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Research Article

Antitumor Activity and Synthesis of 1, 2-Disubstituted Benzimidazoles in One-Pot Diverse Using Bismuth (III) Trifluoromethanesulfonate as Catalyst

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A B S T R A C T

Various 1,2-disubstituted benzimidazoles were synthesized in a facile method using Bismuth(III) trifluoromethanesulfonate. It is suggested that formation of an intermediate between the substrate, amine and solvent gives the N-arylation process. This developed protocol is demonstrated by the efficient reactions involving various substituents ranging from electron-withdrawing groups to electron-donating groups.

Key words: *One-pot, Substituted benzimidazoles, N-arylation, Tandem synthesis.*

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INTRODUCTION

N-Containing hetero aromatic compounds are significant designs found in in natural and synthetic compounds. Among them, benzimidazole and its subsidiaries are crucial core structures used to make drugs and materials. 1,2-Disubstituted benzimidazole subordinates are significant in the medicinal science setting as a more thorough library of compounds could be produced by having diverse substituent at positions 1 and 2. It could prompt a superior comprehension of their structure activity-relationship (SAR) and more proper changes of biologically active compounds could then be accomplished in a possibly more shorter time-frame.

Benzimidazole moiety is a bicyclic compound having an imidazole ring containing two nitrogen atoms at nonadjacent positions, fused to benzene. It has been helpful intermediates in the advancement of molecules of drug and biological interest. Benzimidazoles are a significant class of heterocycles that are habitually utilized in drug and agrochemical revelation/discovery programs. For models, the benzimidazole core structure is found in a variety of commercial drugs such as Atacand, Nexium, Micardis, Protonix and Vermox (Figure 1). Benzimidazoles and its derivatives represent one of the most biologically active classes of compounds, possessing a wide spectrum of activities and these are well-documented in literature. 1,2-Disubstituted benzimidazole derivatives are important in the medicinal chemistry context as a more comprehensive library of compounds could be generated by having different substituent at positions 1 and 2. It could lead to a better understanding of their structure activity-relationship (SAR) and more appropriate modifications of biologically active compounds could then be achieved in a potentially shorter time-frame. Previous syntheses of 1,2-disubstituted benzimidazole structures not only led to drug leads such as the hepatitis C virus[1] (HCV) NS5B polymerase inhibitor 1and the agonist 2 against the g-aminobutyric acid A receptor (GABAA), [2] but also resulted in commercial pharmaceutical products such as the antihypertensive telmisartan. [3] Although 1,2-disubstituted benzimidazoles play an important role in pharmaceutical science, the available synthetic strategies that lead to these compounds are limited compared with those that lead to the structurally related indoles. The classical methods

for the assembly of these molecules include acylation/cyclization processes from ortho-aminoanilines, [4] reduction/cyclization processes from ortho-nitroanilines.[5] 1,2-disubstituted benzimidazole show selective neuropeptides YY, receptor antagonists, [6] potent inhibitors of TiE-2 and VEGFER-2 tyrosine kinase receptor,[7] gamma-amino butyric acid (GABA) agonists and 5-HT3 antagonists. [8] They have been showing promising activities in the treatment of several diseases like epilepsy, diabetes, and antifertility. [9] For these reasons, they gained much attention as important pharmacophore and privileged structure in medicinal chemistry [10] encompassing a diverse range of biological activities.[11] These benzimidazoles derivatives have found commercial application in veterinarian medicine as anthelmintic agents and diverse human therapeutic areas. [12] Realizing the importance of these compounds, numerous methods have been reported in the literature for the synthesis of benzimidazoles like condensation reaction of 1,2-phenylenediamine with carboxyaldehydes, carboxylic acids or their derivatives [13,14] such as chlorides, nitriles and orthoesters, under strong acidic conditions with high temperatures. This benzimidazoles are also synthesized by the condensation of o-aryldiamines and aldehydes in refluxing nitrobenzene. [15] The condensation of o-aryldiamines with carboxylic acids or their derivatives in the presence of strong acids such as polyphosphoric acid [16] or mineral acids. [17] Direct condensation of *o*-aryldiamines and aldehydes are not a good synthetic reactions, as it is well known to yield a complex mixture, being 1,2-disubstituted benzimidazoles. In this case, however, the addition of transition metal, namely dipyridine copper (II) chloride. [18] Copper acetate, [19] or lead tetracetate [20] allows a partial selective synthesis of benzimidazoles. In recent years, solvent-free synthesis of benzimidazoles under microwave irradiation using Yb(OTf)3, [21] MoO3/CeO2-ZrO2, [22] metal halide supported alumina [23] and SbCl3–Al2O3 [24] have been reported. But some of these processes have certain limitations, such as harsh reaction conditions, tedious work up procedures, long reaction times, low yields and cooccurrence of several side reactions.

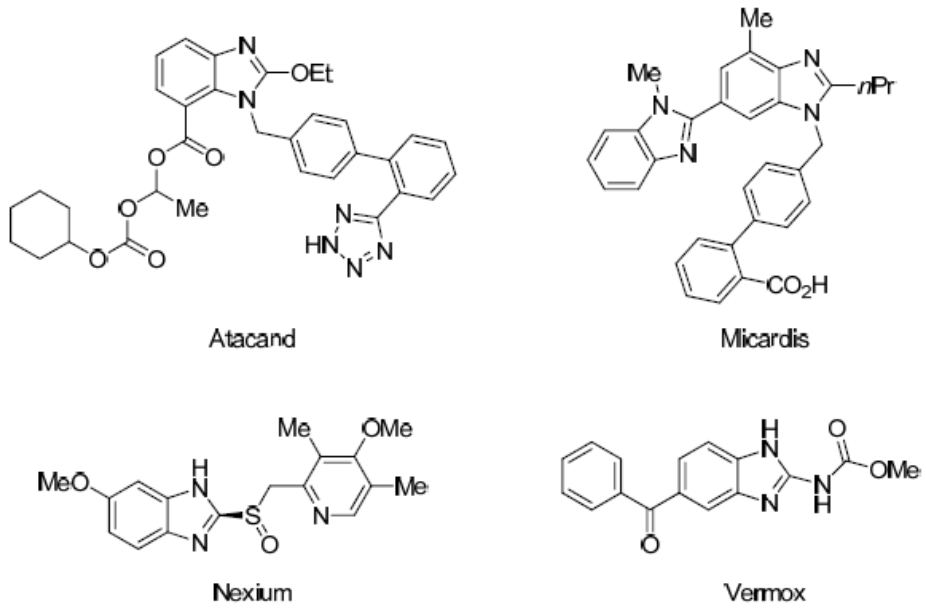


Figure 1: Structure of some pharmacologically important benzimidazoles

Recently, many metal oxides based catalytic systems are widely used in variety of organic reactions like cyclization oxidation reaction. [25,26] Though, those based catalyst are used in number of reactions, these reactions takes place over a longer period, gives low yield and forms byproducts. [27] These limitations can be overcome by using metal containing metal oxide, X-Meng et.al [28] have reported catalytic oxidation by molecular oxygen catalyzed Ni-TiO2, [29] the similar catalyst like SO4/ZrO2, [30] Li/MgO, [31] CeO/CoO [32] etc. now used for a variety of enantioselective reaction such as Knovendgel reaction and oxidation reaction.

However, most of these protocols involve multistep synthetic transformations and engage a complex isolation process leading to a high cost and they suffer from poor availability of starting materials. In some cases the use of strong acid-catalyzed conditions also limits the functional group tolerance. In addition, the employed metals are not environmentally friendly and are not attractive for commercial adoption due to a low catalyst activity and the generation of corrosive waste. These drawbacks prompted us to investigate a more practical access to the 1,2-disubstituted benzimidazole scaffold. It has been received more attention due to its high thermal stability, large specific surface area, easy recovery and good ability to perform organic reactions at lower temperatures.

In such consequence we have developed a new protocol for the preparation of Benzimidazole moiety with short times and high yields. In our present work, we unzip our results for preparation of Benzimidazole moiety with high yields which is superior to other methods. We now report synthesize 1,2-disubstituted benzimidazoles from *O*-fluoronitrobenzene and different substituted aldehyde using Bismuth(III) trifluoromethanesulfonate in DCM as

solvent at 100-130^{0}C. The expected substituted benzimadazole derivatives were obtained in 82-94% yield.

MATERIALS AND METHODS

Melting points were determined in open-end capillaries and are uncorrected. Compounds were checked for their purity by TLC on silica gel G plates and spots were located by iodine vapors. The IR spectra were recorded on Perkin-Elmer spectrum RX IFT-IR System using KBr pellets. Elemental analyses of the newly synthesized compounds were carried out on Perkin Elmer model 2400 C H N analyzer. All the compounds gave satisfactory elemental analysis within ±0.4% of theoretical values. Ultra sonication was performed using BANDELIN SONOREX ® (Germany) 4D ultrasound cleaner with a frequency of 50 KHz and an output power of 480 W. The flask was located at the maximum energy area in the cleaner and addition or removal of water was used to control the temperature of the water bath.

All reactions were carried out under argon in oven-dried glassware with magnetic stirring. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. All solvents were reagent grade. Unless otherwise noted, organic extracts were dried with anhydrous Na_2SO_4, filtered through a fritted glass funnel, and concentrated with a rotary evaporator (20–30 Torr). Flash chromatography was performed with silica gel (200–300 mesh) by using the mobile phase indicated. The NMR spectra were measured with a 400 MHz Bruker Avance spectrometer at 400.1 and 100.6 MHz, for ^{1}H for ^{13}C, respectively, in $CDCl_3$ solution with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ) and are referenced to the residual proton resonances of the solvents. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded using tetramethylsilane (TMS) in the solvent of $CDCl_3$-*d* or DMSO-*d*6 as the internal standard (^{1}H NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.26 ppm, DMSO at 2.50 ppm; ^{13}C NMR: $CDCl_3$ at 77.16 ppm, DMSO at 40.00 ppm.

Experimental section:

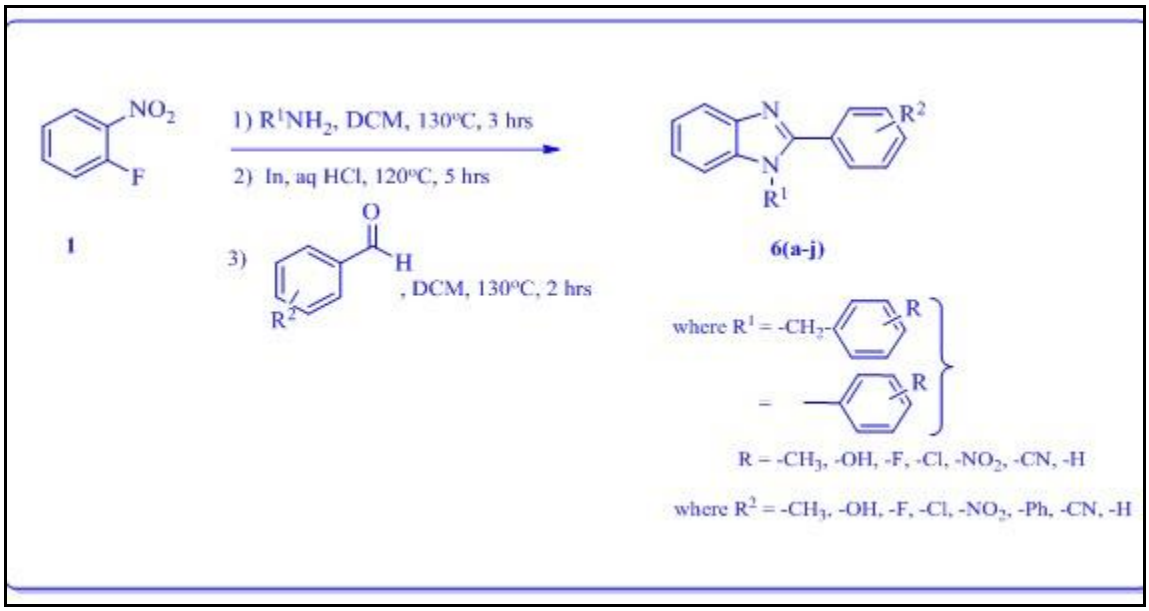
Typical procedure for one-pot tandem N-arylation reduction condensation for synthesis of 1,2-disubstituted benzimidazole (6a-j):

O-fluoronitrobenzene **1** (282 mg, 2 mmol) and **2** (214 mg, 2 mmol) are combined in DCM (10 mL) which was stirred magnetically at 130 °C (oil-bath) for 3 hrs (TLC) followed by addition of In (574 mg, 5 mmol), HCl (5 mL, 10 mmol) and stirring continued for a further 5 hrs at 120 °C. The resultant mixture was treated with **5** (212 mg, 2 mmol) and Bismuth(III) trifluoromethanesulfonate (0.656 mg) in DCM (5 mL) for 2 hrs at 130 °C. The workup and purification procedure was also very simple. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, neutralized with solid $NaHCO_3$ and extracted with ethyl acetate (2 × 15 mL). The combined EtOAc extracts were washed with water (10 mL), dried ($MgSO_4$) and concentrated under rotary vacuum evaporation. The crude products were obtained with very high purity. Further purification was achieved by column chromatography from ethylacetate: n-hexane mixcture (30:70) and obtained pure product **6(a-j)** (89-94%). The chemical structures of the title compounds were elucidated by IR, ^{1}H-NMR, ^{13}C-NMR, mass spectral data and elemental analysis. The data are in agreement with the proposed structures.

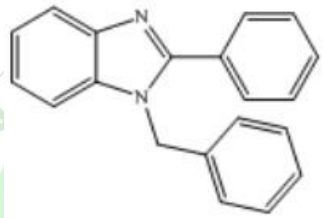
Table-1: The reaction of (**1**) with (**2**) in water under different experimental conditions

Entry	solvent	Yield
1	None	Traces
2	Hexane	Traces
3	Toluene	23
4	THF	26
5	EtOH	36
6	MeOH	38
7	1,4-Dioxane	37
8	Benzene	81
9	Ether	83
10	DCM	93

REACTION SCHEME:



1-benzyl-2-phenyl-1*H*-benzo[d]imidazole (6a):



White solid (93%), mp:129–130°C;

^{1}H NMR(DMSO-d6, 500 MHz): δ 7.75-7.23 (m, 3 H), 7.53-7.45 (m, 4 H), 7.29-7.21 (m, 5 H), 7.00 (d, 2 H, J = 7.5 Hz), 5.58 (s, 2 H)

^{13}C NMR(DMSO-d6, 125 MHz): δ 154.42, 143.89, 138.10, 137.08, 131.33, 130.99, 130.21, 129.95, 128.64, 127.25, 123.86, 123.39, 120.46, 112.27, 48.63

ESI-MS [M+H^{+}]: m/z = 285.

4-(1-(4-hydroxybenzyl)-1*H*-benzo[d]imidazol-2-yl)phenol (6b):

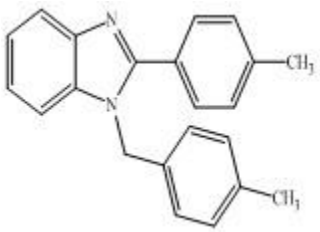
Pale yellow solid (90%), mp: 252-254^{o}C

^{1}H NMR (DMSO-d6, 500 MHz): δ 10.82 (s, 1 H), 9.66 (brs, 1 H), 7.86 (d, 1 H, J = 8.0 Hz), 7.80 (d, 1 H, J = 8.0 Hz), 7.77 (d, 2 H, J = 8.5 Hz), 7.60-7.53 (m, 2 H), 7.10 (d, 2 H, J = 8.4 Hz), 6.98 (d, 2 H, J = 8.3 Hz), 6.71 (d, 2 H, J = 8.4 Hz), 5.63 (s, 2 H)

13C NMR (DMSO-d6, 125 MHz): δ 162.94, 158.54, 151.91, 133.73, 133.08, 132.28, 129.35, 127.36, 126.88, 125.81, 117.56, 116.66, 115.57, 114.66, 113.92, 49.45

ESI-MS [M+H^{+}]: m/z = 317

1-(4-methylbenzyl)-2-(p-tolyl)-1*H*-benzo[d]imidazole (6c):



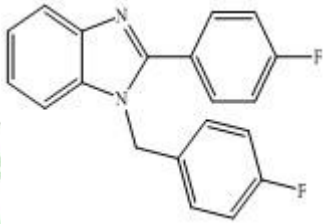
White solid (89%), mp: 128-129 ^{o}C;

^{1}H NMR (DMSO-d6, 500 MHz): δ 7.70 (d, 1 H, J = 7.4 Hz), 7.62 (d, 2 H, J = 7.5 Hz), 7.42 (d, 1 H, J = 7.5 Hz), 7.33 (d, 2 H, J = 7.6 Hz), 7.25-7.20 (m, 2 H), 7.09 (d, 2 H, J = 7.5 Hz), 6.88 (d, 2 H, J = 7.5 Hz), 5.51 (s, 2 H), 2.37 (s, 3H), 2.22 (s, 3H)

^{13}C NMR (DMSO-d6, 125 MHz): δ 154.52, 143.88, 140.71, 137.84, 137.06, 135.13, 130.53, 130.11, 128.49, 127.19, 123.69, 123.29, 120.32, 112.23, 48.41, 22.11, 21.77

ESI-MS [M+H^{+}]: m/z = 313.

1-(4-fluorobenzyl)-2-(4-fluorophenyl)-1*H*-benzo[d]imidazole (6d):



White solid (92%), mp: 110-112^{o}C

^{1}H NMR (DMSO-d6, 500 MHz): δ 7.79-7.74 (m, 3 H), 7.49 (d, 1 H, J = 9.0 Hz), 7.36 (t, 2 H, J = 8.8 Hz), 7.26-7.24 (m, 2 H), 7.10 (t, 2 H, J = 8.8 Hz), 7.05-7.01 (m, 2 H), 5.56 (s, 2 H)

^{13}C NMR (DMSO-d6, 125 MHz): δ 165.11, 163.56, 163.14, 161.62, 153.50, 143.81, 136.99, 134.19, 132.60, 129.40, 127.83, 123.99, 123.50, 120.50, 116.98 (m), 112.25, 47.96

ESI-MS [M+H^{+}]: m/z = 321.

1-(4-chlorobenzyl)-2-(4-chlorophenyl)-1*H*-benzo[d]imidazole (6e) :

Pale White solid (90%), mp: 137-139^{o}C

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.81 (d, J = 7.6 Hz, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.29-7.19 (m, 4H), 7.14 (d, J = 8 Hz, 1H), 6.96 (d, J = 8 Hz, 2H), 5.33 (s, 2H)

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 152.8, 142.9, 136.3, 135.8, 134.6, 133.8, 130.4, 129.3, 129.1, 128.2, 127.2, 123.5, 123.1, 120.1, 110.3, 47.8

ESI- MS: m/z 353, 355 [M + H]$^{+}$

1-(4-chlorobenzyl)-2-(4-chlorophenyl)-1*H*-benzo[d]imidazole (6f):

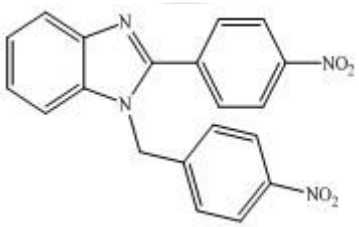
White solid (94%), mp: 189-191^{o}C

^{1}H NMR (DMSO-d6, 500 MHz); δ 8.33 (d, 2 H, J = 8.6 Hz), 8.15 (d, 2 H, J = 8.4 Hz), 8.00 (d, 2 H, J = 8.5 Hz), 7.80 (d, 1 H, J = 9.0 Hz), 7.54 (d, 1 H, J = 8.1 Hz), 7.34-7.31 (m, 2 H), 7.26 (d, 2 H, J = 8.4 Hz), 5.82 (s, 2 H)

^{13}C NMR (DMSO-d6, 125 MHz): δ 152.26, 149.22, 148.10, 145.52, 143.84, 137.26, 137.14,131.56, 128.63, 125.13, 125.15, 124.92, 124.15, 121.02, 112.45, 48.39

ESI-MS [M+H^{+}]: m/z = 374

4-[1-(4-Cyanobenzyl)-1*H*-benzimidazol-2-yl]benzonitrile (6g):

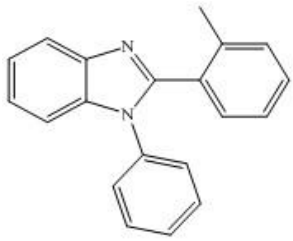


White solid (92%), mp : 136−137 °C

^{1}H NMR (DMSO, 400 MHz, TMS) δ: 7.62 (d, J = 6.71 Hz, 1H), 7.55 (d, J = 7.91 Hz, 2H), 7.40 (d, J = 6.71 Hz, 1H), 7.16 (s, 2H), 6.88 (d, J = 7.98 Hz, 2H), 6.81 (d, J = 7.76 Hz, 2H), 6.64 (d, J = 7.76 Hz, 2H), 5.40 (s, 2H).

MS (EI) m/z: 318.2 (M + H)$^{+}$

1-Phenyl-2-(o-tolyl)-1*H*-benzo[d]imidazole (6h)



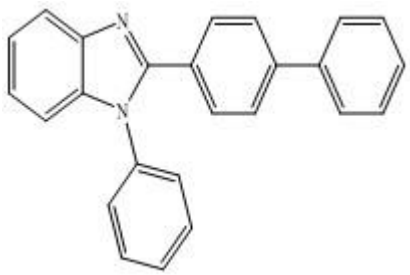
Brown yellow solid (79%), m.p: 80-83ºC

^{1}H NMR (400M Hz, $CDCl_3$, ppm): δ = 7.90 (d, J = 7.6 Hz, 1H), 7.39-7.24 (m, 8H), 7.21-7.11 (m, 4H), 2.17 (s, 3H)

^{13}C NMR (100M Hz, $CDCl_3$, ppm): δ 153.0, 143.1, 137.8, 136.4, 135.7, 130.9, 130.3, 130.2, 129.5, 129.4, 127.9, 126.5, 125.4, 123.2, 122.8, 120.0, 110.5, 20.0

HRMS: [M]$^{+}$ calculated for $C_{20}H_{16}N_2$: 284.1313, found: 284.1315

2-([1,1'-biphenyl]-4-yl)-1-phenyl-1*H*-benzo[d]imidazole (6i):



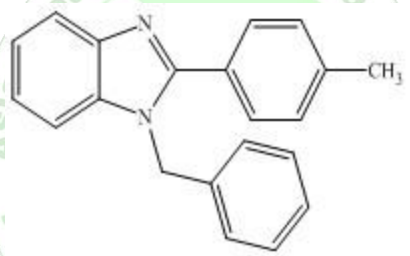
White solid (79%), Mp: 181–182 °C.

^{1}H NMR (400 MHz, $CDCl_3$); δ 13.45 (s, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.56–7.52 (m, 3H), 7.50–7.46 (m, 2H), 7.38–7.27 (m, 6H), 7.24 (dd, J = 8.4, 6.2 Hz, 1H), 7.19–7.14 (m, 1H), 7.00 (d, J = 8.1 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.70 (dd, J = 8.4, 1.8 Hz, 1H)

^{13}C NMR (100 MHz, $CDCl_3$); δ 158.9, 149.6, 143.0, 138.9, 138.8, 136.1, 135.5, 128.6, 127.7, 126.7, 126.8, 126.5, 125.9, 122.7, 122.5, 117.5, 115.9, 115.1, 110.2, 109.3

HRMS (ESI-TOF+): m/z calcd for $C_{25}H_{18}N_2$: [(M + H)+W], 346.15 found, 347.15

1-benzyl-2-(*p*-tolyl)-1*H*-benzo[d]imidazole (6j) :



White solid (88%), m.p: 267–269 °C

^{1}H NMR (DMSO, 400 MHz) δ: 7.80 (d, J = 8.0 Hz, 1H), 7.60 (d, J= 6.96 Hz, 2H), 7.37–7.31 (m, 4H), 7.29–7.21 (m, 4H), 7.14 (d, J= 7.24 Hz, 2H), 5.49 (s, 2H), 2.43 (s, 3H).

MS (APCI) m/z: 299.3 $(M + H)^+$.

Anti-tumour docking studies:

Materials and methods. For receptor-oriented flexible docking, the Autodock 4.2 software package was used. Ligands were prepared using the MGL Tools 1.5.6 program. The Ligand optimization was performed using the Avogadro program. To perform calculations in the Autodock 4.2 program the output formats of the receptor and ligand data were converted to a special PDBQT format. In our previous studies, a similar software package was used [1]. The active macromolecule center of the tyrosine kinase receptor EGFR (PDB ID: 1M17) from the Protein Data Bank (PDB) was used as a biological targets for docking. The receptor maps were made in MGL Tools and AutoGrid programs. Water molecules, ions, and the ligand were removed from the PDB file ID: 1M17.

The following docking parameters were determined:

The maximum RMS tolerance for the conformational cluster analysis – 2 Å; t

The free energy coefficient for torsional degrees of freedom – 0.2983;

The cluster tolerance – 2 Å;

The external grid energy – 1000;

The maximum initial energy – 0;

The maximum number of retries – 10 000;

The number of individuals in the population – 150;

The maximum number of energy evaluations – 2500000;

The maximum number of generations – 27 000;

The number of top individuals to survive to the next generation – 1;

The rate of gene mutation – 0.02;

The rate of crossover – 0.8;

The crossover mode – arithmetic;

The α-parameter of Gauss distribution – 0;

The β-parameter of Gauss distribution – 1.

The visual analysis of complexes of substances in the active center of the tyrosine kinase receptor (PDB ID: 1M17) was performed using the Discovery Studio Visualizer program.

The choice of crystallographic models of tyrosine kinase PDB ID: 1M17 (Epidermal Growth Factor Receptor tyrosine kinase domain with 4-anilinoquinazoline inhibitor erlotinib) (Fig.1) as a biological target for the study of the possible antitumor activity is due to the existing crystallographic model co-crystallized with a derivative of 4-anilinoquinazoline.

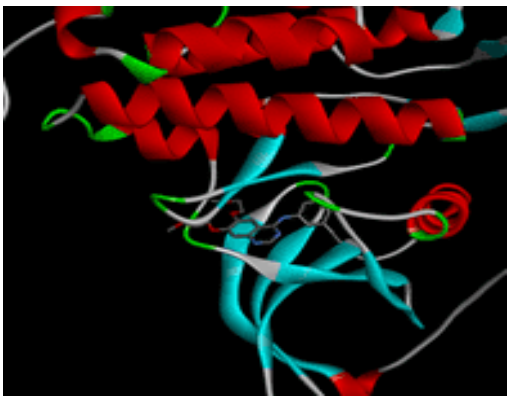


Fig.1. Crystallographic models of PDB ID: 1M17 co-crystallized with a derivative of 4-anilinoquinazoline

The crystal structure of the epidermal growth factor kinase domain EGFRK (PDB ID: 1M17) assumes a conformation that is similar to the phosphorylated active form of the kinase domain, which leads to significant intermolecular contacts [2].

Results and discussion:

Based on the results of molecular docking the following data were calculated:

- The scoring function indicating the enthalpy contribution to the value of the free energy of binding (Affinity DG) for the best conformational positions (Tab. 1);
- The values of the free energy of binding and binding constants (EDoc kcal/mol and Ki mM (millimolar)) for a specific conformational position of the ligand; they allow assessing the stability of complexes formed between ligands and the corresponding receptor (Tab. 2)

Table 1: Affinity DG values for best conformational positions of the test compounds in combination with tyrosine kinase (PDB ID: 1M17)

Molecule	*Affinity DG kcal/mol*	*Molecule*	*Affinity DG kcal/mol*
1	-8,4	13	-9,2
2	-8,4	14	-8,9
3	-9,2	15	-9,8
4	-10,3	16	-9,3
5	-9,2	17	-8,5
6	-9,0	18	-8,2
7	-8,9	19	-8,7
8	-8,8	20	-10,0
9	-9,0	21	-9,3
10	-9,3	22	-9,4
11	-9,3	23	-9,3
12	8,8		

Table 2: Values of the free energy of binding and binding coefficients of the test antitumor agents in combination with tyrosine kinase (PDB ID: 1M17)

Molecule	EDoc kcal/mol	Ki uM micromolar	Molecule	EDoc kcal/mol	Ki uM micromolar
1	-5.49	94.83 uM	13	-6.39	20.69 uM
2	-4.64	395.00 uM	14	-6.06	36.04 uM
3	-5.43	105.53 uM	15	-6.12	32.88 uM
4	-7.91	1.59 uM	16	-5.89	47.77 uM
5	-6.10	33.85 uM	17	-6.42	19.75 uM
6	-5.31	127.14 uM	18	-7.18	5.50 uM
7	-6.83	9.82 uM	19	-6.16	30.59 uM
8	-6.41	20.00 uM	20	-7.66	2.43 uM
9	-5.26	139.59 uM	21	-5.60	78.50 uM
10	-7.02	7.20 uM	22	-6.79	10.57 uM
11	-6.97	7.79 uM	23	-6.09	34.12 uM
12	-6.17	29.90 uM			

Thus, it can be assumed that the inhibitory activity of the molecules tested relative to the receptor PDB ID: 1M17can be actualized by forming complexes between them; their stability is provided mainly due to the energy favorable geometric location of ligands in the active center of this acceptor, the formation of hydrogen bonds between them, intermolecular electrostatic and donor-acceptor interactions. As a consequence, the thermodynamic probability of such binding is confirmed by negative values of the scoring function (Affinity DG, kcal/mol), calculated values of the free energy of binding EDoc (kcal/mol), and binding constants Ki (mM/ μM) (Tab. 2).

In order to understand how the affinity of the molecules studied to the target occurred a detailed analysis of the geometric location of these molecules in the active site of the receptors was conducted.

According to the obtained results, the absolute leaders are molecules ***4, 15, 18*** and ***20***. Therefore, a detailed analysis of the geometric location was performed for them.

Molecule **4** with the tyrosine kinase receptor forms a complex due to hydrogen bonds between the nitrogen atoms of the nitrile groups and the amino acid residues of lysine Lys721 and glycine Gly772. The complex 4 c with tyrosine kinase is formed due to the π-cation and π-anion interactions between phenyl and benzimidazole fragments and Asp831 and Lys721 residues, respectively. Additional stabilization of complexes is facilitated by π-Alk intermolecular interactions between phenyl and benzimidazole fragments with amino acid residues Lys721, Ala719, Val702, Leu768, Leu694 and Leu820 (Fig.2).

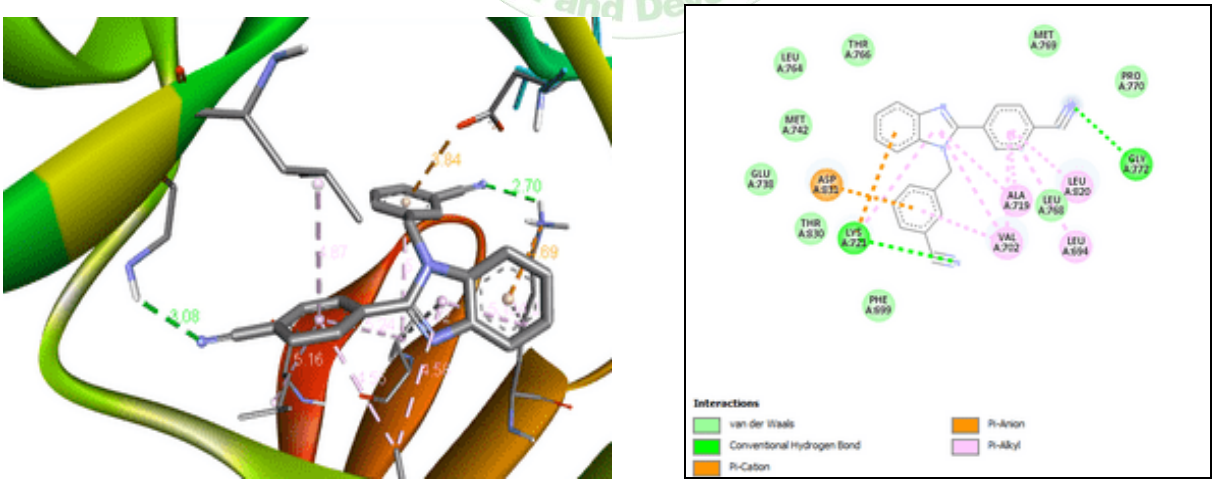


Fig 2. The molecule ***4*** superposition and the diagram of intermolecular interactions in the complex with the biotarget PDB ID: 1M17

The formation of the complex of molecule ***15*** with tyrosine kinase (PDB ID: 1M17) is facilitated by the π-anion and π-sulfur bonds between the phenyl rings of the molecule and the Asp831 and Met742 residues, respectively. π-σ Interactions occur between benzimidazole and phenyl fragments with residues

Val702 and Leu820. Additional stabilization of complexes is facilitated by π-π and π-Alk intermolecular interactions between the test molecule and amino acid residues Phe699, Ala719, Lys721 and Val720 (Fig.3). The complex between molecule ***18*** and the biotarget is formed by the π-cation interaction between the phenyl ring and the lysine residue Lys721. Stabilize the complex of π-Alk and Alk interactions between benzimidazole, phenyl and methyl fragments of the molecule with the corresponding amino acid residues Leu820, Val702, Ala719, Cys773 (Fig.4).

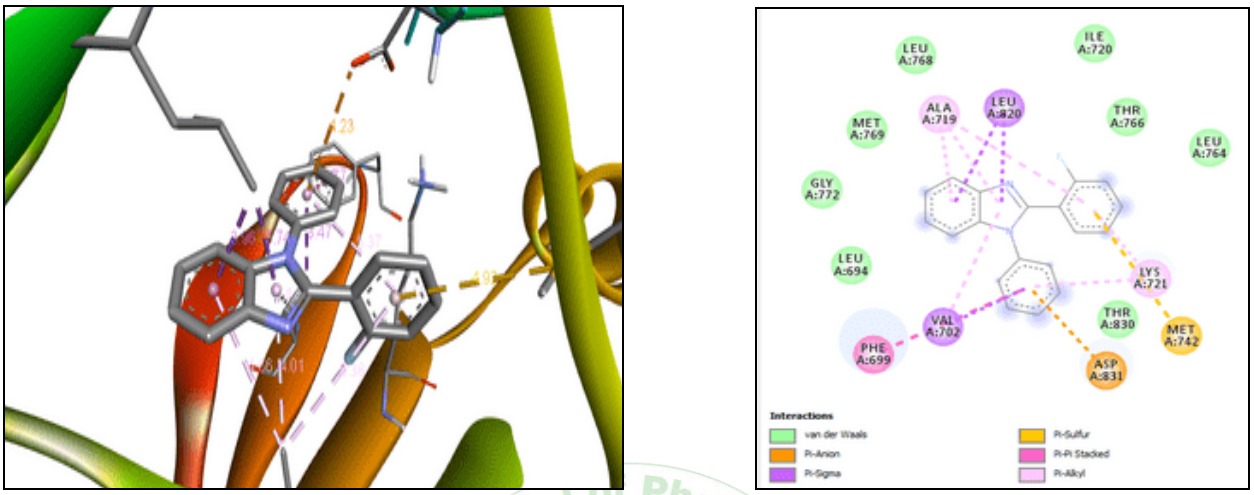


Fig 3. The molecule ***15*** superposition and the diagram of intermolecular interactions in the complex with the biotarget PDB ID: 1M17

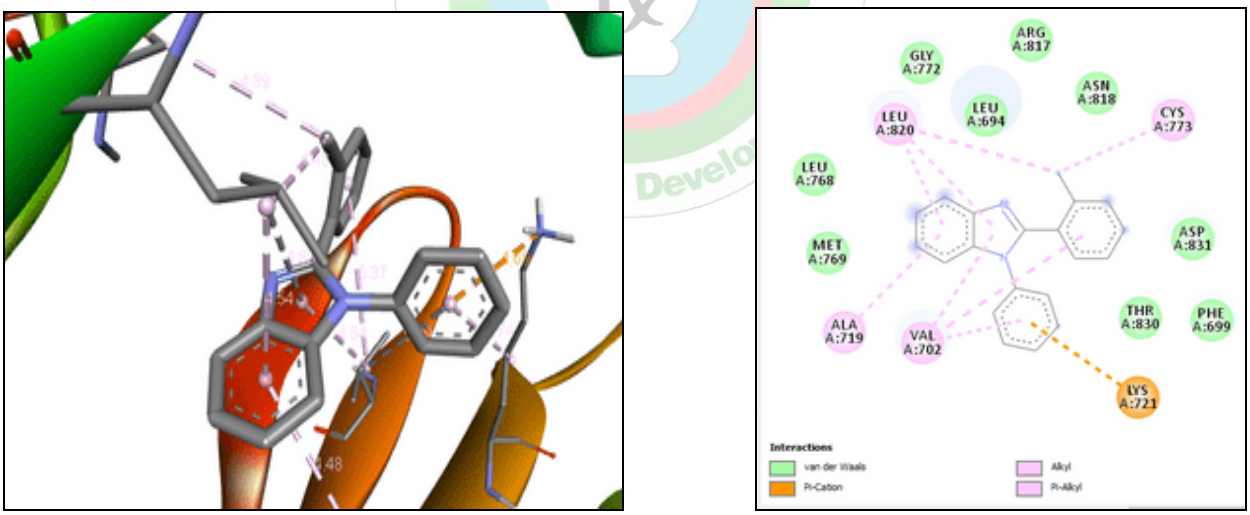


Fig 4. The molecule ***18*** superposition and the diagram of intermolecular interactions in the complex with the biotarget PDB ID: 1M17

In the case of interaction of molecule ***20*** with tyrosine kinase (PDB ID: 1M17), the complex is formed by π-σ and π-anion bonds between the benzimidazole and phenyl rings of the molecule with leucine residues Leu820, Leu694 and Asp831, respectively. The π-sulfur bond forms a methionine Met742 residue with the benzimidazole fragment. Stabilization of complexes is facilitated by π-Alk interactions in which all fragments of the molecule with residues Lys721, Ala719, Val702, Leu694 and Leu820 participate (**Fig.5**).

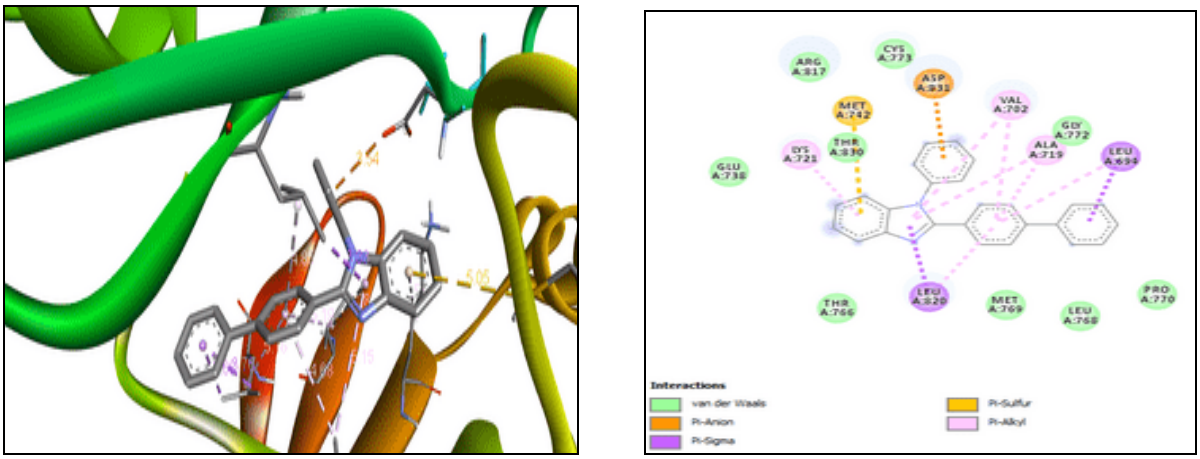


Fig 5. The molecule ***20*** superposition and the diagram of intermolecular interactions in the complex with the biotarget PDB ID: 1M17

The values of interatomic distances in the active site of the tyrosine kinase receptor between fragments of molecules ***4, 15, 18***, ***20*** and amino acid residues, categories and types of intermolecular interactions are given in Tab. 3.

Table 3: The values of interatomic distances, categories and types of intermolecular interactions of molecules 4, 15, 18, 20 in the active site of the tyrosine kinase receptor PDB ID: 1M17

Molecule 4			Molecule 15			Molecule 18			Molecule 20		
Distance, Å	Category	Types	Distance, Å	Category	Types	Distance, Å	Category	Types	Distance, Å	Category	Types
2,70	Hydrogen Bond	Conventional Hydrogen Bond	4,23	Electrostatic	Pi-Anion	4,68	Electrostatic	Pi-Cation	3,54	Electrostatic	Pi-Anion
3,08	Hydrogen Bond	Conventional Hydrogen Bond	3,47	Hydrophobic	Pi-Sigma	4,89	Hydrophobic	Alkyl	3,76	Hydrophobic	Pi-Sigma
4,68	Electrostatic	Pi-Cation	3,95	Hydrophobic	Pi-Sigma	4,48	Hydrophobic	Alkyl	3,68	Hydrophobic	Pi-Sigma
3,84	Electrostatic	Pi-Anion	3,74	Hydrophobic	Pi-Sigma	4,48	Hydrophobic	Pi-Alkyl	3,83	Hydrophobic	Pi-Sigma
5,10	Hydrophobic	Pi-Alkyl	4,92	Other	Pi-Sulfur	4,53	Hydrophobic	Pi-Alkyl	5,05	Other	Pi-Sulfur
4,72	Hydrophobic	Pi-Alkyl	5,77	Hydrophobic	Pi-Pi Stacked	4,64	Hydrophobic	Pi-Alkyl	5,05	Hydrophobic	Pi-Alkyl
4,57	Hydrophobic	Pi-Alkyl	4,66	Hydrophobic	Pi-Alkyl	4,69	Hydrophobic	Pi-Alkyl	5,28	Hydrophobic	Pi-Alkyl
5,13	Hydrophobic	Pi-Alkyl	4,84	Hydrophobic	Pi-Alkyl	5,37	Hydrophobic	Pi-Alkyl	5,15	Hydrophobic	Pi-Alkyl
4,22	Hydrophobic	Pi-Alkyl	4,01	Hydrophobic	Pi-Alkyl	5,08	Hydrophobic	Pi-Alkyl	5,16	Hydrophobic	Pi-Alkyl
5,16	Hydrophobic	Pi-Alkyl	5,38	Hydrophobic	Pi-Alkyl	4,74	Hydrophobic	Pi-Alkyl	5,19	Hydrophobic	Pi-Alkyl
5,23	Hydrophobic	Pi-Alkyl	4,44	Hydrophobic	Pi-Alkyl				4,67	Hydrophobic	Pi-Alkyl
4,54	Hydrophobic	Pi-Alkyl	5,37	Hydrophobic	Pi-Alkyl				4,85	Hydrophobic	Pi-Alkyl
4,86	Hydrophobic	Pi-Alkyl									

CONCLUSION:

In conclusion, a novel method of synthesizing of various 1,2-disubstituted benzimidazole using aryl amino arylation or aryl amino alkylation-reduction with cyclization in water medium has been developed. Hydrogen bond formed during the arylamino arylation or arylamino alkylation of *o*-fluoro anilines since water has hydrogen bond donor and also hydrogen bond acceptor than other organic solvents and it evidence for better yield. In nitro reduction and condensation steps, water has good effect. Water mediated arylamino arylation or arylamino alkylation processes are environmentally friendly and provides numerous advantages over earlier ones such as a simple procedure, eco-friendly, economical, recyclable catalyst, excellent yields in short reaction times and an easy work-up. Thus, the present onepot method proves the synthesis of a wide range of 1,2-disubstituted benzimidazoles. The present protocol exhibits good functional group tolerance, readily available and inexpensive starting materials, and operational simplicity. To further explore novel synthetic approaches toward other nitrogen-containing heterocyclic compounds is underway in our laboratory.

RESULTS AND DISCUSSION

In our preliminarily investigation on the model reaction of 2-fluoro nitrobenzene and various aldehyde in water. It was found that the reaction could be finished under very simple reaction conditions in water medium. The reaction was extended with Bismuth (III) trifluoromethanesulfonate one-pot tandem N-arylation reduction condensation for the synthesizing N-aryl/aryl alkyl/alkyl-2-aryl/heteroaryl/cycloalkyl benzimidazoles (**Scheme 1**). Thus, various substituted *o*-fluoro nitrobenzenes **1** were subjected to react with different amines **2** in DCM at 130°C and formed N-arylated products **3** treated with In and aq. HCl to form the N-monoalkylated/arylated *o*-phenylenediamines **4** which without isolation were treated with various aldehydes **5** to give 1,2-disubstituted benzimidazoles **6(a-j)**. The excellent results were given in the synthesis of 1,2-disubstituted benzimidazoles **6(a-j)**.

In order to investigate the scope of the reaction, different substituted aldehydes were employed and it was clear that yield is not affected by the position of the substituent on aromatic ring of aldehyde. Although the condensation takes place in water without any metal catalyst, the presence (10 mol%) of In or $InCl_3$ offers an advantage in that the condensation may be performed at optimum temperature. However, the use of aprotic solvents such as toluene, 1,4- dioxane, THF, DMF, and DCE under similar conditions gave lower yields in the presence or absence of In and demonstrated the advantage of using water in the condensation stage. The reaction was carried out under very simple reaction conditions which gives the desired various 1,2-disubstituted benzimidazole derivatives in good yield. These methods are more convenient and reactions can be carried out in higher yield. In such consequence we have developed a new protocol for the preparation of various 1,2-disubstituted benzimidazole with short times and high yields. Formation of products was confirmed by recording their ^{1}H NMR, ^{13}C, mass spetra.

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