Unveiling the Full Potential of 2-aryl-1H-phenanthro [9,10-d] imidazoles as Cytotoxic Agents *vs* AGS, HepG2, and MCF-7 Cell lines

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ABSTRACT: *A few 2-aryl-1H-phenanthro [9,10-d] imidazoles were synthesized and assessed for their cytotoxicity against MCF-7, HepG2, and AGS cell lines using MTT assay. Cellular assessments showed that phenanthroimidazoles were extremely potent cytotoxic agents (sub-nanomolar IC_{50}s). Maximum effect was recorded for para-N-phenyl acetamide containing derivative against AGS cells (IC_{50} 0.07 nM). It was also revealed that phenanthroimidazole derivatives showed better cytotoxicity against MCF-7 and AGS cells when compared to HepG2 cells. Minimum cytotoxicity was reported for para-methylphenyl derivatives within HepG2 cancer cells (IC_{50} 7608.07 nM). Structure-activity relationship studies indicated that incorporation of nitrogen/oxygen-containing polar groups such as N-acetyl or nitro into para/meta positions of phenyl ring significantly enhanced the cytotoxicity against AGS cells. A similar trend was observed in meta-nitro derivatives vs MCF-7 cells. It was revealed that even the least potent compound exhibited cytotoxic activity in the range of low micromolar IC_{50}. The results of this study proposed 2-aryl-1H-phenanthro [9,10-d] imidazoles as privileged structures for further in vivo studies.*

KEYWORDS: *Cancer; Cytotoxicity; Phenanthroimidazole; AGS, HepG2, MCF-7.*

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INTRODUCTION

Developed urbanism and alterations of lifestyle faced people with different chemical agents and water/air pollution. These factors along with genetic and other aspects led to the enhanced cancerous population and it has been estimated that by 2020, almost 15 million cases of cancer may be reported per year. [1]Nowadays, cancer is the second cause of mortality in industrial countries and a lot of money is spent on cancer therapy via different strategies.

According to the World Health Organization (WHO) on cancer statistics, the high importance of cancer in death rates is highlighted [2] and due to the high prevalence of the disease, its treatment or control is a key priority [3] Numerous anticancer agents are in hand for chemotherapeutic purposes, but due to the low selectivity of these drugs and resistance concerns, cessation of therapies is expected and hence there is an ever-growing requirement toward design and development of novel small molecule chemotherapeutic agents. [4,5]

Heterocyclic compounds are privileged structures with considerable pharmacological activities and so many drugs possess different types of heterocycles making them similar to the biologically active compounds within biologic systems [6,7]. Within such molecules, *N*-heterocycles are very important building blocks in organic and medicinal chemistry. [8]

Many scientific efforts have been attributed to the synthesis of various imidazole derivatives as appropriate *N*-heterocyclic structures since they exhibit interesting biological activities. [9.10]Besides synthetic agents, the imidazole ring system is one of the most prominent substructures found in a large number of bioactive natural products. [11] Moreover**;** a great number of synthetic methods have been reported for the preparation of multi-substituted imidazoles which has paved the way toward the development of novel imidazole-based structures as bioactive compounds. [12]

A literature survey indicates that besides several pharmacologic activities, particular imidazole structures have been reported as potential anticancer agents. To explain more, 2-substituted-*N*-[4-(1-methyl-4,5-diphenyl-1*H*-imidazole-2-yl) phenyl] acetamides, [13] imidazole piperazines, [14] 2-amino-1-arylidenamino imidazoles [15] are some examples. Some new literature reported the synthesis of imidazole derivatives. [16-19]

In the light of the above explanations and also due to our interest in the design and synthesis of novel cytotoxic nitrogen-containing heterocycles, [20-22] herein we report the synthesis, characterization, and *in vitro* cytotoxic activities of new 2-aryl-1H-phenanthro [9,10-d] imidazole derivatives against MCF-7, HepG2, and AGS cell lines.

EX{ERIMENTAL SECTION

Chemistry

All materials and reagents were purchased from Merck and Aldrich and used without further purification. Melting points were determined on an Electrothermal type 9100 melting point apparatus and are uncorrected. The IR spectra were recorded on a Thermo Nicolet AVATAR-370 FT-IR spectrophotometer and ^{1}H-NMR spectra were obtained on a Bruker DRX400 spectrometer. CHN/CHNS analysis was performed using CHNS-932 Leco analyzer and the results were within ± 0.4% of the theoretical values.

Preparation of silica-supported $La_{0.5}Pb_{0.5}MnO_3$ nanoparticles (30%w/w)

Nano $La_{0.5}Pb_{0.5}MnO_3$ Perovskite was prepared according to the reported method. [23] Silica was put into the oven for 2 hours under 90° C, then catalyst (0.3 g) along with silica (1 g) were worn out into glass mortar for about 1 hour until the mixture was bright and unified. For more clarification, IR spectra of $La_{0.5}Pb_{0.5}MnO_3$ nanoparticles in the silica-free and silica-supported cases were incorporated as supplementary Fig. 1.

After synthesis of $La_{0.5}Pb_{0.5}MnO_3$ nanoparticles, for characterization of this catalyst, the morphology of the sample was determined using SEM analysis. Fig. 1 demonstrates the micrograph related to the samples prepared through the sol-gel modified Pechini technique and calcined 650 °C.

According to the SEM images, the surface is obviously porous and it appears that the size of grown particles is uniform. The size of pores is in the range of 30-188 nm. Moreover, SEM image shows that besides the presence of bigger particles, there were relatively smaller particles on the surface. However, the main particles on the surface were the bigger ones. The aggregation of smaller particles (in the nm scale) may cause the creation of larger LPMO NPs on the surface.

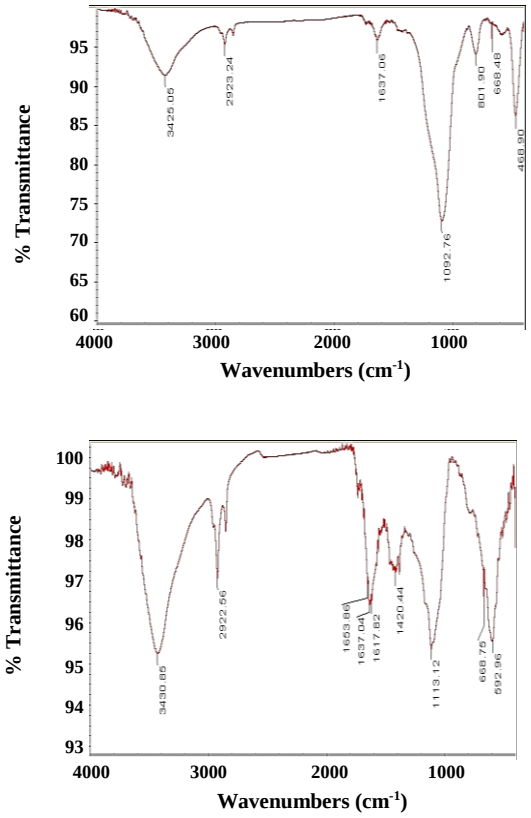


Fig. 1: Infrared spectra of (a) $La_{0.5}Pb_{0.5}MnO_3$ and (b) silica-supported $La_{0.5}Pb_{0.5}MnO_3$ nanoparticles

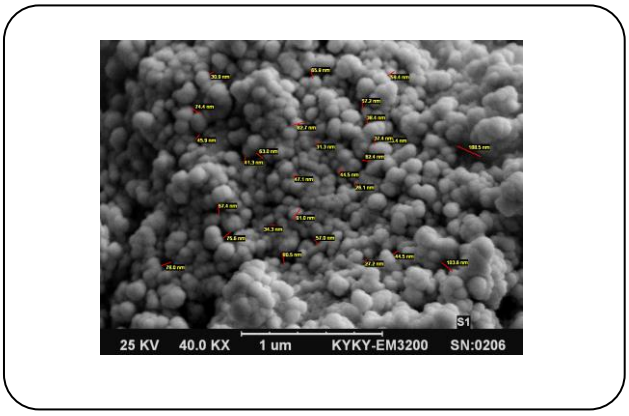


Fig 2: SEM image of $La_{0.5}Pb_{0.5}MnO_3$ nanoparticles

FT-IR spectra were obtained for single LPMO and S-LPMO samples in the range of 400-4000 cm^{-1}. Fig. 2 shows the FT-IR spectrum of LPMO perovskite nanoparticles, and Fig.3 shows the FT-IR spectrum of S-LPMO sample. The IR bands at 3430 and 1638 cm^{-1} are due to the stretching and bending vibration of H_2O molecules, respectively. The very strong IR band at 1113 cm^{-1} is usually assigned to the Si-O-Si asymmetric vibrations. The picks at 668 and 592 cm^{-1} corresponding to LPMO perovskite coated on SiO_2 are clearly observed in this spectrum [23].

A typical procedure for the synthesis of phenanthrene imidazole derivatives

A mixture of 9, 10-phenanthraquinone (**1**) (1 mmol), aldehyde (**2**) (1 mmol), ammonium acetate (2.5 mmol), and nano-catalyst (0.04 g) in ethanol (10 mL) was stirred and refluxed for 2 hours. After completion of the reaction (the reaction progress was monitored by TLC using *n*-hexane: ethyl acetate as eluent) the catalyst was separated via filtration and the organic phase was evaporated. The resulting solid product was washed with cold water (3×20 mL) and recrystallized in ethanol to give a pure product. Physical and characteristic data of a few final compounds are listed below. Other compounds were compared with a synthesized compound that was reported in a published paper [24]. All the compounds are summarized in Table 1.

2-(3-Nitrophenyl)-1H-phenanthro [9,10-d] imidazole (**3b**)

Yellow crystal, M.p.: 316 °C; IR (KBr) ν_{max} (cm^{-1}): 3195, 1615, 1531, 1511, 1347; ^{1}HNMR (300 MHz, DMSO-d_6) δ (ppm) 7.63-8.83 (m, 12 H, Ar-H), 13.80 (s, 1H, NH). Anal. Calcd for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31. Found: C, 73.32; H, 4.54; N, 12.38.

2-(p-tolyl)-1H-phenanthro [9,10-d] imidazole (**3c**)

Yellow crystal, M.p.: 290-292 °C; IR (KBr) ν_{max} (cm^{-1}): 3420, 2922, 1606, 1463, 1416; ^{1}HNMR (300MHz, DMSO-d_6) δ (ppm) 2.38 (s, 3H, CH_3), 7.28-8.82 (m, 12 H, Ar-H), 13.36 (s, 1H, NH). Anal. Calcd for $C_{22}H_{16}N_2$: C, 85.69; H, 5.23; N, 9.08. Found: C, 85.78; H, 5.15; N, 9.18.

2-(2-Chlorophenyl)-1H-phenanthro [9,10-d] imidazole (**3e**)

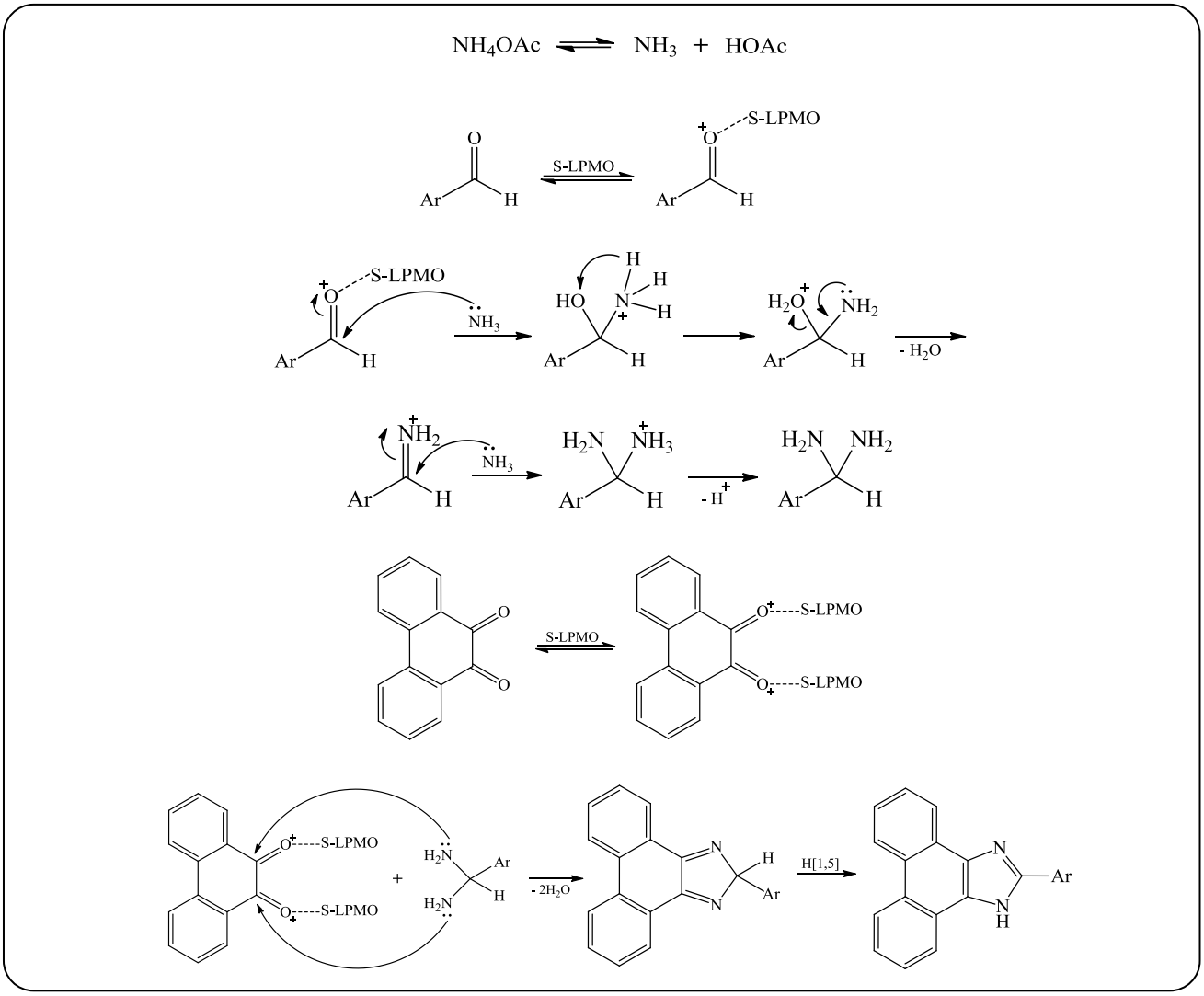
Yellow crystal, M.p.: 233-234 °C; IR (KBr) ν_{max} (cm^{-1}): 3584, 1674, 1592, 1451; ^{1}HNMR (300MHz, DMSO-d_6) δ (ppm) 7.37-8.88 (m, 12H, Ar-H), 13.57 (s, 1H, NH). Anal. Calcd for $C_{21}H_{13}ClN_2$: C, 76.7; H, 3.99; N, 8.52; Cl, 10.78. Found: C, 76.82; H, 3.93; N, 8.46; Cl, 10.71 .

N-(4-(1H-phenanthro [9,10-d] imidazol-2-yl)phenyl) acetamide (**3i**)

Yellow crystal, M.p.: 246-248 °C; IR (KBr) ν_{max} (cm^{-1}): 3461, 2480, 1673, 1593; ^{1}HNMR (300 MHz, DMSO-d_6) δ (ppm) 2.08 (s, 3H, CH_3), 7.28-8.82 (m, 12H, Ar-H), 10.17 (s, 1H, NH), 13.40 (s, 1H, NH). Anal. Calcd for

Table 1: One-pot three component synthesis of substituted imidazoles using $La_{0.5}Pb_{0.5}MnO_3$ nanoparticles supported on silica as an acidic catalyst

Entry	Ar	Product	Yield (%)	m.p. (°C) Found/reported[Ref.]
1	C_6H_5	3a	89	286-288/>300[24]
2	4-$NO_2C_6H_4$	3b	92	>300/>300[24]
3	3-$NO_2C_6H_4$	3c	89	269-271/278-280[25]
4	4-CNC_6H_4	3d	86	>300/>300[24]
5	2-ClC_6H_4	3e	87	232-234/236-237[24]
6	4-ClC_6H_4	3f	94	268-270/263-265[25]
7	4-$MeOC_6H_4$	3g	83	258-260/265-267[25]
8	4-MeC_6H_4	3h	84	290-292/292-294[25]
10	4-$CH_3CONHC_6H_4$	3i	74	246-248/ new



Scheme 1: Mechanism for the formation of imidazole derivatives in the presence of nanocatalyst.

Table 2: Comparison of some reported methods with the present protocol for the synthesis of imidazole derivatives.

entry	condition	Time(min)	Yield (%)	ref
1	I2 (5 mol%)/ 75 °C/ solvent -free	15	98	26
2	L-proline (15 mol%)/ 60 °C/ CH3OH	540	88	27
3	(WD/ SiO2) (0.6 g)/ r.t./ solvent -free	120	88	28
4	Nano SiO2/H3PO4 (0.1 g)/ 140 °C / solvent -free	180	85	29
5	NBS (15 mol%)/ 120 °C/ solvent -free	45	92	30
6	SBA/TFE (0.1 g/3 mL)/ 90 °C/ solvent -free	180	92	31
7	$La_{0.5}Pb_{0.5}MnO_3$ *nanoparticles*	20	89	This work

C30H22N2O: C, 84.48; H, 5.19; N, 6.57. Found: C, 84.58; H, 5.28; N, 6.68.

We prepared a range of replaced imidazoles (Table 4). In all cases, aldehydes reacted effectively with replaced carrying either electron-donating (entries 7-10) or electron-withdrawing (Entries 2-4) groups and provided the estimated products in good yields. (Table 1)

The mechanism of the reaction was proposed in Scheme 2. Ammonia molecules are obtained from ammonium acetate. We think that the aldehyde and 1,2-dicarbonyl compounds including [9,10] phenanthraquinone at first activated by S-LPMO as Lewis acid, in the rate-determining step.

The data in Table 1 affirm the high efficacy of the synthesized nanocatalyst to gain the multi-substituted imidazoles. The general applicability of catalysts for various derivatives of imidazoles was investigated. It was observed that benzaldehyde and its activated derivatives as well as deactivated aromatic aldehydes gave their corresponding imidazoles 3a-i successfully.

A comparison between the present studies for the synthesis of imidazoles with some other reported results in the literature have been shown in Table 2. Performing the reaction at room temperature, utilizing a small amount of the catalyst, reusability within several runs, relatively short reaction time, and high yield, in addition to simple preparation of nano $La_{0.5}Pb_{0.5}MnO_3$ are interesting advantages of this newly synthesized nanocatalyst in the synthesis of multi-substituted imidazoles. (Table 2)

Biological activity

Reagents and Chemicals

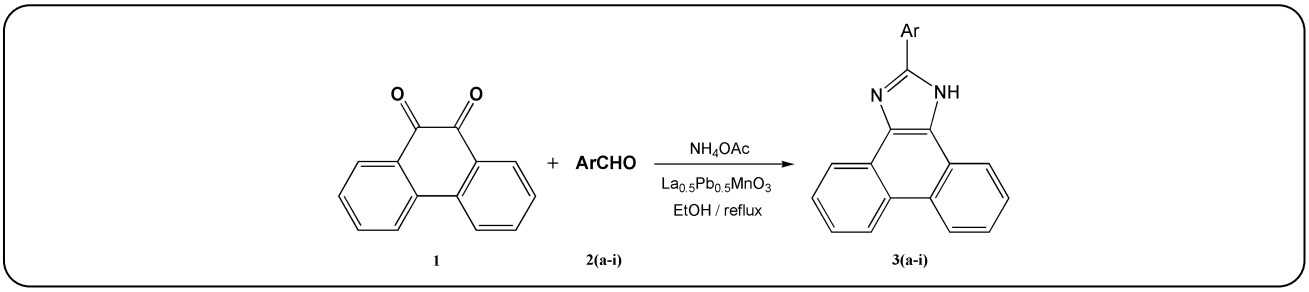
RPMI 1640, Fetal Bovine Serum (FBS), trypsin, and phosphate-buffered saline (PBS) were purchased from Biosera (Ringmer, UK). 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was obtained from Sigma (Saint Louis, MO, USA) and penicillin/streptomycin was purchased from Invitrogen (San Diego, CA, USA). Cisplatin and dimethyl sulphoxide was obtained from EBEWE Pharma (Unterach, Austria) and Merck (Darmstadt, Germany), respectively.

Cell lines

MCF-7 (human breast adenocarcinoma), HepG2 (human liver cancer), and AGS (human gastric cancer) cells were obtained from the National Cell Bank of Iran, Pasteur Institute, Tehran, Iran. All cell lines were maintained in RPMI 1640 supplemented with 10% FBS, 100 units/mL penicillin-G, and 100 μg/mL streptomycin. Cells were grown in monolayer cultures.

Cytotoxic effect

Cell viability following exposure to synthetic compounds was estimated by using the MTT reduction assay [32]. Cells were plated in 96-well microplates at a density of 1×10^4 cells per well (200 μL per well). Control wells contained no drugs and blank wells contained only a growth medium for background correction. After cell attachment, the medium was removed, and cells were incubated with a serum-free medium containing 1 mg/mL of the synthetic compounds by 1/4 serial dilutions. Compounds were all first dissolved in DMSO and then diluted in a medium so that the maximum concentration of DMSO in the wells did not exceed 0.5%. Cells were further incubated for 24 h. At the end of the incubation time, the medium was removed and MTT was added to each well at a final concentration of 0.5 mg/mL, and plates were incubated for another 4 h at 37°C. Then formazan crystals were solubilized in 200 μL DMSO. The optical density



Scheme 2: Multi-component synthesis of phenanthroimidazoles in the presence of Perovskite catalyst.

measured at 570 nm with background correction at 655 nm using a Bio-Rad microplate reader (Model 680). The percentage of inhibition of viability compared to control wells was calculated for each concentration of the compound and IC_{50} values were calculated with SigmaPlot version 12.5. The absorbance of wells containing no cells was subtracted from sample well absorbance before calculating the percentage of inhibition. Each experiment was carried out in triplicate.

RESULTS AND DISCUSSION

In continuation to our efforts toward using solid acids as a heterogeneous catalyst in organic reactions [20]. we reported the synthesis of 2-aryl-1H-phenanthro [9,10-d] imidazoles via one-pot three-component condensation of [9,10] phenanthraquinone (**1**), aromatic aldehyde (**2a-i**), and ammonium acetate in the presence of $La_{0.5}Pb_{0.5}MnO_3$ nanoparticles supported on silica as a catalyst. The chemical structures of all synthesized 2-aryl-1H-phenanthro [9,10-d] imidazoles were confirmed by spectroscopic methods. Synthetic routes to compounds **3a-i** are depicted in Scheme 1.

Cytotoxic activity

Prepared 2-aryl-1H-phenanthro [9,10-d] imidazole derivatives (**3a-i**) were assessed for their cytotoxic activity against three human cancer cell lines (MCF-7, HepG2, and AGS) in terms of their IC_{50} values (Table 3).

Analysis of SAR

On the basis of obtained cytotoxicity data (Table 2), following SARs may be ruled out:

● 2-aryl-1H-phenanthro [9, 10-d] imidazoles exhibited the maximum cytotoxic effect against AGS cell lines while the least cytotoxic effects were observed for HepG2 cancer cells. Similar studies on bulkier derivatives of 2-(4-methoxynaphthalen-1-yl)-1-(4-methoxyphenyl)-1H phenanthro[9,10-d] imidazole indicated moderate activities against KB cancer cells. [32,33]

● The incorporation of nitrogen and oxygen-containing polar substituents into the *para* or *meta* positions of phenyl ring enhanced the cytotoxic effect of 2-aryl-1H-phenanthro [9,10-d] imidazoles within all of the assessed cell lines. Careful inspection of the data revealed that such effect was maximum in the case of AGS cells (**3i** and **3b**; IC_{50}=0.07 & 0.14 nM, respectively). The observed effect might be attributed to the enhancement of some favorable electrophilic or nucleophilic interaction sites within structures of ligands. Anticancer effects of 2-substituted-*N*-[aryl-1*H*-imidazole-2-yl) phenyl compounds with *para*-acetamide substituents against colon carcinoma cells were reported before. [13]

● Evaluation of cytotoxicity data against HepG2 cells revealed the superior activity of compounds **3b**, **3d,** and **3i**. A characteristic structural feature of these derivatives could be explained via their polar substituents on the *meta* (**3b**) and *pa*ra (**3d** & **3i**) positions of phenyl ring. Such a trend proposed the possible enhancing effects of electron-withdrawing group (EWG) at *meta* position and electron-donating ones at *para* position [34]. The effect might be detectable for resonance EDGs in HepG2 and AGS cells since compound **3c** with 4-methyl substituent exhibited decreased cytotoxic effect. The effect on MCF-7 cell lines was found to be significantly different since superior cytotoxicity (IC_{50}=2.59 nM) could be achieved.

● Compound **3c** contained *para*-methyl group on the phenyl ring and was significantly a weaker cytotoxic agent than its analogs within AGS cancer cells **(**IC_{50}=1051.28 nM). A similar trend could be detected for HepG2 cells (**3c**; IC_{50}=7608.07 nM). Such results along with other cytotoxic data of more polar derivatives emphasized the possible role of electrostatic or H-bond interactions of these locations with the site of action in AGS cell lines.

Table 3: Cytotoxic activity of 2-aryl-1H-phenanthro [9, 10-d] imidazoles assessed by the MTT reduction assay.

Compound No.	IC_{50} (nM)		
	MCF-7	HepG2	AGS
3a	101.42±11.72	285.37±116.95	90.62±7.51
3b	1.27±0.14	12.71±0.37	0.14±0.06
3c	2.59±0.26	7608.07±234.60	1051.28±296.636
3d	3.78±0.03	30.79±9.14	11.26±1.79
3e	220.43±6.78	1523.59±80.32	190.98±12.48
3f	4.88±0.01	1525.72±69.85	113.63±10.95
3g	65.10±9.82	130.78±4.32	99.03±11.95
3h	8.22±0.18	463.45±40.85	179.94±1.05
3i	2.46±0.49	28.51±3.07	0.07±0.02
Cis-platin	6090±2.29	23650±2.86	11490±2.99

● It was interestingly found that compounds **3e** and **3f** exhibited relatively similar cytotoxic effects against HepG2 cells. These results indicated that, unlike other cell lines, the position of the chlorine atom was not a determinant of the HepG2 cell growth inhibition of chlorophenyl substituted phenanthro [9, 10-d] imidazoles. Such rationalization was could not be considered for HepG2 and MCF-7 cells since in both of these, and especially in the case of MCF-7, para-Cl substituted compound (**3f**) was a better cytotoxic agent than *ortho*-Cl substituted one (**3e**).

● Compound **3b** seemed to be an appropriate candidate for developing multi-target anti-tumoral agents since it exhibited excellent cell growth inhibitory activities in all three cell lines.

CONCLUSIONS

It was revealed that 2-aryl-1H-phenanthro [9,10-d] imidazole analogues showed good to excellent cytotoxic activities against MCF-7, HepG2, and AGS human cancer lines, while a superior potency could be detected in the case of AGS cells (**3i**; IC_{50}=0.07 nM). SAR exploration indicated that polar substituents including nitrogen and oxygen atoms on the *para* or *meta* positions of phenyl ring considerably enhanced the cytotoxic effect particularly against AGS cell lines. These results might emphasize the possible electrostatic/H-bond interactions of such polar compounds in their site of action. The outcomes of this study may provide structural features of 2-aryl-1H-phenanthro [9,10-d] imidazoles for the rational design of potent cytotoxic molecules.

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REFERENCES

[1] Dueñas-González A., García-López P., Herrera L A., Medina-Franco J.L., González-Fierro A., Candelaria M., The Prince and the Pauper. A Tale of Anticancer Targeted Agents, *Mol*ecular *Cancer*, **7** :82 (2008).

[2] Bray F., Ferlay J., Soerjomataram I., Siegel RL., Torre LA., Jemal A., Global Cancer Statistics: GLOBOCAN, Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries, *CA Cancer Journal Clinic*, **68(6)**: 394-424(2018).

[3] Farhood B., Geraily G., Alizadeh A., Incidence and Mortality of Various Cancers in Iran and Compare to other Countries: a Review Article, *Iranian Journal of Public Health*, **47(3)**: 309-316 (2018).

[4] Hassan G S., Kadry H H., Abou-Seri S.M., Ali M.M., El-Din Mahmoud A.E., Synthesis and *in vitro* Cytotoxic Activity of Novel Pyrazolo [3,4-d] Pyrimidines and Related Pyrazole Hydrazones Toward Breast Adenocarcinoma MCF-7 Cell Line, *Bioorganic and Medicinal Chemistry*, **19:** 6808 (2011).

[5] Spaczyńska E., Mrozek-Wilczkiewicz A., Malarz K., Kos J., Gonec T., Oravec M., Gawecki R., Bak A., Dohanosova J., Kapustikova I., Liptaj T., Jampilek J., Musiol R., Design and Synthesis of Anticancer 1-hydroxynaphthalene-2-carboxanilides with a p53 Independent Mechanism of Action, *Scientific. Report.*, **9**: 6387(2019).

[6] Bajaj S., Asati V., Singh J., Roy P.P., 1,3,4-Oxadiazoles: An Emerging Scaffold to Target Growth Factors, Enzymes and Kinases as Anticancer Agents, *European Journal of Medicinal Chemistry*, **97**: 124 (2015).

[7] Heidary Alizadeh B., Vosooghi M., Khoobi M., Javidnia A., Panah F., Safavi M., Ardestani S., Shafiee A., Synthesis and Cytotoxic Activity of Novel 9-[hydroxy (substituted phenyl) Methyl]-2,2-dimethyl-2,3,8,9-tetrahydro-4H,10H-Pyrano [2,3-f]chromene-4,10-diones, *Iran. J. Chem. Chem. Eng. (IJCCE)*, **29**: 189 (2010).

[8] Vessally E., Soleimani-Amiri S., Hosseinian A., Edjlalid L ., Bekhradnia A., New Protocols to Access Imidazoles and Their Ring Fused Analogues: Synthesis from *N*-Propargyl Amines, *RSC Advance*, **7**: 7079 (2017).

[9] Alkahtani H M., Abbas A Y., Wang S., Synthesis and Biological Evaluation of benzo[d]imidazole Derivatives as Potential Anti-Cancer Agents, *Bioorganic and Medicinal Chemistry Letters*, **22(3)**: 1317(2012).

[10] Navidpour L., Shadnia H., Shafaroodi H., Amini M., Dehpour A.R., Shafiee A., Design, Synthesis and Biological Evaluation of Substituted 2-Alkylthio-1,5-Diarylimidazoles as Selective COX-2 Inhibitors, *Bioorg*anic *and Medicinal Chem*istry, **15**: 1976 (2007).

[11] Forte B., Malgesini B., Piutti C., Quartieri F., Scolaro A., Papeo G.A., A Submarine Journey: The Pyrrole-Imidazole Alkaloids Drugs, *Marine Drugs*, **7**: 705 (2009).

[12] Bharti A., Pandeya S.N., Various Approaches for Synthesis of Imidazole Derivatives, *International journal of research in Ayurveda Pharmacology*, **2(4)**: 1124 (2011).

[13] Özkay Y., Isikdag I., Incesu Z., Akalin 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, *European Journal of Medcinal Chemistry*, **45:** 3320 (2010).

[14] Finlay M.R.V., Acton D.G., Andrews D.M., Barker A.J., Dennis M., Fisher E., Graham M.A., Green C.P., Heaton D W., Karoutchi G., Loddick S A., Morgentin R., Roberts A., Tucker J.A., Weir H.M., Imidazole Piperazines: SAR and Development of a Potent Class of Cyclin-Dependent Kinase Inhibitors with a Novel Binding Mode *Bioorg*. *Bioorganic and Medicinal Chemistry Letters*, **18**: 4442 (2008).

[15] Li W.T., Hwang D.R., Song J.S., Chen C.P., Chuu J.J., Hu C.B., Lin H.L., Huang C.L., Huang C.Y., Tseng H.Y., Lin C.C., Chen T.W., Lin C.H., Wang H.S., Shen C.C., Chang C.M., Chao Y.S., Chen C.T., Synthesis and Biological Activities of 2-amino-1-arylidenamino Imidazoles as Orally Active Anticancer Agents, *Journal of Medicinal Chemistry*, **53(6)** :2409 (2010).

[16] Sim Y., Kang S., Shin D., Park M., Kay K-Yo., Jongwook P., Synthesis and Properties of New Imidazole Derivatives Including Various Chromophore for OLEDs, *Molecular Crystals and Liquid Crystals*, **687(1)**: 27–33 (2019).

[17] Zhiqiang L., Ning X., Yincai X., Chenglong L., Xiaoyue M., Yue W., Fluorine-Substituted Phenanthro [9,10-d]imidazole Derivatives with Optimized Charge-Transfer Characteristics for Efficient Deep-Blue Emitters, *Organic Materials*, **2**:11–19 (2020).

[18] Singh I., Uxami V., Pau K., Synthesis of Naphthalimide-Phenanthro[9,10-*d*]Imidazole Derivatives: *In vitro* Evaluation, Binding Interaction with DNA and Topoisomerase Inhibition, *Bioorganic Chemistry*, **96**:103631 (2020).

[19] Shaofeng Y., Shaoqing Z., Biao P., Runda G., Lei W., Imidazole Derivatives for Efficient Organic Light-Emitting Diodes, *Journal of Information Display*, **21(3)**: 173-196 (2020).

[20] Mohammadi M.K., Firuzi O., Khoshneviszadeh M., Razzaghi-Asl N., Sepehri S., Miri R., Novel 9-(alkylthio)-Acenaphtho[1,2-e]-1,2,4-triazine Derivatives: Synthesis, Cytotoxic Activity and Molecular Docking Studies on B-cell Lymphoma 2 (Bcl-2), *Daru*, **22:** 2 (2014).

[21] Azizian J., Mohammadi M.K., Firuzi O., Razzaghi-Asl N., Miri R., Synthesis, Biological Activity and Docking Study of Some new Isatin Schiff Base Derivatives, *Medicinal Chem*istry *Research*, **21**: 3730 (2012).

[22] Razzaghi-Asl N., Miri R., Firuzi O., Assessment of the Cytotoxic Effect of a Series of 1,4-dihydropyridine Derivatives Against Human Cancer Cells, *Iranian Journal of Pharmaceutical Research*, **15(3)**: 413 (2016).

[23] Tavakkoli H., Moayedipour T., Fabrication of Perovskite-type Oxide $La_{0.5}Pb_{0.5}MnO_3$ Nanoparticles and its Dye Removal Performance, *Journal of Nanostructure Chemistry*, **4**: 116 (2014).

[24] Behmadi H., Roshani M., Saadati S.M., Synthesis of Phenanthrimidazole from 9,10-Phenanthraquinone and Aldehydes by Molecular Iodine as Catalyst, *Chinese Chemistry Lett*ers, **20**: 5-8 (2009).

[25] Mohammadi Ziarani G., Tavaf E., Fathi Vavsari V., Badiei A., Synthesis of 2,4,5-Trisubstituted Phenanthroimidazole Derivatives using SBA-Pr-SO_3H as a Nanocatalyst, *Acta Chimica. Slovenia*, **64** 701 (2017).

[26] Kidwai M., Mothsra P., Bansal V., Somvanshi R K., Ethayathulla A.S., Dey S., Singh T.P., One-pot Synthesis of Highly Substituted Imidazoles using Molecular Iodine: A Versatile Catalyst, *Journal of Molecular Catalyst A: Chem*istry, **265**: 177-182 (2007).

[27] Samai S., Nandi G.C., Singh P., Singh M S., L-Proline: an Efficient Catalyst for the One-Pot Synthesis of 2, 4, 5-Trisubstituted and 1, 2, 4, 5-Tetrasubstituted Imidazoles, *Tetrahedron*, **65**:10155-10161 (2009).

[28] Karimi A R., Alimohammadi Z., Amini M.M., Wells–Dawson Heteropolyacid Supported on Silica: A Highly Efficient Catalyst for Synthesis of 2, 4, 5-Trisubstituted and 1, 2, 4, 5-Tetrasubstituted Imidazoles, *Molecular Diversity*, **14**: 635-641 (2010).

[29] Janeeka J., Vineet J., An Iodine/DMSO-Catalyzed Sequential One-Pot Approach to 2,4,5-Trisubstituted-1H-Imidazoles from a Methylene Ketones, *RSC Advance* **8**: 37557–37563(2018).

[30] Maleki B., Sedigh Ashrafi S., N-Bromosuccinimide Catalyzed Three-Component One-Pot Efficient Synthesis of 2,4,5-Triaryl-1H-imidazoles from Aldehyde, Ammonium Acetate, and 1,2-Diketone or α-Hydroxyketone, *Journal of Mexican Chemical Society*, **58:** 76-81(2014).

[31] Rostamnia S., Zabardasti A., SBA-15/TFE (SBA-15/2,2,2-Trifluoroethanol) as a Suitable and Effective Metal-free Catalyst for the Preparation of the tri- and tetra-Substituted Imidazoles *via* One-Pot Multicomponent Method, *Journal of Fluorine Chemistry*, **144**: 69-72 (2012).

[32] Bohlooli S., Jafari N., Jahed S., Cytotoxic Effect of Freeze-dried Extract of Ecballium Elaterium Fruit on Gastric Adenocarcinoma (AGS) and Esophageal Squamous cell Carcinoma (KYSE30) Cell Lines, *Journal of Gastrointest Cancer*, **43(4)**: 579 (2012).

[33] Ramanathan P., Synthesis, Spectral Characterization and Biological Studies of 2-(4- Methoxynaphthalen-1-yl)-1-(4-methoxyphenyl)-1H-phenanthro[9,10-D] Imidazole, *Modicianl Chemistry Application*, **5**: 1000242 (2017).

[34] Azarifar D., Asadpoor R., Tavakoli E., Bazouleh M., Sulfonated-Titanomagnetite Nanoparticles as Potential and Recyclable Catalyst for the Synthesis of Dihydroquinazoline and Hexahydroquinoline Derivatives under Solvent-Free Condition, *Iran. J. Chem. Chem. Eng. (IJCCE)*, **40(2)**: 367-381(2021).