J Mol Model (2007) 13:229–232
DOI 10.1007/s00894-006-0143-x

ORIGINAL PAPER

# Theoretical studies of the reduction reaction of the anti-tumor drug FR900482

**Anne-Marie Sapse · Duli C. Jain**

Received: 31 March 2006 / Accepted: 28 July 2006 / Published online: 23 September 2006


**Abstract** A number of analogs of the anti-tumor drug FR900482 have been investigated with quantum chemical calculations, at the HF/6-31G(d,p) and B3LYP levels from the point of view of their energy, optimum geometry and the energetics of the reduction reaction. It was found that the parent molecule is the most prone to reduction, followed closely by fluorine-containing analogs.

**Keywords** FR900482 · Reduction · Hartree–Fock · B3LYP (Density functional theory)

## Introduction

The anti-tumor antibiotic FR900482, obtained from the fermentation of *Streptomyces sandaensis* No. 6897 at Fujisawa Pharmaceutical Co.Ltd., Japan, belongs to a very important class of alkylating agents, the bioreductive alkylating agents, which become selectively activated when delivered to cancerous tissues [1].

**Electronic supplementary material** Supplementary material is available in the online version of this article at http://dx.doi.org/10.1007/s00894-006-0143-x and is accessible for authorized users.

A.-M. Sapse (✉)
John Jay College and Graduate Center,
City University of New York,
445 W 59th St,
New York, NY 10019, USA
e-mail: acransg6@aol.com

D. C. Jain
Department of Natural Sciences, York College of CUNY,
94-20 Guy R. Brewer Boulevard,
Jamaica, NY 11451, USA

FR900482 is close in structure and activity to the alkylating bioreductive drug mitomycin C [2, 3], which is at present clinically employed. It is now established that mitomycin C is reductively activated both in vivo and in vitro, leading to the formation of a highly reactive species called mitosene, which cross-links DNA preferentially at 5′–3′ sites [4]. During the reductive pathway, the quinone moiety is reduced to a semi-quinone radical anion, which can transfer an electron to molecular oxygen, thus producing a superoxide radical anion, leading to reactions causing non-selective tissue damage [5], such as cardiotoxicity.

Some studies [6] have shown FR900482 to be three times as potent as mitomycin C and it also exhibits lower toxicity. The later is thought to be related to the absence of the quinone moiety and to the presence of the hydroxylamine hemi-ketal [1], as such, excluding the mechanism that would lead to the formation of superoxide radical anions.

The FR900 class of agents have been found to exhibit minor-groove specificity. This way, the minor groove binding HMG I/Y proteins might represent a target for the drug [7]. This might be part of the anti-tumor activity of FR900482, since artificial overexpression of HMG I/Y leads to cancerous changes in cells [7].

In a previous study, we investigated the effect of changing the aldehyde group on the aromatic nucleus of the drug to a number of other groups on the energy of oxidation of the hemi-acetal to quinone. It was found that the $NH_2$ group-containing drug is the most prone and the F or $CF_3$ containing drugs are the least prone to oxidation [8].

This work applies quantum chemical methods to the study of the effect of these substituents on the reducing reaction of the N–O bond, leading to the formation of the compound shown in Fig. 1b and its analogs.

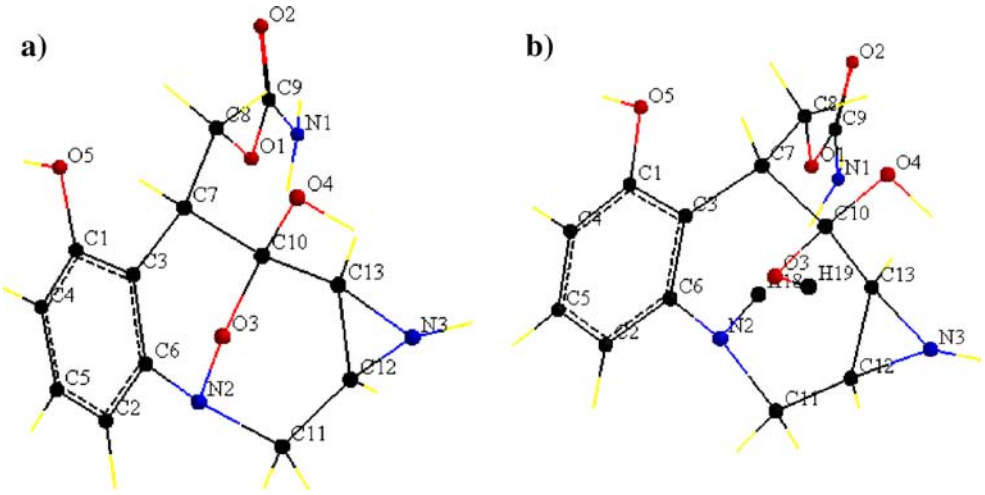


**Fig. 1** **a** FR900482 featuring the oxygen bridge **b** Reduced FR900482, with the oxygen bridge open into an OH group and a hydrogen atom attached to the nitrogen

## Methods and results

Several analogs of FR900482 have been investigated. Figure 1 shows the numbering of the atoms for the drug featuring no substituent at C5. The same numbering applies to the other compounds, except for the substituents. Figure 2 shows the substituents for the various compounds investigated. Compound 2 is the parent molecule, with an aldehyde group attached to C5.

Energies and optimum geometries were obtained. The calculations were performed at the Hartree–Fock level, with the 6-31G(d,p) basis set, using the Titan program [9]. In addition, DFT (density functional theory) calculations were performed with the B3LYP method.

The computational effort for both types of calculations, as implemented by the Titan program, is practically the same. The advantage of using the B3LYP method is the fact that it takes into account the correlation energy, making it more appropriate for situations when the correlation energy might play a role. In these calculations, the N–O bond is broken, so the correlation energy might affect the results.

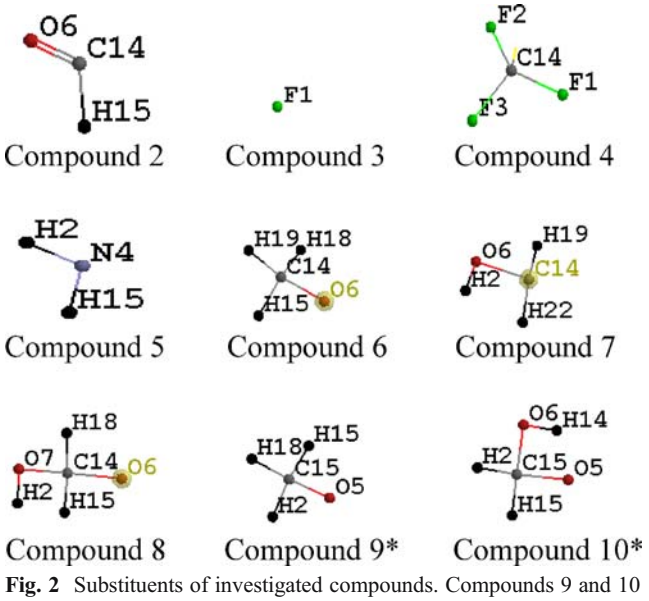


**Fig. 2** Substituents of investigated compounds. Compounds 9 and 10 have OCH3 and OCH2OH, respectively, as substituents at C1, and CF3 as substituent at C5

Two kind of compounds were considered:

- compounds featuring the oxygen bridge, as shown in Fig. 1a.
- reduced compounds, with the oxygen bridge open into an OH group and a hydrogen atom attached to the nitrogen, as shown in Fig. 1b.

The optimized parameters of interest of both categories of compounds, obtained at both levels, are given as supplementary material.

Table 1 shows the optimized energies of all the compounds at both HF/6-31G(d,p) and at B3LYP levels.

Table 2 shows the solvation energies of the compounds, as obtained by semiempirical methods [10].

Table 3 shows the energy of the reaction:

$$\text{Oxidized compound (figure a)} + H_2 = \text{Reduced compound (figure b)}.$$

## Discussion

Examining the supplementary material one notices that at HF/6-31G(d,p) calculational level, the changes for the bond lengths are not significant upon changing the substituents at C5 or at C1. However, there are changes from the oxidized forms (a) to the reduced forms (b). For instance, the C6N2 bond length increases by 0.004 to 0.008 A. The O3C10 bond length decreases by 0.03 A from a to b. These changes are similar for the B3LYP calculations, but the bond lengths, in general, are found to be longer. No significant changes are

**Table 1** Energies (au) of the compounds

| Compound | Energy | |
|---|---|---|
| | HF/6-31G(d,p) | B3LYP |
| 1a | −1038.63986 | −1044.72970 |
| 1b | −1039.84439 | −1045.97148 |
| 2a | −1151.36967 | −1158.05501 |
| 2b | −1152.57559 | −1159.29781 |
| 3a | −1137.49005 | −1143.36109 |
| 3b | −1138.69464 | −1145.20316 |
| 4a | −1374.25993 | −1381.76620 |
| 4b | −1375.46541 | −1383.00846 |
| 5a | −1093.67670 | −1100.08846 |
| 5b | −1094.87962 | −1101.32819 |
| 6a | −1152.52372 | −1159.25393 |
| 6b | −1153.72778 | −1160.49558 |
| 7a | −1152.53275 | −1159.25913 |
| 7b | −1153.73532 | −1160.49828 |
| 8a | −1227.39045 | −1234.47615 |
| 8b | −1228.59482 | −1235.71812 |
| 9a | −1413.28334 | −1421.07157 |
| 9b | −1414.48802 | −1422.31289 |
| 10a | −1488.15287 | −1496.29869 |
| 10b | −1489.35002 | −1497.52988 |

observed in the bond angles upon change of substituent. Upon reduction, some angles change by a few degrees in either direction. The C2C6N2C11 dihedral angle increases upon reduction by approximately 30°.

**Table 2** Solvation energies (kcal $mol^{-1}$) for the HF/6-31G(d,p) and the B3LYP optimized structures

| Compound | Energy | |
|---|---|---|
| | HF/6-31G(d,p) | B3LYP |
| 1a | −17.30 | −19.24 |
| 1b | −16.69 | −18.77 |
| 2a | −18.62 | −20.94 |
| 2b | −18.22 | −20.34 |
| 3a | −15.86 | −17.71 |
| 3b | −15.89 | −17.90 |
| 4a | −14.78 | −16.67 |
| 4b | −14.79 | −16.93 |
| 5a | −20.95 | −22.88 |
| 5b | −20.98 | −23.23 |
| 6a | −17.91 | −20.17 |
| 6b | −17.97 | −20.20 |
| 7a | −20.43 | −22.80 |
| 7b | −20.36 | −22.80 |
| 8a | −19.70 | −22.51 |
| 8b | −19.67 | −22.41 |
| 9a | −11.77 | −12.79 |
| 9b | −12.10 | −13.70 |
| 10a | −16.86 | −19.28 |
| 10b | −14.46 | −17.49 |

Examining Table 3, it can be seen that the most favorable reduction occurs for the drug FR900482 itself. Indeed, a highly negative energy for the reduction reaction shows the compound to be more prone to reduction. Out of the investigated analogs, the most prone to reduction is 4a, which features a $CF_3$ group replacing the aldehyde group at C5. Another analog featuring a favorable reduction is 9a, which features both $CF_3$ at C5 and the OH at C1 replaced by a $OCH_3$ group. These results are obtained at HF/6-31G (d,p) level. At the B3LYP level, in addition to 4a, the analogs 3a, featuring an F at C5 and 8a featuring a $OCH_2OH$ group at C5 also present a favorable energy for the reduction reaction. Table 2 shows that the solvation energies, as calculated for the geometries obtained at both calculational levels, are higher for the reduced entities in compounds 3, 4 and 9. Since the parent drug exhibits a more favorable energy of reduction than compounds 9a and 3a by approximately 0.8 kcal $mol^{-1}$, and for compound 4a of 0.3 kcal $mol^{-1}$ and the difference in solvation energy is more favorable for the above mentioned analogs by few tenths of a kcal $mol^{-1}$ at HF/6-31G(d,p) level, with similar

**Table 3** The energies (kcal $mol^{-1}$) of the reduction reactions of the investigated compounds

| Compound | Energy[a] | |
|---|---|---|
| | $\Delta E^b$ | ΔE+Solv. |
| | HF/6-31G(d,p) | |
| 1 | −45.933 | 0.8722 | 1.4822 |
| 2 | −46.805225 | 0 | 0.4 |
| 3 | −45.97065 | 0.8346 | 0.8946 |
| 4 | −46.529125 | 0.2761 | 0.2661 |
| 5 | −45.2553 | 1.5499 | 1.5199 |
| 6 | −45.638075 | 1.1671 | 1.1077 |
| 7 | −44.7031 | 2.1021 | 2.2721 |
| 8 | −45.8326 | 0.9726 | 1.026 |
| 9 | −46.027125 | 0.7781 | 0.4481 |
| 10 | −41.30205 | 5.5031 | 7.9031 |
| | B3LYP | | |
| 1 | −39.6831 | 0.64 | 0.687 |
| 2 | −40.32315 | 0 | 0.6 |
| 3 | −39.865075 | 0.458 | 0.268 |
| 4 | −39.9843 | 0.3388 | 0.0788 |
| 5 | −38.396725 | 1.9264 | 1.5764 |
| 6 | −39.601525 | 0.7216 | 0.6916 |
| 7 | −38.032775 | 1.2903 | 1.2903 |
| 8 | −39.802325 | 0.5208 | 0.6208 |
| 9 | −39.39445 | 0.9287 | 0.0187 |
| 10 | −33.0316 | 7.2915 | 8.0815 |

[a] The solvation energy is the difference in solvation energy between the compounds b and a. A higher negative number indicates a more favorable reduction reaction as far as the solvation is concerned.
[b] The difference between the energy of the parent compound and the other compounds.

results at B3LYP level. Table 3 shows these analogs to be very close in energy to the parent compound.

As mentioned before, previous calculations [8] performed by our group on some of the compounds have shown compound 4a to be less prone to oxidation than other analogs with the exception of compound 3a. This reaction might be related to the toxicity of the compounds (Ciufolini, M, personal communication). Accordingly, compound 4a, which reduces readily but oxidizes less than others, might be interesting to prepare experimentally and tested for activity and toxicity.

These results suggest that it might be interesting to synthesize the analogs investigated and investigate the relationship between their activity and their toxicity to their oxidation and reduction potentials.

## References

1. Williams WM, Rajski SR, Rollins SB (1997) Chem Biol 4 (2):127–137
2. Uchida I, Takase S, Kayskiri H, Kiyoto S, Hashimoto M (1987) J Am Chem Soc 109:4108–4109
3. Torano H, Takase S, Hosoda J, Kohsaka M (1989) J Antibiot 42:145–148
4. Tomasz M (1995) Chem Biol 2:575–579
5. Sartorelli AC, Pristos CA (1988) Cancer Res 46:3528–3532
6. Hirai O, Shimomura K, Mizota T, Matsumoto S, Mori J, Kikuchi H (1987) J Antibiotics 40:607–611
7. Beckerbauer L, Tepe JJ, Cullison J, Reeves R, Williams RM (2000) Chem Biol 7(10):805–812
8. Sapse AM, Rothchild R, Hernadez G, Jain DC (to be published)
9. Titan, Version 1.05 (1999) Wavefunction Inc, California
10. Chambers CC, Hawkins GD, Cramer CJ, Truhlar DG (1996) J Chem Phys 100:16385