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Synthesis of 1, 2-Disubstituted Benzimidazoles at Ambient Temperature Catalyzed by 1-Methylimidazolium Tetraflouroborate ([Hmim] BF_4) and Investigating Their Anti-ovarian Cancer Properties Through Molecular Docking Studies and Calculations

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Abstract

An environmentally benign method for the synthesis of 1, 2-disubstituted benzimidazoles by the reaction of aromatic aldehydes and o-phenylenediamines (OPD) in the presence of 1-methylimidazolium tetraflouroborate ([Hmim] BF_4) at ambient temperature under green conditions is described. A broad range of structurally diverse benzaldehydes were applied successfully, and corresponding products were obtained in good to excellent yields in very short times. All products were identified by the melting points, ^1H and ^{13}C NMR techniques. Furthermore, with the help of computational chemistry and drug design methods, the anti-ovarian cancer properties of these compounds were studied and investigated. All the synthesized compounds bind to an agonist at the active site of the 6LAD protein, which leads to the inactivation of this protein and produces beneficial effects during ovarian cancer treatment. In this study, it was found that these compounds have the potential to become an oral anti-cancer drug.

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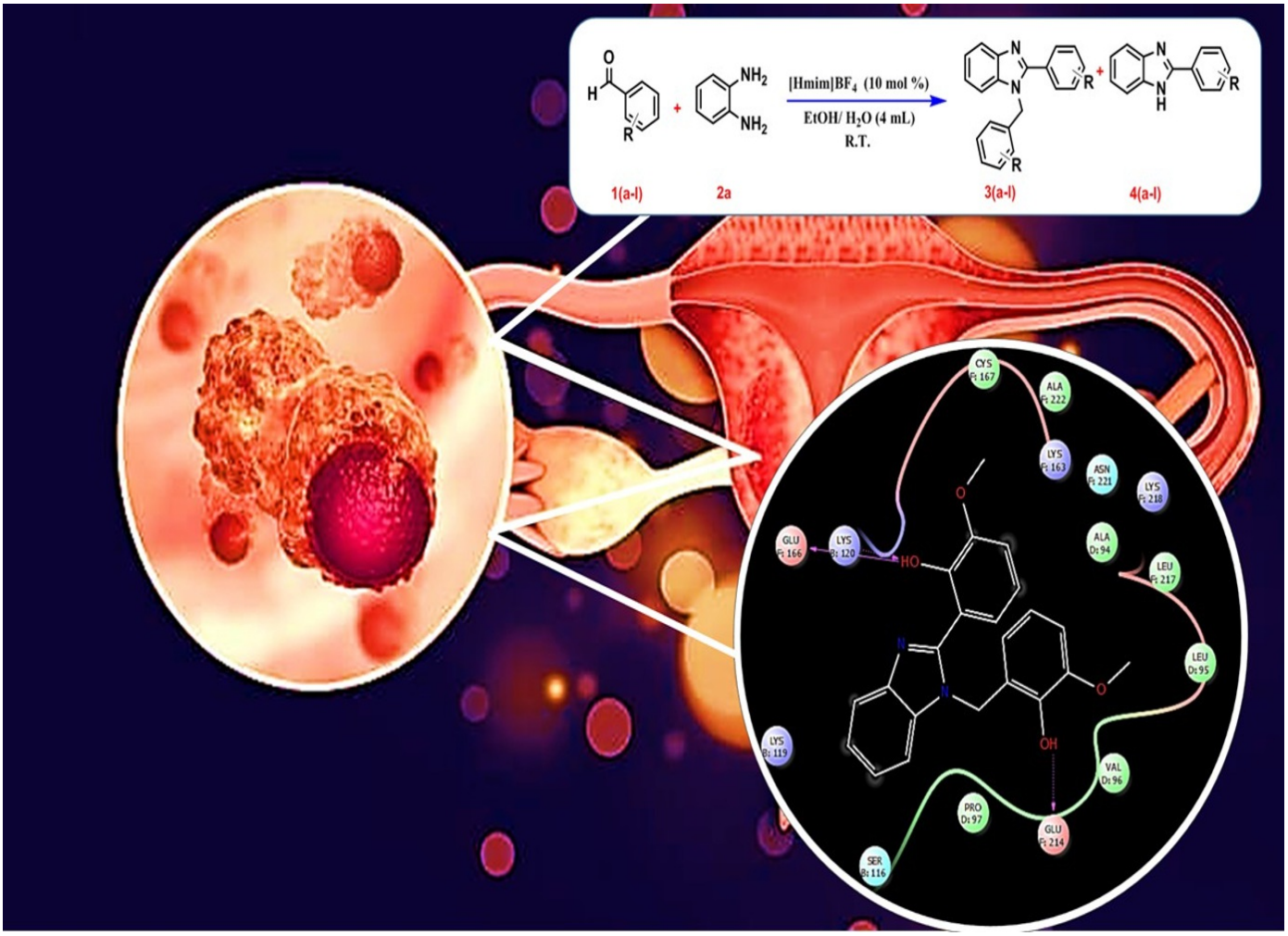
Keywords: Benzimidazoles, Ionic liquid, 1-methylimidazolium tetraflouroborate ([Hmim] BF_4), Molecular docking, Anti-ovarian cancer.

Graphical Abstract



Introduction

Organic compounds have various structures, many of these structures have a ring system that consists of carbon atoms and at least one other element, which are called heterocyclic compounds. These compounds are of great importance in the design of modern drugs and the improvement of medicinal properties due to their wide range among various pharmaceutical, veterinary, and herbal compounds. More than 90 % of clinically available drugs contain heterocyclic nuclei. {m/1-3/} Among the heterocyclic compounds, the heterocyclic compounds containing nitrogen and sulfur are of

special importance and due to their many applications and wide structural range, they play a prominent role as active chemical and biological compounds. {m/4-5/} Benzimidazoles are compounds that have received much attention in medicinal chemistry. Benzimidazole and purine-based nucleic acid are isosteres of each other. Benzimidazole is an aromatic heterocyclic compound consisting of two fused rings of benzene and imidazole. Benzimidazole is an important pharmacophore and a privileged structure in medicinal chemistry and is one of the constituents of vitamin B12. [1][2][3][4] Benzimidazole and its derivatives are considered a heterocyclic motif that is used in a wide range of medicinal applications including antihypertensive, antifungal, anticancer, antiviral, anti-HIV, antidiabetic, anticonvulsant, anti-neoplastic and anti-trichinosis properties. In addition, these compounds are used to treat nematode and trematode infections in domestic animals. Benzimidazole drugs, for example, fenbendazole, mebendazole, thiabendazole, pantoprazole, oxfenbendazole and lansoprazole represent substances used in human and veterinary medicine. [5][6][7][8]{m/14/} Other applications of benzimidazole and their derivatives can be mentioned in agriculture, electronics, and polymer chemistry. Due to the great importance of benzimidazole, efforts are made from time to time to produce various derivatives of these compounds. [9][10][11]

Ionic liquids are organic salts that typically melt below 100°C. These compounds are generally formed by charged species and may contain more than one cation or anion. The most important advantages of ionic liquids are non-volatility, high transparency, stability and heat resistance, high polarity, high electrical conductivity, and wide operating temperature range. {m/18-19/}[12][13] Ionic liquids are divided into two categories protic ionic liquids and aprotic ionic liquids. Most of the ionic liquids are of the type aprotic and compared to the types with protic, they often have more conductivity and fluidity and also have a lower melting point. Also, protic ionic liquids can form networks with the help of hydrogen bonds, which limits their ionization power compared to types of aprotic ionic liquids. The applications of ionic liquids can be mentioned as a potential candidate in supercapacitors, solar cells, and energy storage devices. [14][15][16][17] By changing the type of charged species, the properties of ionic liquids can be changed and adjusted, hence ionic liquids are also called designer solvents. In addition, ionic liquids can catalyze reactions in chemistry. In the case of catalytic reactions, ionic liquids lead to higher yields and selectivity of the reaction and enable easy isolation of catalysts after the reaction. [18][19][20]

The ovary is the main source of estrogen and progesterone hormones and plays an important role in female fertility. Ovarian cancer is the seventh most common type of cancer and the eighth cause of cancer-related death in women. [21][22][23] Ovarian cancer occurs when normal cells in the fallopian tubes turn into abnormal cells grow out of control and enter the ovaries. These cells can invade or spread to other parts of the body. Ovarian tumours appear in different forms, including epithelial tumours, germ cell tumours, and stromal tumours. [24][25][26][27] Ovarian cancer symptoms can include abdominal swelling, bloating, pelvic pain, irregular bleeding, indigestion, fatigue, diarrhoea, urinary disorders, and urgent urination. Areas where cancer is likely to spread include the abdominal wall, liver, lungs, and lymph nodes. Early symptoms of ovarian cancer may be weak or invisible and these symptoms can be confused with irritable bowel syndrome. [28][29][30][31]

The risk of ovarian cancer is higher in those who ovulate more, so it can be concluded that those who have never had children are at a higher risk. Also, those who ovulate at a younger age or go through menopause at an older age, are

more prone to ovarian cancer. The effective factors of ovarian cancer include obesity, family history, endometriosis, ageing and menopause before 40 years of age. [32][33][34] Ovarian cancer treatment methods include surgery, chemotherapy, hormone therapy, radiation therapy, and immunotherapy (biotherapy). Ovarian tumours are very sensitive to chemotherapy, which in most cases leads to a reduction in tumour size and a significant number of cases to the disappearance of microscopic tumour remnants after surgery. This method is used before or after surgery to destroy cancer cells. [35][36][37][38] Ovarian cancer chemotherapy involves the use of certain cytotoxic or antiblastic drugs to destroy cancer cells. Chemotherapy is usually administered intravenously or orally. Carboplatin, topotecan, docetaxel, gemcitabine, and trabectedin are the most commonly used drugs for the treatment of ovarian cancer. Ovarian cancer chemotherapy drugs destroy cancer cells, but at the same time temporarily reduce the number of leukocytes and white blood cells. [39][40][41][42]

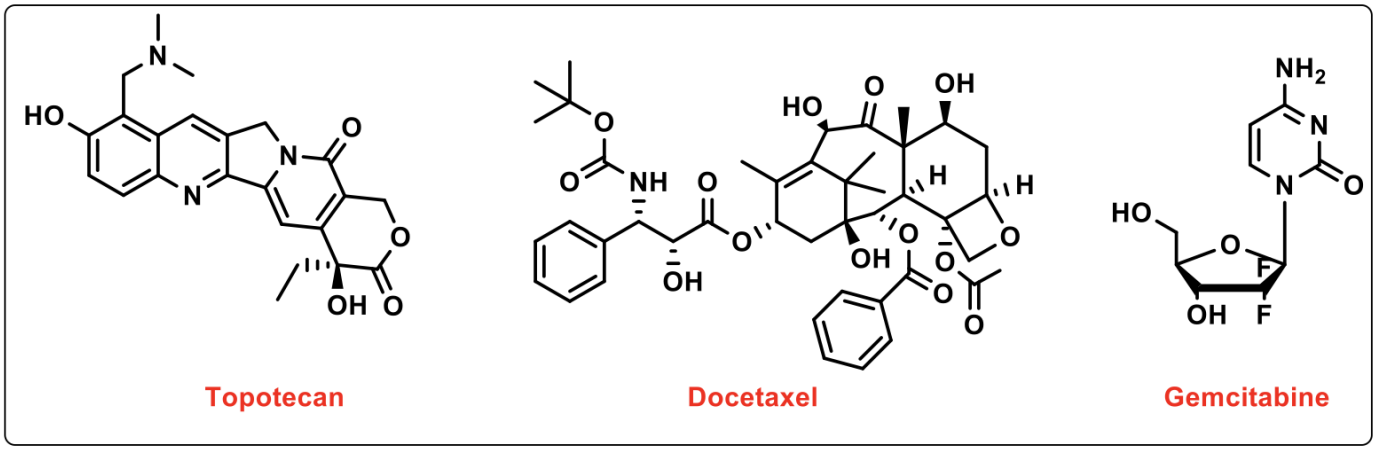
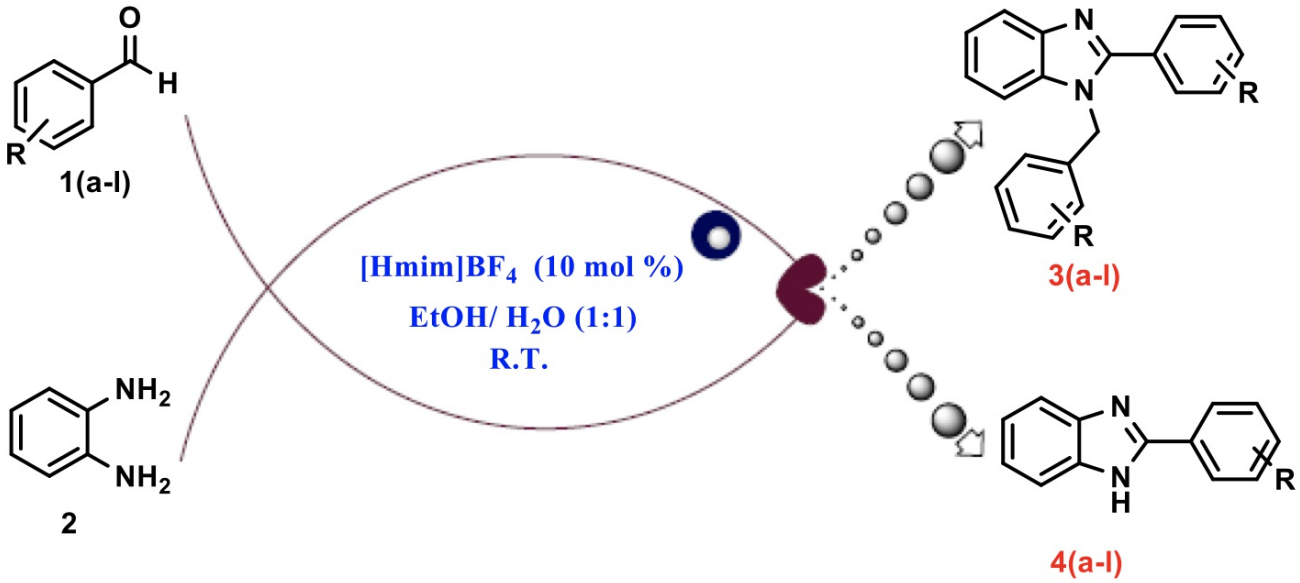


Figure 1. The most common drugs used in the treatment of ovarian cancer.

In this research, the authors try to evaluate the performance of 1-methylimidazolium tetraflouroborate ([Hmim] BF_4) as an effective catalyst in the synthesis of benzimidazoles by arylaldehydes with o-phenylenediamine (OPD) with high efficiency and short reaction times. In addition, the anti-ovarian cancer properties of these compounds were investigated through molecular docking calculations.



Scheme 1. Synthesis of 1,2-disubstituted benzimidazoles (**3a–l**), and 1-substituted benzimidazoles (**4a–l**) in the presence of 1-methylimidazolium tetraflouroborate ([Hmim] BF_4) as a catalyst.

Experimental section

All reagents and solvents were purchased and used without further purification. The progress of the reactions was followed by TLC using silica gel polygrams SIL G/UV 254 plates. NMR spectra were recorded on a Brucker Avance DPX-400 (^{1}H NMR 400 MHz and ^{13}C NMR 101 MHz) spectrometer in pure deuterated dimethyl sulfoxide (DMSO-d6) solutions. Chemical shifts are given in parts per million (ppm) downfield from tetramethyl silane (TMS) as an internal reference, and coupling constants (*J*-values) are in hertz (Hz). ^{1}H NMR assignment abbreviations are the following; singlet (s), doublet (d), triplet (t), doublet of doublets (dd) and multiplet (m). Melting points were recorded using a Barnstead electro-thermal 9100 BZ circulating oil melting point apparatus by using the open capillary method. The mode of interaction was investigated by docking. The ligand-receptor interaction pictures were created using Schrödinger 2018.10 software.

General procedure for the preparation of 1, 2-disubstituted benzimidazoles derivatives (3a-l)

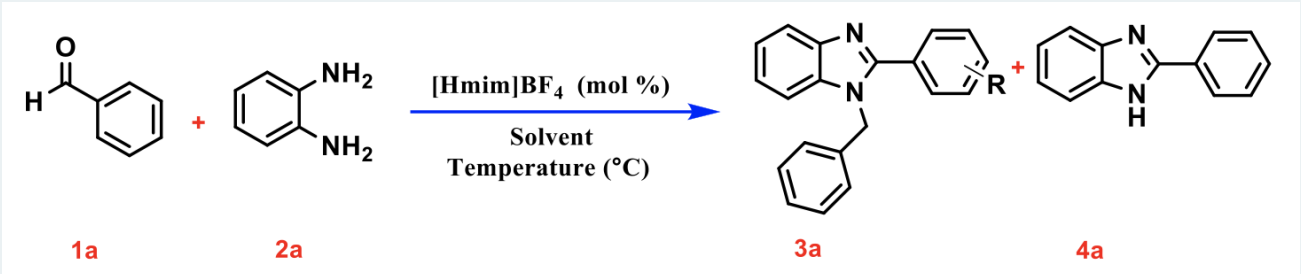
A mixture of benzaldehyde (2 mmol), o-phenylenediamine (1 mmol) and EtOH/H_2O (4 mL), was stirred in the presence of 1-methylimidazolium tetraflouroborate (10 mol %) at room temperature in appropriate times. After the completion of the reaction, as indicated by TLC, the reaction mixture was cooled to room temperature. Then the reaction mixture was diluted with EtOAc and centrifuged to remove the catalyst. The filtrate was extracted with EtOAc and water. The organic layer was dried with Na_2SO_4. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate 10:2) to afford desired pure product.

Results and discussion

Catalytic performance

In order to establish the optimum conditions, the catalytic activities of 1 methylimidazolium tetraflouroborate ([Hmim] BF_4) was examined in a model reaction. To this regard, the reaction of benzaldehyde (1a) and orthophenylenediamine (2a) was selected as a model reaction and the time and the yield of the reaction were monitored under different conditions such as solvent, temperature and the amount of catalyst and obtained results were summarized in Table 1. As it is clear from Table 1, moderate to good yields were obtained in EtOH and H_2O (entries 1 and 2), while the yield of the model reaction in MeOH and DMF, was not effective and very low yields were obtained after a long time (entries 4 and 5). The best results were obtained using 10 mol % of the catalyst in EtOH: H_2O as a solvent (entry 8). Furthermore, the reaction temperature directly affects the yield and time of the reaction. The shortest reaction time and the best reaction yield were obtained at room temperature (Table 1, entry 3). The best results were obtained using 10 mol % of the catalyst, while the decrease in the quantity of catalyst led to a significant increase in reaction times and a decrease in yields (Table 1, entries 10-11). Therefore, considering all of these results, the best reaction conditions for the reaction of benzaldehyde (**1a**) and orthophenylenediamine (**2a**) in the presence of 1-methylimidazolium tetraflouroborate is the use of EtOH: H_2O (1:1) as a solvent, 10 mol % of the catalyst and conduction of the reaction at room temperature.

Table 1. Synthesis of 1,2-disubstituted benzimidazole derivatives catalyzed by 1 methylimidazolium tetraflouroborate ([Hmim] BF_4)



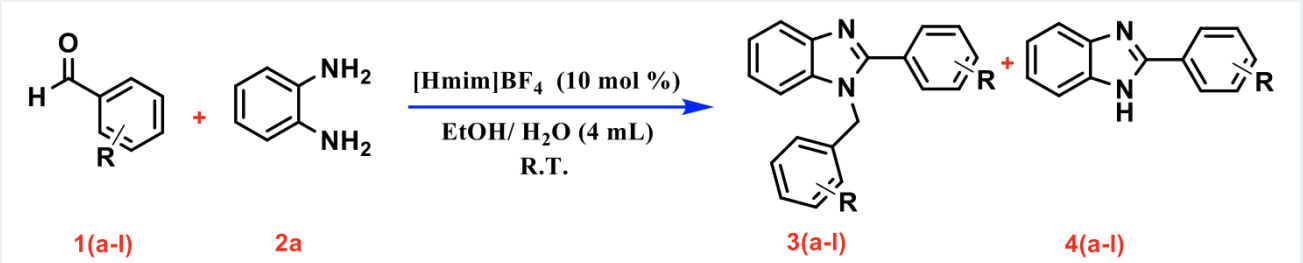
Entry	Catalyst (mol %)	Solvent	Temp. (°C)	Time (h)	3a/4a [b]
1	[Hmim] BF_4 (10 mol %)	EtOH	R.T	0.45	63: 5
2	[Hmim] BF_4 (10 mol %)	H_2O	R.T	0.30	71: 4
3	**[Hmim] BF_4 (10 mol %)**	**H_2O/EtOH (1:1)**	**R.T**	**0.16**	**85: 5**
4	[Hmim] BF_4 (10 mol %)	MeOH	R.T	0.50	45: 5
5	[Hmim] BF_4 (10 mol %)	DMF	R.T	0.50	30: 5
6	[Hmim] BF_4 (10 mol %)	-	R.T	6	70: 10
7	[Hmim] BF_4 (10 mol %)	H_2O/EtOH (1:1)	30	0.30	73: 4
8	[Hmim] BF_4 (10 mol %)	H_2O/EtOH (1:1)	40	0.50	61: 5
9	[Hmim] BF_4 (10 mol %)	H_2O/EtOH (1:1)	50	0.50	45:8
10	[Hmim] BF_4 (5 mol %)	H_2O/EtOH (1:1)	R.T	0.50	64:5
11	[Hmim] BF_4 (7 mol %)	H_2O/EtOH (1:1)	R.T	0.25	76: 4

[a] *Reaction conditions*: benzaldehyde (2 mmol) and o-phenylenediamine (1 mmol), catalyst and solvent (4 mL).

[b] Isolated yield.

In the following, the optimal reaction conditions for the preparation of a wide range of benzimidazole derivatives using different aryl aldehydes and o-phenylenediamine (OPD) were investigated using 1-methylimidazolium tetraflouroborate, and the related results are listed in Table 2. Aryl aldehydes were investigated in terms of electron and space in this reaction. The results showed that electron-withdrawing and electron-releasing groups of aryl aldehydes react without significant differences to obtain the corresponding benzimidazoles in excellent yields.

Table 2. Synthesis of 1, 2-disubstituted benzimidazole derivatives catalyzed by 1-methylimidazolium tetraflouroborate



Entry	R (a-l)	Product	Time (h)	Yield 3: 4 [b] (%)	m.p	Lit. m.p
1	H	3a	0.16	85: 5	132-133	132-133 [43]
2	3-NO_2	3b	0.11	91: 4	154-156	154-155 [44]
3	4-OMe	3c	0.16	83: 5	127-130	127-129 [45]
4	3,4-di OMe	3d	0.28	71: 4	170-173	170-172[46]
5	4-Me	3e	0.16	82: 4	127-130	126-129[47]
6	3-OH	3f	0.16	73: 7	256-257	250-252[48]
7	4-OH	3g	0.16	76: 5	206-209	250-252[49]
8	3-OH,4-OMe	3h	0.41	63: 12	228-230	229-231[50]
9	3-OMe, 4-OH	3i	0.41	65: 11	186-186	187-189[51]
10	4-Cl	3j	0.16	92: 4	131-133	131-134[52]
11	4-NO_2	3k	0.11	95: 3	190-192	190-192[53]
12	Thiophene-2-carbaldehyde	3l	0.28	86: 5	146-149	146-149[54]

[a] *Reaction condition*: different aromatic aldehyde (2 mmol), o-phenylenediamine (1 mmol), [Hmim] BF_4 (10 mol %), H_2O/EtOH (4 mL), room temperature.

[b] Isolated yield.

Molecular docking study of anti-ovarian cancer activity of synthesized 1, 2-disubstituted benzimidazoles

The docking results of the synthesized compounds are shown in Table 3-5. The results according to Lee Pinsky's rules (rules of medication) are given below. According to Lee Pinsky's laws, the molecular mass of the drug should not be more than 500 g/mol, because the higher the molecular mass, the lower its absorption and permeability. All synthesized compounds follow this. According to Lee Pinsky's laws, the molecular mass of the drug should not be more than 500 g/mol, because the higher the molecular mass, the lower its absorption and permeability. Fortunately, all the synthesized compounds have a molecular mass of less than 500 g/mol (**3a-l**). The second law of Le Pinsky is the octanol-water dissociation coefficient, which shows the balance between hydrophilicity and lipophilicity of the drug molecule. In this balance, the octanol/water partition coefficient should not be more than 5. Ligands **3a**, **3c**, **3d**, **3e**, **3j** and **3l** do not follow this rule. The third and fourth law states the number of hydrogen donor groups and the number of hydrogen acceptor groups, that in the case of the number of hydrogen donor groups, the number of groups such as NH and OH should not

be more than 5, and also in the case of the number of hydrogen acceptor groups, the number of O and N should not be more than 5 that all compounds follow these two rules. In addition to the mentioned rules, cell permeability plays an important role in drug bioavailability and absorption. As shown in Table 5, the docking energy indicates the strength of the binding of the ligand to the receptor. The more negative the docking energy is, the better the binding of the ligand to the receptor.

Solubility and cell permeability are two important factors in drug absorption and bioavailability. The solubility of medicinal compounds plays an important role in the drug design process, and low solubility can cause the deposition of some medicinal compounds in the urinary tract and kidney. Hydrogen bonding plays an important role in drug solubility. In order for proper digestive absorption of the drug, it must first dissolve well in the digestive system, and then these bonds are broken, and then the connection with the cell membrane is established to penetrate and absorb the drug. An excessive increase in hydrogen bonding reduces drug diffusion between the aqueous and lipid phases. On the other hand, the increase in molecular weight due to the decrease in solubility and the decrease in surrounding water molecules causes a decrease in the gastrointestinal absorption of the drug.

Cell permeability optimizes the gastrointestinal absorption of drugs, which should have a cell permeability rate greater than 500 nm/s. Permeability has an inverse relationship with solubility. Increasing solubility decreases permeability. Ligands 3b and 3c do not follow this rule.

Table 3. Results of molecular docking calculations of synthesized compounds (**4a-4l**).

Entry	Molecular weight	Octanol/water ratio	AHB[a]	DHB[b]
3a	284.36	5.284	1.5	0
3b	374.355	3.82	3.5	0
3c	344.412	5.427	3	0
3d	404.465	5.178	4.5	0
3e	312.413	5.945	1.5	0
3f	316.359	3.769	3	2
3g	316.359	3.734	3	2
3h	376.411	4.083	4.5	2
3i	376.411	3.838	4.5	2
3j	353.25	6.301	1.5	0
3k	374.355	3.829	3.5	0
3l	296.404	5.061	1.5	0

[a] **AHB:** Number of acceptor hydrogen bonds

[b] **DHB:** Number of donor hydrogen bonds

Table 4. Results of molecular docking calculations of synthesized compounds (**4a-4l**)

Entry	Central nervous system (CNS)	Cell permeability (QPPCaco)	Aqueous solubility	Dock score
3a	1	6529.465	-5.493	-1.279
3b	-2	96.868	-5.656	-2.16
3c	1	6538.604	-5.832	-2.757
3d	1	6497.772	-4.865	-2.433
3e	1	6537.54	6.728	-3.566
3f	-1	625.996	-4.865	-4.247
3g	-1	602.919	-4.798	-3.67
3h	-2	713.742	-5.494	-4.27
3i	-1	746.221	-4.551	-4.498
3j	2	6542.484	-7.035	-2.684
3k	-2	94.503	-5.745	-2.485
3l	1	6159.06	-5.255	-2.355

Table 5. Results of molecular docking calculations of synthesized compounds (**4a-4l**)

Entry	Persentage oral absorption	Human oral absorption	Blood-brain partition coefficient	Docking energy
3a	100	3	0.27	-26.288
3b	84.863	3	-1.759	-31.642
3c	100	3	0.139	-28.855
3d	100	3	0.03	-34.865
3e	100	1	0.259	-28.695
3f	100	3	-0.864	-37.255
3g	100	3	-0.869	-31.132
3h	100	3	-1.005	-32.325
3i	100	3	-0.851	-36.746
3j	100	1	0.613	-27.331
3k	84.723	3	-1.796	-32.675
3l	100	3	0.428	-27.876

Investigating how protein 6LAD PDB binds to its natural ligand in the treatment of ovarian cancer

CD-125 protein is the most common ovarian cancer marker protein and, is named 6LAD PDB in the protein database. Figure **2** shows the 3D graphs of the ligand-receptor interactions of the synthesized compounds. As shown in Figure **2**, ligand 3j is hydrogen bonded by the hydroxy functional group with glutamic acid 214 residues and serine 120 and glutamic acid 166 residue. These links play a very special and vital role in biological sciences and pharmaceutical connections which leads to the inactivation of this protein and produces beneficial effects during ovarian cancer treatment. Figure **3** depicts 3D graphs of ligand-receptor interactions of the synthesized compounds. As shown in Figure 3, all the synthesized compounds bind to an agonist at the active site of the 6LAD protein, which leads to the inactivation of this

protein and produces beneficial effects during ovarian cancer treatment.

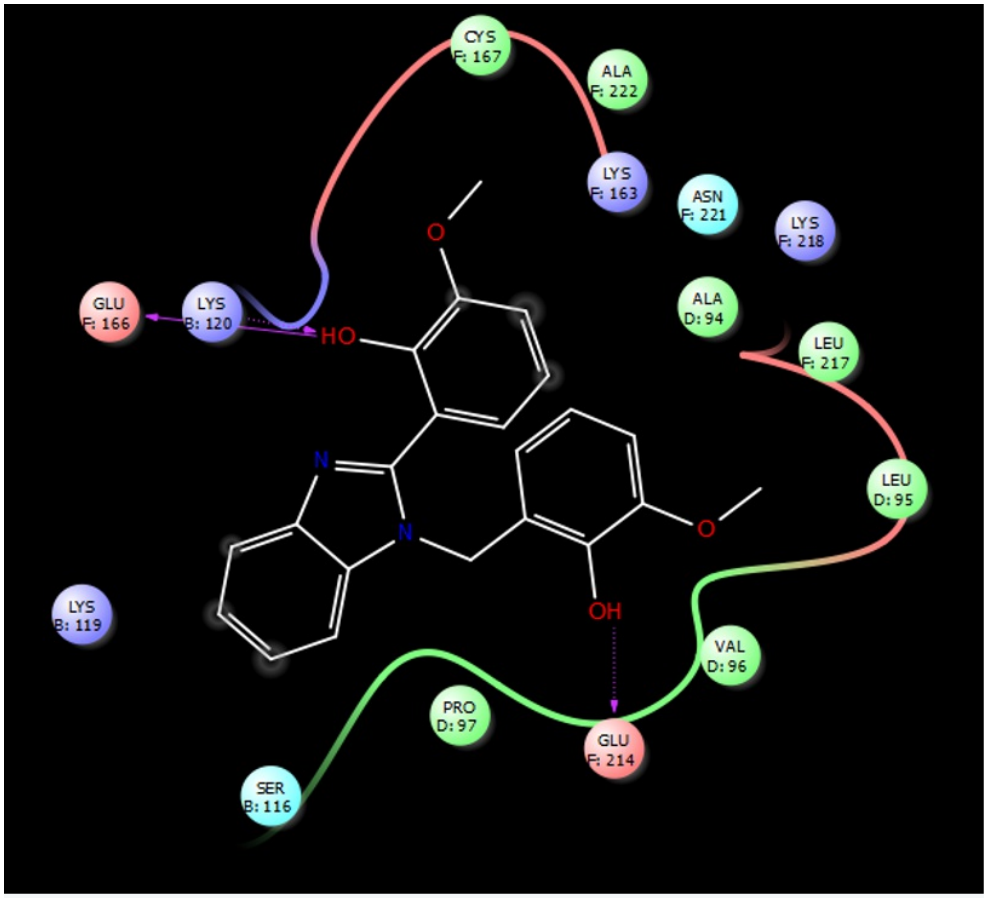


Figure 2. Bonds and interactions between ligand **3j** and protein 6lad.

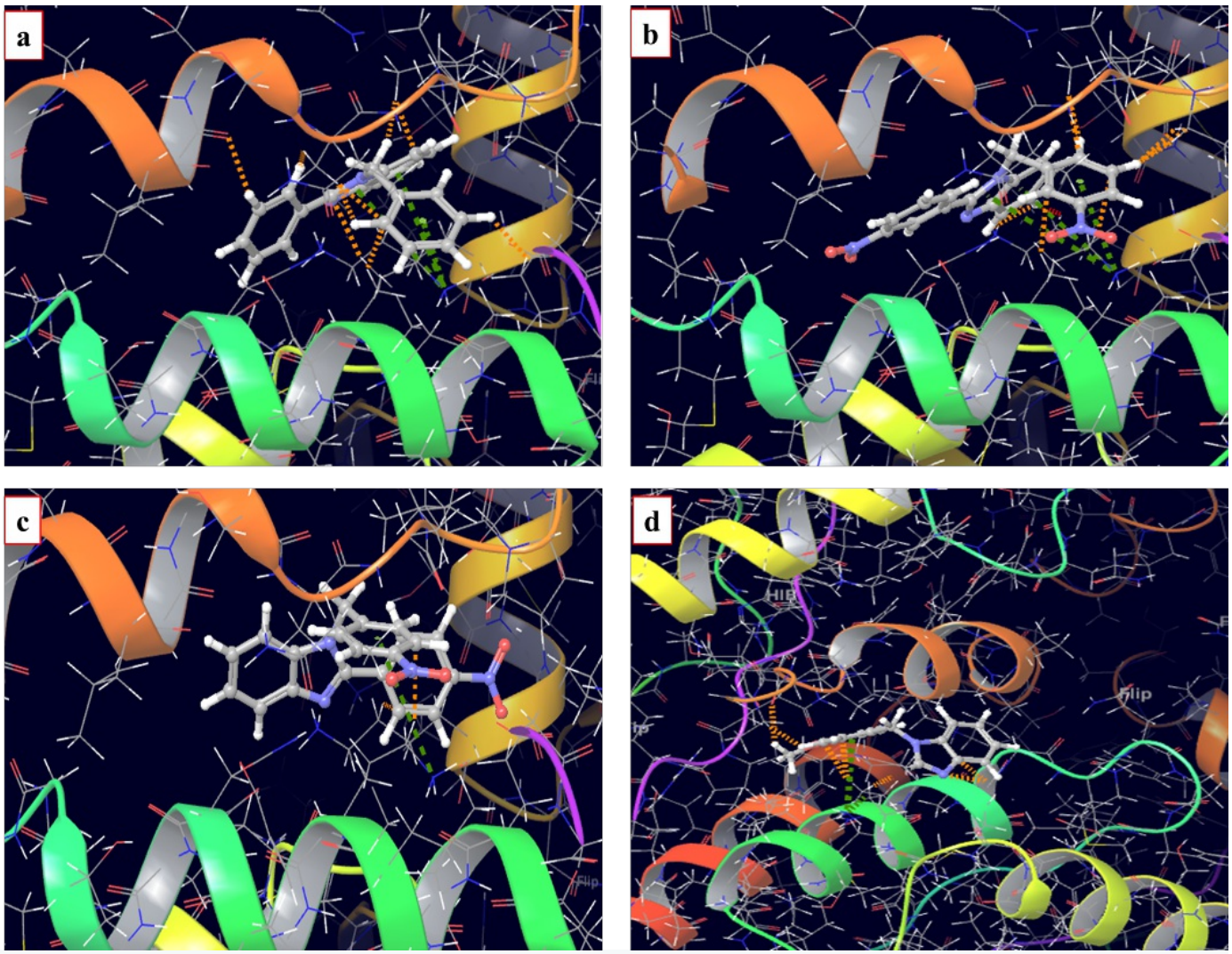


Figure 3. 3D graphs of ligands-protein interactions of four synthesized 1, 2-disubstituted benzimidazole derivatives **3a** (a), **3b** (b), **3c** (c) and **3j** (d).

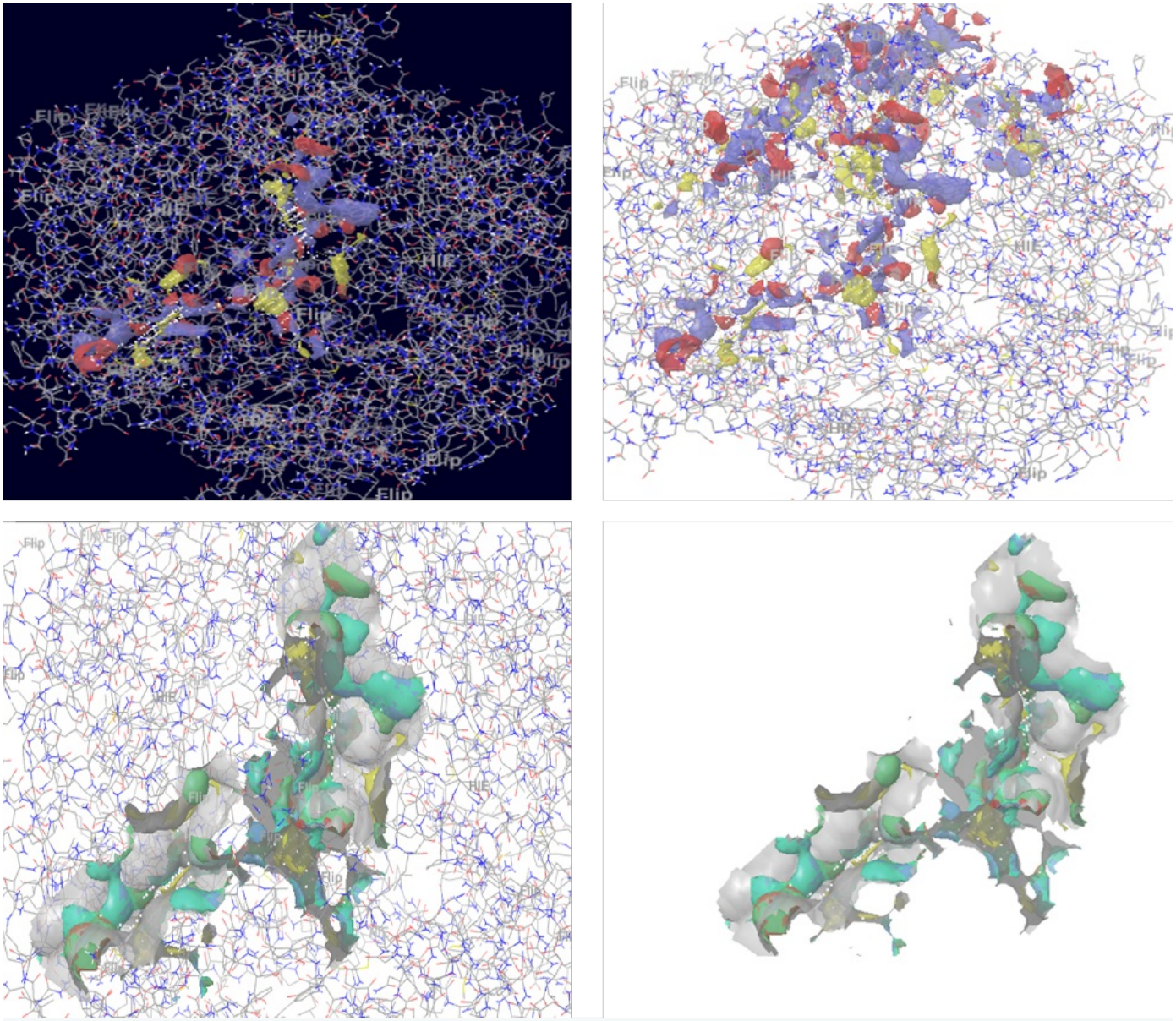
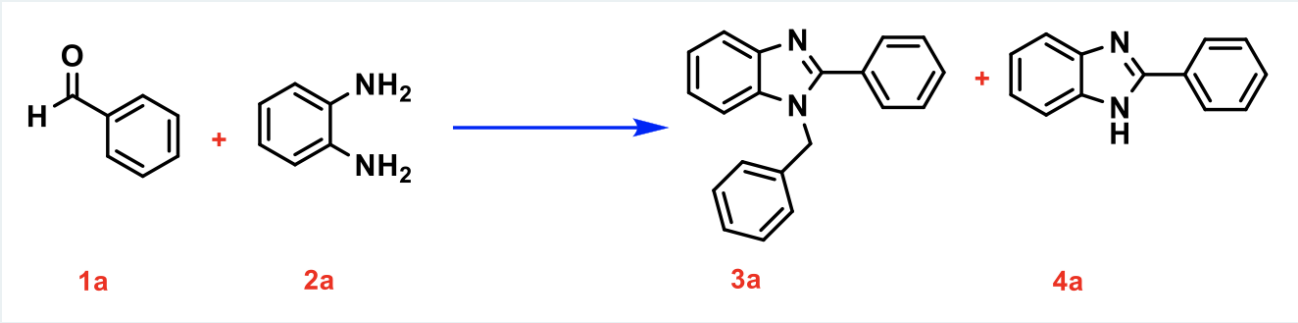


Figure 4. Active site of protein 6lad.

Comparison of the prepared catalyst with reported ones

Finally, to evaluate the efficiency of the 1-methylimidazolium tetraflouroborate as a highly efficient catalyst, its activity in the condensation reaction from benzaldehyde (**1a**) and o-phenylenediamines (**2a**) was compared with some other catalysts, which have been reported previously. The gathered data in Table 6 showed that the reaction was performed in a shorter reaction time using 1-methylimidazolium tetraflouroborate and produce the desired product **(3a**) in excellent yield.

Table 6. The comparison of 1-methylimidazolium tetraflouroborate catalytic activity with some reported catalysts for the preparation of compound **3a** [a]



Entry	Catalyst	Conditions	Time (h)	Yield 3a:4a[b]	*Ref*
1	Silica gel supported trichloroacetic acid	EtOH, H_2O, 50ºC	0.2	91.4: n/a	[44]
2	Erbium(III) triflate	80ºC	0.0333	91: 9	[55]
3	Thiamine hydrochloride	N, N-dimethyl-formamide, 20ºC	1.5	88: 6	[56]
4	1-dodecylimidazolium trifluoromethanesulfonate;	Oxygen, EtOH, 20ºC	3	10: 86	[57]
5	Copper(II) oxide	N, N-dimethyl-formamide, 20ºC	1	82: 10	[58]
6	Sodium dodecyl-sulfate	H_2O, 20ºC	6	78: 10	[59]
7	Zinc(II) oxide	1,4-dioxane, 80°C	1	30: 69	[60]
8	Cerium(III) nitrate hexahydrate	N, N-dimethyl-formamide, 100 ºC	0.3	69: 31	[61]
9	Tetra-(n-butyl) ammonium iodide	H_2O, 20ºC	10	68: 28	[62]
10	Fe_2O_3/silica	Neat, 30ºC	8	65: 22	[63]
11	Silver	MeOH, H_2O, 55ºC	3	65: 34	[64]
12	HY zeolite	CH_3CN, 20ºC	10	61: 17	[65]
13	Aminosulfonic acid	EtOH, 20ºC	1	55: 35	[66]
14	[Cu(N, N-bis(2-oxyphenyl) pyridine-2,6-dicarboxamide) H_2O]	20ºC	4	40: 10	[67]
15	p-toluenesulfonic acid on silica gel	60 - 70ºC	0.25	59: 32	[68]
16	2-aminoterephthalate coordinated zirconium-based porous coordination polymer nanoparticles	EtOH, 20ºC	0.5	38: 60	[69]
17	Citrus limonium	80ºC	3	60: 31	[70]
18	Magnesium hydrogen sulfate	MeOH, 80ºC	3.5	60: n/a	[71]
19	SBA-15-supported poly(4-styrenesulfonyl(perfluorobutylsulfonyl) imide)	Nitromethane, at 25 - 28 ºC	1.33333	65: 5	[72]
20	Iodine	THF, H_2O, 20ºC	2	20: 72	[73]
21	Scandium tris(trifluoromethanesulfonate)	THF, 20ºC	44	1: 97	[74]
22	Phosphoric acid	MeOH, 50°C	0.08	90: 5	{m/5/}
23	[Hmim] BF_4 (10 mol %)	EtOH:H_2O, R.T	0.16	85: 5	-

[a] *Reaction conditions*: benzaldehyde (2 mmol) and o-phenylenediamine (1 mmol).

[b] Isolated yield.

Conclusions

In summary, we have developed a simple and efficient method for the synthesis of 1, 2-disubstituted benzimidazoles via condensation reaction from aromatic aldehydes and o-phenylenediamines (OPD), by using 1-methylimidazolium tetraflouroborate ([Hmim] BF_4) as catalyst under green solvent (EtOH: H_2O) at ambient temperature. This procedure suffers from many advantages such as reduced reaction times, easy purification, high yields, operational simplicity, and cost efficiency and thus significantly contributes to the practice of green chemistry. Furthermore, with the help of computational chemistry and drug design methods, the anti-ovarian cancer properties of these compounds were studied and investigated. All the synthesized compounds bind to an agonist at the active site of the 6LAD protein, which leads to the inactivation of this protein and produces beneficial effects during ovarian cancer treatment. In this study, it was found that these compounds have the potential to become an oral anti-cancer drug.

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