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A GREEN, MICROWAVE ASSISTED AND EFFICIENT PROTOCOL FOR SYNTHESIS OF 2-(4-SUBSTITUTED PHENYL)-1*H*-BENZIMIDAZOLE CATALYZED BY NICKEL NITRATE AND THEIR MOLECULAR DOCKING STUDY

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Abstract
A simple green, efficient method developed here for the one pot synthesis of 2-(4-substituted phenyl)-1*H*-benzimidazole derivatives via cyclocondensation of o-phenylenediamine with aromatic carboxylic acids under microwave irradiation using transition metal nitrates as a catalyst in an organic solvent. This green protocol offers the significant advantages in terms of simplicity, low catalyst loading, very good yields, the use of available catalysts, simple workup procedure, short reaction time andnon toxicnature.The molecular Docking studies carried out using molecular modeling software HEX 8.0.0 for determining the antibacterial activity of synthesized benzimidazoles against β-ketoacyl-acyl carrier protein synthase (1HNJ) and the results shows that the synthesized molecules show moderate to betterbinding affinity.The proposed protocol will discover the novel synthetic route for new bioactive compounds.

Keywords
O-Phenylenediamine, microwave irradiation, nickel nitrate, benzimidazole, green protocol.

Introduction
The Benzimidazoles are a class of heterocyclic, aromatic chemical compounds which share a fundamental structural characteristic of six-membered benzene fused to a five-membered imidazole. Aside from their place in biomedical research, benzimidazoles also have a prominent place in organocatalysis, organometallic and material chemistry. The imidazole is a precursor to N-heterocyclic carbenes and the benzene ring provides a convenient scaffold to which additional functionality easily added to modify the spatial and electronic characteristics of a benzimidazole derivative. This combination of a reactive carbene center with a modifiable backbone is one of the reasons for the recent rise in the study and the use of benzimidazoles and their N-heterocyclic carbene derivatives.

The benzimidazole is an important pharmacophore in modern drug discovery[1].Benzimidazole derivatives exhibit significant activity against several viruses such as [2],herpes (HSV-1) [3], RNA [4], influenza[5] and human cytomegalovirus(HCMV)[*6]*. The bis-benzimidazoles are being developed as DNA minor-groove binding agents with antitumor activity6and can act as ligands to transition metals for modeling biological systems [7]. In addition, benzimidazoles are also important intermediates in organic synthesis, which is why benzimidazoles have gained considerable attention in recent years. Despite their importance from pharmacological, industrial and synthetic points of view, unfortunately very few methods reported for their preparation. One such method involves coupling reaction o-phenylenediamines and carboxylic acids or their derivatives (nitriles, imidates, or orthoesters) using strong acids such as polyphosphoric acid [8] or mineral acids [9]or high-temperature microwave irradiation [10]. Another method involves a two-step procedure involving oxidative cyclodehydrogenation of Schiff bases, which often generated from the condensation of o-phenylenediamines and aldehydes. Various oxidative and catalytic reagents such as sulfamic acid[11], I_2 [12], 2,3-dichloro-5,6-dicyanobenzoquinine(DDQ)[13] , $In(OTf)_3$ [14] and $Sc(OTf)_{3[}$15] employed. Because of the availability of a vast number of aldehydes,
condensation of o-phenylenediamines and aldehydes has been extensively used. Though these published methods are effective, they suffer from one or more disadvantages such as (a) poor yields, (b) the use of expensive reagents, (c) multistage synthesis, (d) long reaction times, (e) tedious workup procedures, and (f) occurrence of several side reactions. Consequently, the introduction of new methods or further work on technical improvements of procedures to overcome these limitations is still an important experimental challenge.

Legislation to maintain environmental friendliness requires us to prevent the generation of waste, avoid the use of auxiliary substances (e.g., organic solvents, additional reagent) and minimize the energy requiredin the development of new procedures for the reaction. Recently, the microwave as a heating source used for the rapid synthesis of a variety of heterocyclic compounds, both in solution phase as well as under solvent-free conditions [16]. Usually, 2-arylbenzimidazoles prepared by classical cyclocondensation of 1,2-phenylenediamines with the corresponding carboxylic acids under harsh dehydrating reaction conditions [17] or aldehydes under oxidative conditions [18]. The condensation of 1,2-phenylenediamines and aldehydes requires an oxidative reagent to generate the benzimidazole core. Moreover, various reagents and catalysts such as nitrobenzene [19], benzoquinone [20], sodium metabisulfite [21] ,air [22], Thiamine hydrochloride [23] and Polyvinylpolypyrrolidone supported chlorosulfonic acid[24] employed for organic synthesis purpose. Because of the availability of commercial aldehydes, this method chosen as the most general procedure. However, in most of the cases, the reaction requires at least 4 to 48 h, giving yields between 30 to 75%. Using microwave irradiation as a heating source, the rates of reactions involving polar components are usually very fast. The reactions that require hours or even days by conventional heating often accomplished in seconds by microwave heating, that is the reason why this technology widely applied to drug discovery.

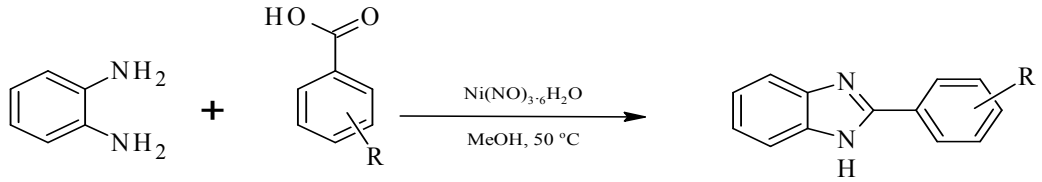
In addition to the use of microwave assisted technology and the use of methanol as a solvent in less quantity is also ecofriendly approach. In this paper,we present a highly selective and efficient method for the synthesis of 2-arylbenzimidazole by using microwave assisted technology inmethanol using $Ni(NO_3)_3$as catalyst.

Experimental

All the chemicals used for the synthesis are of analytical grade and used without further purification. Melting points measured on a digital melting-point apparatus.The IR spectra measured on the Bruker alpha FTIR spectrometer. The ^{1}H NMR spectra measured in dimethylsulfoxide (DMSO-d_6) on a Bruker DRX 300NMR spectrometer (300 MHz) using TMS as an internal standard .

General procedure for the synthesis of 2-(substituted phenyl)-1*H*-benzimidazole:

To a mixture of o- phenylenediamine (1 mmol), aromatic acids (1mmol) and nickel nitrate hexahydrate ($Ni(NO_3)_3 .6H_2O$) (5 mole %) stirred in methanol (10 mL) at 50ºC temperature. The progress of the reaction monitored by TLC. After completion of the reaction the solvent removed under reduced pressure and cold water (15 - 25 mL) added to give the product. The solid product filtered and washed with cold water and air dried. The solid recrystallized from ethanol.The obtained product chromatographed on silca gel and eluted with CH_2Cl_2–MeOH (100:1) to obtain pure product.



O-phenylenediamne Aromatic acid 2-(substituted phenyl)-1*H*-benzimidazole

Figure.1 : Scheme ofsynthesis of 2-(substituted phenyl)-1*H*-benzimidazole

Spectroscopic characterization of compounds (1a-1g) :

2-Phenyl-1H-benzimidazole (1a):

m.p. 287–289 °C .

IR spectrum (ν_{max}/ cm^{-1}):1630 (C=N), 3438 (NH);

^{1}H NMR spectrum (500.1 MHz ; $CDCl_3$; Me_4Si):7.16–7.27 (2H, m, aromatic), 7.51–7.65 (5H, m, aromatic), 8.30–8.33 (2H, d, J = 7.1 Hz, aromatic), 12.92 (1H, bs, NH).

2-(4-chlorophenyl)-1*H*-benzimidazole (1b) :

m.p. 288–290 °C.

IR spectrum (ν_{max}/ cm^{-1}): 1628 (C=N), 3425 (NH) , 650 (C-Cl).

^{1}H NMR spectrum (500.1 MHz ; $CDCl_3$; Me_4Si): 8.026 (4H, m, aromatic), 7.478 (5H, m, aromatic), 7.471 (1H, bs, NH).

2-(4-nitrophenyl)-1*H*-benzimidazole (1c):

m.p. 288–290 °C.

IR spectrum (ν_{max}/ cm^{-1}): 1619 (C=N), 3158 (NH); 1346-1424 (NO_2).

1H NMR spectrum (500.1 MHz ; $CDCl_3$; Me4Si):7.477- 8.303 (5H , m, aromatic), 7.259 (1H, bs, NH).

2-(2-nitrophenyl)-1*H*-benzimidazole (1d):

mp: 209–211 °C .

IR spectrum (ν_{max}/ cm^{-1}): 1340, 1550 (NO_2), 1624 (C=N), 3438 (NH).
^{1}H NMR spectrum (500.1 MHz ; $CDCl_3$; Me_4Si): 7.25–7.40 (4H, m, aromatic), 7.67–7.80 (4H, m, aromatic), 12.89 (1H, bs, NH).

4-(1*H*-benzimidazol-2-yl)phenol (1e):
m.p. 257–259 ℃ .
IR spectrum (ν_{max}/ cm^{-1}): 3399 - 3250 (NH, OH); 2691 (C-H in aromatic ring), 1732 - 1626 (C=N); 1273-1243 (C=C in aromatic ring).
^{1}H NMR spectrum (500.1 MHz ; $CDCl_3$; Me_4Si): 7.481 –7.969 (2H, m, aromatic), 9.857 (1H, bs, OH), 6.855(1H, bs, NH).

2-[2-phenylethenyl]-1*H*-benzimidazole (1f):
m.p. 210-212°C.
IR spectrum (ν_{max}/ cm^{-1}):1665 (C=N), 3250 (NH);1577 (C=C in aromatic ring).
^{1}H NMR spectrum (500.1 MHz ; $CDCl_3$; Me_4Si): 7.61–7.71 (4H, m, aromatic), 7.73–7.79 (2H, m, aromatic), 7.81–7.86 (2H, m, aromatic), 9.89 (1H, bs, OH), 7.471 (1H, bs, NH).

2-(1*H*-benzimidazol-2-yl)-*N*-phenylaniline (1g):
m.p. 257–259 ℃ .
IR spectrum (ν_{max}/ cm^{-1}): 1690 (C=N), 3250 (NH) , 3120 (N-H).
^{1}H NMR spectrum (500.1 MHz ; $CDCl_3$; Me_4Si): 7.25 –8.06 (5H, m, aromatic),7.208 (1H , NH), 6.72 (1H, bs, NH).

The Molecular docking study :
The molecular docking studies of synthesized benzimidazoles against β-ketoacyl-acyl carrier protein synthase (1HNJ) carried by 'HEX' software. The HEXis an interactive molecular graphics program for calculating and displaying feasible docking modes of pairs of protein and DNA molecules. The HEXcan calculate protein ligand docking, assuming the ligand is rigid and it can superpose pairs of molecules using only knowledge of their 3D shape. The spherical polar frontier (SPF) correlation used to accelerate the calculations and it is one of the few docking programs, which has built in graphics to view the result. The molecular docking of all synthesized compounds and standard drugs was done on molecular docking software's Hex 8.0.0.For obtaining the 3D structures of the compounds chemical structure drawing software's like Cambridgsoft ChemDraw Ultra 8.0, Chem3D Ultra 8.0 used. The PDB file of target β-ketoacyl-acyl carrier protein synthase (1HNJ) was taken from Research Collaboratory for Structural Bioinformatics (RCSB)-Protein Data Bank website.
As fatty acid synthesis (FAS) in bacteria is an essential process for cell survival, the enzymes involved in the FAS pathway have emerged as promising targets for antimicrobial agents. Therefore, β-ketoacyl-acyl carrier protein synthase (1HNJ), which is the enzymes involved in the FAS pathway, acts as an essential target for novel antibacterial drug design.Therefore, this enzyme have benn selected for molecular docking study for determination of binding affinity and inhibitory activity of synthesized benzimidazoles. Moreover, The β-ketoacyl-acyl carrier protein synthase (1HNJ) docked with compounds 1a-1g as well as with standard antibacterial drugs Amoxicillin ad Ciprofloxacin.Figures 2-10 shows interaction and binding energy of 1a-1g and standard drugs with β-ketoacyl-acyl carrier protein synthase (1HNJ).The Docking results were evaluated on the basis of binding energy values obtained after docking of benzimidazole derivatives with 1HNJ.

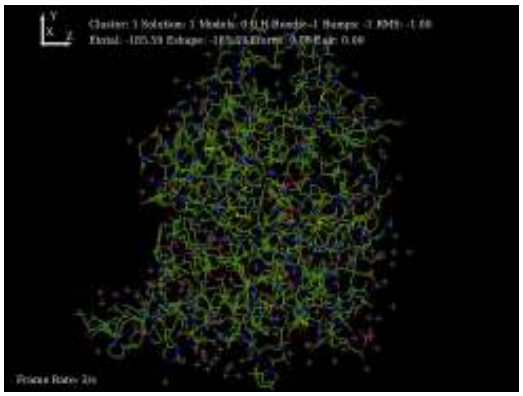


Figure -2: Interaction and binding energy of 1a with 1HNJ

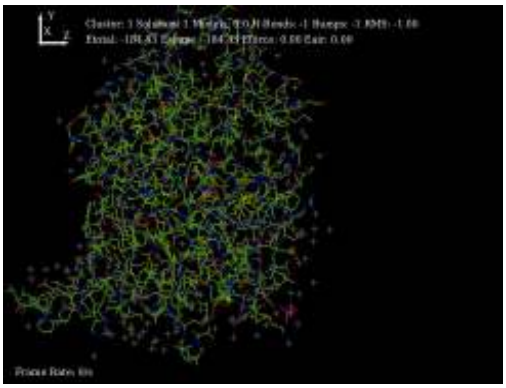


Figure-3: Interaction and binding energy of 1b with 1HNJ

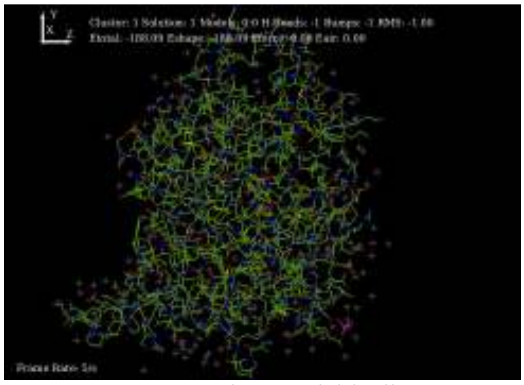


Figure-4: Interaction and binding energy of 1c with 1HNJ

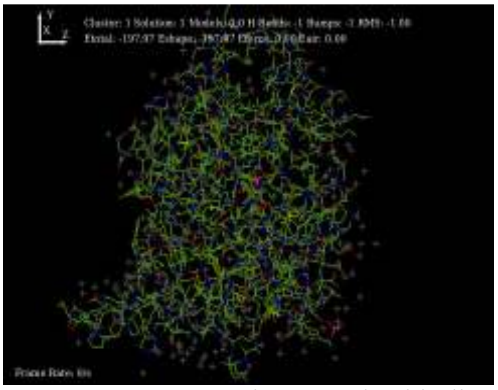


Figure-5: Interaction and binding energy of 1d with 1HNJ

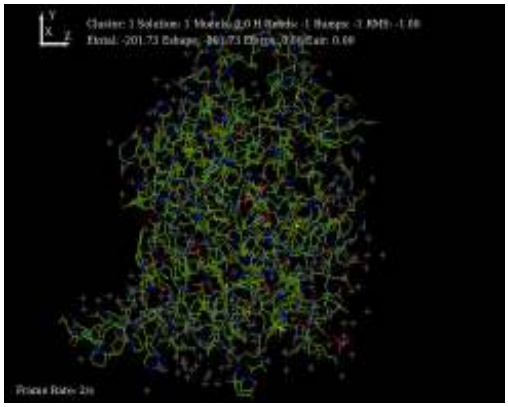


Figure-6: Interaction and binding energy of 1e with 1HNJ

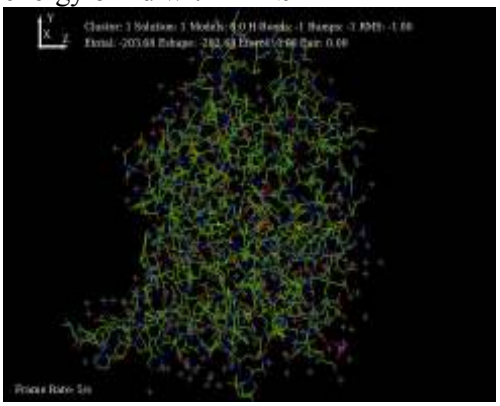


Figure-7: Interaction and binding energy of 1f with 1HNJ

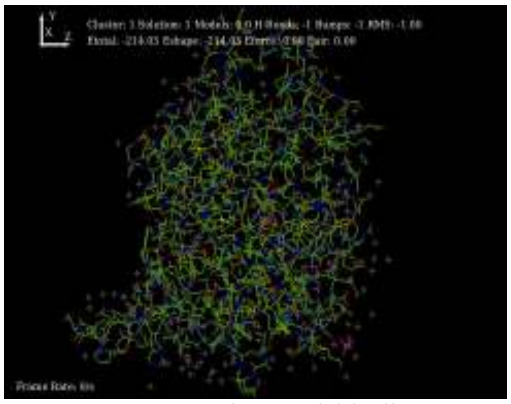


Figure-8: Interaction and binding energy of 1g with 1HNJ

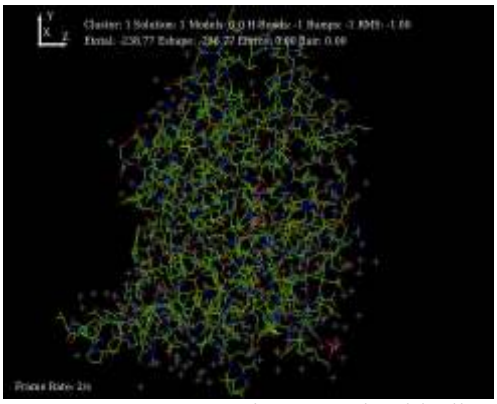


Figure-9: Interaction and binding energy of Amoxicillin with 1HNJ

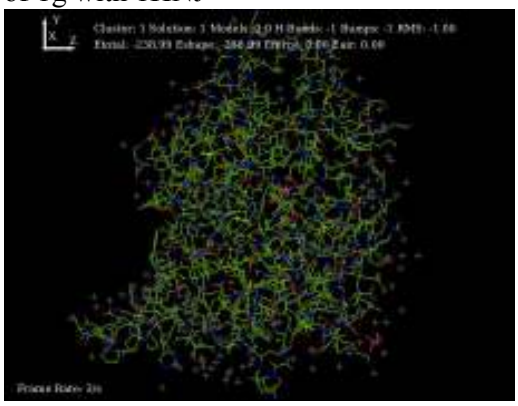
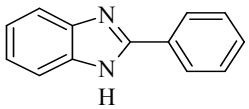
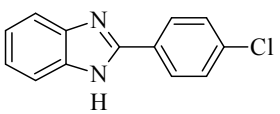
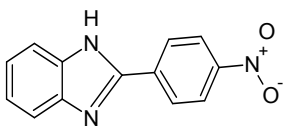


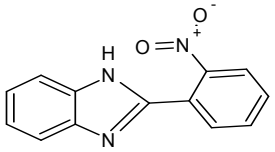
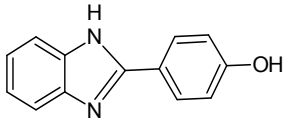
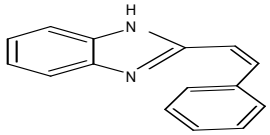
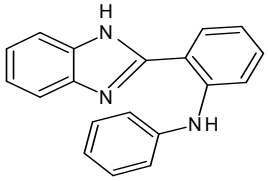
Figure-10: Interaction and binding energy of Ciprofloxacin with 1HNJ

Results and Discussion:

An efficient synthesis of 2-arylbenzimidazoles in methanol in the presence of nickel nitrate asa catalyst reported here. The reaction of aryl acids with o-phenylenediamine afforded benzimidazoles using nickel nitrate as a catalyst under microwave irradiation affords the corresponding products in excellent yields (Table 1).

Table.1: Reaction of o-phenylenediamine with aromatic carboxylic acids under microwave assisted technology

Sr. No.	R	Product	Reaction Time (min)	Yield (%)	Rf
1	2-C_6H_5		2.5	90	0.65
2	4-Cl-C_6H_5		3.5	80	0.76
3	4- NO_3-C_6H_5		4.0	83	0.53

4	2- NO_3-C_6H_5		4.5	90	0.80
5	4-OH-C_6H_5		4.0	95	0.78
6	4-CH=CH-C_6H_5		6.5	94	0.56
7	4-C_6H_5-NH-C_6H_5		7.0	82	0.74

The effect of solvent studied by reacting o-pehenylenediamine and substituted aromatic acids in an equimolar ratio in different solvents at 50ºC as shown in Table 2. The yield of the product varied with the nature of the solvent.

Table 2: Optimization study of different metal nitrates (catalyst) , catalyst concentration and solvents with yield of product.

Sr.No.	**Catalyst**	**Catalyst loading (%)**	**Solvent**	**Yield (%)**
1	Cu $(NO_3)_3.6H_2O$	5	EtOH	70-75
2	Cu $(NO_3)_3.6H_2O$	5	CH_3CN	75-80
3	Ni $(NO_3)_3.6H_2O$	5	MeOH	80-85
4	Ni $(NO_3)_3.6H_2O$	10	MeOH	75-78
5	Ni $(NO_3)_3.6H_2O$	15	MeOH	65-72
6	Ni $(NO_3)_3.6H_2O$	20	MeOH	60-67
7	Mn $(NO_3)_3.6H_2O$	5	MeOH	45-53
8	Fe$(NO_3)_3.6H_2O$	5	MeOH	25-30
9	Co $(NO_3)_3.6H_2O$	5	MeOH	70-78
10	Ni $(NO_3)_3.6H_2O$	5	EtOH	75-80
11	Ni $(NO_3)_3.6H_2O$	5	DMSO	55-60
12	Ni $(NO_3)_3.6H_2O$	5	DMF	70-75

From the table, it is clear that methanol stands out as the solvent of choice, because it is nontoxic and results in better yield when the reaction carried out for the same time.

With extended heating times, a decrease of the yield due to the formation of several by-products observed. For comparison, Benzimidazoles(1a-1g) also prepared by the classical thermal method (i.e., refluxing the 1,2-phenylendiamine, the acids and nickel nitrate in methanol for 3 –4.5 h). Consequently, the classical heating afforded lower yields for almost all compounds and other by-products, for which separation was difficult. Moreover, the reaction proceeded smoothly under microwave irradiation within 3.5- 7.0 minutes, whereas under reflux conditions, it needed 3 – 4.5 h. The most important result of our approach is the optimization of yields and reaction times using microwave irradiation.

To test the general scope and versatility of this procedure, we repeated the reaction with a number of different substituted aromatic acids. The formation of benzimidazole reported here in each case in better yields. The results summarized in Table 2. Consequently, the aromatic acids bearing both electron-donating and electron-withdrawing substituents gave the desired benzimidazoles in better yields.

Molecular dockingstudy :

All the synthesized benzimidazoles(1a-1g) subjected to the Molecular Docking Studies for inhibitory activity against β-ketoacyl-acyl carrier protein synthase (1HNJ) using HEX 8.0.0. molecular docking software.The results were compared by docking the same receptor with standarddrugs Amoxicillin ad Ciprofloxacin.

The results of docking done withHex8.0.0 were represented in Table 3.

Discussion

The inhibitory activities of Synthesized benzimidazole derivatives against β-ketoacyl-acyl carrier protein synthase (1HNJ) were investigated by molecular docking using the HEX docking software.The Protein-Ligand interaction molecular docking study plays a significant role in structural based drug designing.

The results of docking done withHex8.0.0 were represented in Table 3.

Table 3: Docking results of 1HNJ,enzyme with benzimidazolederivatives

Compound Docked	**E-Value**
	1HNJ
1a	-185.59
1b	-184.43
1c	-188.09
1d	-197.97
1e	-201.73
1f	-203.68
1g	-214.05
Amoxicillin	-238.77
Ciprofloxacin	-238.99

The binding energy obtained in Kcal. Table 3 shows that 1a shows low binding energy (-185.59).It may be due to the presence of the phenyl ring. Compound 1b shows lowest binding energy (-184.43) attributed to the presence of p-chlorobenzenering which is a deactivating substituent.Compound 1c and 1d shows significantly high binding energy values i.e.-188.09 and -197.97 respectively. It may be due to the presence of electron withdrawing $–NO_2$ group at para and meta position to the benzene ring. High binding energy

(-201.73) of Compound 1e attributed to the presence of p-hydroxybenzene substituent which is strong activating electron donating group.Compound 1f shows binding energy (-203.68) may be due to the presence of vinylbenzene (-CH=CH-Ph) group.The highest binding energy (-214.05) of compound 1g is due to the presence of diphenylamine (Ph-NH-Ph) group. Moreover , the results were compared with the standard drugs Amoxicillin ad Ciprofloxacin. For standard amoxicillin and ciprofloxacin energy values obtained were -238.77 and -238.99 respectively. When it is compared with the binding energy of 1a-1g , they shows binding energy values very close to the standard. This indicates that synthesized benzimidazoles 1a-1g have good inhibitory activities against β-ketoacyl-acyl carrier protein synthase.Among all the designed compounds, the compound 1g shows more binding energy values (-214.05) Therefore , it can be concluded that the designed benzimidazoles can be used as a potent antibacterial agents.

Conclusion

A novel, simple, and efficient procedure for the synthesis of 2-arylsubstituted benzimidazoles explored. Short reaction time, large-scale synthesis, easy and quick isolation of the products, and excellent yields are the main advantages of this procedure, which make this method more attractive. We believedthat thismethod is a useful contribution to the existing methodologies and a new addition of the catalytic activity of nickel (II) nitrate hexahydrate in the synthesisof organic synthesis.The synthesized compounds (1a-1g) docked with β-ketoacyl-acyl carrier protein synthase (1HNJ) and found to have a betterbinding affinity with 1HNJ.

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