A Novel One-Pot Three-Component Approach to Orthoaminocarbonitrile Tetrahydronaphthalenes Using Triethylamine (Et_3N) as a Highly Efficient and Homogeneous Catalyst Under Mild Conditions and Investigating Its Anti-cancer Properties Through Molecular Docking Studies and Calculations

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Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.

Abstract

An efficient and environmentally friendly method for the one-pot synthesis of ortho-aminocarbonitrile tetrahydronaphthalenes has been developed in the presence of triethylamine (Et_3N) as a homogeneous catalyst. The multicomponent reactions of benzaldehydes, cyclohexanone and malononitrile were carried out under mild conditions to obtain some ortho-aminocarbonitrile tetrahydronaphthalene derivatives. A broad range of structurally diverse benzaldehydes were applied successfully, and corresponding products (**4a-l**) were obtained in good to excellent yields (87-98%) in very short times (10-25 minutes). The present approach provides several advantages including simple workup, high yields, very mild reaction conditions, short reaction times, little catalyst loading and not requiring specialized equipment. Furthermore, with the help of computational chemistry and drug design methods, the anti-cancer properties of these compounds were studied and investigated. All the synthesized compounds bind to an agonist at the active site of the 3A8P protein, which leads to the inactivation of this protein and produces beneficial effects during cancer treatment. In synthesized compounds, the ligands establish hydrogen bonds with leucine A:728 residues through nitrogen, which has a very special and vital role in biological sciences and pharmaceutical connections. In this study, it was found that these compounds have the potential to become an oral anti-cancer drug.

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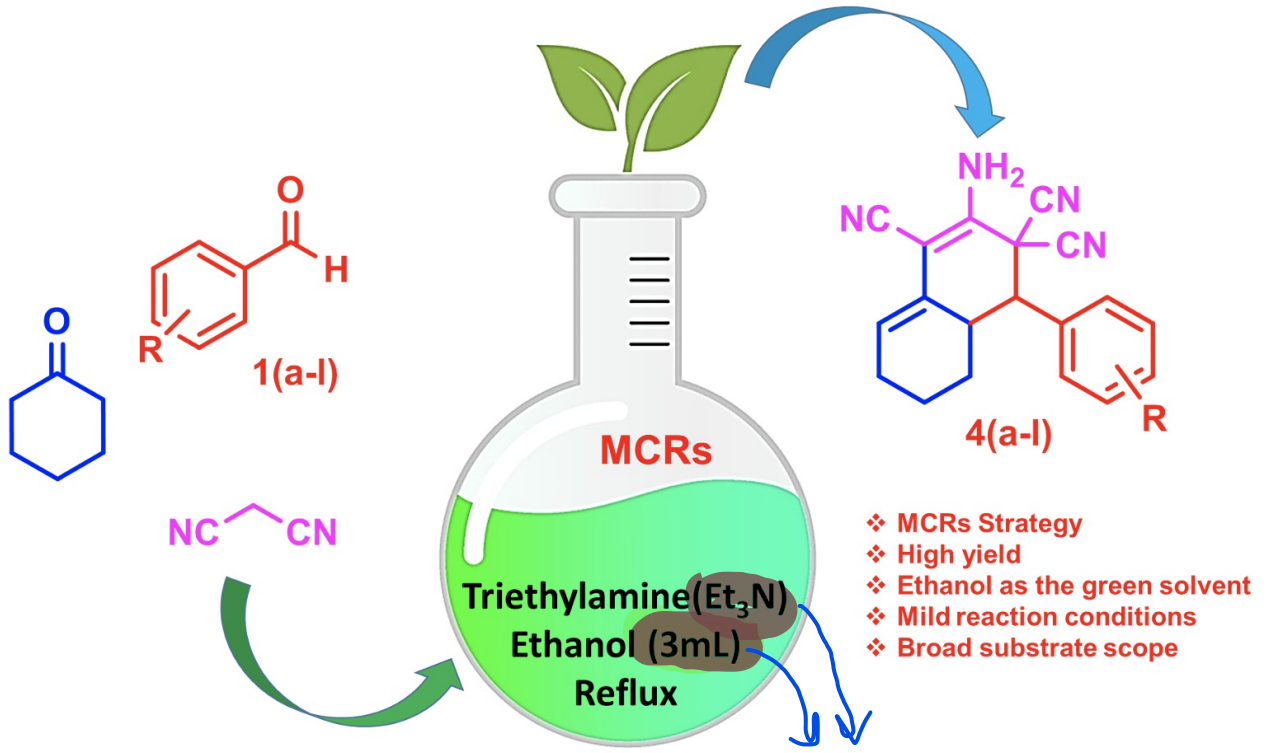
Keywords: Anti-cancer, Molecular docking, Homogeneous catalyst, Triethylamine(Et_3N), Orthoaminocarbonitrile tetrahydronaphthalenes.

Graphical abstract



Comment 1: It is better to remove (Et3N) and 3 mL

Introduction

One of the important goals of green chemistry is the efficient synthesis of complex molecules with high-added value and the use of green solvents [1][2][3]. Multicomponent reactions (MCRs) are synthesis productivity and reaction design tools and are a suitable alternative to multi-step syntheses. The advantages of these reactions include high efficiency, the use of available raw materials, a wide range of products, ease of automation, and simple work methods. These characteristics,

which correspond to most of the principles of green chemistry, have turned the use of multicomponent reactions (MCRs) into an idea synthesis method [4][5][6][7]. In the last few decades, multicomponent reactions (MCRs) have been considered as one of the potential techniques for the synthesis of heterocyclic compounds and new biologically active compounds [8][9][10]. It is worth noting that the heterocyclic compound shows significant biological activity. Heterocyclic compounds play an important role in drug discovery, and to date, a large number of synthesis molecules based on these structures have been reported with high potential in medicinal chemistry. Medicines containing heterocyclic compounds are found in all fields of treatment, including cardiovascular diseases, anti-cancer, anti-viral, anti-inflammatory, anti-tumour, anti-ulcer drugs, etc [11][12][13][14][15].

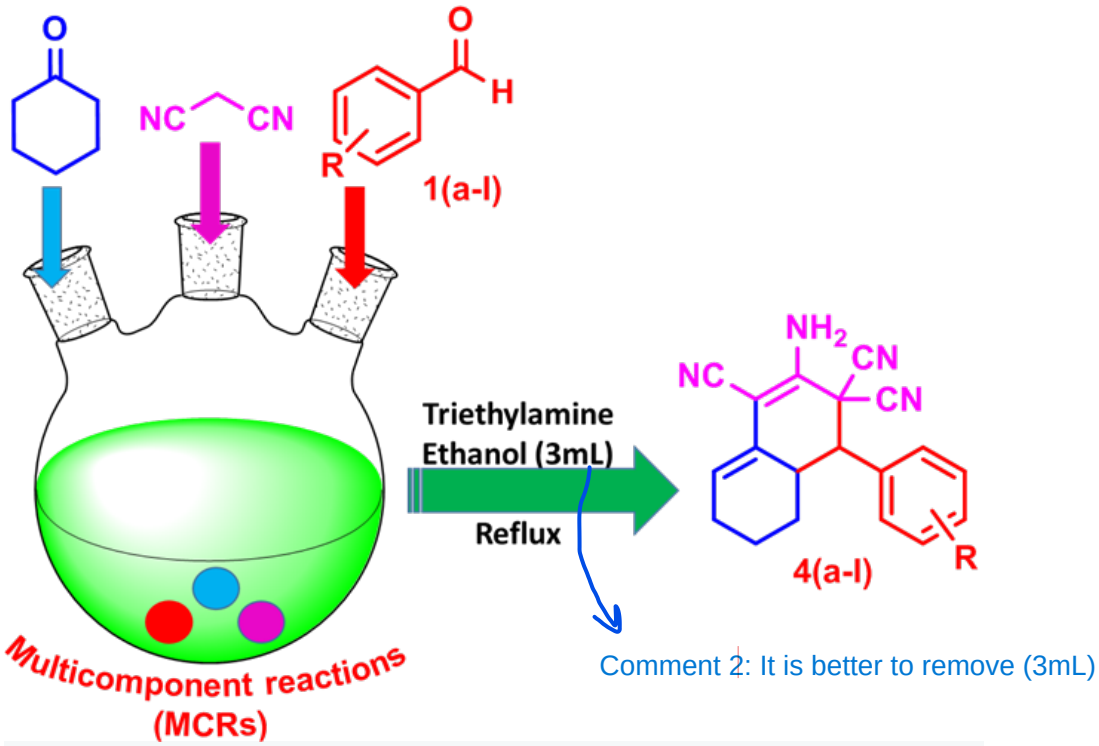
Among other applications of heterocyclic compounds, we can mention their use in a wide range of industries, including cosmetics, antioxidants, plastics, solvents, and vulcanization accelerators. In the CMC database, more than half (67%) of the compounds listed contain heterocyclic rings. Every year, a large number of articles in the field of heterocyclic drugs are introduced in chemical and pharmaceutical journals, and the structure of these heterocyclic can be aromatic or non-aromatic. The type and size of the heterocyclic compounds, together with the substituted groups on them, can affect the physicochemical properties of the medicinal compound. The type and size of the heterocyclic compounds, along with the substituted groups on these compounds, can affect the physicochemical properties of the medicinal compound [16][17][18][19][20][21].

One of the goals of medicinal chemistry is the design and synthesis of molecules that have high value and properties in the treatment of diseases [22][23][24]. In this regard, tetrahydronaphthalene derivatives are one of the compounds that have been considered in medicinal chemistry. Tetrahydronaphthalene is a heterocyclic compound and an important pharmacophore in medicinal chemistry. This compound is bicyclic in nature with two chiral centres and exhibits a wide range of medicinal applications including anticancer and antidepressant [25][26][27].

A neoplasm is an abnormal and excessive growth of tissue, the growth of a neoplasm is inconsistent with the growth of the surrounding normal tissue, and even if the main trigger is removed, it continues to grow abnormally, and usually, with this abnormal growth, a mass is formed, which is called a tumour. Tumours are divided into two categories, malignant and benign. A benign tumour can grow but not spread, while a malignant tumour can invade nearby tissues or spread to other parts of the body [28][29][30]. A malignant tumour is called cancer, and according to the Global Burden of Disease Study, cancer is the second leading cause of death and loss of life for many people on the planet. Cancer can be defined as uncontrollable growth with loss of differentiation power and usually accompanied by metastasis. It should be noted that in a healthy organism, there is always a balance between the rate of cell division, natural cell death and differentiation. Cancer depends on factors such as age, gender, genetics and environmental factors [31][32][33][34]. Fortunately, during these years, the chemotherapy method and the use of chemotherapy drugs have helped to treat some cancer patients. Chemotherapy is a method of treating cancer, which uses drugs that prevent fast-growing cells from dividing [35][36][37]. Almost all people with this deadly disease undergo a course of chemotherapy to cure or stabilize and prevent the disease from progressing. During the course of chemotherapy, chemotherapy drugs are used orally or by injection to go through the treatment process. Using different mechanisms, these drugs target specific aspects of the cancer process and prevent

cell division or induce cell death. Anticancer drugs, from traditional chemotherapy to targeted therapies and modern immunotherapies, play an important role in cancer treatment [38][39][40][41].

In this research, the authors try to investigate the effect of triethylamine as an effective catalyst for the synthesis of a wide range of structurally diverse orthoaminocarbonitrile tetrahydronaphthalenes via a three component one-pot reaction under mild condition. In addition, the anti-cancer properties of these compounds were investigated through molecular docking calculations.



Scheme 1. synthesis of a wide range of structurally diverse orthoaminocarbonitrile tetrahydronaphthalenes via a three component one-pot reaction under mild condition.

Experimental section

General information

All substrates and solvents with high quality were prepared from Fluka (Buchs, Switzerland), Aldrich (St. Louis, Missouri United States), and Merck (Darmstadt, Germany) chemical companies and used without purification. ^{1}H NMR was run on a Bruker Ascend 400MHz and applying deuterated DMSO-d_6 with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ) deshield from tetramethylsilane and coupling constant are indicated in Hertz. Abbreviations used for ^{1}H NMR signals are: s= singlet, d= doublet, t= triplet, q=quartet, m= multiplet, br=broad and etc. Melting points were specified on a Büchi 510 melting point apparatus (Büchi Labortechnik, Flawil, Switzerland). The molecular docking studies were achieved by applying the Schrödinger 2015.10 software (Maestro 10.2).

General procedure for the synthesis of orthoaminocarbonitrile tetrahydronaphthalenes

Benzaldehydes (1 mmol), malononitrile (2 mmol) and cyclohexanon (1 mmol) were transferred to 10 mL round bottom flask in addition to the addition of triethylamine (0.3 mmol) in 3 mL of ethanol. The mixture was refluxed for an appropriate time. The precipitate was separated from the filtrate and washed with ethanol. Afterwards, the mixture was concentrated under reduced pressure and dried in an oven at 70°C for 8 h. Spectral information related to the prepared products (**4a-l**) is given below.

Representative spectral data (compound 4a-4l)

Comment 3: It is better to write DMSO-d6 instead of DMSO in all spectral information section.

Compound 4a: White solid; Yield: 98%; ^{1}H NMR (400 MHz, DMSO) δ(ppm) = 7.61 – 7.38 (m, 7H), 5.73 (s, 1H), 3.55 (d, J = 12.0 Hz, 1H), 2.84 – 2.78 (m, 1H), 2.23 – 2.02 (m, 2H), 1.75 – 1.63 (m, 1H), 1.52 – 1.41 (m, 2H), 0.98 – 0.72 (m, 1H).

Compound 4b: Yellow solid; Yield: 87%; ^{1}H NMR (400 MHz, DMSO): δ (ppm) = 8.09 (d, J = 8.0 Hz, 1H), 8.02 (d,J = 8.0 Hz, 1H), 7.92 (t, J = 8.0 Hz, 1H), 7.75 (t,J = 8.0 Hz, 1H), 7.45 (s, 2H), 5.79 (s, 1H), 4.07 (d,J = 12.0 Hz, 1H), 3.0 (s, 1H), 2.38 – 2.01 (m, 2H), 1.69 (s, 1H), 1.49 (d, J = 8.0 Hz, 2H), 1.01-0.97 (m, 1H).

Compound 4c: White solid; Yield: 92%; ^{1}H NMR (400 MHz, DMSO) δ(ppm) = 7.48 – 7.19 (m, 6H), 5.73 (s, 1H), 3.47 (d, J = 12.0 Hz, 1H), 2.78 (t,J = 12.0 Hz, 1H), 2.34 (s, 3H), 2.21 – 2.12 (m, 1H), 2.05– 2.01 (m, 1H), 1.50 - 1.40 (m, 2H), 1.55 – 1.35 (m, 1H), 0.91 – 0.75 (m, 1H).

Compound 4d: Yellow solid; Yield: 93%; ^{1}H NMR (400 MHz, DMSO) δ(ppm) = 7.71 – 7.39 (m, 6H), 5.73 (s, 1H), 3.63 (d, J = 12.0 Hz, 1H), 2.80 (s, 1H), 2.21 – 2.01(m, 2H), 1.67 (s, 1H), 1.46 (d,J = 4.0 Hz, 2H), 0.90 – 0.81 (m, 1H).

Compound 4e: White solid; Yield: 95%; ^{1}H NMR (400 MHz, DMSO) δ(ppm) = δ 7.85 – 7.54 (m, 3H), 7.50 – 7.41 (m, 3H), 5.73 (s, 1H), 3.65 (d, J = 12.0 Hz, 1H), 2.83 (d,J = 12.0 Hz, 1H), 2.6 1.98 (m, 2H), 1.67 (s, 1H), 1.46 (d,J = 12.0 Hz, 1H), 0.87 (d, J = 12.0 Hz, 1H).

Compound 4f: White solid; Yield: 92%; ^{1}H NMR (400 MHz, DMSO) δ(ppm) = 7.81 – 7.74 (m, 1H), 7.67 – 7.60 (m, 1H), 7.56 – 7.39 (m, 4H), 5.73 (s, 1H), 3.89 (d, J = 12.0 Hz, 1H), 2.97 – 2.78 (m, 1H), 2.27 – 2.05 (m, 2H), 1.76 – 1.55 (m, 1H), 1.47 – 1.23 (m, 2H), 0.86 – 0.75 (m, 1H).

Compound 4g: White solid; Yield: 93%; ^{1}H NMR (400 MHz, DMSO) δ(ppm) 7.70 – 7.32 (m, 6H), 5.73 (s, 1H), 3.65 (d,J = 12.0 Hz, 1H), 2.80 (t, J = 12.0 Hz, 1H), 2.28– 2.01 (m, 2H), 1.75 – 1.67 (m, 1H), 1.42 (t, J = 8.0 Hz, 2H), 0.94 – 0.74 (m, 1H).

Compound 4h: Yellow solid; Yield: 96%; ^{1}H NMR (400 MHz, DMSO) δ(ppm): 7.96 – 7.40 (m, 5H), 5.77 (s, 1H), 3.88 (d,J = 12.0 Hz, 1H), 2.96 – 2.74 (m, 1H), 2.31 – 2.00 (m, 2H), 1.66 (s, 1H), 1.45- 1.27 (m, 1H), 0.95- 0.63 (m, 1H).

Compound 4i: White solid; Yield: 92%; ^{1}H NMR (400 MHz, DMSO) δ(ppm) = 7.35 (s, 1H), 7.19 – 7.03 (m, 2H), 6.97 (s, 1H), 5.72 (s, 1H), 3.76 (d, J = 24.0 Hz, 6H), 3.52- 3.41 (m, 1H), 2.85- 2.69 (m, 1H), 2.21- 2.06 (m, 2H), 1.67 (s, 1H), 1.58-1.44 (m, 2H), 0.87 (d, J = 8.0 Hz, 1H).

Compound 4j: Yellow solid; Yield: 90%; ^{1}H NMR (400 MHz, DMSO) δ(ppm): 7.40 (d, J = 16.0 Hz, 2H), 6.85 (d, J = 20.0 Hz, 2H), 5.73 (s, 1H), 3.80- 3.70 (m, 10H), 3.45 (d, J = 12.0 Hz, 1H), 2.81 (s, 1H), 2.22 – 2.01 (m, 2H), 1.99 – 1.44 (m, 2H), 0.96 – 0.81 (m, 1H).

Compound 4k: Yellow solid; Yield: 95%; ^{1}H NMR (400 MHz, DMSO) δ(ppm) = 9.66 (s, 1H), 7.42 – 7.29 (m, 3H), 7.24 – 7.16 (m, 1H), 6.93 – 6.72 (m, 1H), 5.70 (s, 1H), 3.38 (d, J = 12.0 Hz, 1H), 2.77 – 2.62 (m, 1H), 2.21 – 1.98 (m, 2H), 1.76 – 1.60 (m, 1H), 1.53 – 1.38 (m, 2H), 0.93 – 0.68 (m, 1H).

Compound 4l: Yellow solid; Yield: 94%; ^{1}H NMR (400 MHz, DMSO) δ(ppm) = 7.56 – 7.23 (m, 6H), 5.72 (s, 1H), 3.48 (d, J = 12.0 Hz, 1H), 2.98 – 2.88 (m, 1H), 2.84 – 2.70 (m, 1H), 2.21 – 1.97 (m, 2H), 1.73 – 1.62 (m, 1H), 1.53 – 1.40 (m, 2H), 1.29 – 1.17 (m, 6H), 0.91 - 0.78 (m, 1H).

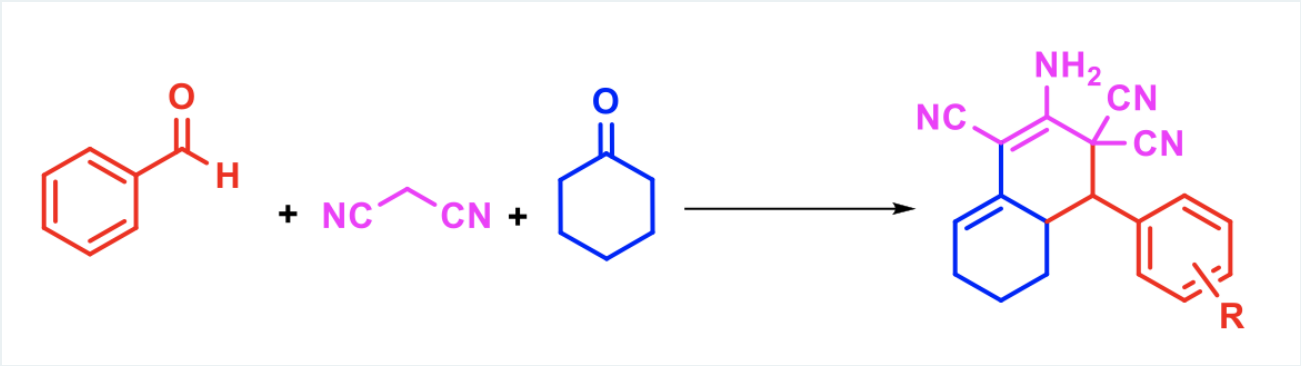
Results and Discussion

Screening the conditions for the synthesis of orthoaminocarbonitrile tetrahydronaphthalenes in the presence of triethylamine (Et_3N)

In order to establish the optimum conditions, the catalytic activities of various bases were examined in a model reaction using benzaldehyde (**1a**, 1 mmol), malononitrile (**2a**, 2 mmol), and cyclohexanone (**3a**, 1 mmol). Initially, the effect of base, on the model reaction was investigated. Because of the critical role of bases in reaction, the effectiveness of various bases such as NaOH, Na_2CO_3, K_3PO_4, Pyridine and triethylamine(Et_3N) were studied in the model reaction. Although all of the bases applied showed good activity (Table 1, entries 1-6) the most effective base was triethylamine (Table 1, entry 6). Afterwards, for choosing the reaction media, different solvents such as EtOH, MeOH, CH_3CN and $CHCl_3$ were examined (Table 1 and entries 6-9) and the best results were obtained in the ethanol (Table 1 and entry 6). In the next step, the amount of the catalyst on the reaction rate was investigated. Then, 1, 3, and 5 mmol of catalyst were used in the model reaction (Table 1 and entry 6, entries 10-11). When we used 3 mmol of catalyst, the highest efficiency in the product was observed (Table 1 and entry 10). In order to measure the effect of temperature on reaction efficiency and reaction time, the reaction was studied at four temperatures 50°C, 60°C, 70°C, and 80°C (Table 1, entry 10 and entries 12-14). The best efficiency was observed when the reaction temperature was 70°C (Table 1, entry 13). Thereupon, the optimized conditions were found to be using ethanol as a solvent in the presence of 3 mmol of catalyst (triethylamine), 70°C (reflux), at 10 min reaction time.

Table 1. Optimization of the reaction conditions for the synthesis of 2-Amino-4-phenyl-4a,5,6,7-tetrahydronaphthalene-1,3,3(4 *H*)-tricarbonitrile **(4a)** [a]

2-amino ...



Entry	Solvent	Catalyst (mmol)	Temperature (ºC)	Yield (%)[b]	Time (min)
1	EtOH	-	50	Trace	30
2	EtOH	NaOH (0.1)	50	17	30
3	EtOH	Na_2CO_3 (0.1)	50	36	30
4	EtOH	K_3PO_4 (0.1)	50	39	30
5	EtOH	Pyridine (0.1)	50	36	30
6	EtOH	Et_3N (0.1)	50	55	30
7	CH_3Cl	Et_3N (0.1)	50	38	30
8	MeOH	Et_3N (0.1)	50	44	30
9	CH_3CN	Et_3N (0.1)	50	37	30
10	EtOH	Et_3N (0.3)	50	65	30
11	EtOH	Et_3N (0.5)	50	65	30
12	EtOH	Et_3N (0.3)	60	85	20
13	**EtOH**	**Et_3N (0.3)**	**70**	**98**	**10**[c]
14	EtOH	Et_3N (0.3)	80	98	10

[a] *Reactionconditions:* Benzaldehyde (**1a**, 1 mmol), malononitrile (**2a**, 2 mmol), and cyclohexanone (**3a**, 1 mmol), catalyst and solvent (3 mL).

[b] TLC yield.

Comment 4: It is necessary for the author to provide clear explanations about "TLC yield" in the Experimental section - general information.

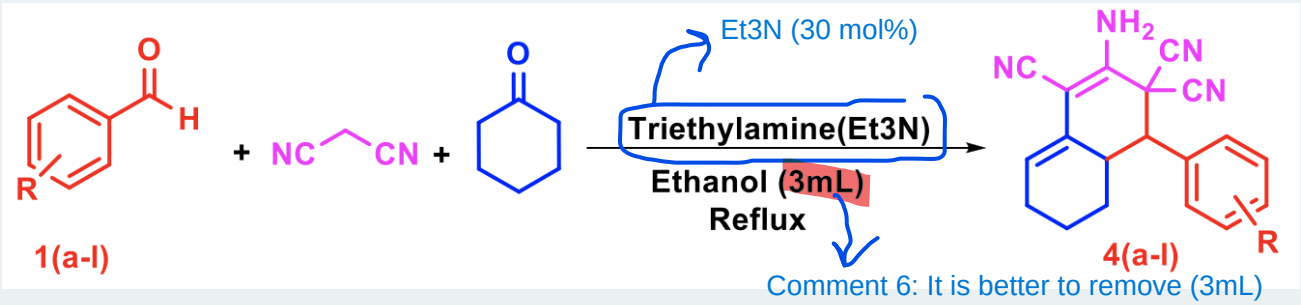
[c] Isolated yield.

Isolated

Comment 5: It is enough to write the numbers of the compounds and the numbers of intermediates in bold, and there is no need to write them in parentheses.

Encouraged by the initial success in the production of 2-Amino-4-phenyl-4a,5,6,7-tetrahydronaphthalene-1,3,3(4*H*)-tricarbonitrile (**4a**) via the multicomponent reaction strategy, to show the general scope and versatility of this strategy in the preparation of substituted orthoaminocarbonitrile tetrahydronaphthalenes, different substituted aromatic aldehydes (**1a-l**), malononitrile (**2a**) and cyclohexanone (**3a**) were examined under optimized conditions. Excitingly, the corresponding substituted orthoaminocarbonitrile tetrahydronaphthalene derivatives (**4a-l**) were successfully and smoothly obtained, and the results are listed in Table **2**.

Table 2. The one-pot three-component reaction of aryl aldehydes (**1**, 1 mmol), malononitrile (**2**,2 mmol) and cyclohexanone (**3**, 1 mmol) under optimized conditions

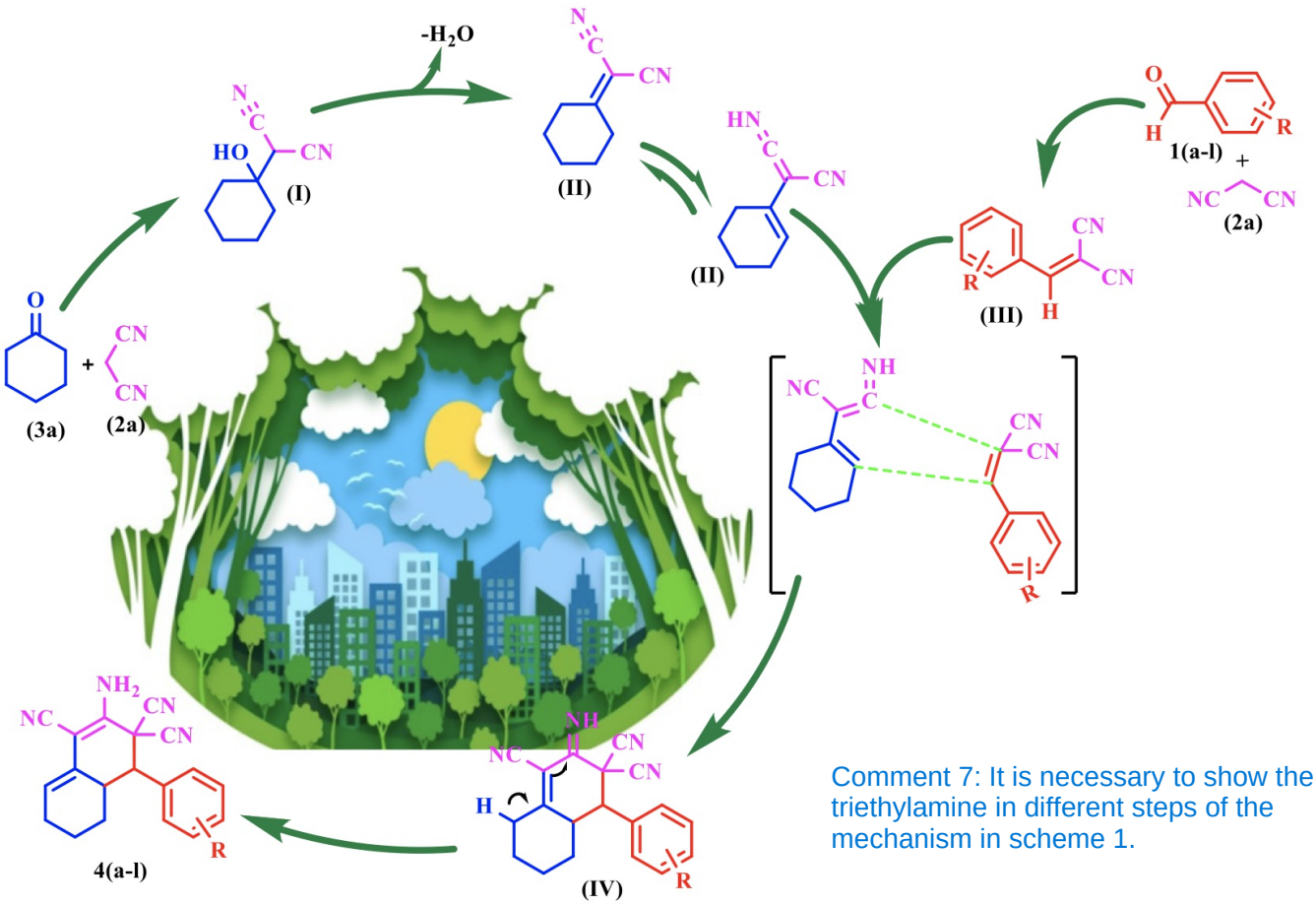


Entry	R	product	Time (min)	Yield (%)[a]	m.p. (°C)	Lit. m.p.[ref.]
1	h	**4a**	10	98	255-257	255-256 [42]
2	2-NO_2	**4b**	25	87	245-247	244-246 [25]
3	4-Me	**4c**	25	92	235-238	235-237 [25]
4	4-Br	**4d**	25	93	244-246	244-246 [42]
5	3-Br	**4e**	20	95	250-252	251-254 [25]
6	2-Cl	**4f**	20	92	271-272	282-284 [26]
7	4-Cl	**4g**	15	93	247-250	248-250 [43]
8	2,4-diCl	**4h**	20	96	256-258	257-259 [25]
9	3,4-diOMe	**4i**	20	92	289-290	289-291 [25]
10	3,4,5-triOMe-	**4j**	20	90	234-236	233-235 [26]
11	4OH	**4k**	25	95	239-241	239-240 [25]
12	4-$CH(CH_3)_2$	**4l**	20	94	196-198	197-199 [25]

[a] Isolated yield.

Mechanism of the catalytic reaction

Scheme **1** illustrates possible mechanisms for the synthesis of orthoaminocarbonitrile tetrahydronaphthalenes (**4a-l**). In the first step, the triethylamine plays a major role in the condensation of cyclohexanone (**3a**) and malononitrile (**2a**) by absorbing the acidic hydrogen of malononitrile (**2a**), and the intermediate (**I**) is obtained which results in the intermediate (**II**) through the loss of a water molecule, and then is followed by tautomerization to form intermediate**II**). In the next step, similarly, the treatment of malononitrile (**2a**) with a benzaldehyde (**1a-l**) produces the intermediate (**III**). Afterwards, intermediate (**II**) reacts with intermediate (**III**) through a Diels-Alder reaction to form intermediate (**VI**). Finally, the corresponding orthoaminocarbonitrile tetrahydronaphthalene (**4a-l**) is formed through tautomerization of intermediate (**VI**).



Scheme 1. illustrates possible mechanisms for the synthesis of orthoaminocarbonitrile tetrahydronaphthalenes (**4a-l**).

Molecular docking study of anti-cancer activity of synthesized ortho-aminocarbonitrile tetrahydronaphthalenes

The results of molecular docking calculations of the synthesized compounds are shown in Tables **3 and 4**. According to the obtained results, the docking energy indicates the strength of the binding of the ligand to the receptor, the more negative the number is, the better the binding of the ligand to the receptor. The following are the results according to Lee Pinsky's rules (rules of medication):

Molecular mass: In this law, the mass of the drug molecule should not be more than 500 g/mol, because the heavier the molecule becomes, the possibility of its absorption and permeability also decreases. All synthesized compounds follow this rule.

Ligand dissociation factor: This item tries to create a balance between hydrophilicity and lipophilicity of the drug molecule. In this balance, the octanol/water partition coefficient should not be smaller than 5. This applies to all synthesized compounds.

Number of hydrogen donating groups: This item indicates the number of hydrogen donating groups (such as NH and OH) in the drug molecule. The number of these groups should not be more than 5. All synthesized compounds follow this

rule.

The number of hydrogen acceptor groups: This item indicates the number of hydrogen acceptor groups (groups such as O and N). The number of these groups should not be more than 10. Fortunately, all synthesized compounds follow this law.

Cell permeability (QPPCaco): This item plays an important role in bioavailability and drug absorption. Cell permeability optimizes the gastrointestinal absorption of drugs, which should have a permeability rate greater than 500 nm/s. All combinations except **4k** follow this case.

Prediction of human oral absorption (PHOA): Edible potential is moderate to high for all ligands (Recommended values < 80% is high and > 25% is weak).

PHOA: Prediction of human oral absorption on a scale of 0 to 100 percent.

Drug solubility (**QlogPs)** This has an important role in gastrointestinal absorption and oral biological supply of the drug. The drug solubility standard should be between 0.5 and -6.5. Fortunately, all synthesized compounds follow this law.

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

Entry	Molecular weight	Octanol/water ratio	Number of donor hydrogen bonds	Number of acceptor Hydrogen bonds	Cell permeability (QPPCaco)
4a	300.362	1.703	6.25	2.5	74.978
4b	345.360	1.156	5.5	1.5	16.114
4c	314.389	2.003	5.5	1.5	75.044
4d	379.258	2.264	5.5	1.5	75.552
4e	379.258	2.264	7.75	1.5	74.99
4f	334.807	2.125	5.5	1.5	102.089
4g	334.807	2.19	6.5	1.5	75.556
4h	369.252	2.673	5.5	1.5	100
4i	360.415	1.980	5.5	1.5	74.94
4j	390.441	2.113	5.5	1.5	91.452
4k	316.362	1.002	7	1.5	22.922
4l	342.443	2.657	5.5	1.5	75.989

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

Entry	Potential Energy-OPLS3	RMS Derivative-OPLS3	Central nervous system (CNS)	Blood-brain partition coefficient	PHOA	QlogPs	Docking energy
4a	90.267	0.044	-2	-1.662	70.476	-4.673	-2.871
4b	125.816	0	-2	-2.364	55.319	-4.607	-3.208
4c	101.182	0.008	-2	-1.73	72.237	-5.215	-3.856
4d	98.456	0.006	-2	-1.531	73.819	-5.49	-3.79
4e	97.966	0.003	-2	-1.539	73.758	-5.502	-3.069
4f	102.471	0.023	-2	-1.465	75.343	-5.053	-2.673
4g	98.554	0.02	-2	-1.533	73.384	-5.38	-3.818
4h	91.597	0.001	-2	-1.32	78.456	-5.881	-3.122
4i	161.202	0.015	-2	-1.921	72.092	-5.21	-3.305
4j	178.822	0.032	-2	-1.81	74.421	-4.983	-3.466
4k	93.287	0.001	-2	-2.234	57.158	-4.48	-3.103
4l	109.859	0.006	-2	-1.879	76.166	-5.99	-3.372

In the following, the interactions and bonds of the ligand with the protein are shown in two dimensions. As shown in the **Figure 1 and 2**, ligand 4c hydrogen bonds with leucine A:728 residue by nitrogen, which has a very special and vital role in biological sciences and pharmaceutical connections.

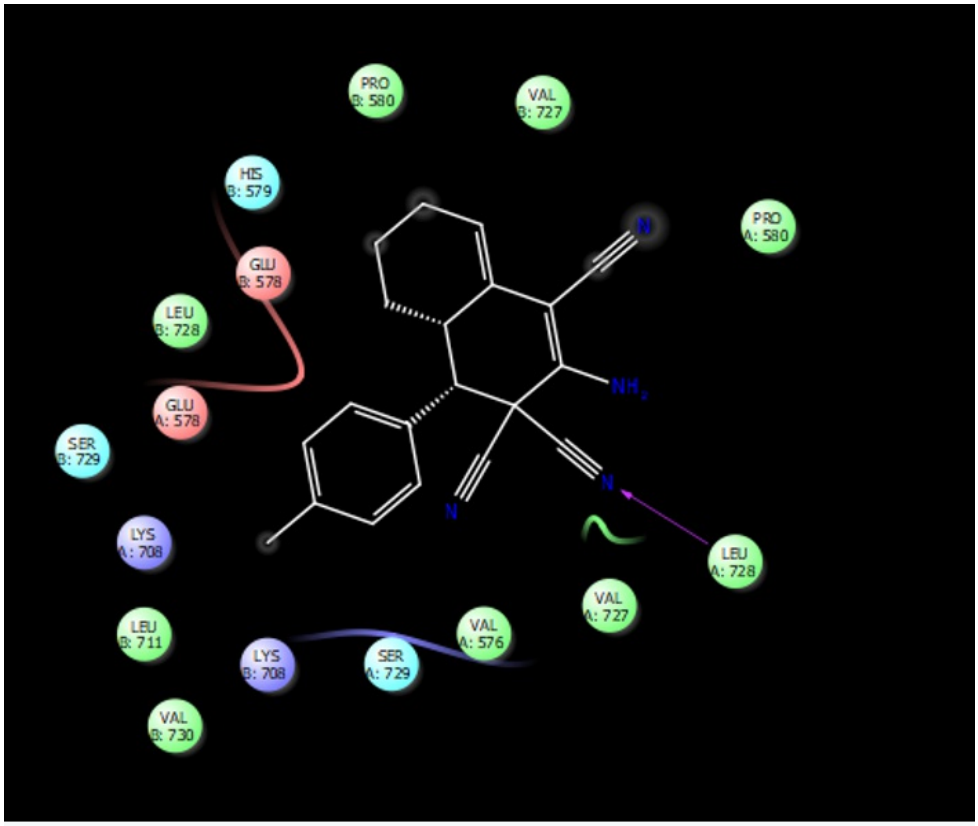


Figure 1. Bonds and interactions between ligand **3c** leucine A:728 residue.

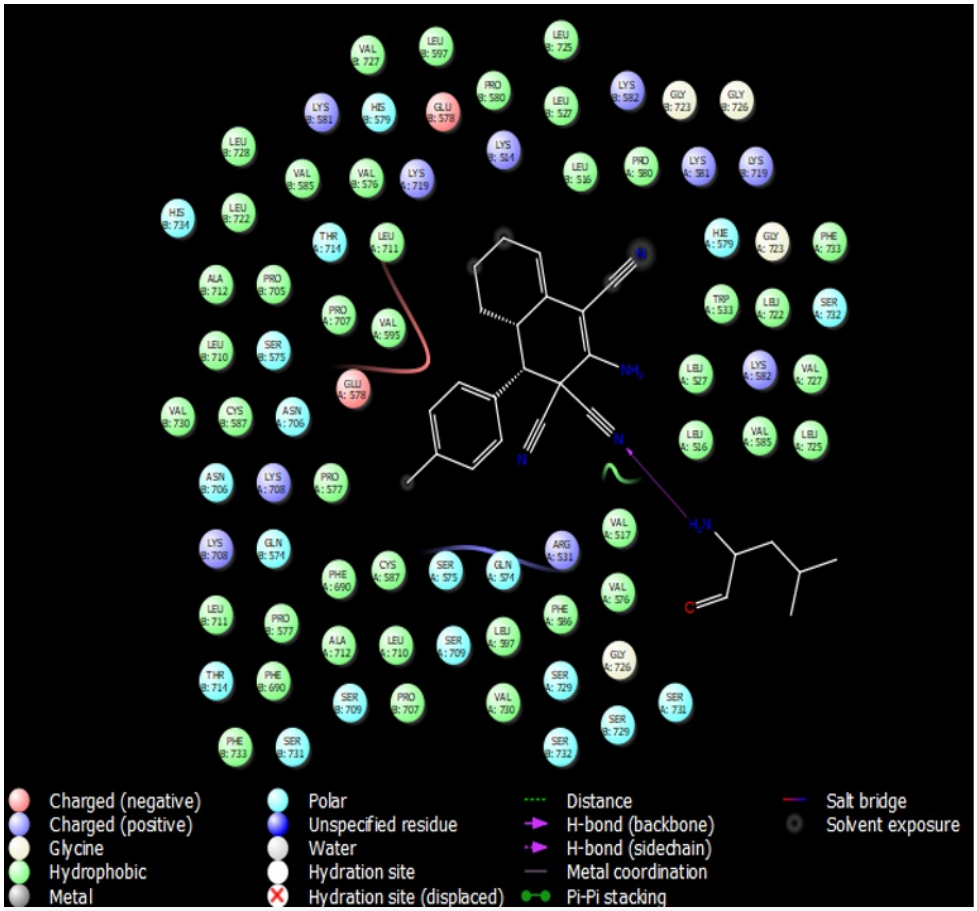


Figure 2. Links and connections of ligand **4c** and extended leucine A:728 residue.

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 3A8P protein, which leads to the inactivation of this protein and produces beneficial effects during cancer treatment.

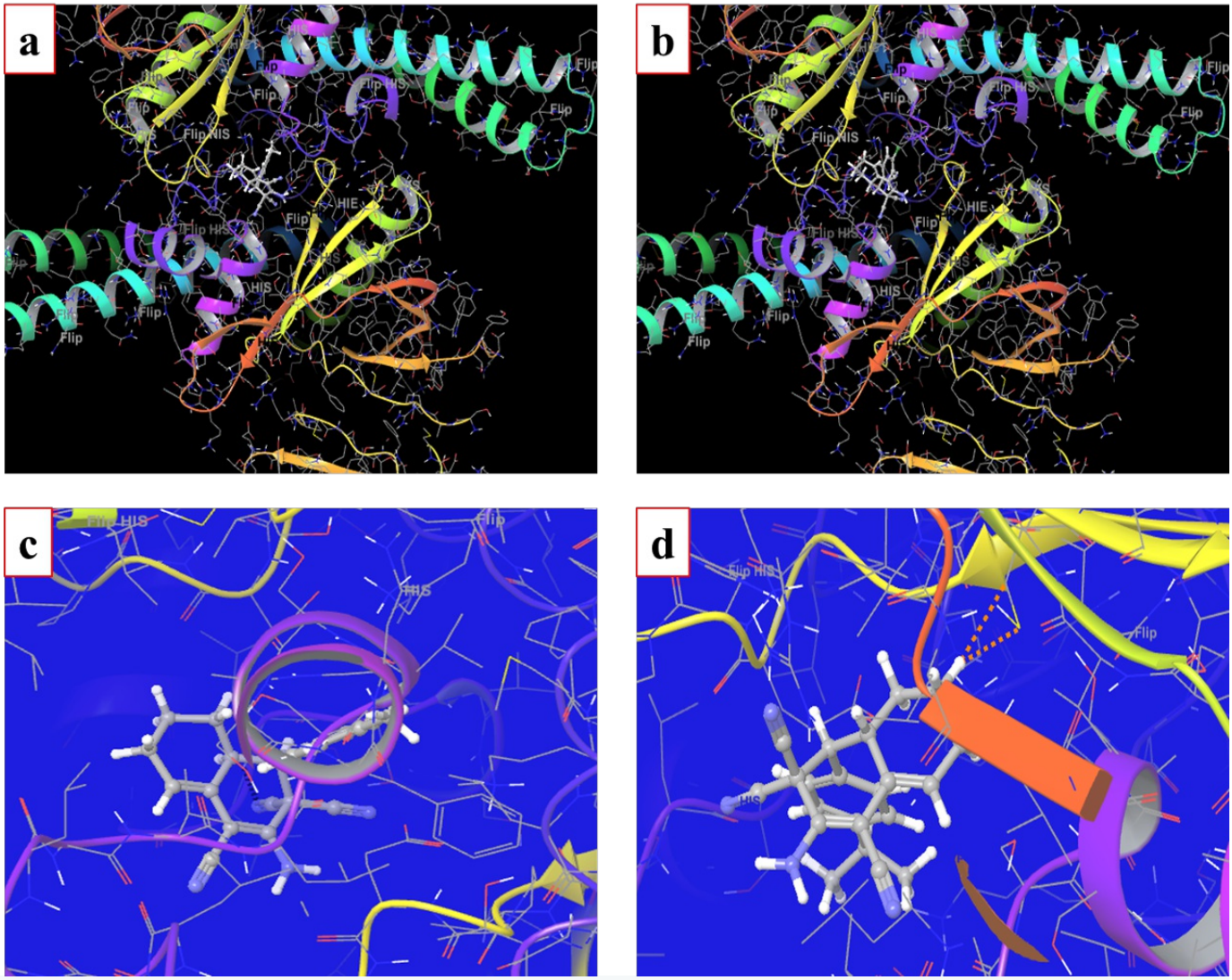


Figure 3. 3D graphs of ligands-protein interactions of four synthesized ortho-aminocarbonitrile tetrahydronaphthalene derivatives **4c** (a), **4f** (b), **4g** (c) and **4l** (d).

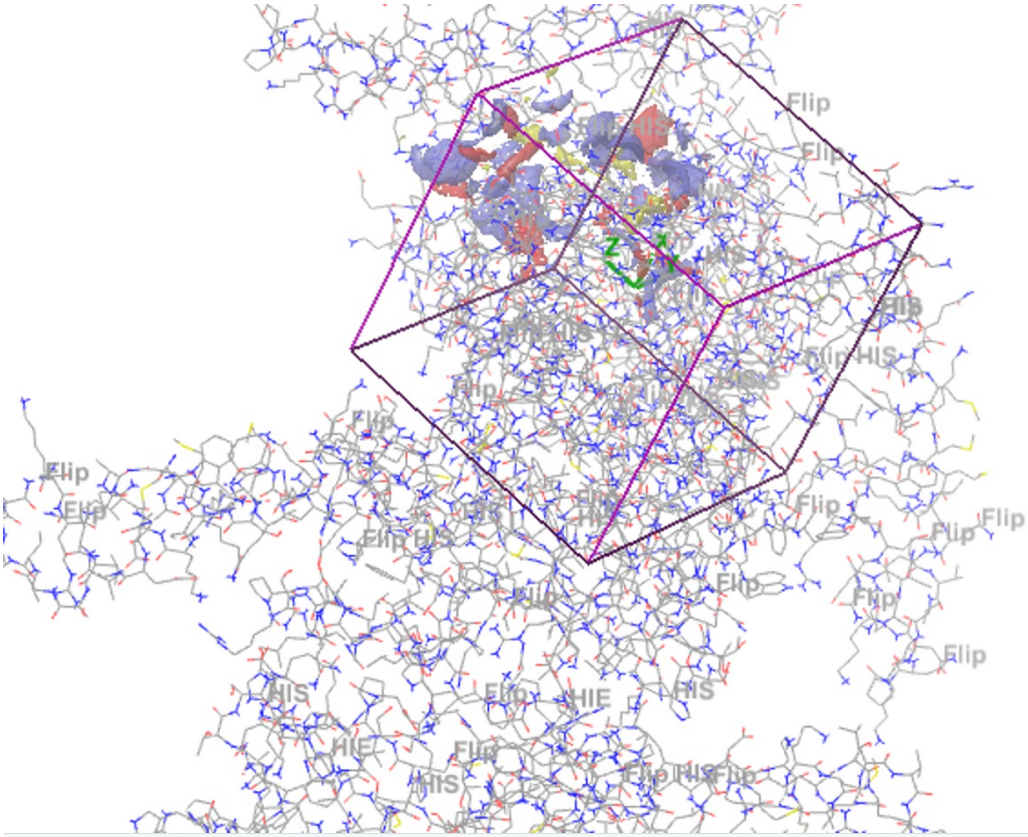


Figure 4. Active site of protein 3A8P.

Comparison of the prepared catalyst with reported ones

Comment 8: It is better to move this section be

To demonstrate the uniqueness, advantages, novelty, and to further evaluate the presented catalytic activities of the triethylamine catalyst, were compared with those of the reported catalyzed for the synthesis of orthoaminocarbonitrile tetrahydronaphthalene derivatives (**4a**) in terms of the reaction time and yield. Although the reported catalysts have advantages, the use of triethylamine as a catalyst provides a shorter reaction time and higher yield of products. Fortunately, the method used in our current work has advantages over other works such as simplicity, short reaction time and mild conditions, which makes this method a green and environmentally friendly protocol.

Table 5. Comparison among efficiency of triethylamine (Et_3N) with the reported catalysts for the preparation of compound **4a**

Entry	Catalyst	Conditions	Time (h)	Yield[b] (%)	*Ref*
1	[BPy] BF_4 (2 mL)	60ºC	5	83	[44]
2	DDIL (20 mol%)	H_2O, RT, U.S	0.25	86	[45]
3	BMIM.PF_6 (0.3 mmol)	Ethanol, Reflux	0.16	95	[26]
4	Morpholine (0.1 mmol)	Ethanol, RT	0.75	95	[46]
5	CaMg@MYS (5 mg,	Ethanol, Reflux	0.16	96	[25]
6	$[Bmim\text{-}G]^+[Br]^-$ (10 mol %)	Solvent-free, RT	6	83	[44]
7	Triethylamine (Et_3N)	Ethanol, Reflux	0.16	98	This work

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[a] *Reaction conditions*: Benzaldehyde (1 mmol), malononitrile (2 mmol) and cyclohexanone (1 mmol), in various conditions.

[b] Isolated yield.

Conclusions

In summary, an efficient and green method for the synthesis of ortho-aminocarbonitrile tetrahydronaphthalene derivatives has been developed in the presence of triethylamine (Et_3N) as a homogeneous catalyst under mild conditions. The products were obtained in good to excellent yields (87-98%) and the reaction times were significantly short (10-25 minutes). This method is bestowed with several unique merits such as simple workup, use of ethanol as a solvent, high yields, very mild reaction conditions, short reaction times, little catalyst loading, not requiring specialized equipment and thus significantly contributes to the practice of green chemistry. Additionally, all the synthesized compounds bind to an agonist at the active site of the 3A8P protein, which leads to the inactivation of this protein and produces beneficial effects during cancer treatment. In synthesized compounds, the ligands establish hydrogen bonds with leucine A:728 residues through nitrogen, which has a very special and vital role in biological sciences and pharmaceutical connections. In this study, it was found that these compounds have the potential to become an oral anti-cancer drug.

Acknowledgments

The authors thank the Research Committee of University of Kashan and Shiraz University for financial support of this work.

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