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IMIDAZOLE AND CARBAZOLE DERIVATIVES AS POTENTIAL ANTICANCER AGENTS: MOLECULAR DOCKING STUDIES AND CYTOTOXIC ACTIVITY EVALUATION

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ABSTRACT. Carbazoles and imidazole represent two important classes of heterocycles which exhibit diverse biological activities such as antitumor properties. In this study, imidazole (**C1-C3**) and carbazole (**C4** and **C5)** derivatives were evaluated for their cytotoxic activity against three human cancer cell lines namely, MCF7 (human breast cancer), HT29 (human colon cancer), and HeLa (human cervical cancer). Carbazole derivatives (**C4** and **C5)** with $IC_{50} < 10$ μM showed greater cytotoxic effect than imidazole derivatives (**C1-C3**). Furthermore, all compounds exhibited better anticancer activity against MCF-7 than other two cell lines (HT-29, HeLa) and compound **C4** was the most potent compound with the IC_{50} values of 2.5, 5.4 and 4.0 μM, against MCF-7, Hela and HT-29 cell lines, respectively. Physicochemical properties of compounds were calculated and their correlation with the IC_{50} values on MCF-7 cell line investigated. Surface area and polarizability of compounds showed good correlation by $R^2 = 0.8396$ and $R^2 = 0.834$, respectively. Docking studies of these compounds were also performed on the DNA as proposed target to comprehend their binding interactions and binding energies. The docking energy of compounds ranged from - 11.32 to -13.48 kcal/mol. Compound **C3** with energy of -13.48 kcal/mol had the highest docking energy. Docking results indicated that these compounds (**C1-C5**) had strong affinity in binding to the DNA.

KEY WORDS: Imidazole, Carbazole, Molecular docking, Cancer, MTT assay

INTRODUCTION

Cancer after the cardiovascular problems is one of the most spread and mortal disease in the world. Hence, the development of new and potent anticancer agents, is one of the fundamental goals in the medicinal chemistry [1].

Carbazole heterocyclic ring is a major constituent of many natural alkaloids and synthetic derivatives, possessing variant biological activities [2]. These activities including anticancer [3], anti-inflammatory and analgesic effects. Fujita *et al.* [4] reported that the carbazole derivatives, NP-10, NP-14 and HND-007, exhibit significant anticancer activity as a novel anti-microtubule agents (Figure 1). Moreover, Kamble and co-worker synthesized carbazoles derivatives which indicate partial anticancer and significant antitubercular activities [2]. In addition to these reports, Lansiaux *et al.* synthesized and screened novel carbazole derivatives for cytotoxic along with topoisomerase II inhibitory activities which the best compound (**53**) displayed a high cytotoxicity (IC_{50} = 150 nM), higher than etoposid (IC_{50} = 490 nM) (Figure 1) [5].

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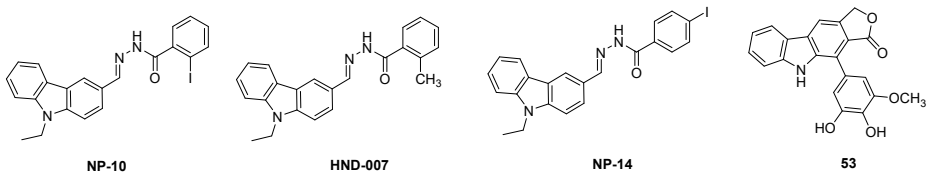


Figure 1. Chemical structures of NP-10, HND-007, NP-14 and 53.

It is well known that imidazole heterocyclic nucleus is main part of many therapeutic agents with antifungal (econazole, miconazole, metranidazole, ketoconazole and itraconazole), and anticancer (dacarbazine, azathioprine and zoledronic acid) activity [6]. The importance of this nucleus has drawn attention of researchers to synthesize and develop new agents bearing imidazole ring. For example, Yurttas *et al.* synthesized new imidazole derivatives and evaluated their cytotoxicity against 60 human tumor cell lines along with antimicrobial and antifungal activities [7]. Furthermore, Salerno and co-workers designed and synthesized novel imidazole derivatives based on azalanstat and investigated their antiproliferative properties in prostate ((DU-145, PC3, LnCap) and breast cancer cell lines (MDA-MB-231, and MCF-7) [8].

Based on these premises and importance of imidazole and carbazole heterocyclic nucleuses in medicinal chemistry, we investigated imidazole and carbazole derivatives, which were synthesized recently [9-11], for cytotoxic activity.

Physicochemical properties of compounds, to indicate their correlation with the IC_{50} values on MCF-7 cell line, were calculated. Docking study of these compounds was also carried out to determine the best binding mode and binding energies of these compounds with DNA as proposed targets.

EXPERIMENTAL

Chemicals

All cell lines were purchased from Pasteur Institute of Iran (Tehran, Iran). RPMI-1640 and DMEM medium were purchased from Sigma Aldrich. Fetal bovine serum (FBS) and L-glutamine, were purchased from Gibco Invitrogen Co. (Scotland, UK). Dimethyl sulfoxide (DMSO), doxorubicin (DOX), penicillin, streptomycin and sulforhodamine B (SRB) were purchased from Sigma Chemical Co. (Saint Louis, USA).

Cell cultures and MTT assay

The cytotoxic activity of five carbazole and imidazole derivatives were evaluated using a 3-(4, 5-dimethylthiazol-2-y-2,5-diphenyl tetrazolium bromide (MTT) assay. In briefly, for the assay, three cell lines (MCF-7, HT-29 and HeLa) were freshly isolated and seeded in 96-well flat bottom tissue culture plate at a concentration of 1×10^5 cells/well containing 100 µL of RPMI-1640 (supplemented with 10% FBS) tissue culture medium. Then the microplate was incubated in incubator at 37 °C for 24 h. After discarding the medium, 100 µL of compounds with different concentration (0.1, 1, 10, 25, 50 75, 100 µM) were added to each deep plate. The plates were incubated for 48 h. After incubation, 100 µL of the supernatant media was removed and 100 µL of MTT solution (0.5 mg/mL) added and incubated at 37 °C for 3h. After the incubation, the MTT solution was discarded and 80 µL of DMSO was added to dissolve formazan. The optical density was determined at 540 nm using an ELISA plate reader (Bio-Tek, Winooski, VT, USA). The cell growth inhibition was calculated based on the following expression:

$$\% \text{ Cell Viability} = \frac{\text{Optical Density of Test}}{\text{Opatical Density of Control}} \times 100 \quad (1)$$

% Cell Inhibition = 100 - % Cell Viability (2)

IC_{50} value was calculated by extrapolating a graph with % cell inhibition on Y-axis against concentration of test compound on X-axis.

Statistical analysis

The IC_{50} values were calculated using Curve Expert 1.4. and were expressed as mean ± SD. One-way analysis of variance (ANOVA) were used for analysis of MTT cytotoxicity results and the level of $P < 0.05$ was considered to indicate statistically significant differences.

Physicochemical properties

Physicochemical properties of compounds including SA (surface area), volume, HE (hydration energy), Log P, polariability, reflectivity and mass, after minimizing of energy based on two methods (molecular mechanic (MM^+) and semiempirical (AM1) were calculated using HyperChem 8.

Docking procedure

The docking studies were performed using an *in house* batch script (DOCKFACE) [12-16] of AutoDock 4.2. HyperChem 8 was applied to optimized energy of each ligand with MM+ and AM1 minimization methods. Then the partial charges of atoms were calculated using Gasteiger-Marsili procedure. Non-polar hydrogens of compounds were merged and then rotatable bonds were assigned. Then mol2 format was converted PDBQT by MGL tools 1.5.6 [17].

The 3D crystal structure of DNA (PDB ID: 1BNA) as potential targets for our compounds were retrieved from protein data bank (http://www.rcsb.org/pdb/home/home.do). After removing water molecules, missing hydrogens were added and non-polar hydrogens were merged into their corresponding carbons using AutoDock Tools [18]. As search algorithms, Lamarckian Genetic Algorithm (LGA) was applied and performed by AutoDock 4.2. [17, 19-21]. Finally, the PDBQT file of the receptors was obtained using MGLTOOLS 1.5.6.

For Lamarckian GA, a maximum number of 2,500,000 energy evaluations, 27,000 maximum generations; 150 population sizes, a gene mutation rate of 0.02; and a crossover rate of 0.8 were applied. The grid maps of the receptors were calculated using AutoGrid tools of AutoDock 4.2. The grid box parameters for these targets were shown in the Table 1. The grid box parameters of 1BNA were 60×74×120 points in x, y, and z directions. gpf and dpf as grid and docking parameter files were built by AutoDock Tools.

Table 1. Gridbox parameters in AutoDock 4.2.

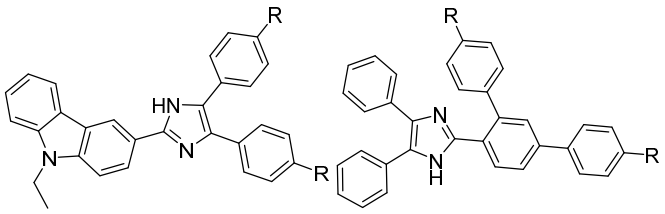
Parameter Name	DNA
PDB ID	1BNA
Grid spacing	0.375
Box X center	15.81
Box Y center	21.31
Box Z center	9.88

RESULTS AND DISCUSSION

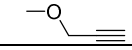
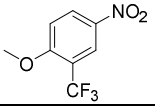
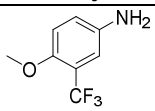
In vitro cytotoxicity

In this study, all heterocyclic compounds were evaluated against three cell lines including MCF-7, HT-29 and HeLa by standard MTT assay method (Table 2).

Table 2. Chemical structure of the compounds C1-C5 and their IC_{50} values.



C1-C3 **C4-C5**

Compound	R	(IC_{50} ± SD) µM		
		MCF-7	HeLa	HT-29
C1		28.7 ± 4.1	39.6 ± 8.3	>100
C2		48.3 ± 4.1	>100	>100
C3		75.3 ± 12.4	>100	76.8 ± 15.5
C4	—NO_2	2.5 ± 1.2	5.4 ±1.3	4.0 ± 0.9
C5	—NH_2	8.2 ± 3.7	6.6 ± 2.8	4.5 ± 1.3
Doxorubicin	-	1.4 ± 0.3	0.9 ± 0.2	0.7 ± 0.2

Comparison between these compounds on MCF-7 cell line indicated that after standard drug (doxorubicin), compound **C4** had better cytotoxic effect with IC_{50}=2.50 µM.

As shown above, carbazole derivatives, compounds namely: **C4** and **C5** with IC_{50} < 10 µM showed greater cytotoxic effect than imidazole derivatives (**C1-C3**). Furthermore, all compounds exhibited better anticancer activity against MCF-7 than other two cell lines (HT-29, HeLa). The order of the cytotoxic effect of the compounds on different cell lines is as follows: MCF7 cell line: DOX > C4 > C5 > C1 > C2 > C3; HT-29 cell line: DOX > C4 > C5 > C3 > C2 > C1 and HeLa cell line: DOX > C4 >C 5 > C1 >C2 > C3.

Compound **C4** was the most potent compound against all cell lines MCF-7, Hela and HT-29 with the IC_{50} values 2.5, 5.36 and 4.03 µM, respectively. As shown in Table 2, among compounds **C1-C3** as imidazole derivatives, compound **C1** with IC_{50} 28.7 and 6.63 µM against MCF-7 and Hela, respectively, showed significant anticancer activity than **C2** and **C3**.

As mentioned above, imidazole and carbazole derivatives have attracted considerable attention because of variable biological activity such as anticancer activity. Thus, selected compounds which bearing imidazole and carbazole rings, were subjected to MTT assay and structure-activity relationship (SAR) of compounds was investigated. Comparison between carbazole derivatives **C2** and **C3**, which contain NO_2 and NH_2 substitution, respectively, indicated that the NO_2 group had a greater effect on cytotoxic activity against MCF-7 cell line than NH_2 group.

Compound **C4** and **C5**, similar to imidazole derivatives **C2** and **C3**, showed that NO_2 group had higher anticancer effect than NH_2 group against all tested cell lines. Overall, all compounds have no significant effect against HT-29 cell line and none of them shown more cytotoxic effect than doxorubicin as positive control.

Carbazole derivatives (**C4** and **C5)** showed higher cytotoxic activity against MCF-7 cell line in comparison to the other anticancer agents such as imidazolylphenylheterocyclic-2-

ylmethylenethiazole-2-amine derivatives [22]. Furthermore, compound **C4** and **C5**, had more cytotoxic activity on HeLa cell line than most of hybrid compounds of imidazole scaffold-based 2-benzylbenzofuran and carbazole alkaloide [23]. In addition,these compounds are effective on the greater number of cell lines than those mentioned above [22, 24], which showed the broader spectrum activity of our studied compounds against different cancer cell lines.

Physicochemical properties

Physicochemical properties of compounds including surface area, volume, hydration energy, Log P, polariability, reflectivity and mass are presented in Table 3.

Table 3. Physicochemical properties of compounds calculated by HyperChem 8.

Compound	Surface area	Volume	Hydration energy	Log P	Polarizability	Reflectivity	Mass
C1	874	1531	-8.41	6.65	62.99	159	522
C2	1105	1973	-18.51	11.1	80.31	210	824
C3	1083	1921	-16.98	9.67	79.33	204	764
C4	800	1430	-16.72	8.76	59.71	153	539
C5	772	1382	-15.13	7.28	58.73	153	479

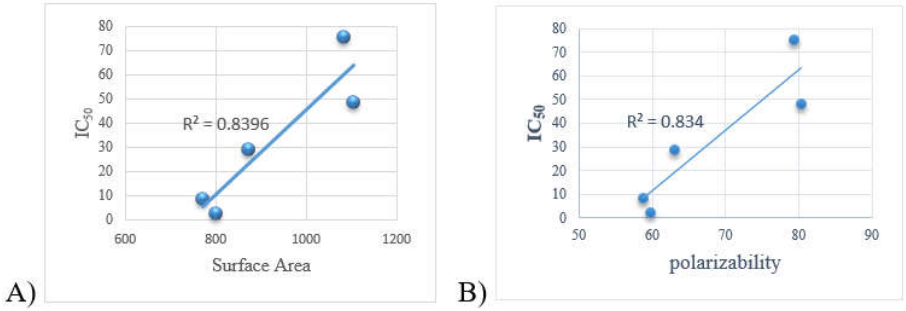


Figure 2. A plot of IC_{50} values on MCF-7 cell line against A) surface area and B) polarizability. Surface area and polarizability of compounds showed good correlation with IC_{50} values on MCF-7 cell line by $R^2 = 0.8396$ and $R^2 = 0.834$, respectively.

The IC_{50} values on MCF-7 cell line and physicochemical properties of compounds were plotted and the results showed that surface area and polarizability had good correlation than the other physicochemical properties.

The IC_{50} values on MCF-7 cell line showed good correlation with surface area and polarizability of compounds by $R^2 = 0.8396$ and $R^2 = 0.834$, respectively. The other physicochemical properties had low to moderate correlation with IC_{50} value (Figure 2).

Docking study

As shown in Table 4, the docking energy of compounds ranged from - 11.32 to -13.48 kcal/mol.

Table 4. Docking binding energy (kcal/mol) of DNA (1BNA) by AutoDock 4.2.

Docking binding energy (kcal/mol)	
Ligand/Receptor	1BNA
C1	-12.77
C2	-11.33
C3	-13.48
C4	-11.32
C5	-12.08

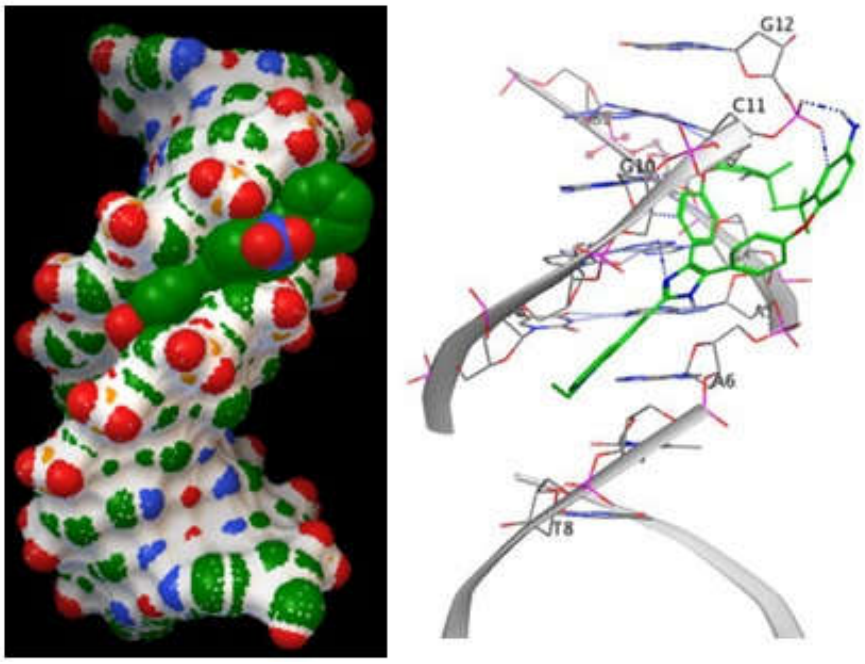


Figure 3. Interaction of compound 3 with DNA (1BNA). The amino groups of compound 3 were involved in hydrogen bonds with Adenosine 6 and Guanosine 4 of DNA. There was also exists an aren-H interaction between the imidazole ring and adenosine 5 of DNA.

Furthermore, 3D interactions of compound **C3** into minor groove of DNA was shown in the Figure 3. The amino groups of compound **C3** were involved in hydrogen bond interactions with adenosine 6 and guanosine 4. There was also exists an aren-H interaction between the imidazole ring and adenosine 5 of DNA.

Docking studies of these compounds were also performed on the DNA as proposed targets to found out their binding interactions and binding energies. Based on molecular docking results, it can be concluded that these compounds had stronger affinity to bound with DNA and compound **C3** with energy of -13.48 kcal/mol had the highest affinity to bound with this target.

CONCLUSIONS

In the present work, the cytotoxic activity of the five imidazole and carbazole compounds were evaluated using MTT test on three cell lines namely breast cancer (MCF-7), cervical cancer (HeLa) and colon cancer (HT-29). The most cytotoxic activity in the entire set was related to

carbazole derivative, compound **C4**. Based on these results, carbazole derivatives had better cytotoxic effects than imidazole derivatives and nitro substituted groups showed more cytotoxic activity than amino substituted groups. The docking simulations were carried out by means of AutoDock 4.2. to find the best pose of each ligand in the active site of the DNA and tubulin as proposed targets. Base on the docking binding energies, these compounds had stronger affinity in binding to the DNA, and the compound **C3** had the highest docking energy when docked into the DNA. Although the molecular weight of these compounds is more than 500, biological results show that these compounds have acceptable anti-cancer effects. The range below 500 is one of Lipinski's rules that usually applies to compounds that can be administered orally. Therefore, one of the limitations of these compounds will probably be the route of their administration. The findings suggest that the new derivatives of imidazole and carbazole had the potential to be considered as cancer treatment and should be further explored in future cancer therapy.

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