Journal of Computational Science 10 (2015) 166–177

Contents lists available at ScienceDirect

Journal of Computational Science

journal homepage: www.elsevier.com/locate/jocs

Assessment of molecular binding of Hoechst 33258 analogues into DNA using docking and MM/GBSA approach

Upasana Issar, Tripti Kumari, Rita Kakkar*

Computational Chemistry Group, Department of Chemistry, University of Delhi, Delhi 110007, India

ARTICLE INFO

Article history:
Received 22 October 2014
Received in revised form 18 May 2015
Accepted 24 May 2015
Available online 27 May 2015

Keywords:
Hoechst 33248
Minor grove binder;
Combinatorial design
Docking
Interaction energies

ABSTRACT

In order to understand every aspect of interaction between minor groove binders based on Hoechst 33258 and the double helical B-DNA dodecamer, a molecular modeling study has been performed on Hoechst analogue-DNA complexes. Using combinatorial design with structural modifications, a diverse ligand library of two hundred and fifty analogues of Hoechst 33258 has been prepared. Molecular interactions and binding affinities of these analogues, differing in their central cores, with nucleic acids are studied using molecular docking and MM-GB/SA methods. Results show that the presence of hydrogen bond donors, aliphatic piperazinyl ring and rotatable bonds is the essential requirement for optimal DNA binding of Hoechst analogues. Mainly, the bisubstituted and trisubstituted phenyl analogues, rich in hydrogen bond donors, display good recognition towards AATT rich DNA sequences, affirming all reported experimental observations. The analogues that have benzoxazole, benzothiazole and pyridine substituted benzimidazole show preference towards GGCC rich DNA rather than CCGG, AATT and TTAA rich DNA. The docking results show that the binding site of these analogues consists mainly of GCCA or TGGC sequences. Here, the guanine base acts as both a hydrogen bond donor and hydrogen bond acceptor for these heteroatom substituted analogues, thereby holding them with greater ease. In all, our work satisfactorily explains the variation in drug-DNA recognition on altering the basic nature of Hoechst.

© 2015 Elsevier B.V. All rights reserved.

1. Introduction

Studies on the noncovalent interactions of molecules with the minor groove of DNA continue to be a prolific area for the discovery of potential new therapeutic agents that can target any predetermined sequence, thus controlling gene expression. In this regard, the minor groove binder Hoechst 33258 is known to selectively bind the adenine-thymine rich region of DNA. It possesses cytotoxic activity [1] and has been in phase I/II clinical trials against pancreatic carcinomas [2]. As a result, Hoechst has received particular attention as a starting point for the design of new potential anticancer drugs and has emerged as a model for synthetic drug design. The properties of Hoechst 33258 and its analogues have been thoroughly reviewed [3].

A number of studies have revealed that altering the basic nature of Hoechst changes the specificity and selectivity of the drug toward DNA. While the basic moiety prefers AT rich DNA, a study [4] showed that replacement of benzimidazole by benzoxazole with inward directed pyridine nitrogen on it confers the property of recognition of a GC base pair within the binding sequence. However, the exact mechanism of its interaction was not explained well enough. A review [5] on the medical implications of benzimidazole derivatives as drugs designed for targeting DNA and DNA associated processes revealed that substitution of the benzimidazole heterocycle by benzoxazole, benzothiazole or indole rings leads to marked reduction in the biological activity. Therefore, the benzimidazole unit is retained in a wide collection of compounds exhibiting topoisomerase I inhibition activity. Nevertheless, the alteration of DNA specificity upon substitution with these rings cannot be neglected and thus the nature of interaction of these analogues with DNA should be explored in detail.

In a continuing effort to develop bisbenzimidazole-type compounds with increased double stranded-DNA binding affinity and specificity, several derivatives of Hoechst have been synthesized [6–8]. An alternative approach used to develop sequence specific agents related to Hoechst 33258 comprise of substitutions at *ortho*, *meta* and *para* positions of the phenyl group of Hoechst.

As far as *para* substitution is concerned, the DNA binding characteristics of a diphenyl ether bis-benzimidazole analogue has been investigated [9]. The authors reported the longer recognition of this analogue toward double stranded DNA. This was attributed to its increased length and preserved crescent-shaped curvature

* Corresponding author. Tel.: +91 1127666313.
E-mail address: rkakkar@chemistry.du.ac.in (R. Kakkar).

http://dx.doi.org/10.1016/j.jocs.2015.05.003
1877-7503/© 2015 Elsevier B.V. All rights reserved.

(required for optimal contact within the minor groove). Moreover, this phenoxy as well as ethoxy analogues were found to exhibit greater cytotoxicity than the parent molecule owing to their greater cellular permeability [10,11]. The radioprotective ability of these analogues has been investigated theoretically, and results show that electron donating substituents at the *para* position of the phenol ring enhance radioprotecting ability [12].

Apart from the *para* substituted analogues, *meta* as well as *ortho* analogues were designed in an attempt to improve the radioprotective activity of Hoechst. The first such study involved the use of ^{125}I-labelled iodoHoechst 33258 that exploited the induction of DNA strand breaks. Comparison of *o*-, *m*- and *p*-iodoHoechst with respect to DNA strand breakage in plasmid DNA indicated remarkable differences in photopotency [13]. The *ortho* isomer was found to be more efficient than the *meta* and *para* isomers [14,15]. Moreover, the photo-induced cytotoxicity by these analogues in K562 cells also displays similar results [16]. Squire et al. [17] reported the first X-ray crystal structure of *m*-iodo Hoechst within DNA.

In addition to monosubstituted derivatives, bisubstituted analogues (like methylproamine, which has the $-CH_3$ and $-N(CH_3)_2$ groups on the phenyl ring) [18], displayed potential for use as topical preparations of a radioprotector. Another molecule, DMA, a dimethoxy analogue of Hoechst, was shown to be a better radioprotector as compared to the parent molecule [19]. It was also reported that these bisubstituted ligands afford two-fold protection due to their ability to alter the DNA structure and directly scavenge free radicals [20,21].

Apart from mono and disubstitutions on Hoechst, trisubstituted derivatives that target DNA and also bind t-RNA in 1:1 stoichiometry with sufficient accuracy [22] have been synthesized. Subsequently, a lot of modifications on the phenylic as well as piperazinylic end of Hoechst have been employed till date. These modifications not only enhance the DNA binding property but are also known to alter sequence specificity. Interestingly, Neidle et al. [23] proposed a novel symmetric head-to-head arrangement of benzimidazole rings in Hoechst that could also effectively bind the minor groove. This arrangement extended the size of the bisbenzimidazole recognition site with distinctive cross-strand H-bonds involving each base pair. Further these analogues were also shown to possess antitumor activity [24,25].

Keeping all the above information in mind, the present work is divided into two main segments. The first portion discusses the nature of interactions of various analogues of Hoechst 33258 with the Dickerson-Drew dodecamer sequence $d(CGCGAATTCGCG)_2$ [26]. The crystal structure of the complex of Hoechst–DNA was used for this purpose and all the analogues were then allowed to interact with the same. In the second segment, we built various canonical oligomeric sequences that vary mainly in the central core of the DNA, and the Hoechst analogues were then tested upon them. The goal of this work is to analyze how various substituents on Hoechst affect its AT selectivity and which factors dictate their binding affinity within various oligomeric sequences.

2. Computational details

2.1. Preparation of compound libraries

A compound library of 250 Hoechst analogues was built using the parental structure of Hoechst 33258 as a template. These analogues were generated by structural modification of the ring structure with sterically and conformationally allowed substituents (most of them reported in the literature) using Maestro, available in Schrödinger 2009. The modifications were done on the Hoechst 33258 extracted from the protein data bank (RCSB). Fig. 1 shows the basic asymmetric **HT** (head to tail bis-benzimidazole) and symmetric **HT'** (head to head bis-benzimidazole) used as a model to build the analogues.

For a better understanding of the influence of structural changes on the binding energy of these analogues with DNA, and their fitness as anticancer drugs, the modifications done on the ligand were divided into three main categories. This was carried out to investigate thoroughly each and every aspect of DNA binding possessed by the Hoechst family. The categories are as follows:

(a)Modifications in the bis-benzimidazole rings – The structural modifications (Table S1, Supplementary information) include replacement of the benzene ring of the benzimidazole moiety by pyridine. In addition, replacement of the benzimidazole unit by a benzoxazole or benzothiazole moiety was considered in two possible orientations: one, where the heteroatoms (O or S) face the concave edge of the minor groove (at W and Y positions; Table S1(a)), and the other where they lie opposite to it (at X and Z positions; Table S1(a)). Apart from these, every possible combination of heteroatoms (—N, —O or —S) on benzimidazole rings was tested to find the analogue of Hoechst 33258 which binds DNA with sufficient accuracy and selectivity. Thus in this category, all variations involve substitutions only at the central bis-benzimidazole unit of Hoechst. Table S1(a) displays a total of 99 structural analogues (S# 1 to 99), with their respective citations [4,27].

The structures from S# 1 to 24 include step by step replacement of first Bz1, and then Bz2, with benzoxazole and benzothiazole units. After this, the benzene ring of each benzimidazole (Bz1 and Bz2) moiety of these 24 structures was replaced by a pyridine ring, making 99 structures in all.

(b) Modifications in the phenyl end of Hoechst – This class involves substitution of various groups at the *ortho, meta* and *para* positions of the phenyl ring of Hoechst, without altering the rest of the Hoechst 33258 moiety. Table S1(b)-(i) give the list of analogues designed under this category. While most of the substituents were collected from the literature, there are some that have been self-generated.

Starting from S# 100 to 126, the -OH of the phenolic ring of Hoechst 33258 was replaced by different groups like $-OCH_2CH_3$ (Hoechst 33342), $N(CH_3)_2$ (proamine), -I (iodo Hoechst), which have been shown to affect the radioprotection ability of the parent molecule [16,17]. Substitutions at Hoechst 33258 [16–19,28–38] also include carbamates and 2-chloroethylnitrosourea derivatives that have already proved as potential anticancer agents and topoisomerase I inhibitors [29,30].

The ligands from S# 127 to 146 are substituted at the *ortho* or *meta* position of the phenyl ring. Molecules from S# 147 to 229 involve bisubstitutions and trisubstituions at the phenyl ring.

(c) Modifications at both ends -phenylic and piperazinylic ends. In this category, the modifications involve substitutions at the phenyl and piperazinyl ends of Hoechst, with the central bis-benzimidazole attached in symmetric or asymmetric manner. In Table S1(j), S# 230 to 242 represent asymmetric analogues [6,39–43], while in Table S1(k), S# 243 to 248 represent symmetric ones [23–25,44,45].

The motivation behind introducing symmetric binding of two-benzimidazole rings is to monitor the extension of the recognition site by these bisbenzimidazoles from three (in Hoechst 33258 and analogues) to four AT base pairs [23]. It was also suggested that replacement of the piperazine group in Hoechst 33258 by pure DNA-binding groups would enhance the cytotoxicity and possibly lead to compounds with antitumor activity [24,25].

Each structure was then minimized using the MMFFs force field [46] and assigned an appropriate bond order using the LigPrep script shipped by Schrödinger.

Download English Version:

https://daneshyari.com/en/article/430345

Download Persian Version:

https://daneshyari.com/article/430345

Daneshyari.com