Original Article

Docking Studies and Evaluation of Antimicrobial Activity of Chroman Carboxamide Derivatives

Pinki Rawat[1,*], Saurabh Manaswita Verma[1], Piyush Kumar[2]

[1]Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology, Ranchi, Jharkhand, INDIA.
[2]Department of Pharmacy, Integral University, Lucknow, Uttar Pradesh, INDIA.

ABSTRACT

Aim: Based on our previous work, a series of chroman derivatives, which were first used as antiepileptic agents, are evaluated for their antimicrobial potency. **Materials and Methods:** The present study involves docking studies, synthesis and evaluation of *in vitro* antimicrobial activity against seven bacterial strains and two fungal strains.The activity was tested by agar well dilution and serial tube dilution methods. **Results:** The majority of the compounds displayed good to excellent antimicrobial activity. The MIC values of the compounds ranged between 25-100 μg/ml against gram-positive bacteria. However, in the case of gram-negative bacteria, the MIC of compounds ranged between 12.5-100 μg/ml. Compounds 4a and 4b displayed the highest antifungal activity (MIC 25 μg/ml) compared with the antifungal drug, fluconazole. **Conclusion:** The compounds showed high potency against gram-negative bacteria as compared to the gram-positive bacteria. These findings indicate that it might be a starting point for the development of novel and more potent antimicrobial agents in the future.

Key words: Antimicrobial agents, Chroman derivatives, Turbidity, Zone of Inhibition, MIC.

INTRODUCTION

Microbes induced diseases in humans and resistance to antibiotic treatment have become the most severe global health problems. Due to the overuse of common antibiotics, there is a development of multidrug-resistant bacteria.[1,2] Now a day's, the development of drug-resistance in serious fungal infections amongst cancer and AIDS patients showed major health problems.[3] The *Candida albicans* is mainly accountable for different nosocomial diseases and infection in medical devices like catheters, artificial joints, vascular bypass grafts, heart valves, central nervous system shunts and dental implants.[4] Resistance of drugs is rising at a dangerous rate and has surfaced out as one of the serious public health concerns. Therefore, there is an essential demand to develop alternative antimicrobial agents. Chroman derivatives constitute an imperative class of benzopyran heterocyclic compounds with several kinds of activities including antimicrobials,[5,6] anti-breast cancer,[7,8] anti-epileptic agents,[8] anti-HIV,[9] antioxidant,[10] antidiabetic[11] and neuroprotective agents.[12]

In our previous work, chroman derivatives were synthesized by condensation reaction between substituted Trolox hydrazide (4a-c) and different anhydrides to afford compounds (5a-t) in 61-91% yield and tested for antiepileptic activity.[13] In view of the above-mentioned findings and as a continuation of our effort toidentify some new activities of these derivatives, we herein report the docking studies and antimicrobial activities of these chroman derivatives. Figure 1 represents the pharmacophoric pattern of some antimicrobial agents and model compound having structural similarities.

Submission Date: 12-09-2020;
Revision Date: 25-11-2020;
Accepted Date: 03-02-2021

DOI: 10.5530/ijper.55.1s.60

Correspondence:
Dr. Pinki Rawat
Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology, Ranchi-835215, Jharkhand, INDIA.
Phone no: +91 9454855617
Email id: pnkrawat@yahoo.co.in

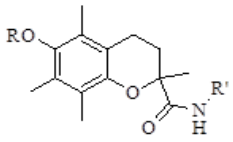
www.ijper.org

RESULTS AND DISCUSSION

Docking Studies

Various compounds were designed by substitution of chroman hydrazides by different anhydride moieties using Chemoffice 2004. Docking of the same was performed on DNA gyrase Glide v5.0 (Schrodinger-Maestro)[14] for all the designed compounds. Docking scores of designed compounds (4a-c and 5a-t) along with standard drugs were given in Table 1. Glide docking procedure was used for validation. The results showed the score of the co-crystallized ligand CBN -5.17 (Figure 2). The RMSD value of the co-crystallized ligand was 0.2 Å which is considered as suitable for docking of the designed molecules.

DNA gyrase is an essential bacterial protein that is required fortranscription and replication and is a common target for antibacterial agents since its blocking leads to bacterial death. Thus, for the design of antimicrobial compounds, docking studies were conducted on DNA gyrase enzyme (PDB: 1KZN). Compounds exhibited docking scores ranging between -2.66 to -5.83. The compound 5e having docking score of -5.83 was ranked most active among the designed compounds. Most of the compounds possess better docking scores (-4.31 to -5.83) than the standard drug, ciprofloxacin (-4.01) except for compounds 5b, 5f, 5k and 5l. The binding mode analysis of three best-docked compounds 5e (-5.83), 5i (-5.81) and 5a (-5.69) revealed the common interaction pattern. The O of >C=O formed H-bond with H of –NH in ASN46 (Figure 3 and Figure 4). It has been observed that the top docking scored compounds interacted within the active site of the enzyme in a similar way. Compounds containing pyridine-3,4-dicarboxylic acid anhydride 5e, 5m and 5r showed good docking scores-5.83, -5.44 and -5.19, respectively. R substitution by benzyloxy group seemed to increase its binding profile, whereas hydroxy substitution gave less active compounds.



Predicted ADME Studies

ADME properties of all compounds (4a-c and 5a-t) such as predicted apparent MDCK cell permeability (PMDCK), predicted aqueous solubility (log S), percent human oral absorption, brain/blood partition coefficient (QPlogBB), octanol/water partition coefficient (QPlogPo/w), SASA and rule of five were

Table 1: Docking scores of designed compounds (4a-c and 5a-t) and standard drug.

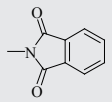
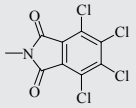
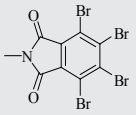
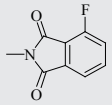
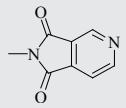
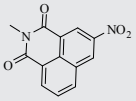
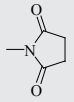
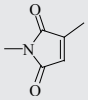
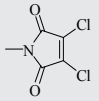
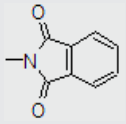
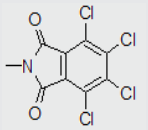
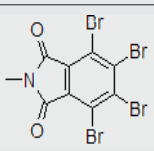
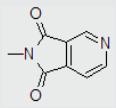
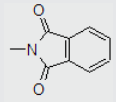
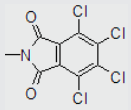
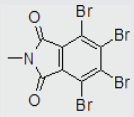
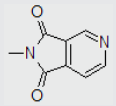
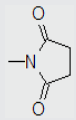
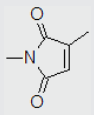
Compounds	R	R'	Docking Score
			1KZN
4a	H	$-NH_2$	-5.37
4b	CH_3	$-NH_2$	-4.31
4c	C_6H_5	$-NH_2$	-5.21
5a	H		-5.69
5b	H		-2.73
5c	H		-4.48
5d	H		-5.65
5e	H		-5.83
5f	H		-3.06
5g	H		-5.32
5h	H		-5.17
5i	H		-5.81
5j	CH_3		-5.47
5k	CH_3		-3.73
5l	CH_3		-2.66

Table 1: Cont'd			
5m	CH_3		-5.44
5n	CH_3		-4.90
5o	C_6H_5		-4.84
5p	C_6H_5		-5.50
5q	C_6H_5		-5.03
5r	C_6H_5		-5.19
5s	C_6H_5		-5.36
5t	C_6H_5		-4.75
Ciprofloxacin			-4.01

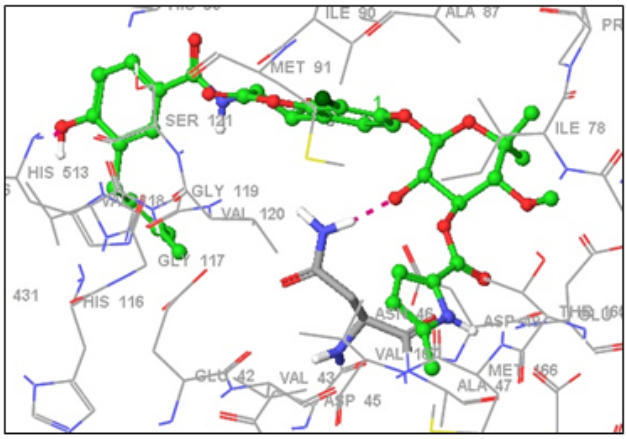


Figure 2: Crystallographic view of DNA gyrase after re-docking of co-crystallized ligand (green) CBN (RMSD: 0.2; GLIDE score: -5.17).

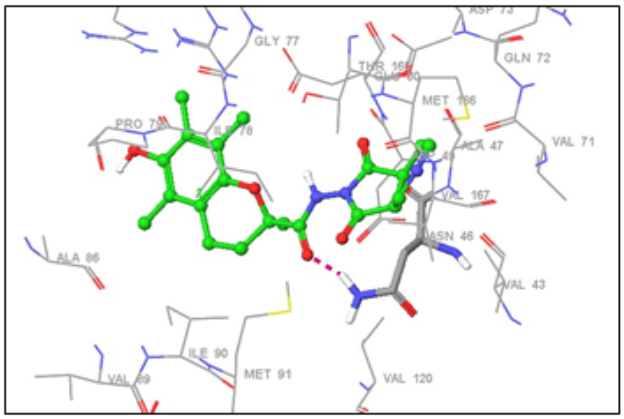


Figure 3: Docked conformations of the compounds 5e showing imperative amino acid residues of DNA gyrase. Ligands are presented as ball and stick and amino acids are presented as sticks. Hydrogen bonds are displayed by the red dotted line.

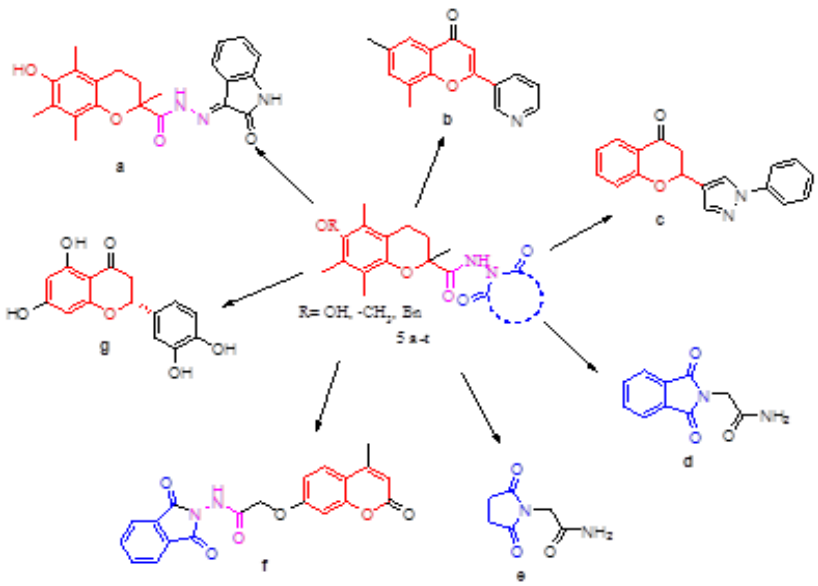


Figure 1: Pharmacophoric pattern of antimicrobial agents and model compound (5a-t).

Table 2: Toxicity analysis results based on Osiris Property Explorer.

Compounds	Toxicity Risks		Osiris Calculations				
	MUT	TUMO	MW	CLP	S	DL	D-S
4a	Green	Red	264	1.10	-3.30	-5.63	0.16
4b	Green	Red	278	1.37	-3.62	-5.56	0.16
4c	Green	Green	354	2.79	-4.94	-0.37	0.11
5a	Green	Green	394	2.18	-4.49	-5.19	0.21
5b	Red	Red	532	4.61	-7.44	0.70	0.03
5c	Red	Red	710	5.08	-7.83	0.29	0.03
5d	Green	Green	412	2.28	-4.81	0.95	0.34
5e	Green	Green	395	1.18	-3.70	-7.15	0.15
5f	Green	Red	489	2.46	-6.56	2.08	0.16
5g	Green	Red	346	0.71	-3.32	-2.9	0.08
5h	Green	Green	358	0.88	-3.22	-7.15	0.15
5i	Green	Green	413	1.28	-4.48	-0.91	0.33
5j	Red	Red	408	2.46	-4.81	1.35	0.08
5k	Green	Green	546	4.88	-7.75	-5.13	0.20
5l	Red	Red	724	5.36	-8.14	0.75	0.03
5m	Green	Green	409	1.46	-4.01	-1.78	0.23
5n	Red	Red	360	0.99	-3.64	0.34	0.03
5o	Red	Red	484	3.88	-6.13	-5.05	0.01
5p	Green	Red	622	6.30	-9.07	2.13	0.15
5q	Red	Red	800	6.78	-9.47	-4.64	0.01
5r	Green	Green	485	2.88	-5.34	-6.22	0.18
5s	Green	Red	436	2.41	-4.95	-3.26	0.06
5t	Green	Green	448	2.57	-4.86	-10.5	0.13

predicted by Qikprop v3.0 and reported in our previously published work.[15]

Toxicity analysis

Toxicity prediction studies were performed by Osiris Property Explorer and Toxtree v2.6.6.[16]

Osiris Property Explorer

Mutagenic (MUT) and tumorigenic (TUMO) properties were predicted using Osiris molecular property explorer (Table 2). Green color depicts low toxicity, yellow shows moderate toxicity, while red color represents a high tendency for toxicity. The compounds 5b, 5c, 5j, 5l, 5n, 5o and 5q were predicted to be mutagenic and compounds 4a, 4b, 5b, 5c, 5f, 5g, 5j, 5l, 5n, 5o, 5p, 5q and 5swere predicted to be carcinogenic. Drug Score (D-S) predicts the potential of a compound to be marketed as a drug. It provides results based on molecular weight, clogP, log S, drug-likeness and toxicity risks. Compounds 5d and 5i were considered a better drug score as compared to other compounds. Druglikeness (DL) values are based on topological descriptors, the fingerprint of molecular structure, or other properties like molecular weight, solubility and clogP (CLP). Compounds 5b, 5c, 5d, 5f, 5j, 5l, 5n and 5p showed positive DL values which indicate that the compounds include principally fragments which are usually present in commercial drugs.

Molecular weight (MW) and aqueous solubility (S) were also predicted. Low aqueous solubility of a compound influences its absorption and distribution characteristics. Compounds 5e, 5g, 5h and 5n displayed better solubility than other compounds. High clogP values are an estimation of low hydrophilicity and therefore cause poor absorption or permeation. The compounds 5g, 5h and 5n displayed excellent clogP values.

Toxtree

The toxicity of the compounds (4a-c and 5a-t) had also been predicted by using Toxtree v2.6.6. Results are compiled in Table 3. The obtained results indicate that some compounds (4a, 4b, 4c and 5g) have the potential to be carcinogenic. The predicted results were also compared with the QSAR model analysis. It was found that none of the compounds were mutagenic or carcinogenic.

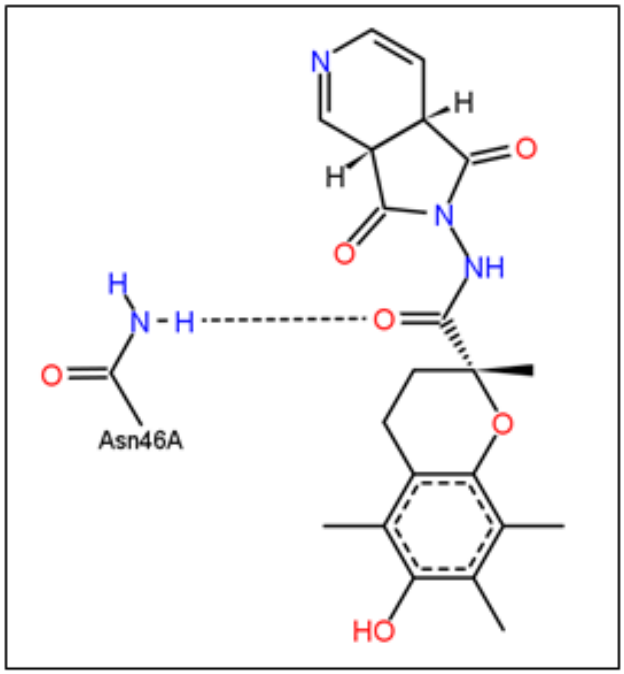


Figure 4: Binding mode interactions of compound 5e. Hydrogen bond interaction represented by dotted lines.

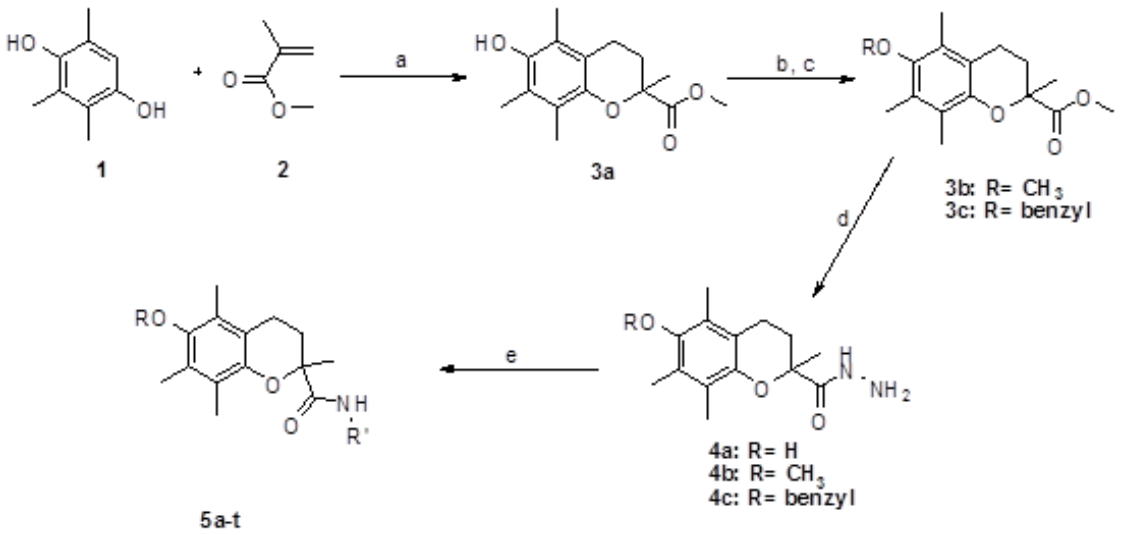
Chemistry

The synthetic routeof targeted compounds (4a-c and 5a-t) is depicted in Scheme 1 and were confirmed by synthetic and spectroscopic evidence as reported in our recent study.[12]

Antimicrobial Activity

The *in vitro* antimicrobial activity of all synthesized compounds (4a-c and 5a-t) was performed by two methods, i.e. serial tube dilution method and agar well diffusion method.[5] Antimicrobial activity was tested against microorganisms (*Escherichia coli* MTCC 118, *Bacillus subtilis* MTCC 3053, *Salmonella typhi* MTCC 3216, *Klebsiella pneumonia* MTCC 4031, *Staphylococcus aureus* MTCC 3160, *Pseudomonas aeruginosa* MTCC 4673, *Vibrio cholera* MTCC 3906, *Aspergillus niger* MTCC 281 and *Candida albicans* MTCC 227). Standard antifungal drug, fluconazole and antibacterial drug, ciprofloxacin were used to compare the antifungal and antibacterial activities shown by chroman carboxamide derivatives. Screening results are summarized in Table 4 and Table 5.

All compounds (4a-c and 5a-t) revealed antibacterial potency against the growth of bacterial strains having diameters of zone inhibition (ZI) ranging between 5-27 mm. The most prominent antibacterial activity was shown by test compound 5p (27 mm) against E. colibacterial strains, at the concentration of 100 *µg*/ml.It could be due to the presence of benzyloxy and teatrachlorophthalic anhydride. It was found that compounds were more active against *E. coli*. The compound 4a having hydroxyl and amine groups was found to be least active among the series. Four compounds (4a, 4b, 4c and 5i) showed better antifungal activity than the standard drug against *C. albicans* fungal strain with ZI value ranging between 10-19 mm. None of the tested compounds showed anyactivity against fungal strain, *A. niger*. The compounds had greater antimicrobial potency against *E. coli* and *C. albicans* than the other microorganisms. The highest antifungal potency was obtained in the compound 5i (19 mm) against *C. albicans* at 100 µg/ml. Compounds containing



Scheme 1: Synthetic pathway for compounds 4a-c and 5a-t. (a) (HCHO)n, $[CH_3(CH_2)_3]2NH$, CH_3COOH, reflux, 20 h; (b) dimethyl sulfate, K_2CO_3, CH_3COCH_3, 50°C, 24 h; (3b); (c) benzyl bromide, DMF, K_2CO_3, RT, 12 h (3c); (d) $NH_2NH_2.H_2O$, C_2H_5OH, reflux, 10 h; (e) Different anhydrides, CH_3COOH, reflux, 2-4 h.

Table 3: Toxicity analysis results by using Toxtree v.2.6.6.

Compounds	Negatif for genotoxic carcinogenity	Negatif for non-genotoxic carcinogenity	Potential *S.Typhiurium* TA 100 mutagen based on QSAR	Potential carcinogen based on QSAR
4a	No	Yes	No	No
4b	No	Yes	No	No
4c	No	Yes	No	No
5a	No	No	No	No
5b	No	No	No	No
5c	No	No	No	No
5d	No	No	No	No
5e	No	No	No	No
5f	No	No	No	No
5g	No	Yes	No	No
5h	No	No	No	No
5i	No	No	No	No
5j	No	No	No	No
5k	No	No	No	No
5l	No	No	No	No
5m	No	No	No	No
5n	No	No	No	No
5o	No	No	No	No
5p	No	No	No	No
5q	No	No	No	No
5r	No	No	No	No
5s	No	No	No	No
5t	No	No	No	No

electron-withdrawing group's ensued significant antimicrobial activities against various micro-organisms except *S. aureus*. Hydroxy substitution attributed to more active compounds as compared to methoxy and benzyl substituted compounds. All compounds showed activity against at least one bacteria.

The compounds which showed ZI against any microorganism was further tested for minimum inhibitory concentration (MIC) at concentrations of 100, 50, 25, 12.5, 6.25 and 3.125 µg/ml via serial tube dilution method. The lowest concentration at which the compound showed no turbidity was considered as its MIC. The results have been presented in Table 5. The MIC values of compounds ranged between 25-100 µg/ml against gram-positive bacteria. The compound 4a possessed good MIC (50 µg/ml) against *K. pneumonia*. Compounds 5a, 5j, 5p and 5r showed moderate MIC of 100 µg/ml against *B. subtilis* whereas compound 4c, 5h and 5j possessed MIC of 100 µg/ml against *S. aureus*. However, in the case of gram-negative bacteria, the MIC of compounds ranged between 12.5-100 µg/ml. Compound 4b, 5a and 5h showed MIC (25 µg/ml) against *E. coli*. Compound 5a showed the highest MIC (12.5 µg/ml) against *Pseudomonas aeruginosa*. While comparing activity against gram-positive bacteria, all compounds possessed high activity against gram-negative bacteria.

The MICs of compounds (4a-c and 5i) were also evaluated against *V. cholera* and *C. albicans*. Compounds4a and 4b displayed the highest antifungal activity (MIC 25 µg/ml) whereas compounds 4c, showed good antifungal activity at MIC of 50 µg/ml when compared with the antifungal drug, fluconazole. It has been shown that compounds exhibited less to potent MIC as compared to standard drugs, ciprofloxacin and fluconazole.

The presence of electron-withdrawing groups (Cl, Br and F) on anhydride moiety of compounds increases theantibacterial activity. The obtained results revealed

Table 4: Results of antimicrobial screening of compounds (4a-c and 5a-t).

Compd (µg/ml)	Zone of Inhibition (mm)																	
	Bacterial Strain														Fungal Strain			
	E. coli		*S. typhii*		*B. subtilis*		K. pneumonia		*P. aurogenosa*		*S. aureus*		*V. cholera*		*C. albicans*		*A. niger*	
	50	100	50	100	50	100	50	100	50	100	50	100	50	100	50	100	50	100
4a	-	-	-	-	-	-	-	5	-	5	-	-	-	-	15	15	-	-
4b	13	10	-	-	-	-	-	-	-	-	-	-	-	-	11	11	-	-
4c	8	10	-	-	-	-	-	-	9	8	-	5	-	-	10	10	-	-
5a	14	15	-	-	-	12	-	-	11	11	-	-	12	12	-	-	-	-
5b	14	15	-	-	-	-	-	-	12	15	-	-	-	-	-	-	-	-
5c	21	24	-	-	-	-	13	13	-	-	-	-	-	-	-	-	-	-
5d	20	23	-	-	-	-	13	13	-	-	-	-	-	-	-	-	-	-
5e	22	23	-	-	15	17	-	-	12	12	-	-	11	11	-	-	-	-
5f	22	23	-	-	-	14	-	-	-	-	-	-	-	-	-	-	-	-
5g	15	15	16	16	-	-	-	-	13	14	-	-	14	14	-	-	-	-
5h	10	15	12	17	-	-	-	-	12	13	13	13	-	-	-	-	-	-
5i	21	22	14	14	16	21	14	14	14	15	13	14	-	-	16	19	-	-
5j	21	21	13	13	11	14	13	14	-	-	-	-	-	-	-	-	-	-
5k	25	25	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5l	23	23	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5m	19	26	-	-	-	-	-	-	12	15	-	-	11	12	-	-	-	-
5n	21	22	-	-	-	-	-	-	-	-	-	-	13	13	-	-	-	-
5o	-	15	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5p	25	27	14	14	15	16	14	14	-	-	-	-	-	-	-	-	-	-
5q	23	23	-	-	15	17	-	17	-	-	-	-	-	-	-	-	-	-
5r	21	23	15	15	-	-	14	14	14	16	-	-	-	-	-	-	-	-
5s	-	-	-	-	-	-	-	-	-	-	11	11	12	13	-	-	-	-
5t	22	22	18	18	14	16	-	-	18	20	-	-	-	-	-	-	-	-
Ciprofloxacin	25	27	25	28	15	15	12	12	35	35	15	15	35	35				
Fluconazole															2	2	-	-

Dash indicates no inhibition

that 6-hydroxy substituent in chroman was more active than the corresponding 6-methoxy and 6-benzyl substituents.

MATERIALS AND METHODS

Molecular Docking

The X-ray crystallographic structure of the DNA gyrase (PDB: 1KZN) was obtained from Protein Data Bank (www.rcsb.org) for antimicrobial activity and prepared for molecular modeling.[17] Ligands were prepared using Maestro (v8.5) and minimized. A comprehensive set of conformations were developed by using Liquid Simulations-2005 (OPLS 2005) force field in solvent water conditions. LigPreps were generated for 3D coordinates of the conformers, their stereochemical, ionization and tautomeric variations. The docking method was validated by extracting ligand CBN (Clorobiocin) from the binding site and re-docking it to the respective active site. All ligands were docked with the obtained LigPrep conformers into the active site DNA gyrase using the extra precision settings of the docking panel with default settings.

Toxicity Studies

Toxicity prediction studies were performed by available online software Osiris Property Explorer and Toxtree v2.6.6. Osiris property explorer is a chemical structural database that used to estimate various drug-related properties like tumorigenic, mutagenic, reproductive

Table 5: MIC values of compounds 4a-c and 5a-t.

Compounds (µg/ml)	MIC (µg/ml)							
	E. coli	*S. typhii*	*B. subtilis*	*K. pneumonia*	*P. aurogenosa*	*S. aureus*	*V. cholera*	*C. albicans*
4a	-	-	-	50	50	-	-	25
4b	25	-	-	-	-	-	-	25
4c	50	-	-	-	50	100	-	50
5a	25	-	100	-	12.5	-	25	-
5b	50	-	-	-	-	-	-	-
5c	-	-	-	100	-	-	-	-
5d	-	-	-	100	-	-	-	-
5e	-	-	-	-	100	-	50	-
5f	-	-	-	-	-	-	-	-
5g	-	100	-	-	-	-	100	-
5h	25	100	-	-	100	100	-	-
5i	-	100	-	100	-	-	-	100
5j	-	100	100	-	-	100	-	-
5k	50	-	-	-	-	-	-	-
5l	100	-	-	-	-	-	-	-
5m	50	-	-	-	100	-	25	-
5n	100	-	-	-	-	-	-	-
5o	-	-	-	-	-	-	-	-
5p	-	-	100	-	-	-	-	-
5q	-	-	-	-	-	-	-	-
5r	-	-	100	100	-	-	-	-
5s	-	-	-	-	-	-	-	-
5t	50	-	-	-	100	-	-	-
Ciprofloxacin	6.25	6.25	12.5	12.5	6.25	12.5	6.25	
Fluconazole								50

effects, irritant, cLog*P*, Log*S*, MW, drug-likeness and overall drug score. Prediction results were colour coded in which the green colour indicated drug-conform behaviour whereas red colour showed a high tendency for toxicity.[18] Toxtree v2.6.6 predicts the toxicity level of compounds by applying various decision tree approaches. Three Toxtree modules, such as Cramer rules with extension, Bengni/Bossa rule base for carcinogenicity and mutagenicity and structure notify for the *in vivo* micronucleus assay in rodents, were used to set up hazard estimations. Various toxicological restraints like carcinogenicity (genotoxic and non-genotoxic), hERG channel inhibition, hepatotoxicity, skin sensitization and reproductive toxicity were presented.

Antimicrobial Activity

In vitro antimicrobial activity of all synthesized compounds (4a-c and 5a-t) was performed by previously reported agar well diffusion and serial tube dilution methods.[5]

CONCLUSION

The objective of the present study is to evaluate the antimicrobial activity of our previously reported chroman carboxamide derivatives (4a-c and 5a-t). All compounds showed antimicrobial activity with the diameters of ZI ranging between 5-27 mm. The MIC value was also recorded, which was ranged between 25-100µg/ml. It had been found that compounds displayed high potency against gram-negative bacteria as compared to gram-positive bacteria. The compounds 4a and 4b showed the highest antifungal activity (MIC 25 µg/ml) compared with the standard drug, fluconazole. The presence of electronegative groups at anhydride ring promotes its antibacterial activity. Further investigation of the activity profile of these derivatives against other serious microbial infections needs to be exploited.

ACKNOWLEDGEMENT

Dr Pinki Rawat is grateful to UGC-RGNF (Rajiv Gandhi National Fellowship) for providing National

Doctoral Fellowship and contingency grant as financial support. The authors also thank the Advanced Centre for Treatment Research and Education in Cancer (ACTREC), Navi Mumbai, Maharashtra, India, for evaluation of the *in vitro* anticancer activity.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

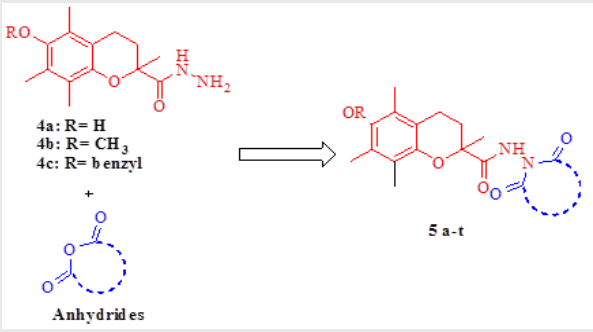
ABBREVIATIONS

ADME: Absorption, Distribution, Metabolism, Excretion; **GI:** Gastro Intestinal; **P-gp:** P-glycoprotein; **BBB:** Blood Brain Barrier; **CYP1A2:** Cytochrome P450 family 1 subfamily A member 2; **CYP2D6:** Cytochrome P450 family 2 subfamily D member 6; **PMDCK:** Predicted apparent MDCK cell permeability; **Log S:** Predicted aqueous solubility; **QPlogBB:** Percent human oral absorption, brain/blood partition coefficient; **QPlogPo/w:** Octanol/water partition coefficient, **SASA:** Solvent accessible surface area; **MUT:** Mutagenic; **TUMO:** Tumorigenic; **D-S:** Drug Score; **DL:** Druglikeness**; ZI:** Zone of Inhibition; **MIC**: Minimum Inhibitory Concentration.

REFERENCES

1. Woodford N, Ellington MJ. The emergence of antibiotic resistance by mutation. Clin Microbiol Infect. 2007;13(1):5-18.
2. Llor C, Bjerrum L. Antimicrobial resistance: Risk associated with antibiotic overuse and initiatives to reduce the problem. Ther Adv Drug Saf. 2014;5(6):229-41.
3. Vandeputte P, Ferrari S, Coste AT. Antifungal resistance and new strategies to control fungal infections. Int J Microbiol. 2011;2012:1-26.
4. Burmølle M, Thomsen TR, Fazli M, Dige I, Christensen L, Homøe P, *et al*. Biofilms in chronic infections - a matter of opportunity - monospecies biofilms in multispecies infections. FEMS Immunol Med Microbiol. 2010;59(3):324-36.
5. Rawat P, Verma SM. Synthesis and pharmacological evaluation of 6-hydroxy-2,5,7,8-tetramethylN'-(2-oxoindolin-3-ylidene)chroman-2-carbohydrazide derivatives as antimicrobial agents. J Chem Pharm Res. 2016;8(3):149-54.
6. Venugopala KN, Jayashree BS. Microwave-induced synthesis of schiff bases of aminothiazolyl bromocoumarins as antibacterials. Indian J Pharm Sci. 2008;70(1):88-91.
7. Kumar P, Rahman MA, Wal P, Singh K. Design synthesis and evaluation of anticancer potential of some new benzopyran schiff base derivatives. Indian J Heterocy Chem. 2020;30(2):297-305.
8. Rawat P, Verma SM. Design and synthesis of chroman derivatives with dual anti-breast cancer and anti-epileptic activities. Drug Des Dev Ther. 2016;10:2779-88.
9. Kraus GA, Mengwasser J, Maury W, Oh CS. Synthesis of chroman aldehydes that inhibit HIV. Bioorg Med Chem Lett. 2011;21(5):1399-401.
10. Foroumadi A, Samzadeh-Kermani A, Emami S, Dehghan G, Sorkhi M, Arabsorkhi F, *et al*. Synthesis and antioxidant properties of substituted 3-benzylidene-7-alkoxychroman-4-ones. Bioorg Med Chem Lett. 2007;17(24):6764-9.
11. Reddy KA, Lohray BB, Bhushan V, Reddy AS, Rao MNV, Reddy PP, *et al*. Novel antidiabetic and hypolipidemic agents. 5. hydroxyl versus benzyloxy containing chroman derivatives. J Med Chem. 1999;42(17):3265-78.
12. Hussain AT, Imaduddin MD, Koti BC, Ronad PM. Evaluation of neuroprotective potential of some newly synthesized benzopyran-2-one derivatives in swiss albino mice. Indian J Pharm Educ Res. 2018;5(4s2):326-32.
13. Rawat P, Verma SM, Kumar P. Novel chroman derivatives as promising heterocyclic compounds: Their synthesis and anti-epileptic activity. Indian J Pharm Educ Res. 2019;53(4):655-65.
14. Friesner RA, Banks JL, Murphy RB, Halgren TA, Klicic JJ, Mainz DT, *et al*. Glide: A new approach for rapid, accurate docking and scoring. 1. method and assessment of docking accuracy. J Med Chem. 2004;47(7):1739-49.
15. Rawat P, Verma SM. Docking studies of substituted chroman derivatives at estrogen receptor. Asian J Pharm Clin Res. 2015;8(6):88-92.
16. Pedrosa LF, Macedo WPD, Furtado ACR, Guedes GP, Pinheiro LCS, Resende JLC, *et al*. Synthesis, crystal structures and *in silico* toxicity prediction of thienopyridine phosphoramidates. Synth Comm. 2013;43(24):3373-86.
17. Tan Q, Blizzard TA, Morgan JD, Birzin ET, Chan W, Yang YT, *et al*. Estrogen receptor ligands. part 10: chromanes: Old scaffolds for new SERAMs. Bioorg Med Chem Lett. 2005;15(6):1675-81.
18. Jawarkar RD, Mahajan DT, Masand VH, Hadda TB, Kurhade GH. COMFA Analysis and toxicity risk assessment of coumarin analogues as MaoA inhibitors: Attempting better insight in drug design. Der Pharmacia Lettre. 2010;2(6):350-7.

PICTORIAL ABSTRACT



SUMMARY

The chromans are important chemical synthon, associated with a broad range of biological activities. The computational studies like docking, ADME and toxicity were performed and based on their results, compounds were designed and synthesized. The antimicrobial study of chroman carboxamide derivatives (4a-c and 5a-t) was carried out by agar well dilution and serial tube dilution methods against seven bacterial strains and two fungal strains. Most of the compounds displayed significant activity. The compounds 4a and 4b showed the highest antifungal activity (MIC 25 μg/ml) compared with the standard drug, fluconazole.

About Authors

Dr. Pinki Rawat, has completed her Ph.D from Birla Institute of Technology, Ranchi, India. Her research interest are in the area of synthesis of heterocyclic compounds, molecular docking, QSAR, antiepileptic, anticancer, antimicrobial and antioxidant.

Dr. Saurabh Manaswita Verma, working as a Professor in Birla Institute of Technology, Ranchi, India. Her research interest are in the area of docking, Synthetic Chemisty, Natural Product Chemistry and Computer Aided Drug Design.

Mr. Piyush Kumar, is Persuing his Ph.D from Integral University, Lucknow, India. He has done MS Pharm from NIPER, Raebareli, India. His research interest in the area of organic chemistry, medicinal chemistry and nanotechnology.

Cite this article: Rawat P, Verma SM, Kumar P. Docking Studies and Evaluation of Antimicrobial Activity of Chroman Carboxamide Derivatives. Indian J of Pharmaceutical Education and Research. 2021;55(1s):s275-s284.