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

Behbood Taheri¹, Mehdi Taghavi², Mansoreh Zarei³, Narges Chamkouri⁴ and Ayyub Mojaddami¹,⁵*

¹Toxicology Research Center, School of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
²Department of Chemistry, Faculty of Science, Shahid Chamran University of Ahvaz, Ahvaz, Iran
³Medical Physics Department, School of Medicine, Ahvaz Jundishapur University of Medical Science, Ahvaz, Iran
⁴Abadan School of Medical Sciences, Abadan, Iran
⁵Department of Medicinal Chemistry, School of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

(Received February 2, 2020; Revised October 7, 2020; Accepted October 20, 2020)

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 IC₅₀ < 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 IC₅₀ 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 IC₅₀ values on MCF-7 cell line investigated. Surface area and polarizability of compounds showed good correlation by R² = 0.8396 and R² = 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 (IC₅₀ = 150 nM), higher than etoposid (IC₅₀ = 490 nM) (Figure 1) [5].

*Corresponding author. E-mail: mojaddami.a@gmail.com
This work is licensed under the Creative Commons Attribution 4.0 International License
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\textsubscript{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-yl)-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\textsuperscript{3} 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:

\[
\% \text{ Cell Viability} = \frac{\text{Optical Density of Test}}{\text{Optical Density of Control}} \times 100
\]
Imidazole and carbazole derivatives as potential anticancer agents

% Cell Inhibition = 100 - % Cell Viability

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

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, polarizability, 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\textsubscript{50} values.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
Compound & R & (IC\textsubscript{50} ± SD) μM & \\
\hline
 & & MCF-7 & HeLa & HT-29 \\
\hline
C1 & - & 28.7 ± 4.1 & 39.6 ± 8.3 & >100 \\
C2 & \begin{array}{c}
\text{NO}_2
\end{array} & 48.3 ± 4.1 & >100 & >100 \\
C3 & \begin{array}{c}
\text{NH}_2
\end{array} & 75.3 ± 12.4 & >100 & 76.8 ± 15.5 \\
C4 & \begin{array}{c}
\text{NO}_2
\end{array} & 2.5 ± 1.2 & 5.4 ± 1.3 & 4.0 ± 0.9 \\
C5 & \begin{array}{c}
\text{NH}_2
\end{array} & 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 \\
\hline
\end{tabular}
\end{table}

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

As shown above, carbazole derivatives, compounds namely: C4 and C5 with IC\textsubscript{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 > C5 > C1 > C2 > C3.

Compound C4 was the most potent compound against all cell lines MCF-7, Hela and HT-29 with the IC\textsubscript{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\textsubscript{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\textsubscript{2} and NH\textsubscript{2} substitution, respectively, indicated that the NO\textsubscript{2} group had a greater effect on cytotoxic activity against MCF-7 cell line than NH\textsubscript{2} group.

Compound C4 and C5, similar to imidazole derivatives C2 and C3, showed that NO\textsubscript{2} group had higher anticancer effect than NH\textsubscript{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-
Imidazole and carbazole derivatives as potential anticancer agents

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 alkaloid [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, polarizability, reflectivity and mass are presented in Table 3.

| 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 polarizibility 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.

| 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.

ACKNOWLEDGEMENTS

The authors would like to thank research deputy of Ahvaz Jundishapur University of Medical Sciences who support this work. The collaboration of Medicinal Chemistry, Faculty of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, in providing the required facilities for this work is greatly acknowledged. This article is extracted from thesis by Behbood Taheri (grant Number: GP96063 and Ethic: IR.AJUMS.REC.1396.525).

REFERENCES

1. Kamel, M.M.; Abdo N.Y.M. Synthesis of novel 1,2,4-triazoles, triazolothiadiazines and triazolothiadiazoles as potential anticancer agents. *Eur. J. Med. Chem.* 2014, 86, 75-80.
2. Taj, T.; Kamble, R.R.; Gireesh, T.; Hunmur, R.K.; Margankop, S.B. One-pot synthesis of pyrazoline derivatised carbazoles as antitubercular, anticancer agents, their DNA cleavage and antioxidant activities. *Eur. J. Med. Chem.* 2011, 46, 4366-4373.
3. Nagarapu, L.; Gaikwad, H.K.; Sarikonda, K.; Mateti, J.; Bantu, R.; Raghu, P.; Manda, K.M.; Kalvendi, S.V. Synthesis and cytotoxicity evaluation of 1-[3-(9H-carbazol-4-yloxy)-2-hydroxypropyl]-3-aryl-1H-pyrazole-5-carboxylic acid derivatives. *Eur. J. Med. Chem.* 2010, 45, 4720-4725.
4. Ohira, M.; Iwasaki, Y.; Tanaka, C.; Kuroki, M.; Matsuo, N.; Kitamura, T.; Yukihiro, M.; Morimoto, H.; Pang, N.; Liu, B. A novel anti-microtubule agent with carbazole and benzohydrazide structures suppresses tumor cell growth in vivo. *Biochim. Biophys. Acta Gen. Subj.* 2015, 1850, 1676-1684.
5. Hajji, Y.; Neagoie, C.; Biannic, B.; Chilloux, A.; Vedrenne, E.; Baldeyrou, B.; Bailly, C., Mérour, J.-Y.; Rosca, S.; Routier, S. Synthesis and biological activities of new furo [3, 4-b] carbazoles: Potential topoisomerase II inhibitors, *Eur. J. Med. Chem.* 2010, 45, 5428-5437.
6. ÖzKay, Y.; Işkıdağlı, I.; Incenas, Z.; Akalın, G. Synthesis of 2-substituted-N-[4-(1-methyl-4,5-diphenyl-1H-imidazole-2-yl) phenyl] acetamide derivatives and evaluation of their anticancer activity. *Eur. J. Med. Chem.* 2010, 45, 3320-3328.
7. Yurttaş, L.; Duran, M.; Demirayak, Ş.; Gencer, H.K.; Tunah, Y. Synthesis and initial biological evaluation of substituted 1-phenylmino-2-thio-4,5-dimethyl-1H-imidazole derivatives. *Bioorg. Med. Chem. Lett.* 2013, 23, 6764-6768.
8. Salerno, L.; Pittala, V.; Romeo, G.; Modica, M.N.; Marrizzo, A.; Siracusa, M.A.; Sorrenti, V.; Giacomo, C.Di.; Vanella, L.; Parayath, N.N. Novel imidazole derivatives as heme oxygenase-1 (HO-1) and heme oxygenase-2 (HO-2) inhibitors and their cytotoxic activity in human-derived cancer cell lines. *Eur. J. Med. Chem.* 2015, 96, 162-172.
9. Ghaemy, M.; Hassanzadeh, M.; Taghavi, M.; Nasab, S.M.A. Synthesis and characterization of trifluoromethylated poly(ether-imidazole-imide) based on unsymmetrical diamine

*Bull. Chem. Soc. Ethiop.* 2020, 34(2)
bearing carbazole and imidazole chromophores in ionic liquids: Study of electrochemical properties by using nanocomposite electrode. J. Fluorine Chem. 2012, 142, 29-40.

10. Ghaemy, M.; Sharifi, S.; Nasab, S.M.A.; Taghavi, M. Synthesis and characterization of novel poly (amide-ether)s bearing imidazole pendants: Study of physical and optical properties. Polym. 2013, 70, 1125-1142.

11. Taghavi, M.; Ghaemy, M.; Hassanzadeh, M.; Nasab, S.M.A. A quick and green ionic liquid-mediated approach for the synthesis of high-performance, organosoluble and thermally stable polyimides. Chinese J. Polym. Sci. 2013, 31, 679-690.

12. Fereidoonnezhad, M.; Faghhi, Z.; Mojaddami, A.; Sakhteman, A.; Rezaei, Z. A comparative docking studies of dichloroacetate analogues on four isozymes of pyruvate dehydrogenase kinase in humans. Dent. 2016, 1(4), 5.

13. Eswar, N.; Eramian, D.; Webb, B.; Shen, M-Y.; Sali, A. Protein structure modeling with MODELLER, structural proteomics: High-throughput methods. Methods in Molecular Biology (Clifton, N.J.) 2008, 426, 145-159.

14. Mojaddami, A.; Sakhteman, A.; Fereidoonnezhad, M.; Faghhi, Z.; Najdian, A.; Khabnadideh, S.; Sadeghpour, H.; Rezaei, Z. Binding mode of triazole derivatives as aromatase inhibitors based on docking, protein ligand interaction fingerprinting, and molecular dynamics simulation studies. Res. Pharm. Sci. 2017, 12(1), 21-30.

15. Rezaei, Z.; Fereidoonnezhad, M.; Faghhi, Z.; Sadeghpour, H.; Mojaddami, A.; Sakhteman, A. Comparison of docking procedures and its efficiency for betasecretase, aromatase and pyruvate dehydrogenase kinase inhibitors. Trends Pharmacol. Sci. 2017, 3, 31-42.

16. Khaledi, M.; Ziyaee Qychan Atiq, H.; Chamkouri, N.; Mojaddami, A. Molecular docking and druggability studies of terpenoid-derived metabolites from marine sponges as IL-17A inhibitors. Eurasian Chem. Commun. 2019, 1, 419-432.

17. Fereidoonnezhad, M.; Faghhi, Z.; Jokar, E.; Mojaddami, A.; Rezaei, Z.; Khosnavianzadeh, M. QSAR, molecular docking and protein ligand interaction fingerprint studies of N-phenyl dichloroacetamide derivatives as anticancer agents. Trends Pharmacol. Sci. 2016, 2, 34.

18. Fereidoonnezhad, M.; Mojaddami, A.; Rezaei, Z.; Sakhteman, A. Comparative QSAR analysis, molecular docking and PLIF studies of some N-arlylphenyl-2,2-dichloroacetamide analogues as anticancer agents. Iran. J. Pharm. Res. 2017, 16, 981-998.

19. Zare, S.; Fereidoonnezhad, M.; Afsar, D.; Ramezani, Z. A comparative QSAR analysis and molecular docking studies of phenyl piperidine derivatives as potent dual NK 1 R antagonistsserotonin transporter (SERT) inhibitors. Comput. Biol. Chem. 2017, 67, 22-37.

20. Shamsimeymandi, R.; Pourshojaie, Y.; Eskandari, K.; Mohammadi-Khanaposhtani, M.; Abiri, A.; Khodadadi, A.; Langarizadeh, A.; Sharififar, F.; Amirheidari, B.; Akbarzadeh, T. Design, synthesis, biological evaluation, and molecular dynamics of novel cholinesterase inhibitors as anti-Alzheimer's agents. Archiv. Der. Pharmazie 2019, 352, 1800352.

21. Pourshojaie, Y.; Abiri, A.; Eskandari, R.; Dourandish, F.; Eskandari, K.; Asadipo, A. Synthesis, biological evaluation, and computational studies of novel fused six-membered O-containing heterocycles as potential acetylcholinesterase inhibitors. Comput. Biol. Chem. 2019, 80, 249-258.

22. Parekh, N.M.; Mistry, B.M.; Pandurangan, M.; Shinde, S.K.; Patel, R.V. Investigation of anticancer potencies of newly generated Schiff base imidazolylphenylheterocyclic-2-ylmethylenethiazole-2-amines. Chin. Chem. Lett. 2017, 28, 602-606.

23. Wang, X-Q.; Liu, L-X.; Li, Y.; Sun, C.J.; Chen, W.; Li, L.; Zhang, H.B.; Yang, X.D. Design, synthesis and biological evaluation of novel hybrid compounds of imidazole scaffold-based 2-benzylbenzofuran as potent anticancer agents. Eur. J. Med. Chem. 2013, 62, 111-121.