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Docking Studies of Piperazine Propyl-4-oxo-3,4-dihydroquinazoline-2-carboxylate Derivatives

Gopi Reddy A[1], Harinadha Babu V[1*], Jaya Prakash Rao Y[2], Saikiran Reddy P[3], Vijjualatha Manga[3]

[1]Department of Pharmaceutical Chemistry, G. Pulla Reddy College of Pharmacy, Hyderabad, India
[2]Department of Chemistry, Telangana University, Nizamabad, India
[3]Molecular Modeling and Medicinal Chemistry Group, Department of Chemistry, University College of Science, Osmania University, Hyderabad-500007, India

ABSTRACT

Molecular docking studies were carried out in order to explore the possible binding modes of these compounds with DNA. The in silico docking results were in good agreement with biological data.

Keywords: Molecular docking studies, Piperazine, DNA intercalates

INTRODUCTION

Quinazolinone derivatives, the privileged structures in the field of medicinal chemistry not only act as good anticancer agents but also act as good DNA intercalates [1,2]. To estimate the possible intercalating ability of newly synthesized compounds molecular docking studies were performed.

The quinazolinone moiety contained in natural products (Luotonin, Rutaecarpine, Tryptanthrin, Chloroqualone, Alloqualone, etc.,) represents medicinally and pharmaceutically important class of compounds [3,4] because of their diverse range of biological activities such as anticancer, diuretic, anti-inflammatory, anticonvulsants and antihypertensives [5,6]. In recent years, quinazolinone embedded numerous natural products have been identified [7]. Several other quinazolinone derivatives have been identified with anticancer, Mitochondrial Permeability Transition Pore (mPTP) modulators, Epidermal Growth Factor Receptor (EGFR) and Vascular Endothelial Growth Factor Receptor-2 (VEGFR-2) inhibitors [8-10]. The cytotoxic alkaloid Luotonin-A (1) and its derivatives infused with quinazolinone moiety is clinically proved as anti-cancer agents (Figure 1) [11-13].

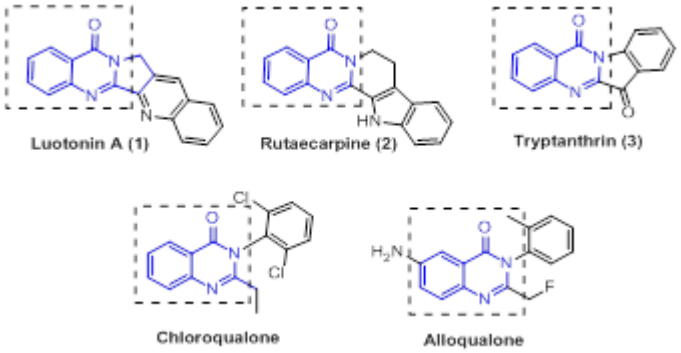

Figure 1: Quinazolinone scaffold containing natural products

METHODOLOGY

The docking studies were carried out using Schrodinger suite 2010 and binding energy values were estimated with Prime MM/GBSA module available in the same suite. Initially the NMR structure of DNA complexed with Respinomycin D (Pdb id: 1N37) was downloaded from protein data bank (www.rcsb.org). It was then prepared, refined and minimized using protein preparation module by applying default parameters. Later receptor grid was generated around the active site of DNA where van der Waals scaling for non-polar atoms was set to 0.9 [14].

Meanwhile the ligands were sketched using maestro build panel and refined geometrically by OPLS force field. All possible states of ligands were then generated using Ligprep module at a physiological pH range of 7± 2. Finally the low energy conformers obtained were docked into the active site using GLIDE 5.6 [15] using extra precision (XP) docking mode.

RESULTS AND DISCUSSION

To gain more insight into the binding modes and corresponding interaction energies the newly synthesized quinazolinone derivatives were docked into the active site of DNA. The docking results revealed that these compounds can act as good intercalating agents. This is due to the fact that they were able to form hydrogen bond interactions with DNA by occupying the position between the base pairs which is a sign of good intercalation. The docking analysis of doxorubicin, the standard with DNA showed three hydrogen bond interactions. Two interactions were observed with nucleotide DG 13 and one with nucleotide DC 12. The binding energy of doxorubicin was found to be -39.819 kcal/mol. The newly synthesized compounds showed hydrogen bond interactions with nucleotides DC 4, DG 5 and DG 13. Compounds 8a and 8b showed one hydrogen bond with nucleotide DG13 whereas other compounds i.e. compounds 8c, 8d, 8e and 8g showed hydrogen bond with nucleotide DG 5. Compound 8f alone showed two hydrogen bonds with nucleotide DC 4. The docking calculations (binding energies) of all compounds are depicted in Table 1.

Table 1: Binding energies

Compound	Binding Energies (Kcal/mol)
8a	-16.541
8b	-25.979
8c	-14.957
8d	-16.375
8e	-9.111
8f	-16.904
8g	-24.995
Doxorubicin	-39.819
Paclitaxel	-22.134

Among newly synthesized compounds, compounds 8b and 8g showed good binding affinity values (-25.979 and -24.995 Kcal/mol). Further a regression analysis was carried out between binding energy values and pGI_{50} (Figure 2a) values which gave a regression coefficient (r^2) of 0.679 indicating a significant correlation between DNA binding and anti-proliferative activity (Figure 1). DNA intercalation with hydrogen bond interactions is depicted in Figure 2b for doxorubicin, Figure 2c for 8b, Figure 2d for 8g and Figure 2e for 8f compounds respectively (Figure 3).

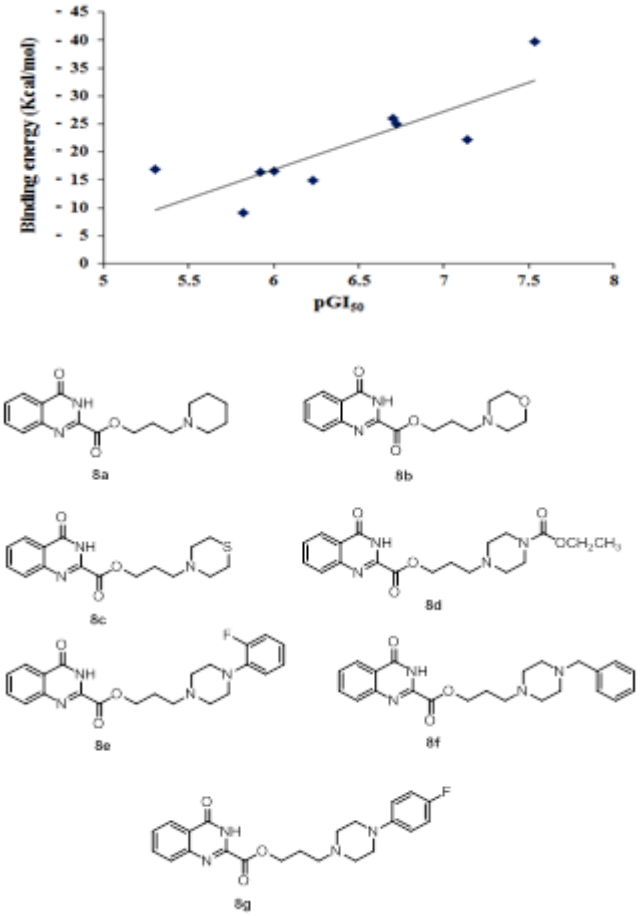

Figure 2: Scatter plot of pGI_{50}versus binding energy. DNA intercalation with hydrogen bond interactions is 2b for doxorubicin, 2c for 8b, 2d for 8g and 2e for 8f

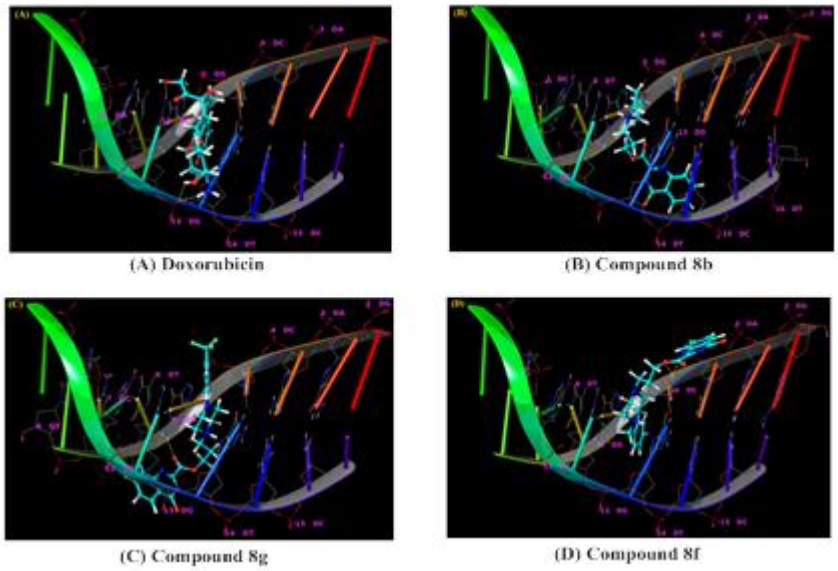

Figure 3: Dock poses of compounds (A) Doxorubicin (B) Compound 8B (C) Compound 8g and (D) Compound 8f, at DNA interaction site showing hydrogen bond interactions (Yellow lines)

CONCLUSION

Molecular docking studies reveal that these quinazolinone derivatives can act as promising lead molecules for the development of new anticancer agents.

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