University of Groningen

A computational study on the nature of DNA G-quadruplex structure

Gholamjani Moghaddam, Kiana

DOI:
[10.33612/diss.159767021](https://doi.org/10.33612/diss.159767021)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):
Gholamjani Moghaddam, K. (2021). *A computational study on the nature of DNA G-quadruplex structure*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen.
<https://doi.org/10.33612/diss.159767021>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

**A computational study on the
nature of DNA
G-quadruplex structure**

**university of
 groningen**

faculty of mathematics and
 natural sciences

zernike institute for
 advanced materials

The work described in this thesis was performed in the research group Theoretical Chemistry and Molecular Dynamics of the Zernike Institute for Advanced Materials at the University of Groningen, the Netherlands.

Printed by: Ridderprint, www.ridderprint.nl

Cover designed by Shekoufeh Izadkhasti

Copyright ©2020 Kiana Gholamjani Moghaddam

university of
 groningen

A computational study on the nature of DNA G-quadruplex structure

PhD thesis

to obtain the degree of PhD at the
University of Groningen
on the authority of the
Rector Magnificus Prof. C. Wijmenga
and in accordance with
the decision by the College of Deans.

This thesis will be defended in public on

Friday 19 March 2021 at 12:45 hours

by

Kiana Gholamjani Moghaddam

born on 23 January 1981
in Rasht, Iran

Supervisors

Prof. S. Faraji

Prof. S.J. Marrink

Co-supervisor

Dr. A.H. de Vries

Assessment Committee

Prof. A. Dreuw

Prof. A. Borschevsky

Prof. R.C. Chiechi

Contents

1	DNA G-quadruplexes in Human Genome and Nanotechnology	1
1.1	G-quadruplex structure	1
1.2	Application Domain	3
1.3	Thesis Outline	5
2	Theoretical Approach	7
2.1	Quantum Mechanical Methods	8
2.1.1	Density Functional Theory.	8
2.1.2	Time-Dependent Density Functional Theory	10
2.1.3	Spin-Flip Time-Dependent Density Functional Theory	11
2.2	Atomistic Molecular Dynamics Simulation	12
2.3	Hybrid Quantum Mechanics/Molecular Mechanics Simulation.	14
2.3.1	Mechanical Embedding	15
2.3.2	Electrostatic Embedding.	15
2.3.3	Polarized Embedding	16
2.4	Coarse-Graining	16
3	The interactions of quinazolone derivatives with c-KIT Gquadruplex	18
3.1	Introduction	19
3.2	Computational Methods	20
3.2.1	Molecular Docking.	21
3.2.2	Molecular Dynamics (MD) Simulation.	21
3.2.3	Molecular Electrostatic Potential (MEP)	22
3.2.4	Free Energy Calculation	22
3.2.5	Solvent Accessible Surface Area (SASA) Calculation	23
3.3	Result and Discussion.	24
3.3.1	Molecular Docking.	24
3.3.2	MD Simulation.	24
3.3.3	Structural Stability	25

3.3.4	Hydrogen Bonding Analysis	25
3.3.5	Molecular Electrostatic Potential.	28
3.3.6	Free Energy Calculations.	31
3.3.7	Solvent Accessible Surface Area Analysis.	33
3.4	Conclusions.	33
3.5	Appendix	34
4	Binding of quinazolinones to c-KIT G-quadruplex	36
4.1	Introduction	37
4.2	Computational Methods	38
4.2.1	Molecular Docking.	38
4.2.2	Molecular Dynamics Simulations	39
4.2.3	Free Energy Analysis	40
4.2.4	Free Energy Decomposition	41
4.3	Results and Discussion	41
4.3.1	Quinazolinones bind to 3' end of G-quadruplex	41
4.3.2	Ligands increase stability of G-quadruplex.	43
4.3.3	Ligands bind via both hydrogen bonds and π - π stacking interactions .	44
4.3.4	Free energy analysis underlines importance of both hydrogen bond and π - π stacking.	47
4.3.5	Identifying two hotspots for G-quadruplex-ligand interactions	50
4.4	Conclusions.	54
4.5	Appendix	55
5	On the nature of the smallest photoswitchable G-quadruplex	61
5.1	Introduction	62
5.2	Computational Methods	64
5.3	Results and Discussion	66
5.3.1	Photoisomerization reactions of AZ1, AZ2 and AZ3 derivatives in the gas phase	66
5.3.2	MD simulations	70
5.3.3	QM/MM simulations	76
5.4	Conclusions.	78
5.5	Appendix	80

6	Insight on the interactions of proteins with G-quadruplex structures	84
6.1	Introduction	85
6.2	Computational Methods	87
6.2.1	Starting Structures	87
6.2.2	Atomistic MD Simulations	87
6.2.3	CG Simulations	88
6.3	Results and Discussion	89
6.3.1	Atomistic MD Simulations	89
6.3.2	CG Simulations	93
6.4	Conclusions.	98
	References	101
	Summary	116
	Samenvatting	118
	List of Publications	121
	Acknowledgements	122