Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 14 (2004) 2677–2680

Threshold interaction energy of NRTI's (2′-deoxy 3′-substituted nucleosidic analogs of reverse transcriptase inhibitors) to undergo competitive inhibition

Arpita Yadav* and Sanjeev Kumar Singh*

Department of Chemistry, Institute of Engineering and Technology, CSJM University, Kanpur 208024, India

Received 11 November 2003; accepted 31 January 2004

Abstract—A quantum pharmacological study has been carried out on nucleosidic inhibitors for HIV-1RT where ab initio HF molecular orbital calculations in conjunction with other quantum mechanical techniques have been utilized in a systematic manner to understand the pharmacophoric features and evaluate specific drug–receptor interactions. The interaction energy between the drug and the closest asp 185 of the catalytic triad has been indicated to be crucial in determining the potency of the nucleosidic drug. This study also emphasizes on identifying important specific drug–receptor interactions and evaluating them at the microscopic level to understand the potency regulation as minor conformational changes may lead to significant difference in interaction energies. Although based on relatively few points our correlation of interaction energies with potency data indicates requirement of ~13 kcal/mol threshold interaction energy for the drug to undergo efficient competitive inhibition.

In the past twenty years or so a lot of research work has been carried out in search of effective drugs against acquired immuno deficiency syndrome (AIDS).[1–3] The best alternative clinically used so far is perhaps the combination therapy where a combination of nucleosidic and non-nucleosidic drug is used.[4] Both the drugs are inhibitors for the enzyme reverse transcriptase (RT) that catalyzes the conversion of RNA retroviral genome into proviral DNA. The nucleosidic inhibitors, are intracellularly converted into their triphosphate derivatives and act as DNA chain terminating analogs of the natural substrate dNTP.[5] Hence, nucleosidic drugs undergo competitive inhibition. The non-nucleosidic inhibitors directly inhibit enzyme RT noncompetitively upon binding to an allosteric site located about 10 Å from the normal substrate dNTP binding site.[6] Inspite of drug resistance towards chemotherapeutics, there is high medical demand to develop more potent, selective and safe antiviral drugs. This would be possible only when we understand the pharmacophoric features of the drugs and drug–receptor interactions, which play a key role in a drugs activity, potency and mechanism. We have recently reported on the pharmacophoric features of nucleosdic[7] and non-nucleosidic[8] drugs.

In this study, we concentrate only on drug–receptor interactions calculated at the microscopic level. The aim of this study is to show that specific drug–receptor interactions (if identified properly) are really the key to understanding the drug's activity and potency. Therefore, a detailed analysis of drug–receptor interactions can lead to design of more specific and potent drugs. In this study we have tried to correlate interaction energies with available potency data (in the form of IC_{50}, etc.). In the past Mickle and Nair[9] have tried to correlate anti-HIV activity/inactivity with the conformation and nature of electrostatic potential surfaces. The nature of electrostatic potential surface can only give an idea about the overall charge environment on the drug. It however cannot be quantitatively correlated with specific potencies. Potency regulation can be understood only by very intricate drug–receptor interaction energies.

A quantum pharmacological study has been performed on selected nucleosidic drugs, which are shown in Figure 1. It is an application of modern quantum mechanical techniques in a systematic manner that will enable us to extract pharmacophoric features, help us understand receptor charge environment and interactions between the drug and the receptor.[10] The whole procedure is best described by a flow chart given in Figure 2. The first step in a quantum pharmacological study is to find out common conformational features (in terms of

* Corresponding authors. Tel.: +91-512-591637; fax: +91-512-590007; e-mail: sanjeevsky@rediffmail.com

0960-894X/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2004.01.108

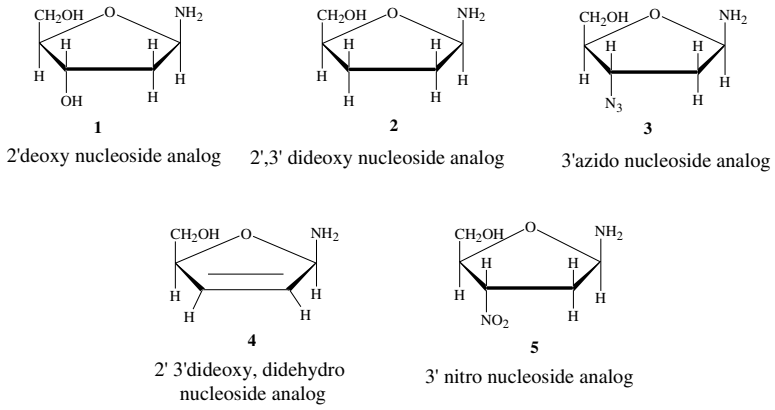

Figure 1. 2′-Deoxy 3′-substituted nucleosidic analogs of reverse transcriptase inhibitors.

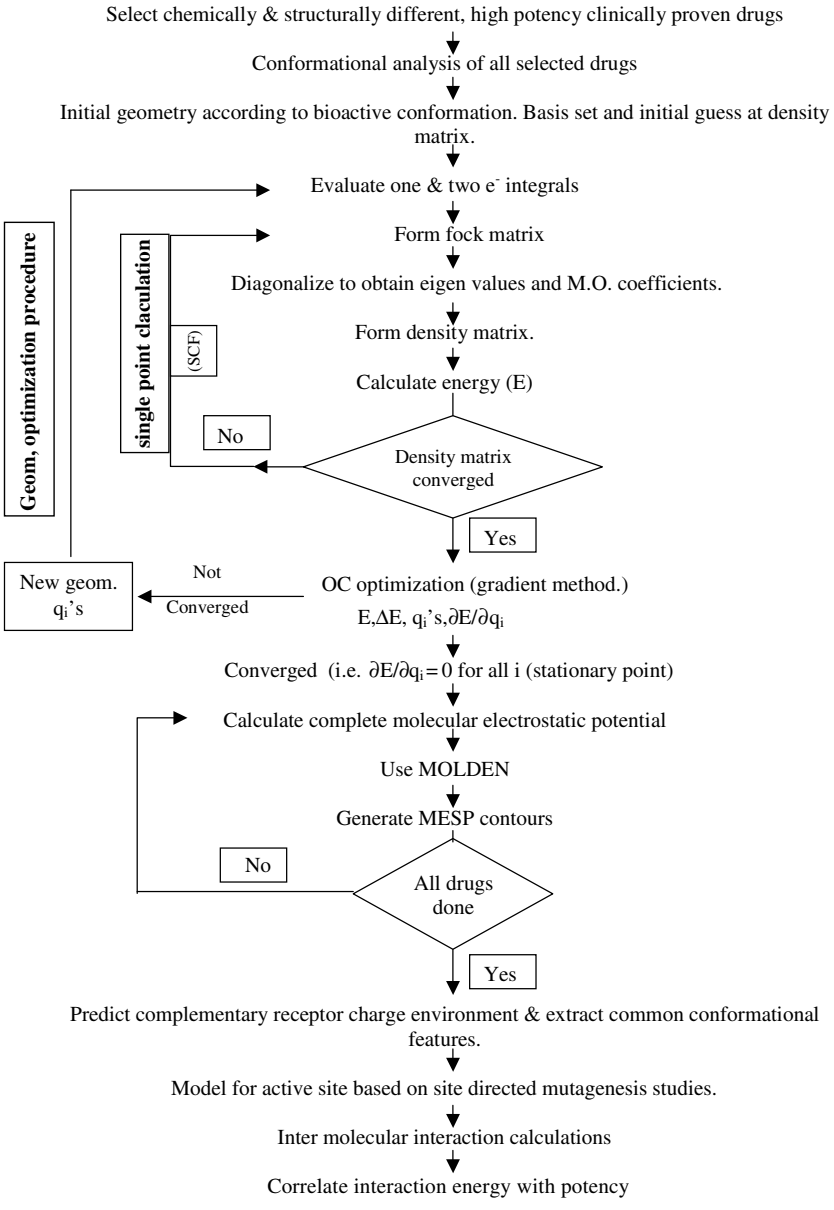

Figure 2. Flow chart showing complete quantum pharmacological procedure.

internuclear distances, specific angles or torsions, etc.) responsible for drug's activity, that is defining the pharmacophore. The next step is the receptor mapping. Our earlier work has dealt with these two steps on nucleosidic and non-nucleosidic drugs. The results of our ab initio HF calculations indicated very little effect of 3′ substituent on ring puckering and suggested that potency regulation may be via very intricate phosphate-catalytic triad interactions.[7] Our molecular electrostatic potential (MESP) maps also showed charge complementarity between the drug and receptor. In this study we try to find a quantitative estimate for the interaction between the phosphate and catalytic triad and correlate it with the potency. Past theoretical calculations regarding interaction energy have been of Monte Carlo simulations type for single system at a time.[11,12]

Table 1. Potency data

NRTI's/NNRTI's	IC_{50} (μM)	References
2′3′-Dideoxy nucleosides	1.6[a]	14
2′3′-Didehydro 2′3′-dideoxy nucleoside	12.0[b]	14
3′-Nitro nucleoside	0.05[c]	15
3′Azidothymidine (AZT)	0.04	14
Nevirapine	0.6	16
Trovirdine	0.8	17
Pyrrolyl hetero aryl sulfone	0.4	16
Efavirenz	0.04	18

[a] This value is for 2′3′-dideoxy cytidine.
[b] This value is for 2′3′-didehydro 2′3′-dideoxy adenine.
[c] This value has been observed for a nitro imidazole compound.

The available potency data along with the relevant references has been collected in Table 1. The relative potency data for nucleosidic drugs is not readily available probably due to the fact that all nucleosidic drugs are incorporated in the growing DNA chain and show-broad-spectrum antiviral activity.

We have applied supermolecule type approach at the 6-31G HF level (with basis set superposition error (BSSE) correction and without BSSE) on truncated analogs for nucleosidic drugs. We have removed the thymidine bases keeping the conformation as optimized with the base. The receptor was modelled by the aspartic catalytic triad placed according to C_α coordinates for protein reported by Jacobo Molina et al. and also a 3-D molecular model reported in 1994.[13] Interactions with only the closest aspartic 185 are reported in Figure 3 (interactions with the other two, asp 110 and asp 186, when calculated were only of repulsive type). Figure 3 indicates that minor differences in ring puckering leads to differences in interaction energies even upto ~9 kcal/mol, which is not evident unless interaction energies are calculated at the microscopic level. This suggests that although the conformational differences induced by the 3′-substituent appear to be minor when compared by conformational mapping, they actually play an important indirect role in monitoring the potency of the drug via interactions with the catalytic triad.

To further substantiate this idea we have correlated the interaction energy with the potency of the drug as shown in Figure 4. Due to lack of potency data for nucleosidic drugs we settle for correlation with relatively few points.

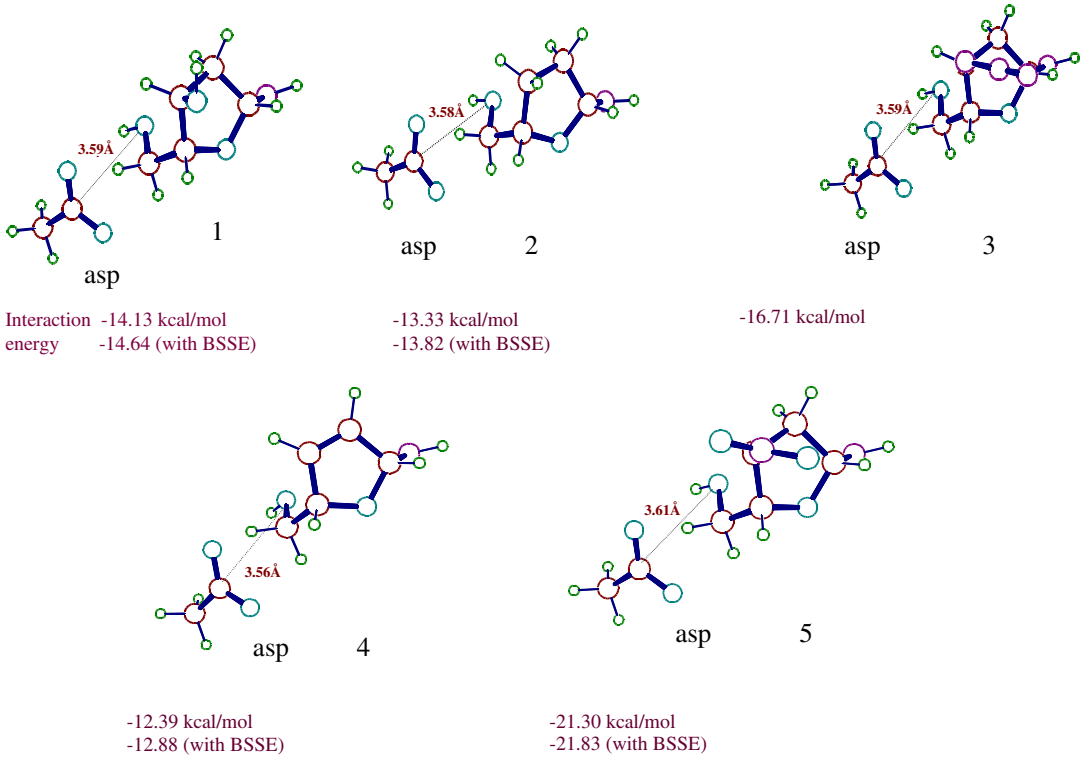

Figure 3. Drug asp 185 interaction energies.

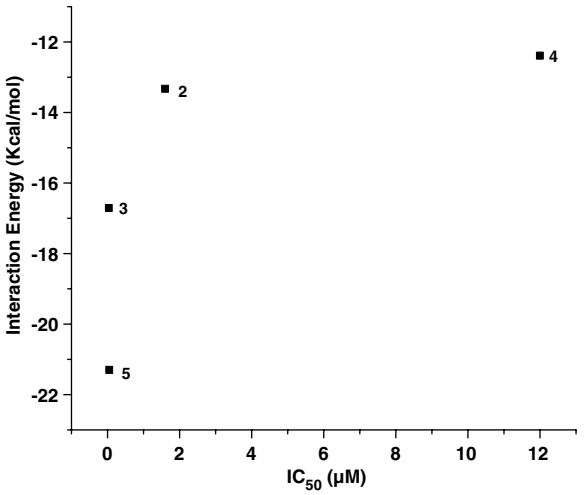

Figure 4. Correlation of interaction energy with potency.

As a preliminary suggestion the data (cf. Fig. 4) indicates that the drug must possess a threshold (minimum) interaction energy to be able to undergo competitive inhibition. If the attractive interaction is less than ~13 kcal/mol a very high concentration of drug would be required for 50% inhibition or else it would not under go competitive inhibition. Small amounts of drug that may bind without possessing threshold interaction energy would only lead to cytotoxicity.

To summarize, this work indicates that potency can be correlated with intricate drug–receptor interaction energies if important parts of receptor have been identified properly and interaction energies have been evaluated at the microscopic level. Our correlation indicates a minimum/threshold interaction energy of ~13 kcal/mol essential for efficient competitive inhibition by the drug.

Acknowledgements

The authors thank the Department of Science and Technology (DST), New Delhi for financial support. One of us (S.K.S.) gratefully acknowledges DST for the Senior Research Fellowship.

References and notes

1. Huryn, D. N.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745.
2. Wlodawer, A.; Erickson, J. *Ann. Rev. Biochem.* **1993**, *62*, 543.
3. Wanacott, A.; Cook, R.; Hayes, F. R.; Hann, M.; Jhoti, M.; McMeekin, H. P.; Mistry, A.; Murray, P.; Rust Singh, O. P. M.; Weir, M. P. *J. Med. Chem.* **1993**, *36*, 3113.
4. (a) Van Leeuwen, R.; Katlama, C.; Murphy, R. L.; Squires, K.; Gatell, J.; Horban, A.; Clotet, B.; Staszewski, S.; van Eeden, A.; Clumeck, N.; Moroni, M.; Pavia, A. T.; Schmidt, R. E.; Gonzalezlahoz, J.; Montaner, J.; Antunes, F.; Gulick, R.; Banhegyi, D.; vander Valk, M.; Reiss, P.; van Weert, L.; van Leth, F.; Johnson, V. A.; Sommadossi, J. P.; Lange, J. M. *AIDS* **2003**, *17*, 987; (b) Podzamczer, D.; Ferrer, E.; Consiglio, E.; Gatell, J. M.; Perez, P.; Perez, J. L.; Luna, E.; Gonzalez, A.; Pedrol, E.; Lozano, L.; Ocana, I.; Llibre, J. M.; Casiro, A.; Aranda, M.; Barrufet, P.; Martinez-Lacasa, J.; Miro, J. M.; Badia, X.; Casado, A.; Lupo, S.; Chan, P.; Manos, M.; Estela, J. A. *Antiviral Ther.* **2002**, *7*, 81.
5. Weil, J. H. In *General Biochemistry*; New Age International Limited, 1997; pp 323–326.
6. Fischl, M. A. *AIDS* **1999**, *13*, 549.
7. Yadav, A.; Singh, S. K. *Bioorg. Med. Chem.* **2003**, *11*, 1801.
8. Yadav, A.; Singh, S. K. *Bioorg. Med. Chem.*, submitted.
9. Mickle, T.; Nair, V. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1963.
10. Singh, S. K. (2003) Quantum pharmacological studies on HIV-1RT inhibitors, Ph.D. thesis, Department of Chemistry, Institute of Engineering and Technology, CSJM University, Kanpur (India).
11. SubbaRao, G.; Kataria, S.; Siddiqui, M. I. *J. Biomol. Struc. Dyn.* **1998**, *16*, 1.
12. Kulkarni, V. M.; Bhalla, D. V. *Ind. J. Chem.* **1994**, *33B*, 941.
13. Yadav, P. N. S.; Yadav, J. S.; Arnold, E.; Modak, M. J. *J. Biol. Chem.* **1994**, *269*, 716.
14. Daluge, S. M.; Good, S. S.; Faletto, M. B.; Miller, W. H.; St. Clair, M. H.; Boone, L. R.; Tisdale, M.; Parry, N. R.; Reardon, J. E.; Dornsife, R. E.; Averett, D. R.; Krenitsky, T. A. *Antimicrob. Agents Chemother* **1997**, *41*, 1082.
15. Silvestri, R.; Artico, M.; Massa, S.; Marceddu, T.; De Montis, F.; La Colla, P. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 253.
16. Silvestri, R.; Artico, M.; De Martino, G.; Novellino, E.; Greco, G.; Lavecchia, A.; Massa, S.; Loi, A. G.; Doratiotto, S.; Lacolla, P. *Bioorg. Med. Chem.* **2000**, *8*, 2305.
17. Vig, R.; Mao, C.; Venkatachalam, T. K.; Tuel-Ahlgren, L.; Sudbeck, E. A.; Uckun, F. M. *Bioorg. Med. Chem.* **1998**, *6*, 1789.
18. Cocuzza, A. J.; Chidesta, D. R.; Cordova, B. C.; Klabe, R. M.; Jeffrey, S.; Diamond, S.; Weigelt, C. A.; Ko, S. S.; Bacheler, L. T.; Erickson-Vitanen, S. K.; Rodgers, J. D. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1389.