NARANDER A, et al, International Journal of Research Sciences and Advanced Engineering [IJRSAE]™
Volume 2, Issue 14, PP: 29 - 39, APR - JUN' 2016.

CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SOME NEW PYRIMIDINES VIA A NOVEL BENZIMIDAZOLES

NARANDER ADDU 1*, Dr. ANBHAZHAGAN 2*

1. Research Scholar, Dept of ORGANIC CHEMISTRY, VINAYAKA MISSION UNIVERSITY.

Abstract Benzimidazole is a heterocyclic sweet-smelling natural compound. It is an essential pharmacophore and a favored structure in restorative science. Benzimidazole and its subsidiaries assume a critical part in therapeutic field with extensive number of Pharmacological exercises, for example, antimicrobial, antiviral, antidiabetic and anticancer movement. This survey is abridged to think about the science of various subordinates of benzimidazoles nearby their natural exercises, for instance, cell fortification, antimicrobial, anthelmintic, torment diminishing, antiprotozoal, antiulcer, antiviral, anticancer, antihypertensive, antineoplastic, quieting, antifungal and anticonvulsant development.

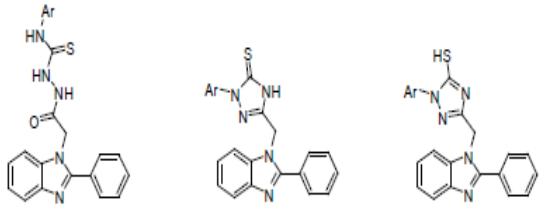
Index Words: Benzimidazoles, Substituted benzimidazoles, Chemistry, Biological actions

Introduction

Benzimidazoles are an imperative gathering of heterocyclic intensifies that are naturally dynamic and of noteworthy significance in therapeutic science. Benzimidazole is a bicyclic compound having imidazole ring, containing two Nitrogen iota at neighboring position combined to benzene ring. The benzimidazole ring is an essential pharmacophore in present day medicate revelation. An assortment of benzimidazole is being used, similar to thiabendazole and flubendazole (anthelmintic), omeprazole and lansoprazole (antiulcerative) and astemizole (antihistaminic). In light of the liking, they show towards an assortment of chemicals and protein receptors, restorative scientific experts would positively order them as favored 'substructures' for sedate dosing. The science and pharmacology of benzimidazoles have been of incredible enthusiasm to restorative science since its subordinates had different natural exercises, for example, antioxidant, antimicrobial, anthelmintic, anticancer, antihyper-tensive, antineoplastic, hostile to inflammatory, analgesic, antiprotozoal, against hepatitis B virus, antiulcer, antiviral, antifungal and anticonvu-lsant movement. All benzimidazole subordinates with their two ring frameworks bear diverse utilitarian substituents and this prompts fundamental alteration of the physico-concoction, metabolic and pharmacokinetic properties of

these medications. In the previous couple of decades, benzimidazole and its subordinates have gotten much consideration because of their chemotherapeutic esteems.

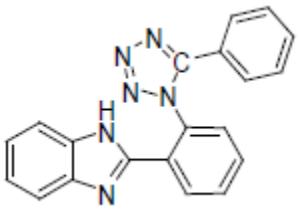
Cancer prevention agent Activity Oxygen-inferred free radicals, for example, the superoxide (O2•-), nitric oxide (NO•), hydroxyl (OH•) and peroxyl (RO2 •) radicals assume an imperative part in human sicknesses including atherosclerosis, rheumatoid joint pain and carcinogenesis. Peroxyl radicals are shaped amid lipid oxidation chain responses. Any species which is equipped for abstracting a hydrogen molecule from polyunsaturated unsaturated fat side chain in lipids display in cell membrane. Antioxidant resistance framework is enacted in the body because of the assault of free radical, Scavenging particular species which including enzymatic frameworks (superoxide dismutase, catalase) and both watery (glutathione-GSH and ascorbate) and nonaqueous scroungers (vitamin E). This is the lopsidedness between the cancer prevention agent security and free radical creation that may prompt different ailments including immune system disease. The medications which have cell reinforcement and free radical searching properties are thought to be utilized for the aversion or treatment of maladies that are specifically identified with the absence of a cancer prevention agent limit of the living beings. Blend of some Indole and benzimidazole subsidiaries and check their action to forestall myocardial harm in rats. Incorporation of thiadiazoles, triazoles and their open-chain partners thiosemicarbazides in the first position of a benzimidazole ring yield more powerful cell reinforcement mixes.



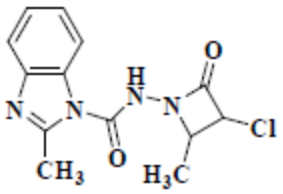
Benzimidazole dihydrochlorides, likewise have cell reinforcement action, these salts additionally have mellow platelet and erythrocyte antiaggregant activity. Presence of trimethyl amass with benzimidazole likewise includes antioxidative property by 5-lipoxygenase inhibitory activity.

Antimicrobial and Antibacterial Activity Benzimidazole demonstrates their antibacterial movement by restraining the bacterial nucleic corrosive and proteins amalgamation. This capacity of benzimidazole is because of their auxiliary likenesses with the purine. 2-substituted benzimidazole subsidiaries are observed to be pharmacologically more intense and

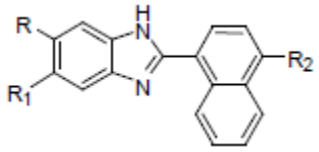
henceforth the plan and blend of 2-substituted benzimidazoles are the potential territory of research. 2-{2-(5-phenyl-1H-tetrazol-1-yl)phenyl}-1H-benzo[d]imidazole were orchestrated and their antimicrobial action product tried against Gram positive Staphylococcus aureus and Gram negative Escherichia coli The impact delivered by the specimen was contrasted and the impact created by the positive control (Reference standard Ciprofloxacin 5 Gg/plate) . The outcome showed that compound were more dynamic against the microorganisms with reference to standard.



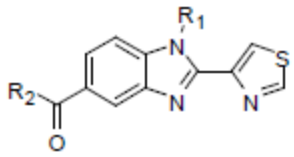
Schiff base of 2-Phenyl benzimidazole subordinates were blended and these mixes demonstrate some great antibacterial action. The essential N=C assemble accepted to upgrade antimicrobial action. Along these lines they might be utilized as lead mixes for assist development. Benzimidazole containing azetidine-2-one moiety are additionally orchestrated and they indicate antimicrobial action against gram positive (S. aureus, S. mutans and B. subtilis) and gram negative (E. coli, S. typhi and P. aeruginosa) microorganisms.



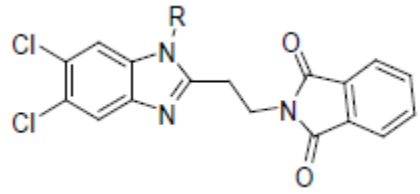
Antimicrobial and Antiviral Activity Late examination has demonstrated that some benzimidazole subordinates could show powerful against HBV movement with low cytotoxicity. Benzimidazole might be viewed as a 1, 3-dideazapurine and may supplant this base in the development of nucleosides in viral replication and demonstrate their inhibitory action. In this manner, A progression of 2-arylbenzimidazole subsidiaries were blended which demonstrate inhibitory movement against Flevivirus, Pestivirus, Reteroviridae, Piconiviridae, Reoviridae, Herpesveridae and Poxviridae.



A library of two basically related thiazolylbenzimidazole subsidiaries was composed and arranged. All the blended mixes were assessed for their against HBV movement and cytotoxity on HepG 2.2.15 cells, with the antiviral medication lamivudine as reference control.



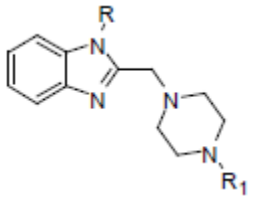
A progression of novel benzimidazole subordinates was orchestrated and assessed for their hostile to hepatitis B infection (HBV) movement and cytotoxicity in vitro. Solid movement against HBV replication and low cytotoxicity were for the most part seen in these benzimidazoles. The most encouraging mixes indicate high antiviral intensity (IC50 = 0.9 and 0.7 μM, individually) and momentous selectivity records (>1111 and 714, separately). They were chosen for promote assessment as novel HBV inhibitors.



An exploration additionally show that N-substituted and 2-Substituted Benzim-idazoles have action against Tobacco Mosaic virus.

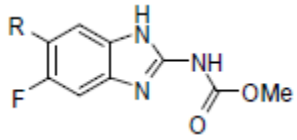
Antimicrobial and Antifungal Activity

The antifungal action of benzimidazoles is because of its cozy association with structure of purines. The purines is one of the basic segment of organic framework and it was found that 5,6-dim-ethyl-1-(α-D-ribofuranosyl) benzimidazole is a vital piece of structure of Vit.B12. A parasitic particular 14α-demethylase inhibitor is relied upon to go about as an antifungal specialist. Extensive exertion has been made for the outline of parasitic – particular 14α-demethylase inhibitors and this has brought about helpful, orally dynamic antifungal specialists which are compelling against both topical and foundational contagious diseases. Various Benzimidazole subordinates were set up by gathering the benzimidazole and substituted piperazinyl gathering. The antifungal action of incorporated mixes was resolved against Candida albicans utilizing Ketoconazole as reference standard. The compound demonstrated equivalent antifungal action to Ketoconazole.

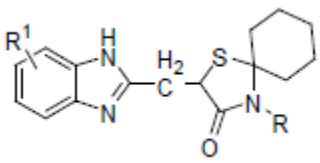


Microtubules are available in every single eukaryotic cell and are imperative as a result of their part in cell mitosis. Benzimidazole subsidiaries have an expansive range antifungal movement and demonstrate their antifungal exercises by hindering the polymerization of α-and β-tubulin subunit. Antitubulin specialists, particularly benzimidazoles, disturb microtubule work in

eukaryotic creatures, for example, organisms, protozoa and helminths. Benzimidazole carbamates are helpful for the treatment of Giardia lamblia, Cryptococcus neoformans, Trichomonas vaginalis, Pneumocystis carinii and Encephalitozoon intestinalis. Subsequently some new methyl benzimidazole carbamate subsidiaries having 5(6)- fluoro-6(5)-substituted heterocyclic rings have been orchestrate and their antifungal exercises were explored against C. albicans.

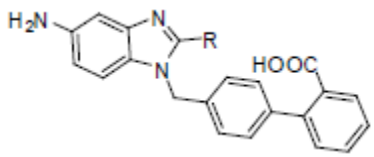


Anthelmintic Activity Benzimidazole core has anthelmintic movement. A progression of 2-(trifluoromethyl)- 1H-Benzimidazole subsidiaries were readied utilizing Phillips cyclocondensation of substituted 1,2-phenylenediamine and trifluoroacetic corrosive. The integrated mixes were screened in vitro against different protozoan parasites, Giardia intestinalis, Entamoeba histolytica, Trichomonas vaginalis and Leishmania mexicana, and they indicated nanomolar exercises against a portion of the previously mentioned protozoa. The mixes were additionally tried in vitro and in vivo against the nematode Trichinella spiralis. In another investigation two arrangement of benzimidazole subordinates were blended. The primary arrangement depended on 5,6-dinitrobenzimidazole and the second arrangement involves 2-thioalkyl-and thioaryl-substituted benzimidazoles. Anti-protozoal action of the recently integrated mixes was examined. Some thioalkyl subordinates demonstrated momentous movement against nosocomial strains of Stenotrophomonas malthophilia, and an action practically identical to that of metronidazole against Gram-positive and Gram-negative microbes. 5,6-dichloro-2-(4-nitrobenzylthio)benzimidazole demonstrated the most particular antiprotozoal activity. Some new mixes were set up by incorporationg two organically dynamic pharmacophore, thiazolidinone and benzimidazole to frame a solitary atom. The combined mixes were assessed for nematicidal action by aq. In vitro screening procedures at different fixations on Ditylenchus myceliophagus and Caenorh-abditis elegans. The outcomes have been communicated as far as LD50. Two mixes indicated promising nematicidal movement on the two species with LD50 estimation of 220ppm and 260ppm.



Substituted 2-trifluorobenzimidazoles additionally announced anthelmintic movement.

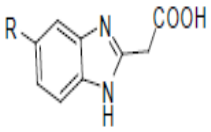
Anticancer Activity Benzimidazole chalcones, benzimidazole mercaptoac-etohydrazide and benzimidazole thiosemicarbazide subsidiaries were integrated and appear strength against PC12 (pheochromocytoma of the rodent adrenal medulla) cells. Benzimidazole-2-isoxazole subordinate too displayed high strength against HEPG2 (human liver carcinoma cell line) and PC12 cells. 4 A Series of new nitrobenzimidazoles were blended and they have cytotoxic action against bosom malignancy. In this detailed research it was additionally discovered that the mixes like thiadiazole, tetrazole, triazines and imidazoles moreover have the movement. 2-substituted benzimidazoles: 2-[(4-oxothiazolidin-2-ylidene) methyl and (4-amino-2- thioxothiazol-5-yl) benzimidazoles, 2-[(4-fluorobenzylidene furthermore, cycloalkylidene) cyanomethyl] benzimidazoles subsidiary combined and items were subjected to in vitro anticancer screening that uncovered that all the tried mixes showed antitumor action against human hepatocellular carcinoma (HEPG2), human bosom adenocarcinoma (MCF7) and human colon carcinoma (HCT 116) cell lines, with IC50's<10 microg/ml.47 Some bis(benzimidazoles), bis(benzoxazoles), benzothiazoles, and their subsidiaries were blended and every one of the mixes subjected to in vitro antitumor exercises against A-549, BFTC-905, RD, MES-SA, and HeLa cell lines. The orchestrated compound show great anticancer action. Hostile to Hypertensive Agents 5-substituted (amino)- 2-phenyl-1-(2'- carboxy biphenyl-4-yl) benzimidazoles contrast from the already announced antihypertensive operators and related mixes on the grounds that they create strong hypertensive impact upon oral organization. It is a sort of non peptide angiotensin (An II) receptor antagonist. 2-position of biphenyl is fundamental for the action. Only ortho substituted corrosive have both high liking for the AII receptor and oral against hypertensive power.

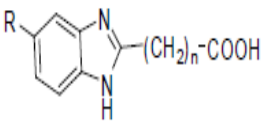


Benzimidazole subsidiaries (2-{6-Chloro-5-nitro-1-[2-(1Htetrazol-5-yl) biphenyl-4-ylmethyl] 1H-benzoimidazol-2-yl}-phenyl)-(Substituted benzylidene) amine was orchestrated and screened for their antihypertensive action. All the orchestrated mixes indicated huge antihypertensive

activity. 5-substituted aryl or alkyl caboxamido subsidiaries were blended and they answer to have Angiotensin-II AT1 receptor hostile activity.

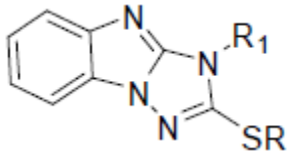
Mitigating Activity Presence of carboxylic corrosive moiety at 2-position of the benzimidazole ring satisfies the base basic prerequisites that are regularly present in the showcased calming drugs. Hence benzimidazole-2-carboxylic corrosive subsidiaries were integrated and tried for intense calming movement against carrageenan incited rodent paw edema display. The tried mixes were observed to be sheltered upto 2000 mg/kg, p.o. measurements and displayed great calming action at 100 mg/kg p.o. also, higher dosages. Their movement to a great extent relies upon substituents at position 5 and chain length at position 2 of benzimidazole moiety. With 1-benzyl substitution, action was found to increment.





A progression of 2-methylaminob-enzimidazole subordinates were blended by the response of 2-(chloromethyl)-1Hbenzimidazole subsidiaries with essential sweet-smelling amines. The recently incorporated mixes demonstrated powerful mitigating exercises contrasted and standard medication Nimesulide individually. 1-(N-Substituted amino) methyl-2-ethyl benzimidazole subsidiaries were incorporated by the response between 2-ethylbenzimidazole and substituted essential and optional amines. All the blended mixes were screened for mitigating action against carrageenan prompted paw oedema in rats. The whole compound show great mitigating.

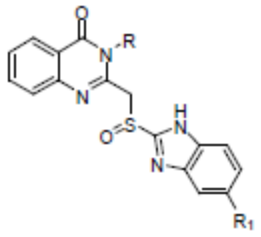
Analgesic Activity Activity 1-acyl-2-alkylthio-1,2,4-triazolo[2,3a] benzimidazole were combined, a large portion of these mixes indicated strong pain relieving impact contrasted with indomethacin.



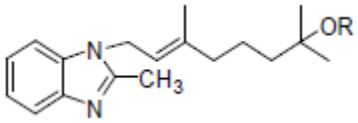
The pain relieving movement of 1,2,5-trisubstituted benzimidazole subordinates have been explored by utilizing the altered Koster test. Among the Synthesized mixes, (1-diethylaminomethyl)- 2-(p-chlorop-henyl)- 5-nitro benzimidazole hydroch-loride) has indicated higher action than acetylsalicylic corrosive (ASA) and indometacin. A progression of N-(acridin-9-yl)- 4-(benzo[d] imidazol/oxazol-2-yl) benzamides has been blended by the buildup of 9-aminoacridine subsidiaries with benzimidazole or benzoxazole subordinates.

Schiff's bases are set up by the buildup of 2-hydroxy naphthaldehyde with functionalized diamines. Incorporated mixes indicated great pain relieving activity.

Antiulcer Activity Benzimidazole sulfinyl methyl pyridine is an entrenched class of H+/K+ATPase inhibitors, helpful in the treatment of intense and endless ulcer conditions. Insertion of pyrimidine ring rather than pyridine in the benzimidazole sulfinyl methyl pyridine moiety, brought about an expansion in antiulcer activity. Substituted benzimidazoles are powerful inhibitors of Parietal cell proton pump, the H+/K+ ATPase, and are fit for blocking gastric corrosive discharge in light of a few boosts. For the action sulfoxide gathering, methylene amass with hetercycles is essential for activity. another arrangement of 2-[5-substituted-1H-benzo(d)imidazol-2-yl sulfinyl] methyl-3-substituted quinazoline-4-(3H)- one subsidiaries were incorporated and tried for antiulcer movement against pylorus ligation-prompted, headache medicine incited and ethanol instigated ulcer in rodent display. A few mixes indicated higher movement than omeprazole utilized as standard.

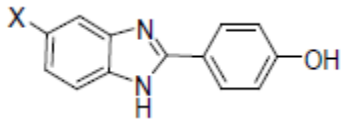


Insecticidal Activity The majority of the creepy crawly developments controllers (IGRs) with adolescent hormone (JH) movement have been accounted for and are gotten from monoterpenes and sesquiterpenes. On the other hand, a few imidazole mixes have been appeared to restrain the epoxidation of methyl farnesoate to JH III in vitro. These realities prompts amalgamation of 1-(3,7-dimethyl-7-methoxy-2-octenyl)- 2-methylbenzimidazole and the 7-ethoxy simple , having an auxiliary likeness to JH imitates, had high insecticidal movement against the housefly.



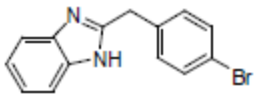
DNA Inhibitory Activity A few benzimidazole subsidiaries are dynamic as inhibitors of sort I DNA topoisomerases (topo I). Three 1Hbenzimidazole subordinates with various electronic qualities at position 5-, specifically 5-chloro-4-(1Hbenzimidazole-2-yl)phenol, 5-methyl-4-(1H-benzimidazole-2-yl)phenol and 4-(1H-benzimidazole-2-yl)phenol , were orchestrated and assessed for their impacts

on mammalian sort I DNA topoisomerase movement utilizing quantitative in vitro plasmid supercoil unwinding measures. Compound 5-methyl-4-(1H-benzimidazole-2-yl) phenol demonstrated intense topoisomerase I restraint.



Some novel combined heterocyclic mixes of 2,5-disubstituted-benzoxazole and benzimidazole subsidiaries were examined for their inhibitory action on both eukaryotic DNA topoisomerase I and II in a cell free framework. A portion of the integrated mixes were observed to be more strong as eukaryotic DNA topoisomerase I harms than the reference medicate camptothecin.

Androgen Receptor Antagonist Activity Oxobenzimidazoles, is a novel arrangement of androgen receptor enemies, were found through all over again configuration guided by structure-based medication design. N-benzyl, N-aceto, and Nethylene ether subordinates of 2-(2,2,2-trifluoroethyl)- 5,6-dichlorobenzimidazole as novel androgen receptor rivals were integrated. SAR ponders prompted the revelation of 4-bromo-benzyl benzimidazole as a powerful androgen receptor foe in the rodent prostate.



Antiallergic Activity 1-[2-{2-(4-hydroxy-2,3,5-trimethylphenoxy)ethoxy}ethyl]-2-(4-methyl-1-homo piperazino) benzimidazole were combined and they powerfully smothered histamine discharge from rodent peritoneal pole cells activated by the antigenantibody reaction. In another study1-[2-{2-(4-Hydroxy-2,3,5-trimethylphenoxy) ethoxy} ethyl]-2- (4-methyl-1-homopip-erazino)- 1H-benzimidazole difumarate indicate antiallergic pharmacological exercises when it is hybridized with trimethylhydroquinone subordinates.

Antidiabetic Activity 4-thiazolidinones and 1,3,4-oxadiazoles containing 2-mercapto benzimidazole moiety were blended and screened for antidiabetic movement utilizing Oral Glucose Tolerance Test (OGTT). A portion of the blend mixes demonstrated brilliant antidiabetic exercises.

Anticonvulsant Activity A progression of new 2-[(1-substituted phenylethylidine) hydrazine]-N-phenyl-1H-benzo[d]imidazole-1-carbothioamides were planned and integrated. All the recently blended mixes were screened for anticonvulsant movement utilizing two most received models, maximal electroshock seizure (MES) and subcutaneous

pentylenetetrazole (scPTZ). A few mixes indicated strong anticonvulsant movement and in the neurotoxicity screening, the greater part of the mixes were without poisonous quality at the dosage of 60 and 100 mg/kg.

Antiproliferative Activity Benzimidazole retinoids have the property to stifle cell development in a measurements subordinate way. These novel Benzimidazole retinoids demonstrating noteworthy measure of antiproliferative impacts on HL-60 might be utilized as potential anticancer agents.

Conclusion Benzimidazole is an imperative heterocyclic moiety for the disclosure of new medications. This has been seen up until now, that adjustments on benzimidazole moiety showed important organic exercises. It will enthusiasm to watch that these adjustments can be used as powerful helpful operators in future. The union of novel benzimidazole subordinates remains a principle center of restorative research. Since now, specialists have been pulled in toward outlining more powerful Benzimidazole subordinates having wide different of natural action.

References

1. Tewari AK, Mishra A. Synthesis and antiviral activities of N-substituted -2-substituted benzimidazole derivatives. Ind J Chem. 2006; 45(B):489- 493.

2. The Merck Index, An Encyclopedia of chemicals, drugs and Biologicals, 13th edition, Merck Research Lab, 2001.

3. Harsch C, Sammes PG, Taylor JB, Ramsden CA. Comprehensive Medicinal Chemistry 1st edition, Oxford: Pergamon Press, 1990; 4:528.

4. Davidse LC, Flach W. Interaction of thiabendazole with fungal tubulin. Biochim. Biophys. Acta 1978;82:543

5. Hollomon DW, Butters JA, Barker H, Hall L. Fungal β-Tubulin, Expressed as a Fusion Protein, Binds Benzimidazole and Phenylcarbamate Fungicides Antimicrob. Agents. Chemother.1998; 42: 2171

6. Kus C, Altanlar N. Synthesis of Some New Benzimidazole Carbamate Derivatives for Evaluation of Antifungal Activity, Turk J Chem 2003; 27: 35-39.

7. Arjmand F, Mohani B, Ahmad S. Synthesis, antibacterial, antifungal activity and interaction of CT-DNA with a new benzimidazole derived Cu (II) complex. Eur J Med Chem. 2005; 40(11):1103-1110.

8. Spasov A, Yozhitsa L, Bugaeva I and Anisimova VA. Benzimidazole derivatives: Spectrum of pharmacological activity and toxicological properties. Pharmaceutical Chemistry Journal 1999; 33(5):232-243.

9. Preston PN. Benzimidazoles and Congeneric Tricyclic Compounds Part 2.Wiley Interscience New York, 1980:531.

10. Foks H, Ksepko DP, Kuzmierkiewicz W, Zwolska Z, Augustynowicz EK, Janowiec M. Synthesis and tuberculostatic activity of new benzimidazole derivatives. Chem Het Comp. 2006; 42: 611-614.

11. Ansari KF, Lal C. Synthesis, physicochemical properties and antimicrobial activity of some new Benzimidazole derivatives. European Journal of Medicinal Chemistry 2009; 44:4028–4033.

12. Gurer-Orhan H, Orhan H, Suzen S, Püsküllü MO, Buyukbingol E. Synthesis and Evaluation of In vitro Antioxidant Capacities of Some Benzimidazole Derivatives. J Enzyme Inhib Med Chem 2006;21(2):241- 247

13. Gardiner JM, Loyns CR, Burke A, Khan A and Mahmood N. Synthesis and HIV-1 inhibition of novel benzimidazole derivatives. BioORG & Med Chem Lett 1995;5(12):1251-1254.

14. Ramla MM, Omar MA, EL Khamry AM, EL Diwani HI. Synthesis and antitumor activity of 1-substituted-2-methyl-5-nitrobenzimidazoles. Bioorg Med Chem. 2006; 14:7324-7332.

15. Refaat HM. Synthesis and anticancer activity of some novel 2- substituted benzimidazole derivatives. Eur J Med Chem. 2010;45(7):2949-56.