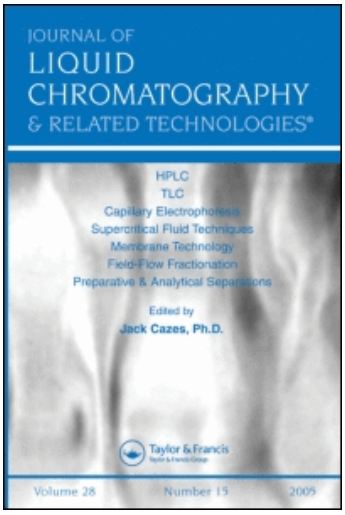

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Lipophilicity Coefficients of [^{11}C]Me-Halo-CGS 27023A Analogs Determined by HPLC

Xiangshu Fei[a]; Qi-Huang Zheng[a]
[a] Department of Radiology, Indiana University School of Medicine, Indianapolis, Indiana, USA

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Lipophilicity Coefficients of [^{11}C]Me-Halo-CGS 27023A Analogs Determined by HPLC

Xiangshu Fei and Qi-Huang Zheng
Department of Radiology, Indiana University School of Medicine, Indianapolis, Indiana, USA

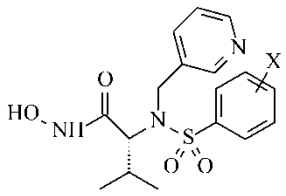
Abstract: New radiolabeled matrix metalloproteinase inhibitors (MMPIs) [^{11}C]Me-Halo-CGS 27023A analogs have been synthesized for evaluation as potential novel positron emission tomography (PET) tumor imaging agents. Their lipophilicity coefficients (log P) were determined by C_{-18} reversed-phase HPLC method. These logP values were compared, and the correlations between lipophilicity and biological activity of selected analogs were made. The results suggest the appropriate level of lipophilic character in this class of compounds as useful imaging agents appears to be in the range of 2.00–2.67.

Keywords: Lipophilicity coefficients, [^{11}C]Me-Halo-CGS 27023A, Positron emission tomography, Tumor imaging agents, HPLC

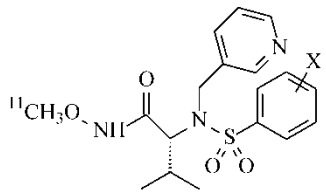
INTRODUCTION

Novel positron carbon-11 labeled matrix metalloproteinase inhibitors (MMPIs) [^{11}C]Me-Halo-CGS 27023A analogs (2-F, **1a**; 4-F, **1b**; 2-Cl, **1c**; 3-Cl, **1d**; 4-Cl, **1e**; 2-Br, **1f**; 3-Br, **1g**; 4-Br, **1h**; 4-I, **1i**), as indicated in Figure 1, have been synthesized for evaluation as potential new radiotracers for biomedical imaging technique positron emission tomography (PET) imaging of MMP enzymes in cancers.[1–6] The ability of [^{11}C]Me-Halo-CGS 27023A analogs to penetrate the blood brain barrier (BBB) in brain

Address correspondence to Qi-Huang Zheng, Department of Radiology, Indiana University School of Medicine, 1345 West 16th Street, L-3 Room 202, Indianapolis, IN 46202, USA. E-mail: qzheng@iupui.edu



2a, X=2-F, 2-F-CGS 27023A
2b, X=4-F, 4-F-CGS 27023A
2c, X=2-Cl, 2-Cl-CGS 27023A
2d, X=3-Cl, 3-Cl-CGS 27023A
2e, X=4-Cl, 4-Cl-CGS 27023A
2f, X=2-Br, 2-Br-CGS 27023A
2g, X=3-Br, 3-Br-CGS 27023A
2h, X=4-Br, 4-Br-CGS 27023A
2i, X=4-I, 4-I-CGS 27023A



1a, X=2-F, [^{11}C]Me-2-F-CGS 27023A
1b, X=4-F, [^{11}C]Me-4-F-CGS 27023A
1c, X=2-Cl, [^{11}C]Me-2-Cl-CGS 27023A
1d, X=3-Cl, [^{11}C]Me-3-Cl-CGS 27023A
1e, X=4-Cl, [^{11}C]Me-4-Cl-CGS 27023A
1f, X=2-Br, [^{11}C]Me-2-Br-CGS 27023A
1g, X=3-Br, [^{11}C]Me-3-Br-CGS 27023A
1h, X=4-Br, [^{11}C]Me-4-Br-CGS 27023A
1i, X=4-I, [^{11}C]Me-4-I-CGS 27023A

Figure 1. Halo-CGS 27023A and [^{11}C]Me-Halo-CGS 27023A.

tumors could be due, at least in part, to their lipophilicity.[7] As part of our efforts to explore novel MMP inhibitor radiotracers, we measured lipophilicity coefficients (log P) of compounds **1a–i** by the C_{-18} reversed-phase HPLC method.[8] The log P of compounds **1a–i** may serve as one of the important parameters to guide selection of new candidates.[9,10] These log P values will be compared, and the correlations between lipophilicity and biological activity of selected analogs will be made.

EXPERIMENTAL

Reagents

MMPIs Halo-CGS 27023A (**2a–i**) and reference standards Me-Halo-CGS 27023A (**1a–i**) for [^{11}C]Me-Halo-CGS 27023A (**1a–i**) were synthesized in our previous works.[1]

Measurement of k′

Based on the literature method,[8] the chromatographic capacity factors (k′) were measured by reversed-phase HPLC using the following conditions: Prodigy 5 μm, 4.6 × 250 mm C_{-18} column; 3 : 1 : 3 CH_3CN/MeOH/20 mM, pH 6.7 $KHPO_4^-$ mobile phase; 1.5 mL/min flow rate; UV (240 nm) and γ-ray (NaI) flow detectors.

$$k' = (RT - RT_0)/RT_0$$

where RT is the compound's retention time and RT_0 is retention of an unretained substance determined by injection of an aqueous solution of potassium nitrite ($RT_0 = 1.84$ min).

Log P Measurements

The method[8] is based on the linear relationship, which has been established between the log k′ values of most compounds and their log P values. Four compounds, benzyl alcohol (log P 1.16), acetophenone (log P 1.66), toluene (log P 2.74), and naphthalene (log P 3.37), were chosen as a "standard" calibration mixture for the evaluation of the log P's of unknowns. log Pexp = partition coefficient calculated from k′ value and calibration curve established by these four compounds. Calibration equation:

$$\log P = 2.222 \log k' + 1.915$$

The experimental capacity factors and literature (standard) partition coefficients of four calibration compounds and standard calibration curve are shown in Table 1 and Figure 2.

Fibril Degradation Assay

In vitro biological assay was performed in our previous work[1] through a fibril degradation assay to determine inhibition effects of the modified compounds (**1a–i**) on enzyme MMP-1 activity in comparison with the parent compound CGS 27023A.[2]

RESULTS AND DISCUSSION

The octanol-water partition coefficient (log P) is an important physical parameter, which has been correlated with the biological activities of a wide variety of organic compounds. As part of our efforts to explore novel

Table 1. Experimental capacity factors and literature (standard) partition coefficients of four calibration compounds

Compound	RT (min)	k′	log k′	log P
Benzyl alcohol	2.60	0.41	−0.384	1.16
Acetophenone	3.43	0.86	−0.063	1.66
Toluene	6.84	2.72	0.434	2.74
Naphthalene	8.92	3.85	0.585	3.37

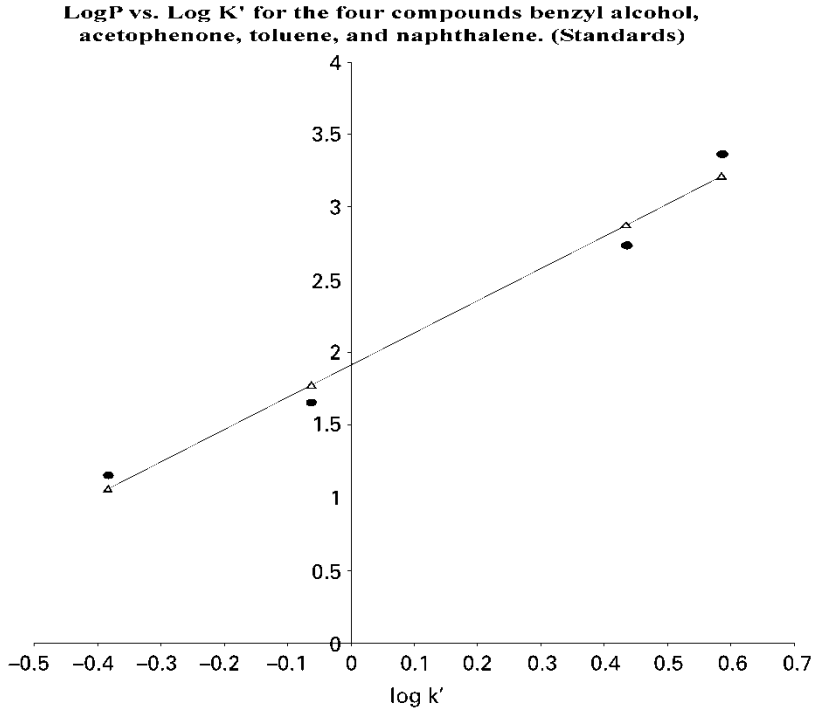


Figure 2. "Standard" calibration curve.

MMPIs as potential radiotracers, we wanted to gain a sense of what the appropriate level of the lipophilic character should be for an *in vivo* MMPI radiotracer. We measured the lipophilicity coefficients log P values of Halo-CGS 27023A (**2a–i**) and Me-Halo-CGS 27023A (**1a–i**) by the C_{-18} reversed-phase HPLC method. The capacity factors log k′ and log P of **2a–i** and **1a–i** are listed in Table 2. The log P values span a range of 1.40–3.34. Me-2-F-CGS 27023A (**1a**) and Me-4-F-CGS 27023A (**1b**) were selected as the lead compounds, since they can be labeled by both positron emitting radionuclides carbon-11 and fluorine-18. The log P values of the lead compounds are 2.67 for **1a** and 2.00 for **1b**, which are more polar than Me-2-Br-CGS 27023A (**1f**, log P 3.34), and more lipophilic than 4-F-CGS 27023A (**2b**, log P 1.40), which is the most polar CGS analog in the group.

In vitro biological data of parent compound CGS 27023A and unlabeled compounds **1a–i** evaluated via a fibril degradation assay, are shown in Figure 3. The nine compounds **1a–i** proved to be potent MMPIs with slight changes in comparison with CGS 27023A.

Table 2. LogP values of MMPIs (**2a–i**; **1a–i**)

Compound	RT (min)	k′	Log k′	Log P
2a	3.27	0.76	−0.12	1.65
2b	2.93	0.59	−0.23	1.40
2c	2.98	0.62	−0.21	1.45
2d	3.51	0.91	−0.041	1.82
2e	3.49	0.90	−0.046	1.81
2f	3.07	0.67	−0.17	1.54
2g	3.69	1.01	0.0043	1.92
2h	3.67	0.99	−0.0044	1.91
2i	5.04	1.74	0.24	2.45
1a	5.84	2.17	0.34	2.67
1b	3.84	1.09	0.037	2.00
1c	3.89	1.11	0.045	2.01
1d	4.82	1.62	0.21	2.38
1e	4.90	1.66	0.22	2.40
1f	9.85	4.35	0.64	3.34
1g	5.10	1.77	0.25	2.47
1h	5.26	1.86	0.27	2.51
1i	8.21	3.46	0.54	3.11

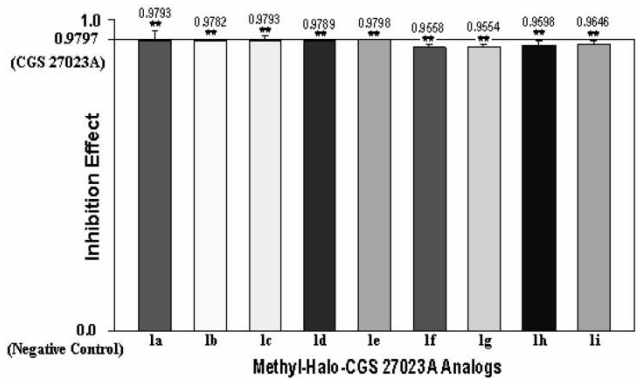


Figure 3. Relative inhibition effects of the modified compounds (**1a–1i**) on MMP-1 activity in comparison with the parent compound CGS 27023A at the concentration of 200 nM determined by a fibril degradation assay. The inhibition levels are normalized with a negative control, which the distilled water was used to replace tested inhibiting substance parent compound CGS 27023A or any modified compound (**1a–1i**). Inhibition Effect = 1 − Relative Activity; Relative Activity = Tested Inhibiting Substance/Negative Control. It was assumed that Relative Activity for Negative Control = 1, then Inhibition Effect of Negative Control = 0. The bar on each column indicates standard deviation in three experiments. The asterisk indicates statistically significant difference ($p < 0.01$) from the negative control.

The correlations between lipophilicity and biological properties of selected lead Me-Halo-CGS 27023A analogs (**1a–b**) showed the appropriate level of lipophilic character in this class of compounds, as useful imaging agents appears to be in the range of 2.00–2.67.

ACKNOWLEDGMENTS

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REFERENCES

1. Zheng, Q.-H.; Fei, X.; Liu, X.; Wang, J-Q.; Sun, H.B.; Mock, B.H.; Stone, K.L.; Martinez, T.D.; Miller, K.D.; Sledge, G.W.; Hutchins, G.D. Synthesis and preliminary biological evaluation of MMP inhibitor radiotracers [^{11}C]methyl-halo-CGS 27023A analogs, new potential PET breast cancer imaging agents. Nucl. Med. Biol. **2002**, *29*, 761–770.
2. Fei, X.; Zheng, Q.-H.; Hutchins, G.D.; Liu, X.; Stone, K.L.; Carlson, K.A.; Mock, B.H.; Winkle, W.L.; Glick-Wilson, B.E.; Miller, K.D.; Fife, R.S.; Sledge, G.W.; Sun, H.B.; Carr, R.E. Synthesis of MMP inhibitor radiotracers [^{11}C]methyl-CGS 27023A and its analogs, new potential PET breast cancer imaging agents. J. Label. Compd. Radiopharm. **2002**, *45*, 449–470.
3. Fei, X.; Zheng, Q.-H.; Liu, X.; Wang, J-Q.; Stone, K.L.; Miller, K.D.; Sledge, G.W.; Hutchins, G.D. Synthesis of MMP inhibitor radiotracer [^{11}C]CGS 25966, a new potential PET tumor imaging agent. J. Label. Compd. Radiopharm. **2003**, *46*, 343–351.
4. Fei, X.; Zheng, Q.-H.; Liu, X.; Wang, J-Q.; Sun, H.B.; Mock, B.H.; Stone, K.L.; Miller, K.D.; Sledge, G.W.; Hutchins, G.D. Synthesis of radiolabeled biphenyl-sulfonamide matrix metalloproteinase inhibitors as new potential PET cancer imaging agents. Bioorg. Med. Chem. Lett. **2003**, *13*, 2217–2222.
5. Zheng, Q.-H.; Fei, X.; DeGrado, T.R.; Wang, J-Q.; Stone, K.L.; Martinez, T.D.; Gay, D.J.; Baity, W.L.; Mock, B.H.; Glick-Wilson, B.E.; Sullivan, M.L.; Miller, K.D.; Sledge, G.W.; Hutchins, G.D. Synthesis, biodistribution, and micro-PET imaging of a potential cancer biomarker carbon-11 labeled MMP inhibitor (2R)-2-[[4-(6-fluorohex-1-ynyl)phenyl]sulfonylamino]-3-methyl-butyric acid [^{11}C]methyl ester. Nucl. Med. Biol. **2003**, *30*, 753–760.
6. Zheng, Q.-H.; Fei, X.; Liu, X.; Wang, J-Q.; Stone, K.L.; Martinez, T.D.; Gay, D.J.; Baity, W.L.; Miller, K.D.; Sledge, G.W.; Hutchins, G.D. Comparative studies of potential cancer biomarkers carbon-11 labeled MMP inhibitors (S)-2-(4′-[^{11}C]methoxybiphenyl-4-sulfonylamino)-3-methylbutyric acid and N-hydroxy-(R)-2-[[(4′-[^{11}C]methoxyphenyl)sulfonyl]benzylamino]-3-methylbutanamide. Nucl. Med. Biol. **2004**, *31*, 77–85.

7. Rubenstein, S.M.; Baichwal, V.; Beckmann, H.; Clark, D.L.; Frankmoelle, W.; Roche, D.; Santha, E.; Schwender, S.; Thoolen, M.; Ye, Q.; Jaen, J.C. Hydrophilic, pro-drug analogues of T138067 are efficacious in controlling tumor growth in vivo and show a decreased ability to cross the blood brain barrier. J. Med. Chem. **2001**, *44*, 3599–3605.
8. Haky, J.E.; Young, A.M. Evaluation of a simple HPLC correlation method for the estimation of the octanol–water partition coefficients of organic compounds. J. Liquid Chromatogr. **1984**, *7*, 675–689.
9. Mullican, M.D.; Wilson, M.W.; Conner, D.T.; Kostlan, C.R.; Schrier, D.J.; Dyer, R.D. Design of 5-(3,5-di-tert-butyl-4-hydroxyphenyl)-1,3,4-thiadiazoles, -1,3,4-oxadiazoles, and -1,2,4-triazoles as orally-active, nonulcerogenic anti-inflammatory agents. J. Med. Chem. **1993**, *36*, 1090–1099.
10. Moret, E.E.; de Boer, M.; Hilbers, H.W.; Tollenaere, J.P.; Janssen, L.H.; Holthuis, J.J.; Driebergen, R.J.; Verboom, W.; Reinhoudt, D.N. In vivo activity and hydrophobicity of cytostatic aziridinyl quinones. J. Med. Chem. **1996**, *39*, 720–728.

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