



SYNTHESIS AND CHARACTERIZATION OF BIOLOGICAL ACTIVE COMPOUNDS CONTAIN BENZIMIDAZOLE PIPERIDINE ANALOGUES

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ABSTRACT

Heterocyclic compounds contain Benzimidazole with piperidine having good importance in Medicinal Chemistry. A series of significant antimicrobial activity compounds Synthesized {[1-(3-Chloro-propyl)-1,3-dihydro-benzimidazol-2-one], (4- substituted secondary piperidine)} 1-[3-(4-substituted piperidine-1-yl)-3-Propyl]-1,3-dihydro-benzimidazol-2-one derivatives by using preamble chemical reactions, which exhibits good antibacterial and antifungal activities. They are structurally related to Domperidone, these results could help full for deriving more potential drug molecules.

KEYWORDS: Synthesis, Novel Analogues, Characterization, antifungal, antibacterial, N-alkylation.

INTRODUCTION

Generally 1,3-dihydro-benzimidazole-2-one with piperidine moiety containing drugs having a good resistance power against Antimicrobial. We based on the collective literature on Antimicrobial and our area of interest is to develop increase to the resistance power of drug of domperidone analogs. Now a days killing of bacteria, fungi and viruses are not easy because of human body resistance decreased due to low-quality food, nature change. Most of the people don't know how much the drug dose used for cure the disease. In general the biotransformations of drugs after oral or intravenous administration in rats dogs and follow oral administration on man. Domperidone is tested on metabolism of rats, dogs and then man and explain work on animal's metabolism in various conditions.^[1]

Domperidone or 5-Chloro-1-[1-3-(2,3-dihydro-2-oxo-1H-benzimidazole-1-yl) propyl]-4-piperidinyl)-1,3-dihydro-2H-benzimidazole-2-one) was synthesized first at Jansen Pharmaceutica in 1974 and carried out the research on antipsychotic drugs.^[2] Jansen Pharmaceutica discovers that many of antipsychotic drug analogs had exact effect on dopamine receptors in the central chemoreceptor trigger zone.^[3] It controlled vomiting and free of the extrapyramidal side effects and are associated with drugs of the proper kind.^[3] Domperidone act as a so much strong anti-emetic with minimal central effects.^[4,5] Selective dopamine D2 receptor antagonist is used as a gastroprokinetic, galactagogue and antiemetic.^[6,7] The drug controlled nausea and vomiting and to improve lactation in breast milk by the release of prolactin.^[8]

Medical uses of Domperidone in the United Kingdom, it is used specified for the curing of nausea and vomiting. In Italy it used for curing of gastroesophageal reflux disease.^[9] Canadian Headache Society's give guidance for the treatment of nausea together with an acute migraine.^[10] Domperidone needful to diabetic and idiopathic gastroparesis,^[11,12] rarely increase the rate of gastric symptoms.^[13] Domperidone can use in the treatment of Parkinson's disease it means poor gastrointestinal function, nausea and vomiting are major problems in Parkinson's disease.^[14] It doesn't cross the blood-brain barrier.^[15] It gives the high dose to cause potential toxicity to the heart due to the lengthening of the QT interval.^[16,17] Domperidone used in functional dyspepsia for both adults and children.^[17,18]

In Australia domperidone drug used as off-label and therapy for mothers who are facing difficulty in breastfeeding^[19,20] within limited dose.^[21] But in 2015 United States, not encourage for this use.^[22,23] The dose of 10 to 20 mg domperidone 3 or 4 times per day through the mouth the result may be seen a minimum 24 hours.^[24] Specialists consider domperidone has active in the treatment of pediatric reflux.^[25] It is extremely powerful drug for treating babies with reflux.^[26] Itraconazole and ketoconazole drugs utilized for treatment of fungal infections.^[27] The effective CYP3A4 inhibitor to improve the plasma density of domperidone.^[28,29] The combination of Domperidone with Erythromycin, certain macrolide antibiotics are CYP3A4 inhibitors and inhibit the metabolism of domperidone drug.^[30] Ketoconazole or other CYP3A4

inhibitors^[31] are hypothetically dangerous but domperidone itself within limits show no such effect.^[32]

Some side effects happened with Domperidone, include dry mouth, abdominal cramps, diarrhea, nausea, rash, itching, hives and hyperprolactinemia.^[33] Hyperprolactinemia suppress the secretion gonadotropin-releasing hormone (GnRH) from the hypothalamus.^[34] It turned suppress the secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in hypogonadism (low sex hormone).^[35] In a few cases male patients expressed low libido, erectile dysfunction and impaired spermatogenesis accordance with hyperprolactinemia and female patients reported the mammoplasia, mastodynia, galactorrhea, amenorrhea.^[36] In the treatment of domperidone gynecomastia and galactorrhea have been reported in male due to blocked of D2 receptors in the central nervous system.^[37]

Domperidone used is an increased risk of sudden cardiac death^[38] through its prolonging effect of the cardiac QT interval and ventricular arrhythmias.^[39,40] The cause is due to blockade of hERG voltage-gated potassium Channels.^[41,42] Conflicting reports exist, neonates and infants, QT prolongation is controversial and uncertain.^[43] In 2014 UK drug regulating authorities (MHRA) has issued a restriction on domperidone used, due to increase the risk of adverse cardiac effects.^[44] In 2014 Co-ordination Group for Mutual Recognition and Decentralized procedures – Human (CMDh) published official press-release suggesting to restrict the used of domperidone as a part of the medicines.^[45] Pharmacovigilance Risk Assessment Committee (PRAC) approved earlier published suggestions and domperidone use only for curing of nausea and vomiting with maximum dosage to 10 mg.^[8] Domperidone was patented in the United States under patent US4066772 A on 3 January 1978.

From all the above observations we were worked on Benzimidazole derivatives those compounds shows good microbial activity. Domperidone and their some derivatives having Benzimidazole moiety with tertiary piperidine derivative compounds show excellent anti-microbial activity. We concentrate on the synthesis of new drug analogues, with the help of commercially available 1-(3-Chloro-propyl)-1,3-dihydro-benzimidazole-2-one treated with secondary piperidine derivatives formed 1-[3-(4-substituted piperidine-1-yl)-3-Propyl]-1,3-dihydro-benzimidazol-2-one derivatives.

This method is useful, all compounds were friendly to nature, low of the cost and get above 92% yield. We were tested anti-microbial activity against bacteria and fungi. Synthesized drug analogues i.e. DAZC, DBPC, DBS, DDAZC, DDPCP, DDPM, DEB, DK9, DPCP and DPHP (Table: 1) compounds having excellent Antibacterial activity against *Bacillus cereus*, *Bacillus Subtilis*, *Escherichia coli*, *staphylococcus aureus*, *Vibrio paraheamolyticus*, *Klebsiella pneumonia*, *Bacillus megaterium* and antifungal activity against *Candida albicans* etc.

MATERIALS AND METHODS

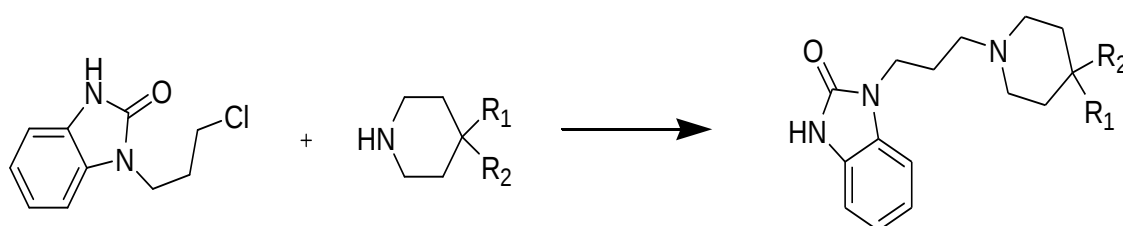
All the below-Desired compound were synthesized from commercially available 1-(3-Chloro-propyl)-1,3-dihydro-benzimidazole-2-one and Corresponding piperidine analogues containing secondary amine in piperidine ring substituted intermediate compounds. Raw materials, Reagents purchased from Sigma Aldrich chemical Pvt Ltd., solvents were taken Analytical grade from Avra chemical Pvt Ltd. And by using conventional chemical reactions to produces feasible and entirely new chemical entities, by adopting the Gabriel synthesis. Instruments used for determination of structural elucidation are ¹H-NMR (Bruker 400 MHZ), ¹³C-NMR (Bruker), Mass (Bruker) and IR by Perkin Elmer. Observed the melting points, boiling points, physical appearance, color and physical state to synthesized analogues.

Test for Microbial

In the below-mentioned compounds DAZC, DBPC, DBS, DDAZC, DDPCP, DDPM, DEB, DK9, DPCP and DPHP (Table: 1) got with good yield. Above mentioned Drug Analogues shows excellent antibacterial activity against *Bacillus cereus*, *Bacillus Subtilis*, *Escherichia coli*, *staphylococcus aureus*, *Vibrio paraheamolyticus*, *Klebsiella pneumonia*, *Bacillus megaterium* and anti-fungal activity *Candida albicans* etc.

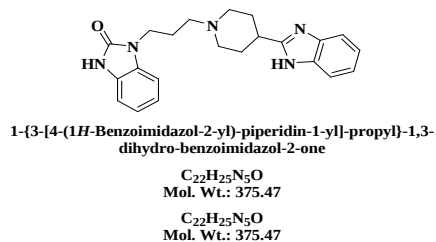
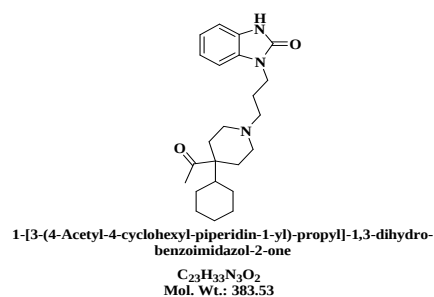
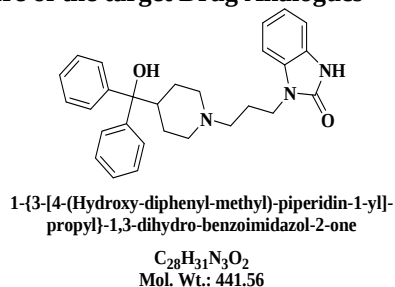
Selected Scheme

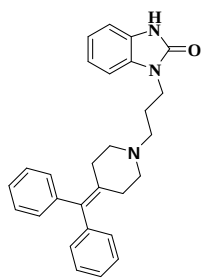
We treated 1-(3-Chloro-propyl)-1,3-dihydro-benzimidazole-2-one treated in presence of an inorganic base potassium carbonate in a solvent acetone under reflux condition with continuous stirring, all reactions were carried out under an inert atmosphere of nitrogen. The yield and purity of all the compounds recorded inadequate manner.



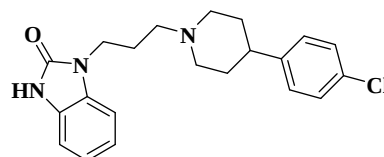
S.NO	R-1	R-2
1.		H
2.		
3.		H
4.		H
5.		H
6.		OH
7.		H
8.		-
9.		H
10.		OH

Structure of the target Drug Analogues

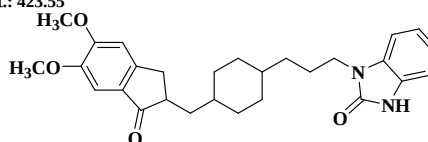




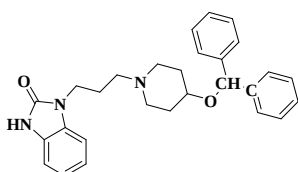
1-[3-(4-Benzhydrylidene-piperidin-1-yl)-propyl]-1,3-dihydro-benzoimidazol-2-one

 $C_{28}H_{29}N_3O$
Mol. Wt.: 423.55


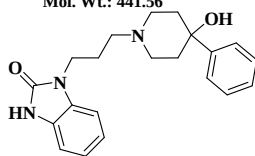
1-[3-[4-(4-Chloro-phenyl)-piperidin-1-yl]-propyl]-1,3-dihydro-benzoimidazol-2-one

 $C_{21}H_{24}ClN_3O$
Mol. Wt.: 369.89


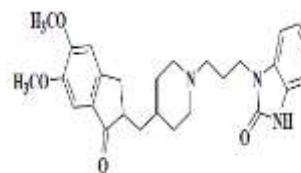
1-[3-[4-(5,6-Dimethoxy-1-oxo-indan-2-ylmethyl)-cyclohexyl]-propyl]-1,3-dihydro-benzoimidazol-2-one

 $C_{28}H_{34}N_2O_4$
Mol. Wt.: 462.58


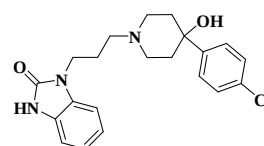
1-[3-(4-Benzhydryloxy-piperidin-1-yl)-propyl]-1,3-dihydro-benzoimidazol-2-one

 $C_{28}H_{31}N_3O_2$
Mol. Wt.: 441.56


1-[3-(4-Hydroxy-4-phenyl-piperidin-1-yl)-propyl]-1,3-dihydro-benzoimidazol-2-one

 $C_{21}H_{25}N_3O_2$
Mol. Wt.: 351.44


1-[3-[4(5,6-Dimethoxy-1-oxo-indan-2-ylmethyl)-piperidin-1-yl]-propyl]-1,3-dihydro-benzoimidazol-2-one

 $C_{27}H_{33}N_3O_4$
Mol. Wt.: 463.57


1-[3-[4-(4-Chloro-phenyl)-4-hydroxy-piperidin-1-yl]-propyl]-1,3-dihydro-benzoimidazol-2-one

 $C_{21}H_{24}ClN_3O_2$
Mol. Wt.: 385.89

RESULT AND DISCUSSION

Domperidone is a benzimidazole derivative and structurally correlated to butyrophenone neuroleptics like haloperidol.^{[65][66]} In the present study we developed the typical compounds, a combination of benzimidazole with substituted tertiary piperidine ring contains different substitution at 4th position on ring. To be formed extremely new drugs analogs 1-[3-(4-substituted piperidine-1-yl)-3-Propyl]-1,3-dihydro-benzoimidazol-2-one derivatives by used preamble chemical reactions, all reactions were carried out in presence of potassium carbonate in acetone under reflux condition with continuous stirring at inert atmosphere of nitrogen and followed Gabriel synthesis. Those compounds DAZC, DBPC, DBS, DDAZC, DDPCP, DDPM, DEB, DK9, DPCP and DPHP (Table: 1) show the good scale of antimicrobial activity.

Chemical Analysis

¹H NMR spectra were recorded on Bruker 400 MHz NMR spectrometer. Chemical shift values are reported in (parts per million, ppm) relative to an internal standard of tetramethylsilane (TMS). The following abbreviations are used for multiplicity of NMR signals: bs = broad singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplets, m = multiplet, s = singlet, t = triplets. ¹³C NMR (Bruker) spectrometer values, Molecular ion peak and Base peak predicted by Mass spectrometry data and IR provide the stretching and bending values. Melting points and boiling points were determined on an electrothermal apparatus and are uncorrected. Anti-microbiology analyses of synthesized analogues were observed in our university Microbiology lab with fully equipped, were within $\pm 0.4\%$ of the calculated values.

Antimicrobial activity

The synthesized Analogs were evaluated for in-vitro (University Microbiology lab) antibacterial and antifungal activity by using of cup and plate method.

Determination of minimum inhibitory concentration (MIC) of compounds

The antimicrobial spectra of the bioactive compounds were determined in terms of minimum inhibitory concentration (MIC) against a wide variety of Gram-positive, Gram-negative bacteria and fungi using agar plate diffusion assay (Cappuccino and Sherman 2002). Nutrient agar and Czapek-Dox agar media were prepared for the growth of bacteria and fungi, respectively. The metabolite dissolved in DMSO at concentrations ranging from 0 to 1000 µg/ml was used to assay against the test bacteria, such as *Bacillus megaterium* (NCIM 2187), *B. cereus* (MTCC 430), *B. subtilis* (ATCC 6633), *Escherichia coli* (ATCC-15597), *Staphylococcus aureus*

(ATCC-6538), *Klebsiella pneumonia* (ATCC-10031) *Vibrio paraheamolyticus* (ATCC-43996) and fungi, *C. albicans* (ATCC-10231). The inoculated plates were examined after 24–48 h of incubation at 37°C for bacteria and 48–72 h at 28°C for fungi. The lowest concentration of the bioactive metabolite exhibiting significant antimicrobial activity against the test microbes was taken as the MIC of the compound.

Determination of MIC of the isolated bioactive Compounds

MIC of the compounds, viz., **DAZC, DDAZC, DDPCP, DDPM, DEB, DK-9 and DPHP** (Table 1) against bacteria and fungi was determined. The sensitivity of bacteria, as well as fungi to the compounds, exhibited variation and the MIC of these compounds ranged from 5–100 µg/ml (Table 1). Compounds showed good antimicrobial activity against test bacteria and fungi in the range of 5–10 µg/ml.

Table 1: Minimum inhibitory concentration (MIC) of the compounds.

		Minimum inhibitory concentration (MIC) of the compounds with (CH CL3)						
Test organism		MIC µg/ml						
Bacteria		DAZC	DDAZC	DDPCP	DDPM	DEB	DK-9	DPHP
<i>Bacillus cereus</i>		5	8	8	8	5	8	8
<i>Bacillus subtilis</i>		5	9	8	8	5	8	9
<i>Escherichia coli</i>		5	8	8	8	5	5	7
<i>Staphylococcus aureus</i>		5	8	8	8	5	5	8
<i>Vibrio paraheamolyticus</i>		5	8	8	8	5	5	-
<i>Klebsiella pneumonia</i>		5	8	8	6	5	8	-
<i>Bacillus megaterium</i>		5	8	8	8	5	8	8
Fungi								
<i>Candida albicans</i>		7	9	8	8	5	8	8

Experimental

General Procedure for formation of 1-[3-(4-substituted piperidine-1-yl)-3-Propyl]-1,3-dihydro-benzoimidazol-2-one derivatives

In a 250 ml round bottom flask equipped with a magnetic stirrer and water bath, taken 1-(3-Chloro-propyl)-1,3-dihydro-benzimidazole-2-one (5g, 0.00mmol), acetone (10 vol) and 4- substituted secondary piperidine contain bi substitution and mono substitution at 4th position on piperidine cyclic compounds (15g, 0.00mmol) in presence of Potassium carbonate (2 vol) at room temperature. The reaction mass stirred for 10 minutes at ambient temperature and slowly heated to reflux temperature, maintain the same temperature for 5-6 hours under stirred. After completion of the TLC solvent distilled off dried 2 vol. Cool the reaction mass to room temperature and add 2 vol of water and then cool the reaction residue 0°–5°C. Filter the residue and Dried. The resultant crude product is purified by column chromatography in a mobile phase Methanol: Chloroform (1:9).

1-{3-[4-(Hydroxy-diphenyl)-piperidin-1-yl]-propyl}-1,3-dihydro-benzoimidazole-2-one

In a 250 ml round bottom flask equipped with a magnetic stirrer and water bath, taken 1-(3-Chloro-propyl)-1,3-dihydro-benzimidazole-2-one (5g, 0.00mmol), acetone (10 vol) and Diphenyl-piperidine-4-yl methanol (5g, 0.00mmol) in presence of Potassium carbonate (2 vol) at room temperature. The reaction mass stirred for 10 minutes at ambient temperature and slowly heated to reflux temperature, maintain the same temperature for 5-6 hours under stirred. After completion of the TLC solvent distilled off dried 2 vol. Cool the reaction mass to room temperature and add 2 vol of water and then cool the reaction residue 0°–5°C. Filter the residue and Dried. The resultant crude product is purified by column chromatography in a mobile phase Methanol: Chloroform (1:9). White color solid is obtained. Yield: 95%.

Melting point: 120-130°C.

¹HNMR: δ7.5 (d) 4H, δ7.3 (d) 4H, δ7.1 (d) 2H, δ7.0 (bs) 4H, δ3.9 (t) 2H, δ3.1 (d) 1H, δ2.9 (t) 2H, δ2.6(m) 1H, δ2.5 (m) 1H, δ2.4 (m) 2H, δ1.9 (t) 4H, δ1.5 (t) 4H.

C13NMR: δ 155 1C, δ 146 1C, δ 130 2C, δ 128 4C, δ 126 4C, δ 125 4C, δ 121 2C, δ 109 2C, δ 79 1C, δ 74 4C, δ 55 1C, δ 54 1C, δ 44 1C, δ 26 1C.

IR Spectra: 629, 664, 700, 974, 1064, 1160, 1195, 1267, 1332, 1430, 1488, 1621, 1692, 2783, 2810, 2943, 3041, 3085, 3280, 3467.

Mass: M+: 441, (M+H)+:442 is the base peak.

1¹-[3-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-propyl]-[1,4¹bipiperidinyl]- 4¹-carboxylic acid.

In a 250 ml round bottom flask equipped with a magnetic stirrer and water bath, taken 1-(3-Chloro-propyl)-1,3-dihydro-benzimidazole-2-one (5g, 0.00mmol), acetone (10 vol) and 4-(4-Chloro-phenyl) -piperidine-4-ol (5g, 0.00mmol) in presence of Potassium carbonate (2 vol) at room temperature. The reaction mass stirred for 10 minutes at ambient temperature and slowly heated to reflux temperature, maintain the same temperature for 5-6 hours under stirred. After completion of the TLC solvent distilled off dried 2 vol. Cool the reaction mass to room temperature and add 2 vol of water and then cool the reaction residue 0°–5°C. Filter the residue and Dried. The resultant crude product is purified by column chromatography in a mobile phase Methanol: Chloroform (1:9). White color solid is obtained. Yield: 95%.

Melting point: 210-220°C.

1HNMR: δ 10.8 (bs) 1H, δ 7.1 (dd) 2H, δ 7.0 (d) 2H, δ 3.7 (t) 2H, δ 2.5 (bs) 2H, δ 2.4 (t) 4H, δ 2.2 (t) 2H, δ 2.0 (t) 4H, δ 1.8 (t) 4H, δ 1.4 (m) 4H, δ 1.3 (m) 2H.

C13NMR: δ 173 1C, δ 154 1C, δ 129 2C, δ 120 2C, δ 108 2C, δ 55 2C, δ 50 2C, δ 49 1C, δ 39 8C, δ 30 1C, δ 26 1C.

IR Spectra: 673, 735, 738, 858, 1018, 1107, 1170, 1267, 1489, 1670, 1719, 2677, 2827, 2934, 2996, 3058, 3155, 3369.

Mass: M+:386 is base peak, (M+H) +:387.

1-{3-[4-(1H-Benzoimidazole-2-yl)-piperidin-1-yl]-propyl}-1,3-dihydro-benzoimidazole-2-one

In a 250 ml round bottom flask equipped with a magnetic stirrer and water bath, taken 1-(3-Chloro-propyl)-1,3-dihydro-benzimidazole-2-one (5g, 0.00mmol), acetone (10 vol) and 2-piperidine-4-yl-1H-benzimidazole (5g, 0.00mmol) in presence of Potassium carbonate (2 vol) at room temperature. The reaction mass stirred for 10 minutes at ambient temperature and slowly heated to reflux temperature, maintain the same temperature for 5-6 hours under stirred. After completion of the TLC solvent distilled off dried 2 vol. Cool the reaction mass to room temperature and add 2 vol of water and then cool the reaction residue 0°–5°C. Filter the residue and Dried. The resultant crude product is purified by column chromatography in a mobile phase Methanol:

Chloroform (1:9). White color solid is obtained. Yield: 92%.

Melting point: 200-210°C.

1HNMR: δ 12.1 (bs) 1H, δ 10.8 (bs) 1H, δ 7.0 (dd) 8H, δ 3.8 (t) 2H, δ 3.6 (q) 1H, δ 2.8 (t) 2H, δ 2.3 (m) 2H, δ 1.9 (m) 4H.

C13NMR: δ 157 1C, δ 154 1C, δ 130 2C, δ 128 2C, δ 121 4C, δ 109 2C, δ 108 2C, δ 55 1C, δ 52 1C, δ 42 1C, δ 39 4C, δ 30 1C.

IR Spectra: 663, 725, 761, 1089, 1134, 1170, 1267, 1391, 1426, 1453, 1497, 1630, 1683, 2686, 2750, 2827, 2934, 3022, 3076.

Mass: M+:375, (M+H)+:376 is base peak.

1-{3-[4-(Benzhydrylidene)-piperidin-1-yl]-propyl}-1,3-dihydro-benzoimidazole-2-one

In a 250 ml round bottom flask equipped with a magnetic stirrer and water bath, taken 1-(3-Chloro-propyl)-1,3-dihydro-benzimidazole-2-one (5g, 0.00mmol), acetone (10 vol) and 5-Chloro-1-piperidine-4-yl-1,3-dihydro benzoimidazole-2-one (5g, 0.00mmol) in presence of Potassium carbonate (2 vol) at room temperature. The reaction mass stirred for 10 minutes at ambient temperature and slowly heated to reflux temperature, maintain the same temperature for 5-6 hours under stirred. After completion of the TLC solvent distilled off dried 2 vol. Cool the reaction mass to room temperature and add 2 vol of water and then cool the reaction residue 0°–5°C. Filter the residue and Dried. The resultant crude product is purified by column chromatography in a mobile phase Methanol: Chloroform (1:9). White color solid is obtained. Yield: 96%.

Melting point: 120-130°C.

1HNMR: δ 7.5 (d) 4H, δ 7.3 (d) 4H, δ 7.1 (s) 2H, δ 7.0 (s) 4H, δ 3.9 (t) 2H, δ 3.1 (s) 1H, δ 2.9 (t) 2H, δ 2.6 (m) 1H, δ 2.5 (m) 1H, δ 2.4 (m) 2H, δ 1.9 (t) 4H, δ 1.5 (t) 4H.

C13NMR: δ 155 1C, δ 146 2C, δ 130 2C, δ 128 4C, δ 126 2C, δ 125 4C, δ 121 2C, δ 109 2C δ 79 1C, δ 74 4C, δ 74 4C, δ 55 1C, δ 54 1C, δ 44 1C, δ 26 1C.

IR Spectra: 629, 664, 700, 752, 974, 1062, 1064, 1160, 1195, 1267, 1392, 1430, 1488, 1621, 1692, 2783, 2810, 2943, 3041, 3085, 3280, 3467.

Mass: M⁺: 424 molecular ion peak is base peak, (M+2):425.

1-{3-[4-(4-Cholo-phenyl)-piperidin-1-yl]-propyl}-1,3-dihydro-benzoimidazole-2-oneIn

a 250 ml round bottom flask equipped with a magnetic stirrer and water bath, taken 1-(3-Chloro-propyl)-1,3-dihydro-benzimidazole-2-one (5g, 0.00mmol), acetone

(10 vol) and) 7-Chloro-10-piperidine-4-ylides-5,10-dihydro-benzo(g) quinoline (5g, 0.00mmol) in presence of Potassium carbonate (2 vol) at room temperature. The reaction mass stirred for 10 minutes at ambient temperature and slowly heated to reflux temperature, maintain the same temperature for 5-6 hours under stirred. After completion of the TLC solvent distilled off dried 2 vol. Cool the reaction mass to room temperature and add 2 vol of water and then cool the reaction residue 0°–5°C. Filter the residue and Dried. The resultant crude product is purified by column chromatography in a mobile phase Methanol: Chloroform (1:9). White color solid is obtained. Yield: 94%.

Melting point: 150-155°C.

¹HNMR: δ10.3 (bs) 1H, δ7.3 (m) 4H, δ7.1 (m) 4H, δ6.0 (bs) 1H, δ4.0 (t) 2H, δ3.1 (t) 2H, δ2.7 (t) 2H, δ2.5 (m) 4H, δ2.0 (m) 2H.

¹³CNMR: δ155 1C, δ139 1C, δ134 1C, δ132 1C, δ130 2C, δ128 2C, δ126 2C, δ122 1C, δ121 2C, δ109 1C, δ108 1C, δ77 2C, δ55 1C, δ53 1C, δ50 1C, δ28 1C.

IR Spectra: 673, 752, 796, 832, 1010, 1045, 1089, 1170, 1355, 1409, 1497, 1683, 2827, 2952, 3067, 3182, 3440.

Mass: M+:368 is base peak, (M+2)⁺:370 due to one chlorine atom.

1-{3-[4-(5,6-Dimethoxy-1-oxo-indan-2-ylmethyl)-piperidin-1-yl]-propyl}-1,3-dihydro-benzimidazole-2-one

In a 250 ml round bottom flask equipped with a magnetic stirrer and water bath, taken 1-(3-Chloro-propyl)-1,3-dihydro-benzimidazole-2-one (5g, 0.00mmol), acetone (10 vol) and) 5, 6 Dimethoxy-2-piperidine-4-indian-1-one (5g, 0.00mmol) in presence of Potassium carbonate (2 vol) at room temperature. The reaction mass stirred for 10 minutes at ambient temperature and slowly heated to reflux temperature, maintain the same temperature for 5-6 hours under stirred. After completion of the TLC solvent distilled off dried 2 vol. Cool the reaction mass to room temperature and add 2 vol of water and then cool the reaction residue 0°–5°C. Filter the residue and Dried. The resultant crude product is purified by column chromatography in a mobile phase Methanol: Chloroform (1:9). White color solid is obtained. Yield: 95%.

Melting Point: 120-130°C.

¹HNMR: δ10.3 (bs) 1H, δ7.2 (s) 1H, δ7.1 (dd) 4H, δ6.9 (s) 1H, δ3.9 (s) 6H, δ3.2 (m) 1H, δ2.9 (t) 2H, δ2.8 (m) 4H, δ2.7 (t) 2H, δ2.4 (t) 2H, δ1.7 (m) 2H, δ1.5 (m) 1H.

¹³C NMR: δ207 1C, δ155 1C, δ149 2C, δ130 2C, δ128 2C, δ121 2C, δ109 2C, δ108 1C, δ77 2C, δ56 1C, δ55 C, δ53 1C, δ45 1C, δ38 2C, δ34 1C, δ33 2C, δ31 1C, δ25 1C.

IR Spectra: 671, 744, 761, 793, 891, 988, 1013, 1045, 1102, 1118, 1151, 1215, 1256, 1305, 1402, 1451, 1500, 1597, 1638, 1687, 1719, 2491, 2685, 2783, 2840, 2865, 2930, 3003, 3068, 3157, 3287, 3401, 3515.

Mass: M+: 463, (M+H)⁺: 464 is base peak.

1-[3-(2-Benzhydroxy-piperidine-1-yl)-propyl]-1,3-dihydro-benzimidazole-2-one

In a 250 ml round bottom flask equipped with a magnetic stirrer and water bath, taken 1-(3-Chloro-propyl)-1,3-dihydro-benzimidazole-2-one (5g, 0.00mmol), Acetone (10 vol) and 4-Benzhydroxyloxy-piperidine (5g, 0.00mmol) in presence of Potassium carbonate (2 vol) at room temperature. The reaction mass stirred for 10 minutes at ambient temperature and slowly heated to reflux temperature, maintain the same temperature for 5-6 hours under stirred. After completion of the TLC solvent distilled off dried 2 vol. Cool the reaction mass to room temperature and add 2 vol of water and then cool the reaction residue 0°–5°C. Filter the residue and Dried. The resultant crude product is purified by column chromatography in a mobile phase Methanol: Chloroform (1:9). White color solid is obtained. Yield: 98%.

Melting point: 155-160°C.

¹HNMR: δ10.3 (bs) 1H, δ7.3 (d) 8H, δ7.2 (dd) 2H, δ7.0 (m) 4H, δ5.5 (t) 1H, δ3.9 (t) 2H, δ3.4 (m) 1H, δ2.7 (t) 2H, δ2.3 (t) 2H, δ2.0 (q) 4H, δ1.7 (m) 2H.

¹³CNMR: δ155 1C, δ142 2C, δ130 2C, δ128 4C, δ127 4C, δ121 2C, δ109 2C, δ108 2C, δ80 1C, δ77 1C, δ55 1C, δ51 1C, δ38 2C, δ31 2C, δ25 1C.

IR Spectra: 606, 695, 753, 768, 1020, 1078, 1321, 1378, 1394, 1451, 1491, 1605, 1678, 1711, 2832, 2930, 3011, 3100, 3132, 3360, 3530.

Mass: M+: 442 Molecular ion peak is base peak; (M+H)⁺: 443.

1-{3-[4-(1³l-dihydro-benzimidazole-2-one)-piperidine-1-yl]-propyl}-1,3-dihydrobenzimidazole-2-one

In a 250 ml round bottom flask equipped with a magnetic stirrer and water bath, taken 1-(3-Chloro-propyl)-1,3-dihydro-benzimidazole-2-one (5g, 0.00mmol), acetone (10 vol) and 1-piperidine-4-yl-1,3-dihydro-benzimidazole-2-one (5g, 0.00mmol) in presence of Potassium carbonate (2 vol) at room temperature. The reaction mass stirred for 10 minutes at ambient temperature and slowly heated to reflux temperature, maintain the same temperature for 5-6 hours under stirred. After completion of the TLC solvent distilled off dried 2 vol. Cool the reaction mass to room temperature and add 2 vol of water and then cool the reaction residue 0°–5°C. Filter the residue and Dried. The resultant crude

product is purified by column chromatography in a mobile phase Methanol: Chloroform (1:9). White color solid is obtained. Yield: 96%.

Melting point: 165-175°C.

¹H NMR: δ 10.6 (bs) 2H, δ 7.0 (m) 8H, δ 4.3 (q) 1H, δ 4.0 (t) 2H, δ 2.9 (t) 2H, δ 2.4 (t) 4H, δ 2.1 (t) 4H, δ 1.7 (m) 2H, δ 1.8 (t) 4H, δ 1.4 (t) 2H.

¹³C NMR: δ 172 1C, δ 150 1C, δ 141 2C, δ 128 6C, δ 127 6C, δ 125 2C, δ 124 1C, δ 69 1C, δ 58 1C, δ 55 1C, δ 40 5C, δ 39 2C, δ 38 1C.

IR Spectra: 704, 768, 1102, 1151, 1370, 1394, 1484, 1622, 1687, 1703, 2832, 2954, 3084, 3149, 3530, 3580.

Mass: M+:392 molecular ion peak is base peak; (M+H)⁺: 393.

1-[3-[4-(4-Chloro-phenyl)-4-hydroxy-piperidin-1-yl]-propyl]-1,3-dihydro-benzimidazole-2-one

In a 250 ml round bottom flask equipped with a magnetic stirrer and water bath, taken 1-(3-Chloro-propyl)-1,3-dihydro-benzimidazole-2-one (5g, 0.00mmol), acetone (10 vol) and 1-[1,4¹]-Bipiperidinenyl-4I-yl-ethanone (5g, 0.00mmol) in presence of Potassium carbonate (2 vol) at room temperature. The reaction mass stirred for 10 minutes at ambient temperature and slowly heated to reflux temperature, maintain the same temperature for 5-6 hours under stirred. After completion of the TLC solvent distilled off dried 2 vol. Cool the reaction mass to room temperature and add 2 vol of water and then cool the reaction residue 0°–5°C. Filter the residue and Dried. The resultant crude product is purified by column chromatography in a mobile phase Methanol: Chloroform (1:9). White color solid is obtained. Yield: 96%.

Melting point: 110-115°C.

¹H NMR: δ 10.8 (bs) 1H, δ 7.5 (d) 2H, δ 7.3 (d) 2H, δ 7.1 (d) 1H, δ 4.0 (t) 1H, δ 7.0 (d) 3H, δ 4.8 (bs) 1H, δ 3.8 (t) 2H, δ 2.6 (t) 2H, δ 2.3 (t) 4H, δ 1.8 (t) 4H, δ 1.5 (m) 2H.

¹³C NMR: δ 154 1C, δ 149 1C, δ 130 2C, δ 128 1C, δ 127 2C, δ 126 2C, δ 120 2C, δ 108 2C, δ 69 1C, δ 58 1C, δ 49 1C, δ 39 4C, δ 25 1C.

IR Spectra: 630, 801, 867, 899, 947, 1028, 1069, 1134, 1232, 1239, 1321, 1443, 1524, 1674, 1880, 1938, 2913, 3027, 3368, 3701.

Mass: M+:368 molecular ion peak is base peak, (M+2)⁺:388 due to one Chlorine atom.

1-[3-(4-Hydroxy-4-phenyl-piperidin-1-yl)-propyl]-1,3-dihydro-benzimidazole-2-one

In a 250 ml round bottom flask equipped with a Magnetic stirrer and a water bath, taken 1-(3-Chloro-

propyl)-1,3-dihydro-benzimidazole-2-one (5g, 0.00mmol), Acetone (10 vol) and 4-phenylpiperidine-4-ol (5g, 0.00mmol) in presence of Potassium carbonate (2 vol) at room temperature. The reaction mass stirred for 10 minutes at ambient temperature and slowly heated to reflux temperature, maintain the same temperature for 5-6 hours under stirred. After completion of the TLC solvent distilled off dried 2 vol. Cool the reaction mass to room temperature and add 2 vol of water and then cool the reaction residue 0°–5°C. Filter the residue and Dried. The resultant crude product is purified by column chromatography in a mobile phase Methanol: Chloroform (1:9). White color solid is obtained. Yield: 96%.

Melting point: 360°C.

¹H NMR: δ 10.1 (bs) 1H, δ 7.5 (d) 2H, δ 7.3 (t) 2H, δ 7.2 (m) 1H, δ 7.0 (m) 4H, δ 4.0 (t) 3H, δ 2.7 (t) 2H, δ 2.4 (t) 4H, δ 2.0 (t) 4H, δ 1.7 (m) 2H.

¹³C NMR: δ 155 (C-1), δ 148 1C, δ 130 2C, δ 128 2C, δ 126 2C, δ 124 1C, δ 121 2C, δ 108 2C, δ 77 4C, δ 71 1C, δ 55 1C, δ 39 1C, δ 25 1C.

IR Spectra: 671, 704, 720, 753, 1004, 1045, 1134, 1142, 1175, 1394, 1411, 1451, 1484, 1638, 1703, 2328, 2840, 2930, 2954, 3035, 3076, 3100, 3132, 3190, 3352, 3636, 3750.

Mass: M+:352, molecular ion peak is the base peak.

CONCLUSION

The results obtained by this enthusiastic research showing that the synthesis, biological activity often new chemical entities DAZC, DDAZC, DDPCP, DDPM, DEB, DK-9 and DPHP were successfully achieved and these molecules may helpful for further research in the process of identifying new drug substance for various therapeutic activities. Hence the attempt is fruitful.

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