful preparation of "3+1" mixed ligand rhenium oxo complex prompted us to make ^{99m}Tc complex to evaluate as an imaging agent that is under development.

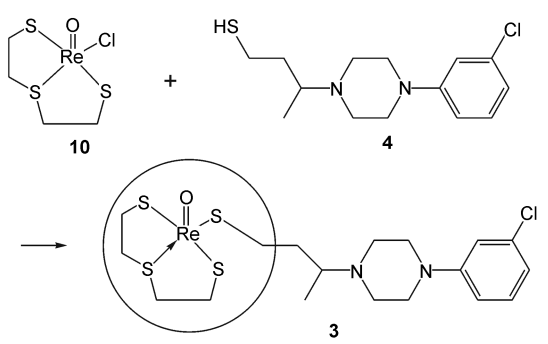

Figure 2. "3+1" Mixed ligand rhenium oxo complex with 2-mercaptoethyl sulfide and 3-(4-*m*-chlorophenyl-piperazin-1-yl)-butane-1-thiol.

Experimental Section

Thiolacetic acid *S*-[2-(2-methyl-[1,3]dioxolan-2-yl) ethyl] Ester (6). Potassium thiolacetate (8.80 g, 77.0 mmol) was added to the solution of 2-[2-methyl-[1,3]-dioxolan-2-yl] ethyl *p*-toluenesulfonate (20.04 g, 70.0 mmol) in CH_3CN. The resultant solution was stirred at 80 ºC for 2 h for the completion. The reaction mixture was cooled down and water (50 mL) was added. The reaction product was extracted with EtOAc (2 × 100 mL). The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to yield yellowish oil that was further purified by chromatography(*n*-Hexane, EtOAc, 1 : 1, V/V) to give 12.04 g of the product in 90% yield. ^1H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.92 (t, J = 8.13 Hz, 2H), 2.31 (s, 3H), 2.93 (t, J = 7.84 Hz, 2H), 3.95 (s, 4H).

2-(2-Methyl-[1,3]dioxolan-2-yl) ethyl disulfide (7). Anhydrous Na_2CO_3 (20.14 g, 190.0 mmol) was added to the solution of thiolacetic acid *S*-[2-(2-methyl-[1,3]dioxolan-2-yl) ethyl] ester (12.04 g, 63.3 mmol) in MeOH and the resultant reaction mixture was stirred at room temperature for 30 h. After the reaction was completed on TLC, water (50 mL) was added. The reaction product was extracted by adding 100 mL of EtOAc twice. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude reaction product was purified by chromatography (*n*-Hexane, EtOAc, 1 : 1, V/V) to give 6.82 g target compound (yellowish oil) in 73% yield. ^1H NMR (300 MHz, $CDCl_3$): δ 1.31 (s, 6H), 2.02 (t, J = 8.1 Hz, 4H), 2.73 (t, J = 8.1 Hz, 4H), 3.92 (s, 8H); ^{13}C NMR (75 MHz): δ 24.0, 30.1, 38.9, 64.6, 109.0; MS (m/z) 294 (M^+).

4-(3-Oxobutyldisulfanyl)butan-2-one (8). Catalytic amount of concentrated hydrochloric acid (0.5 mL) was added into the solution of 2-(2-methyl-[1,3]dioxolan-2-yl) ethyl disulfide (**7**, 6.82 g, 23.2 mmol) in acetone (50 mL). The solution was stirred for 1 h at room temperature for completion. The resultant solution was neutralized with sat. $NaHCO_3$ solution. The reaction product was extracted with EtOAc (2 × 50 mL). The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude reaction product was purified by chromatography (*n*-Hexane, EtOAc, 1 : 1, V/V) to give 4.77 g target compound (yellowish oil) in 99% yield. ^1H NMR (300 MHz, $CDCl_3$): δ 2.14 (s, 6H), 2.82 (s, 8H); ^{13}C NMR (75 MHz): δ 30.5, 31.9, 43.2, 206.0; MS (m/z) 206 (M^+).

3-(4-*m*-Chlorophenylpiperazin-1-yl) butane-1-yl disulfide (9). 4-*m*-Chlorophenylpiperazine (2.86 g, 14.56 mmol), acetic acid (0.83 mL, 14.56 mmol) and $NaBH(OAc)_3$ (4.32 g, 20.38 mmol) were added into the solution of 4-(3-oxo-butyldisulfanyl) butan-2-one (1.50 g, 7.28 mmol) in 1,2-dichloroethane. The resultant solution was stirred for 30 h before quenching the reaction with 1 N NaOH solution to neutralize. The reaction product was extracted with Et_2O (2 × 50 mL). The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated under

reduced pressure. The crude reaction product (brightly yellowish oil) was used for the next reaction without any further purification. Spectral data was obtained from small amount of purified sample by column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (d, J = 6.6 Hz, 6H), 1.63 (m, 2H), 1.92 (m, 2H), 2.56 (m, 2H), 2.65 (m, 2H), 2.76 (m, 8H), 2.94 (m, 2H), 3.22 (m, 8H), 6.79 (t, J = 8.1 Hz, 4H), 6.68 (s, 2H), 7.15 (t, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz): δ 13.2, 21.8, 36.8, 47.3, 48.2, 57.4, 113.8, 115.7, 119.3, 129.8, 134.8, 152.0.

3-(4-*m*-Chlorophenylpiperazin-1-yl)butane-1-thiol (4). Zn dust (1.32 g, 20.15 mmol) was added to 3-(4-*m*-chlorophenyl piperazin-1-yl)butane-1-yl disulfide in mixed solvent AcOH and water (4 : 1, V/V) and the resultant solution was stirred for 2 h at 75 ºC. After the reaction was completed on TLC, 3 N HCl solution (10 mL) was added and the solution was stirred for 0.5 h. The reaction product was extracted with CH_2Cl_2 (50 mL) twice. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude reaction product was loaded on the silica gel column and that was eluted by the mixed solvent (CH_3CN, AcOH, 99.5 : 0.5 V/V) and followed another solvent (*n*-Hexane, EtOAc, 3 : 1, V/V) to give 0.42 g of pure thiol (yellowish oil) **4** in 28% yield for two steps. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 (d, J = 6.6 Hz, 3H), 1.62 (m, 1H), 1.84 (m, 1H), 2.63 (m, 7H), 3.18 (m, 4H), 6.79 (m, 2H), 6.86 (s, 1H), 7.14 (t, J = 5.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 22.4, 38.0, 48.3, 49.4, 57.9, 114.3, 116.2, 119.6, 130.4, 135.3, 152.8; MS (m/z) 284 (M^+).

ReO($SCH_2CH_2SCH_2CH_2S$)Cl (10). A solution of [BnEtN]-[$ReOCl_4$] (500 mg, 0.93 mmol) in 5 mL MeOH and 15 mL CH_2Cl_2 was cooled by ice bath. The 2-mercaptosulfide (0.11 mL, 0.75 mmol) in 40 mL chloroform was added to the solution of rhenium complex very slowly. The resultant solution was stirred for 1 h at 0 ºC. The color of solution was kept blue. The solvent of mixture was removed to obtain a crude powder under reduced pressure. It was treated with chloroform and filtered to obtain a blue powder. The clean blue crystal of needle type was obtained by recrystallization from CH_3CN in 40% (146 mg) yield. m.p. 163-165 ºC. ^{1}H NMR (200 MHz, CD_3CN): δ 2.52-2.58 (m, 2H, CH_2), 3.10-3.27 (m, 2H, CH_2), 4.10-4.24 (m, 4H, CH_2).

ReO($SCH_2CH_2SCH_2CH_2S$)(3-(4-*m*-chlorophenylpiperazin-1-yl)butane-1-thiol (3). A solution of 3-(4-*m*-chlorophenylpiperazin-1-yl)butane-1-thiol (**4**, 120 mg, 423 μmol) in 5 mL CH_3CN was added to ReO($SCH_2CH_2SCH_2CH_2S$)Cl (**10**, 30 mg, 77 μmol) in CH_3CN 10 mL. The color of the mixture changed to deep pink. The resultant solution was stirred for 1 h at 25. The solvent of mixture was removed to yield an oily residue under reduced pressure. Solidification of oily residue was performed with CH_3CN and ethyl ether (v/v) to obtain pink powder and the yield was 30% (14 mg). mp: decomposed >200 ºC, ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.58-1.60 (m, 3H), 2.01-2.09 (m, 2H), 2.15-2.19 (m, 1H), 2.49-2.59 (br, 1H), 3.08-3.17 (m, 4H), 3.47-3.84 (br, 1H), 3.50-3.70 (br, 5H), 3.76-3.81 (m, 1H), 3.90-4.04 (m, 4H), 4.31-4.34 (m, 2H), 6.74-6.76 (m, 1H), 6.86-6.89 (m, 2H), 7.16-7.19 (m, 1H). FT-IR (cm^{-1}, KBr pellet): 909 (Re=O).

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References

1. (a) *Technecium and Rhenium in Nuclear Medicine*; Nicoloni, M.; Bandoli, G.; Mazzi, U.; Editoali, S. G., Eds.; Padova: 1995; Vol. 4. (b) *Topics in Current Chemistry; Technetium and Rhenium*; Yoshihara, K.; Omori, T., Eds.; Springer: 1996; Berlin, p 123. (c) Hom, R. K.; Katzenellenbogen, J. A. *Nucl. Med. Biol.* **1997**, *24*, 483. (d) Jurisson, S. S.; Lydon, J. D. *Chem. Rev.* **1999**, *99*, 2205.
2. Oh, S. J.; Ha, H.-J.; Chi, D. Y.; Lee, H. K. *Curr. Med. Chem.* **2001**, *8*, 999.
3. (a) Tan, P.-Z.; Baldwin, R. M.; Van Dyck, C. H.; Al-Tikriti, M.; Roth, B.; Khan, N.; Charney, D. S.; Innis, R. B. *Nucl. Med. Biol.* **1999**, *26*, 601. (b) Biver, F.; Lotstra, F.; Monclus, M.; Dethy, S.; Damhaut, P.; Wikler, D.; Luxen, A.; Goldman, S. *Nucl. Med. Biol.* **1997**, *24*, 357. (c) Berridge, M.; Comar, D.; Crouzel, C.; Baron, J. C. *J. Labelled Compd. Radiopharm.* **1983**, *20*, 73. (d) Burns, H. D.; Dannals, R. F.; Langstrom, B. *J. Nucl. Med.* **1984**, *25*, 1222. (e) Amokhtari, M.; Andersen, K.; Ibazizene, M.; Dhilly, M.; Dauphin, F.; Barre, L. *Nucl. Med. Biol.* **1998**, *25*, 517. (f) Petit-Taboue, M.-C.; Landeau, B.; Barre, L.; Onfroy, M.-C.; Noel, M.-H.; Baron, J. C. *J. Nucl. Med.* **1999**, *40*, 25.
4. (a) Samnick, S.; Brandau, W.; Nolken, G.; Gerhards, H. J.; Schober, O. *Nucl. Med. Biol.* **1997**, *24*, 295. (b) Baeken, C.; Dhaenen, H.; Flamen, D.; Mertens, J.; Terriere, D.; Chavatte, K.; Boumon, R.; Bossuyt, A. *Eur. J. Nucl. Med.* **1998**, *25*, 1617.
5. (a) Mastrostamatis, S.; Rapadopoulos, M. S.; Pirmettis, I. C.; Paschali, E.; Vatvarigou, A. D.; Stassinipoulous, C. I.; Terzis, A.; Chiotellis, E. *J. Med. Chem.* **1994**, *37*, 3212. (b) Spyriounis, D. M.; Pelecanou, A. T.; Stassinipoulous, C. I.; Raptodopoulos, C. P.; Terzis, A.; Chiotellis, E. *Inorg. Chem.* **1995**, *34*, 1077. (c) Seifert, S.; Pietzsch, H.-J.; Scheunemann, M.; Spies, H.; Syhre, R.; Johannsen, B. *Appl. Radiat. Isot.* **1998**, *49*, 5.
6. (a) Johannsen, B.; Scheunemann, M.; Spies, H.; Brust, P.; Wober, J.; Syhre, R.; Pietzsch, H.-J. *Nucl. Med. Biol.* **1996**, *23*, 429. (b) Pietzsch, H.-J.; Scheunemann, M.; Kretzschmar, M.; Elz, S.; Pertz, H. H.; Seifert, S.; Brust, P.; Spies, H.; Syhre, R.; Johannsen, B. *Nucl. Med. Biol.* **1999**, *26*, 865.
7. Giannangeli, M.; Cazzolla, N.; Luparini, M. R.; Magnani, M.; Mabilia, M.; Picconi, G.; Tomaselli, M.; Baiocchi, L. *J. Med. Chem.* **1999**, *42*, 336.
8. Chapman, J. H.; Owen, L. N. *J. Chem. Soc.* **1950**, 579.
9. (a) Abdel-Magid, A. F.; Maryanoff, C. A.; Caron, K. G. *Tetrahedron Lett.* **1990**, *31*, 5595. (b) Abdel-Magid, A. F.; Caron, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.
10. (a) Kabalka, G. W.; Pace, E. D.; Wadgaonkar, P. P. *Synth. Commun.* **1990**, *20*, 2453. (b) Sera, A.; Yamaguchi, H.; Yamada, H.; Itoh, K. *Synlett* **1990**, 447.