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INSILICO DESIGN, SYNTHESIS, AND ANTHELMINTIC ACTIVITY SCREENING OF SOME 6-BENZIMIDAZOYL PYRANS

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ABSTRACT

An extension of our research for novel anthelmintic agents, some hybrid derivatives containing C-2 pyran of benzimidazole were made by Michael condensation of ethyl cyano acetate in presence of pyridine. Molecular docking studies were then used to find the structural prerequisites for activity of this series of compounds. Whip worms were used in the study to screen the anthelmintic activity of the compounds synthesized. The results indicated that, all the compounds were found to be moderately effective against whip worm (*Trichuris trichuria*) at 1 and 2 mg/ml compared to the standard reverence drug mebendazole. The benzimidazole pyran analogue's percentage yield obtained was found to be in the array of 55-79. The molecular docking studies revealed that, the compounds1 &3 showed good binding affinity with β-tubulin receptors.

INTRODUCTION

Following the discovery of thiobendazole in 1961, several benzimidazoles are introduced afterwards as broad spectrum anthelmintics. The imidazole or imidazoline with benzene moiety are termed as benzimidazole. Benzimidazoles are found to effective against intestinal round worms. Benzimidazole ring system[1,2,3,4,5] can be seen commonly in different classes of therapeutically effective synthetic drugs. Normally the characteristics of the drugs may vary from one to the other in terms of the substitutions to the basic moiety at 1, 2, or 5 positions.[6] Usually anthelmintic drugs contain 2 and 5 substituted benzimidazole ring systems.[7, 8] Large substitutions at 1, and 2 positions can be observed in antihistamines (H1).[10] Proton pump inhibitors have large substituent groups at position 2 of benzimidazole ring system.[9]

The N-ribosyl – dimethyl benzimidazole which serves as an axial ligand for cobalt in vitamin B_{12} is considered as a noticeable benzimidazole compound in nature.[11] Reports[12] on benzimidazole includes in the fused heterocyclic system normally associated with diverse pharmaceutical activities showed that on pyridine ring substitution by electron donating groups increase the activity of the parent compound.

Anthelmintic drugs are used generally to treat worm infestations from flat worms, (fluke worms, tapeworms etc.) and round worms (hook worms, whip worm, ring worms, pin worms etc.).[13,14] As per WHO[15] about 2 billion people are suffering from parasitic worm infections round the world. The livestock and crops also diseased by the parasitic worms which may end up in an economic impact. Yet, the majority of drugs are limited in their action, e.g., praziquantel, a drug used in the treatment of schistosomiasis has no activity against other round worms.

Satyavan Sharma et al[16] synthesized 5 substituted 2 alkyl /aryl –carbonyl amino benzimidazoles. These compounds showed 74-100% reduction of microfilariae and adult filarial worm, *Litomosoides carini.* C.V Reddy & Sastry et al[17] synthesized a series of methyl 5, 6 -3 -oxo -1, 4 benzo thiazin – 7-glyoxyl] benzimidazole – 2-carbamates and screened for their anthelmintic activity. M.Himaja Rajiv et al[22] synthesized 6-nitro benzimidazole-1-acetyl-amino acids and peptides and observed the highly potent activity of these compounds against nematodes.

Benzimidazoles exerts their anthelmintic activity[18,19] by the selective inhibition of β- tubulin (a receptor protein) polymerization thereby suppressing the cellular transport and energy metabolism in the worm cells. Again, benzimidazoles gradually exhaust the energy reserves and obstruct the excretion of waste products from parasitic cells. Slight structural alteration of the beta tubulin receptor in the resistant organism results in lowering of the binding affinity of benzimidazoles, finally results in cross resistance. Many studies[20,21]

showed that beta tubulin substituted with a single amino acid result in anthelmintic drug resistance.

The whip worm (*Trichuris trichuria*) was estimated to infect 750 million people throughout the world, chiefly in the tropics. Man becomes infected by ingesting contaminated soil, food, or water containing infective Trichuris eggs previously passed in faeces. The lifetime of the adult *Trichuris* is normally a year. Sigmoidoscopy is the diagnosis tool for finding trichuris eggs or the adult worms in stool.

In the present study, likely derivatives of benzimidazole pyran compounds were predicted and docked by using β tubulin (Protein Data Bank id TUBB 5). The *insilco* molecular study of these all these predicted compounds are found to obey "Lipinski rule of five". Autodock 4.2, Cygwin and Schrodinger software were used to predict the anthelmintic activity for the selected derivatives. *Molinspiration* (online server) was used to evaluate the molecular properties of the compounds selected. The compounds with high glide score are considered for synthesis as per our earlier communication.[26]

MATERIALS AND METHODS

All the chemicals were obtained from Loba Cheme, S.D. Fine Chem, Himedia (for substituted ketones), Sigma (for substituted benzaldehydes) and Hayman Ltd (for ethanol).

The UV and IR spectra of the synthesized derivatives were documented[26] on JASCO V 530 UV/VIS spectrophotometer and JASCO FT/IR-410 at the Department of Pharmaceutical analysis, SRIPMS, Coimbatore, India. Finnegan MAT 8230 at Indian Institute of Technology, Chennai was utilized for recording the Mass spectra of the prepared compounds. The PMR spectra of the compounds were recorded on Burker 200 MHz at the Dept. of Chemistry, Bharathidasan University, Trichy. The melting points of all the prepared derivatives were taken and uncorrected using melting point apparatus MP-DS, TID 2000.

Outline of synthesis -1

Stage-1

Synthesis of 2-(α-hydroxyl ethyl) benzimidazole:

The reaction mixture contains 27 g (0.25mol) of o-phenylene diamine, 25.5ml (30.6g, 0.34 mol) of lactic acid which was refluxed for around 3h, cooled and made alkaline by the slow addition of sodium hydroxide (10%) solution. The final product obtained was dissolved in 400 ml of boiling water, and digested with 2 g of activated charcoal for 15 min. The final solution was filtered using a Buchner funnel, and the filtrate was cooled to around10^{O}C. The product was again washed with 25 -30 ml of cold water and dried at 100 ^{O}C in a desiccator.

Stage-2

Synthesis of 2-acetyl benzimidazole:

The compound obtained from step -1 (5 mmoles) was added to a ground mixture of $KMnO_4$ (2g, 12.65 mmoles) and solid neutral alumina (2.5 g). Then acetone (20ml) was added to the reaction mixture with forceful stirring and the filtrate was evaporated and the rude residue was taken up in chloroform (15ml) and washed with water (30ml) in order to remove inorganic matter and dried using anhydrous sodium sulfate. Hot water was used to recrystallize the final product as needle like crystals.

Stage-3

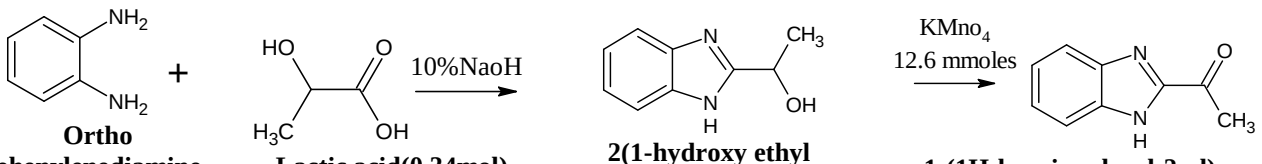
Synthesis of chalcones[25]

The compound obtained from stage-2 (20 mmoles) and sodium hydroxide (4 g, 100mmoles) were mixed thoroughly to a fine powder at room temperature. Different aromatic aldehydes (30mmoles) were added to the mixture and stirred well at room temperature for a 5-10 min. until the condensation was over. The solid residue was washed with water to remove inorganic impurities and dried.

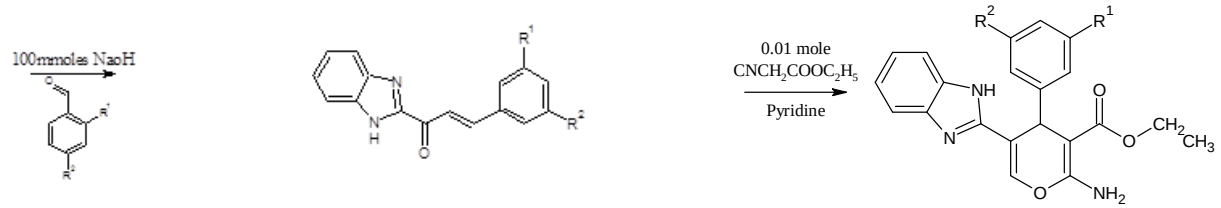
Stage-4

Synthesis of pyrans

A mixture of chalcones (0.01mole) and ethyl cyano acetate (0.01mol) in pyridine was treated for 48h, cooled and decanted in water. The solid residue obtained was recrystallized from $CHCl_3$-*Pet.ether* mixture (1:2).



Ortho phenylenediamine (0.25mol) + **Lactic acid(0.34mol)** → **2(1-hydroxy ethyl benzimidazole)** → **1-(1H-benzimadazol-2-yl) ethanone**

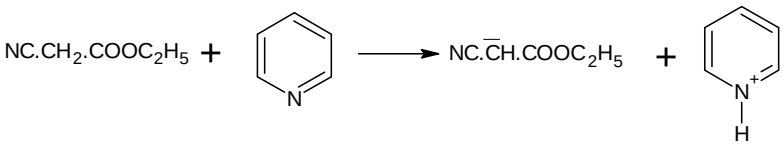


Aromatic aldehyde (30mmoles) | **0.01mol 1-(1H-benzimadazol-2-yl)-3-[4-(dimethylamino) phenylprop-2-en-1-one** | **Ethyl-2-amino-6(1H-benzimadazol-2-yl)-4-Phenyl-4H-Pyran-3-Carboxylate**

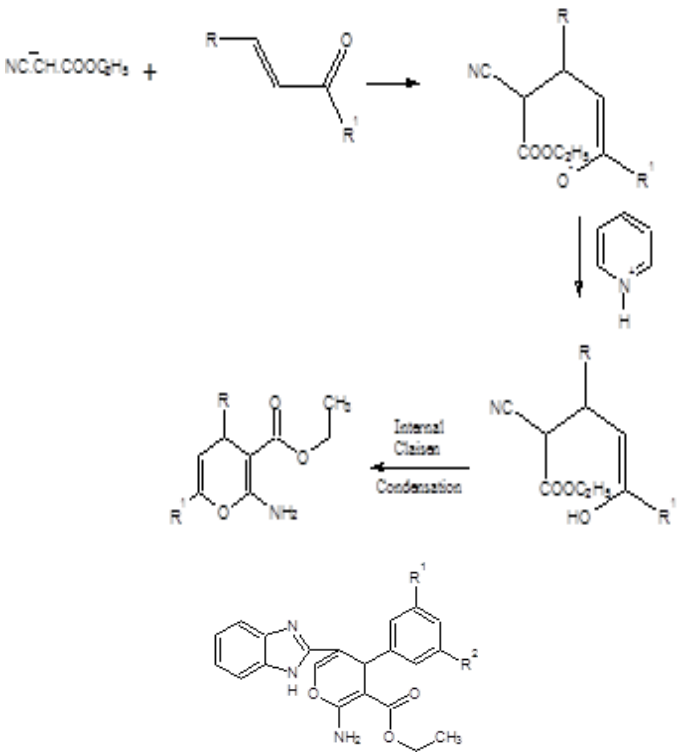
Outline of synthesis - 2

This stage explains the reaction of chalcones with ethyl cyanoacetate in pyridine for the development of the pyran ring system in the mixture.

Stage-1



Stage 2



Compound	R^1	R^2	Molecular formula	Melting point	%yield	Rf value	Molecular weight
C-1	H	H	$C_{21}H_{19}N_3O_3$	204.5	59	0.57	361.4
C-2	Cl	H	$C_{21}H_{18}N_3O_3Cl$	211.0	65	0.74	395.8
C-3	H	OCH_3	$C_{22}H_{21}N_3O_4$	231.5	78.3	0.55	391.4
C-4	OCH_3	H	$C_{22}H_{21}N_3O_4$	219.0	70.5	0.61	391.4
C-5	NO_2	H	$C_{21}H_{18}N_4O_5$	236.0	64.5	0.67	406.4

The spectral, chromatographic, and elemental analysis of the compounds selected for synthesis were compared with the previously reported[26] physical and spectral data by the authors and compared the similarity for all the synthesized compounds. Compound -1($C_{21}H_{19}N_3O_3$, m.p.:204-205^{0}C), Compound-2 ($C_{21}H_{18}N_3O_3Cl$, m.p.:210-212^{0}C), Compound-3($C_{22}H_{21}N_3O_4$, m.p.:210-212^{0}C), Compound-4 ($C_{22}H_{21}N_3O_4$, m.p.:218-220^{0}C), Compound -5 ($C_{21}H_{18}N_4O_5$, m.p.:235-237^{0}C).

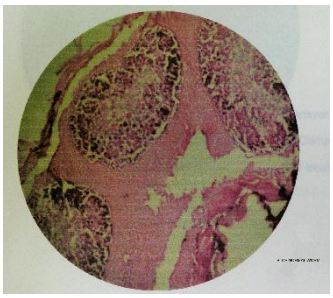
Invitro anthelmintic activity screening[23]

Live whip worms were collected in 0.9 % physiological saline from the pigs slaughtered at local abattoirs. After through washing in physiological saline, the worms were maintained in climatic chamber at 37.0± 1°C. Each concentration (five synthesized compounds) of compounds synthesized was tested against single batch of six worms that are maintained separately in ten petrifies containing 45 ml of medium. Dilutions of compounds were made in dimethyl sulfoxide. Diluted compound was added to the medium to give 1, 2 mg/ml concentration. Mebex, a broad spectrum anthelmintic was used as reference drug. The latter was also dissolved in DMSO and tested at similar to those of synthesized compounds.

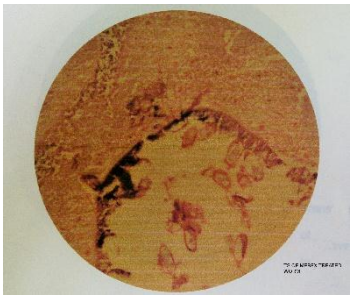
For each such concentration one petridish containing 5 ml of DMSO on the medium served as a control. The experiments were repeated for two times. The efficacy of the synthesized compounds was evaluated in terms of the motility and histomorphological changes of the worms. The time taken for complete paralysis of the worms were recorded and death was confirmed by dipping the worms in warm water. Soon after the worms got paralyzed, a set of those treated with 2 mg/ml of drug along with the ones of controls were picked up and fixed in formalin were subjected to scanning light microscopy studies by standard techniques.

No	Compound code	Paralysis (in h)	
		Concentration 1mg/ml	Concentration 2mg/ml
1	C-1	10-12	8-10
2	C-2	12-13	10-12
3	C-3	11-15	9-11
4	C-4	14-16	10-12
5	C-5	13-15	10-13
6	Standard drug: Mebendazole	4-6	2-4

Worms incubated in control medium showed physical activity till 54 to 68 hours.



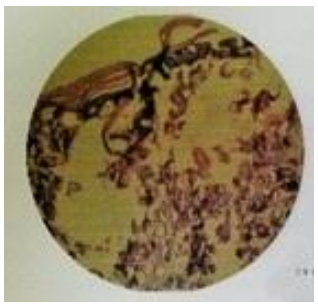
T.S of normal whip worm



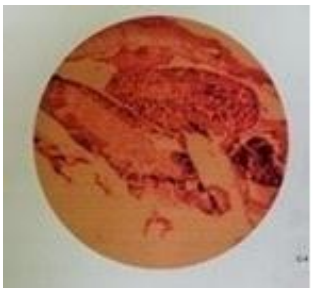
T.S of mebendazole treated worm

T.S of worm treated with C-1

T.S of worm treated with C-2

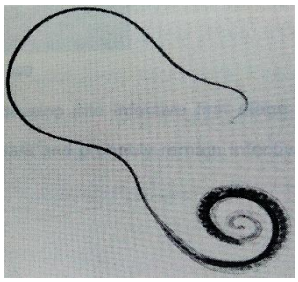


T.S of worm treated with C-3

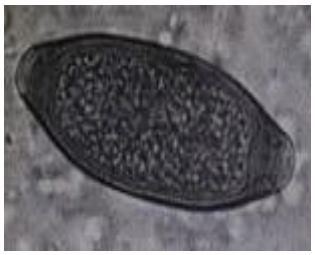


T.S of worm treated with C-4

T.S of worm treated with C-5

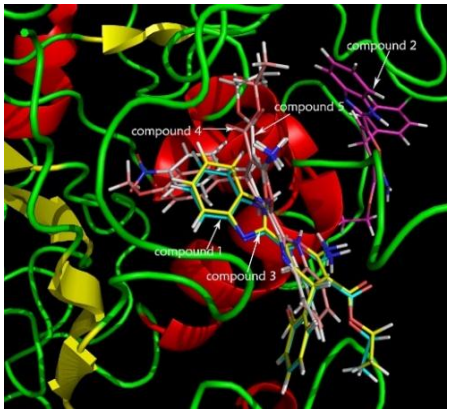


Whip worm

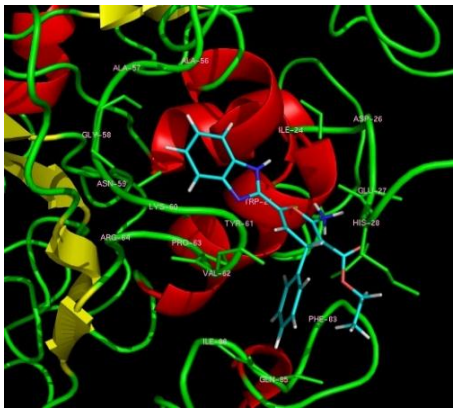


Egg of whip worm

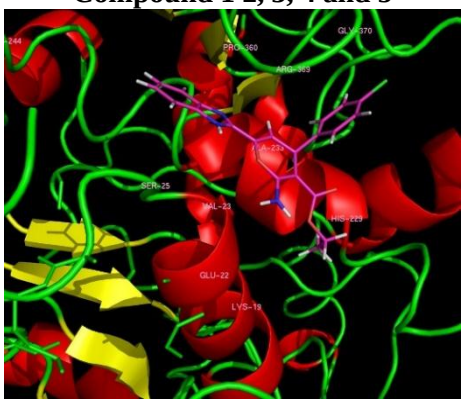
Photomicrograph of the T.S of the whip worm of different drug treated groups, standard drug treated and control



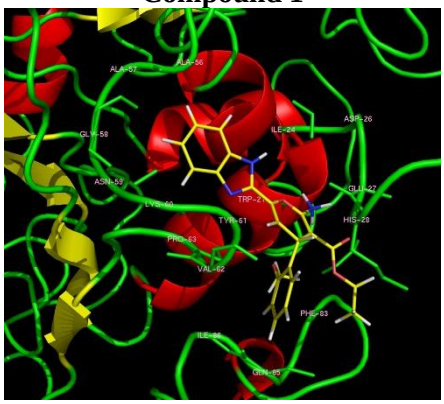
Compound 1 2, 3, 4 and 5



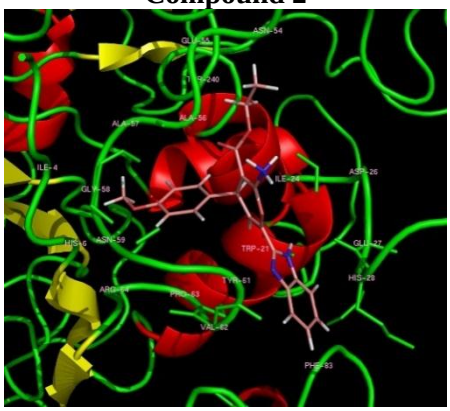
Compound 1



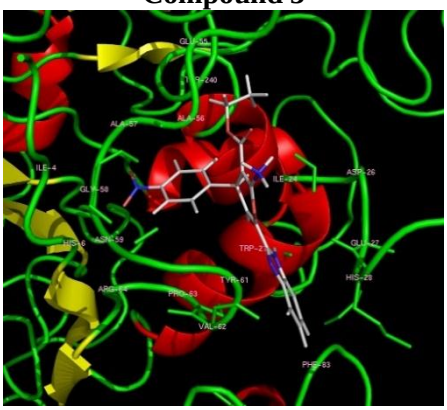
Compound 2



Compound 3



Compound 4



Compound 5

The impulsive photos of the docked compounds with β-tubulin (with high binding energy) showing the binding sites

Table 2: The predicted glide scores of the different benzimidazole pyran derivatives.

Compound	Chemical name	Glide score
C-1	ethyl 2-amino-6-(1*H*-benzimidazol-2-yl)-4-phenyl-4H-pyran-3-carboxylate	-6.092395
C-2	ethyl 2-amino-6-(1H-benzimidazol-2-yl)-4-(4-chlorophenyl)-4H-pyran-3-carboxylate	-4.927417
C-3	ethyl 2-amino-6-(1H-benzimidazol-2-yl)-4-(2-methoxyphenyl)-4H-pyran-3-carboxylate	-6.032163
C-4	ethyl 2-amino-6-(1H-benzimidazol-2-yl)-4-(4-methoxyphenyl)-4H-pyran-3-carboxylate	-5.533157
C-5	ethyl 2-amino-6-(1H-benzimidazol-2-yl)-4-(3-nitrophenyl)-4H-pyran-3-carboxylate	-5.888931
C-6	ethyl 2-amino-6-(1H-benzimidazol-2-yl)-4-(3-chlorophenyl)-4H-pyran-3-carboxylate	-5.853321
C-7	ethyl 2-amino-6-(1H-benzimidazol-2-yl)-4-(2-chlorophenyl)-4H-pyran-3-carboxylate	-5.832231
C-8	ethyl 2-amino-6-(1H-benzimidazol-2-yl)-4-(3-methoxyphenyl)-4H-pyran-3-carboxylate	-5.653202
C-9	ethyl 2-amino-6-(1H-benzimidazol-2-yl)-4-(3-nitrophenyl)-4H-pyran-3-carboxylate	-4.544211
C-10	ethyl 2- amino-6-(1H benz imidazole-2-yl) -4-(2-nitrophenyl)-4H-pyran-3-carboxylate	-4.552231
C-11	ethyl 2-amino-6-(1H-benzimidazol-2-yl)-4-(3-bromophenyl)-4H-pyran-3-carboxylate	-5.7544225
C-12	ethyl 2-amino-6-(1H-benzimidazol-2-yl)-4-(4-bromophenyl)-4H-pyran-3-carboxylate	-5.6745322
C-13	ethyl 2-amino-6-(1H-benzimidazol-2-yl)-4-(2-bromophenyl)-4H-pyran-3-carboxylate	-5.556734

C-14	ethyl 2-amino-6-(1H-benzimidazol-2-yl)-4-(4-methylphenyl)-4H-pyran-3-carboxylate	-4.234542
C-15	ethyl 2-amino-6-(1H-benzimidazol-2-yl)-4-(3-methylphenyl)-4H-pyran-3-carboxylate	-4.185443
C-16	ethyl 2-amino-6-(1H-benzimidazol-2-yl)-4-(2-methylphenyl)-4H-pyran-3-carboxylate	-4.2045331
C-17	ethyl 2-amino-6-(1H-benzimidazol-2-yl)-4-(4-fluorophenyl)-4H-pyran-3-carboxylate	-5.6725522
C-18	ethyl 2-amino-6-(1H-benzimidazol-2-yl)-4-(3-fluorophenyl)-4H-pyran-3-carboxylate	-5.5654434
C-19	ethyl 2-amino-6-(1H-benzimidazol-2-yl)-4-(2-fluorophenyl)-4H-pyran-3-carboxylate	-5.6433111
C-20	ethyl 2-amino-6-(1H-benzimidazol-2-yl)-4-(4-ethoxy phenyl)-4H-pyran-3-carboxylate	-5.0845542
C-21	ethyl 2-amino-6-(1H-benzimidazol-2-yl)-4-(3-ethoxy phenyl)-4H-pyran-3-carboxylate	-5.2333511
C-22	ethyl 2-amino-6-(1H-benzimidazol-2-yl)-4-(2-ethoxy phenyl)-4H-pyran-3-carboxylate	-5.2114544
C-23	ethyl 2-amino-6-(1H-benzimidazol-2-yl)-4-(2-hydroxyphenyl)-4H-pyran-3-carboxylate	-5.2054435
C-24	ethyl 2-amino-6-(1H-benzimidazol-2-yl)-4-(3-hydroxyphenyl)-4H-pyran-3-carboxylate	-5.19335421
C-25	ethyl 2-amino-6-(1H-benzimidazol-2-yl)-4-(4-hydroxyphenyl)-4H-pyran-3-carboxylate	-5.1877556

Benzimidazole compounds are structurally similar to naturally occurring nucleotides therefore they interact easily with the biological system.[24] Anthelmintics with broad spectrum of activity are found effective against parasitic flat worms and round worms.[25]

The current work targeted mainly on the design and progress of benzimidazole pyran derivatives as anthelmintic drugs with preliminary *insilco* screening of various derivatives. The data showed that, all the compounds were found to be moderately active against *Trichuris trichuria* (whip worm) at 1 and 2 mg/ml compared to the standard reference - mebendazole. The yield of all the benzimidazole pyran derivatives were found to be in the range of 55-79%. The pyran with unsubstituted phenyl grouping took only less time for immobilization of whip worms as compared to substituted phenyl derivatives.

The compound-1and compound-3, showed good binding affinity with tubulin receptors, (glide score: -6.092395 and-6.032163), in the docking studies. These values were in good match with the invitro anthelmintic activity reports for the real-time synthesized compounds.

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