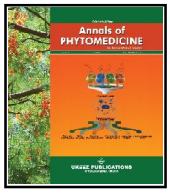
Annals of Phytomedicine 11(2): 385-390, 2022

DOI: http://dx.doi.org/10.54085/ap.2022.11.2.46

Annals of Phytomedicine: An International Journal

http://www.ukaazpublications.com/publications/index.php

Print ISSN : 2278-9839 Online ISSN : 2393-9885



Original Article : Open Access

Design and synthesis of chroman isatin hybrid derivatives as antitubercular agents

R. K. Kushwaha, Kuldeep Singh◆, S. P. Kushwaha, D. Chandra*, A. Kumar and P. Kumar**

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Integral University, Kursi Road, Lucknow-226026, Uttar Pradesh, India

** G.C.R.G. College of Pharmacy, BKT, Lucknow-226201, Uttar Pradesh, India*

*** Department of Chemistry, Indian Institute of Technology, Jagti-181221, Jammu & Kashmir, India*

Article Info

Article history

Received 15 October 2022

Revised 1 December 2022

Accepted 2 December 2022

Published Online 30 December-2022

Keywords

Chroman derivatives

Carbohydrazide

Isatin

Diels-Alder reaction

Abstract

Chromans are an important medicinal group. The chroman nucleolus (3, 4-dihydro-2H-chromene) consists of two rings, among these two rings, one ring is cyclic, aromatic, and another is a saturated heterocyclic ring. In this study, chroman derivatives were integrated with the aid of various substituted isatins. By using thin layer chromatography, melting point, solubility and spectroscopic analysis, all the synthesized compounds were identified. The *in vitro* antitubercular activity of synthesized substances was evaluated against the *Mycobacterium tuberculosis* MTB H37Rv strain using the microplate alamar blue assay (MABA) method. Two substances, with MIC values of 64 µg/ml and 8 µg/ml, were found to have good activity against *M. tuberculosis*. These substances might be thought of as a good place to start when looking for a new lead in the fight against tuberculosis.

1. Introduction

Chroman is a combination of bicyclic and saturated heterocyclic compounds. The chroman nucleolus (3, 4-dihydro-2H-chromene) contains two rings; one ring is cyclic, aromatic and another ring is saturated heterocyclic, with the molecular formula $C_9H_{10}O$. Chromans are a significant class of chemicals linked to a variety of biological processes, including the prevention of breast cancer (Kanbe *et al*., 2006), oral contraceptives (John, 2007), antifertility (Waterbeemd and Mannhold, 2008), anti-inflammatory (Lal, 2010), antitubercular (Joshi *et al*., 2012; Desai *et al*., 2021), anticonvulsant, neuroprotective (Napoleon and Sharma, 2017; Gezici *et al*., 2018), antimicrobial (Angelova *et al*., 2017; Kumari *et al*., 2020), and antiestrogens (Khare and Deshmukh, 2018). Chroman nucleolus is useful for compounding as a water-soluble analogue of γ-tocoferol. Trimethyl hydroquinone reacts with excess methyl methacrylate, dibutyl amine, acetic acid, and para-formaldehyde to produce the substance 2-methyl ester, also referred to as trolox. The basic mechanism involved in the synthesis of chroman in the scheme is the hetero Diel's-Alder reaction, in which the dienophile contains a hetero atom, most often oxygen or nitrogen, which reacts with a substituted alkene to form a substituted cyclohexane derivative. This further creates a powerful tool for the integration of six-member heterocyclic rings (Alghamdi *et al*., 2020). Several methods and mechanisms are available for the integration of chroman derivatives (Bardasov and Alekseeva, 2015; Hu *et al*., 2017; Ismail and Aziem, 2001), and the biological functions are influenced by their substitutions (Dogamanti *et al*., 2021). It is crucial to the creation of novel drugs with exceptional biological and chemical properties (Kumar and Parumasivam, 2013). The bacteria known as *M. tuberculosis* is what causes tuberculosis (TB). Lung tissue is mainly affected by TB bacteria. According to a World Health Organization report 2021, 10 million people have the airborne disease TB, of which 1.5 million have died.

The SAR of chroman reveals that the introduction of hydroxyl (-OH) and halogens (Cl, Br, I, F) increases the potency to treat bacterial infections and diseases (Khan *et al*., 2017). Halogens are electronegative in nature (Khosneviszadeh and Edraki, 2021), Due to this electronegativity, halogens are lethal to microorganisms (Kandar and Haveliwala, 2010) and increase hydrophobicity by making the molecule size bigger and more polarized (Lopez and Blanco, 2007). Halogens act on peptide linkage and alter its antimicrobial potential and property. The destruction of a specific protein function causes the death of microorganisms. Most of the enzymes are proteinous in nature, and protein molecules are composed of amino acids through peptide (-CONH-) linkage. Halogens act by halogenating peptide linkages in protein molecules. The substitution of the halogen atom on the nitrogen atom of the peptide linkage causes a change in hydrogen bonding forces, which is responsible for the proper orientation of the protein molecule. Hydroxyl groups (-OH) are polar, hydrophilic in nature, and found in alcohols. The methyl group ($-CH_3$) is electron donating in nature, making the molecule more reactive. Based on the literature study, we can justify the antibacterial property of compounds (Motamen and Quinn, 2020). These groups will improve the antitubercular and antibacterial properties of the chroman skeleton (Mashana *et al*., 1998).

2. Material and Methods

All of the chemicals used to synthesize the chroman derivatives were analytical standards that were bought from Spectrochem and Avra Synthesis Pvt. Ltd. A capillary tube melting point instrument

Corresponding author: Dr. Kuldeep Singh

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Integral University, Kursi Road, Lucknow-226026, Uttar Pradesh, India

E-mail: kulintegral@gmail.com

Tel.: +91-9453604762

was used to record each derivative's melting point (Macro Synthetic Works Pvt Ltd., MSW 403D). At predetermined intervals, each reaction was observed and examined using thin layer chromatography (Silica gel 60 GF_{254}). The mobile phase was made up of a 40:60 mixture of ethyl acetate and n-hexane. On the Bruker AV-III HD 400 MHz, the ^1H NMR spectra were captured in DMSO (dimethyl sulfoxide) and $CDCl_3$ (deuterated chloroform). At the Central Drug Research Institute in Lucknow, India, the microplate alamar blue assay (MABA) was used in an *in vitro* antitubercular study to determine the minimum inhibitory concentration (MIC) using tetramethyl silane (TMS) as a reference.

2.1 Predicted toxicity study

Ion channel modulators, kinase inhibitors, GPCR ligands, and enzymes are examples of drug targets for which various molecular properties can be calculated in order to forecast bioactivity scores. Different molecular properties, such as the partition coefficient (Log P), topological polar surface area (TPSA), hydrogen bond donors and acceptors, rotatable bonds, number of atoms, molecular weight, and violations of Lipinski's rule of five, were calculated to determine how much the synthetic compounds resembled drugs (Lipinski, 1997).

2.2 Synthesis

Research involves the design and synthesis of chroman isatin hybrid derivatives as antitubercular agents. The synthetic route of synthesis of chroman derivatives is shown in Figure 1. The general structure of the final compounds is depicted in Figure 2.

2.2.1 Synthesis of 2, 5, 7, 8-tetra-methyl-6-hydroxy chromen-2-carboxilic acid methyl ester (III)

The 500 ml round bottom flask (RBF) used in the reflux assembly contained 22.5 ml of acetic acid, 79.5 ml of methyl methacrylate, 4.5 g of para-formaldehyde, 2.4 g of dibutyl amine, and 4.5 g of dibutyl amine. The contents of the flask were stirred at room temperature. After that, 22.8 g of trimethyl hydroquinone was added, and the mixture was refluxed for 20 h while being stirred continuously. To bring the contents of the flask to room temperature, they were set aside. Methanol was used to recrystallize the dark-colored solid after filtering it with a filter pump. The obtained solid could be used in other applications.

2.2.2 Synthesis of 3, 4-dihydro-6-hydroxy-2, 5, 7, 8-tetramethyl-2H-chromene-2-carbohydrazid (IV)

To make carbohydrazide, 10 ml of hydrazine hydrate (80% in ethanol) was refluxed with 1 mole of solid compound (III) for 10 h at 80°C. Under reduced pressure, ethanol was evaporated; the solid, white residue was then removed with water and dried in a hot air oven. Figure 1 depicts the structure of the intermediate compounds (III) and (IV).

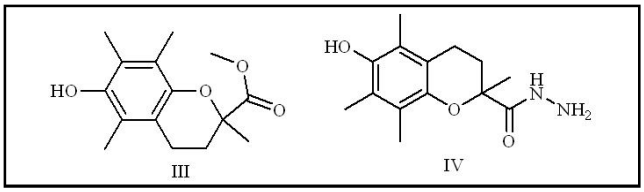


Figure 1: 2, 5, 7, 8-tetra-methyl-6-hydroxy chromen-2-carboxilic acid methyl ester (III), 3,4-dihydro-6-hydroxy-2, 5, 7, 8-tetramethyl-2H-chromene-2-carbohydrazid (IV).

2.2.3 Common method for synthesis of chroman isatin hybrid (RKK-1 to RKK-7)

The final compounds were synthesized by condensing 1 mole of substituted isatin in 10 ml of acetic acid and 1 mole of carbohydrazide (IV) in 500 ml of a RBF, then refluxing the entire mixture for 4 to 12 h. After that, about 20 ml of purified water was mixed into the round bottom flask. The final compound was filtered and dried in a hot air oven. All compounds were recrystallized with ethanol. The general structure of the final compound is shown in Figure 2.

2.3 *In vitro* antitubercular study

Utilizing the MABA assay, the *in vitro* antitubercular activity was carried out (Nalla *et al.*, 2018; Patil *et al.*, 2015). We used a formula to produce stock solutions. Plates were made with test and standard compound concentrations of 0.03, 0.06, 0.125, 0.25, 0.5, 1, 2, 4, 8, 16, 32, and 64 µg/ml and dried in a spotless cabinet with laminar flow. Isoniazid was used as the standard. Each strain was incubated for 48 h at 36°C. Using an automatic micropipette, 5 µl of each bacterial suspension from each strain was added to the surface of the culture medium as an inoculum (usually 15-20 drops per plate). As soon as the drops were absorbed, the plates were placed in a sterile laminar flow cabinet. 48 h were spent keeping the plates at 36°C. Each tested strain had grown on the control plate without an antibiotic following incubation, it was confirmed. The pink color was interpreted as bacterial growth, while the blue color indicated no bacterial growth. A thin film of growth or one or two colonies growing should not be taken seriously (Pini *et al.*, 2018; Pires *et al.*, 2020; Sethumathi *et al.*, 2021).

3. Results

3.1 Physical and analytical study

The TLC profile (ethyl acetate/n-hexane, 40:60) gives details about the reaction's development and the compound's purity. Table 1 displays physical and analytical information.

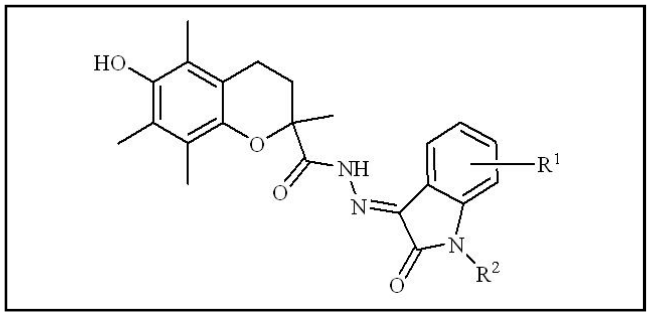


Figure 2: General structure of final compounds.

3.2 Predicted toxicity results

To assess the pharmacokinetic parameters of chroman derivatives, such as solubility, overall drug likeness, and toxicity, a toxicity study was carried out using the online tool Osiris software. The screening results are colored-coded and valued. Green colour indicates low toxicity risk and safety, yellow indicates moderate toxicity, and red indicates high toxicity risk. Based on Clog P, solubility, molecular weight, TPSA, druglikeness, (Hydrogen bond acceptor) HBA, HBD (Hydrogen bond donor), Nb stereo centres, Nb rotatable bonds, and drug score, software produces results.

Table 1: Physicaland analytical data

S.No.	Compound code	R^1	R^2	Time (h)	Yield (%)	M.P. (°C)	Molecular formula	Molecular weight	R_f
1.	RKK-1	H	H	4	74	240-242	$C_{22}H_{23}O_4N_3$	393.44	0.7
2.	RKK-2	H	CH_3	6	72	237-239	$C_{23}H_{25}O_4N_3$	407.46	0.7
3.	RKK-3	5-Cl	H	6	87	255-257	$C_{22}H_{22}O_4N_3Cl$	427.88	0.6
4.	RKK-4	5-Br	H	6	56	260-262	$C_{22}H_{22}O_4N_3Br$	472.33	0.4
5.	RKK-5	6-Cl	H	5	56	283-285	$C_{22}H_{22}O_4N_3Cl$	427.88	0.5
6.	RKK-6	5-F	H	4	51	290-292	$C_{22}H_{22}O_4N_3F$	411.43	0.4
7.	RKK-7	5-Cl	CH_3	5	58	257-260	$C_{23}H_{24}O_4N_3Cl$	441.91	0.5

Table 2: Predicted toxicity risk by Osiris software

Compound Code	$_c$log P	Solubility	TPSA	Drug likeness	HBA	HBD	Nb sterio centers	Nb rotatable bonds	Drug score
RKK-1	2.94	-5.29	100.02	4.26	7	3	1	2	0.50
RKK-2	3.30	-5.27	91.23	4.96	7	2	1	2	0.48
RKK-3	3.55	-6.03	100.02	4.27	7	3	1	2	0.46
RKK-4	3.67	-6.13	100.02	2.12	7	3	1	2	0.40
RKK-5	3.55	-6.03	100.02	4.56	7	3	1	2	0.46
RKK-6	3.04	-5.61	100.02	2.57	7	3	1	2	0.47
RKK-7	3.91	-6.00	91.23	5.24	7	2	1	2	0.44

3.3 Biological study results

The MABA method was used to confirm the synthetic compounds' *in vitro* antitubercular activity. At the conclusion of the experiment, the blue wells showed no evidence of bacterial growth while the pink wells displayed bacterial growth. The MICs (minimum inhibitory concentration), which inhibit bacterial growth and change colour from blue to pink, are expressed in µg/ml. It was discovered that the substances RKK-1 and RKK-2 had good activity against *M.tuberculosis* bacteria. There were two different MIC values observed, each at 64 and 8 µg/ml. The outcomes demonstrated the anti-tubercular activity of the chroman isatin hybrid derivatives. The results of the assay are shown in table 3.

Table 3: MICs (µg/ml) of chroman derivatives RKK-1-RKK-7

S.No.	Sample code	MIC (µg/ml) *M. tuberculosis* H37Rv ATCC 27294
1.	RKK-1	64
2.	RKK-2	8
3.	RKK-3	>64
4.	RKK-4	>64
5.	RKK-5	>64
6.	RKK-6	>64
7.	RKK-7	>64
8.	Isoniazid	0.03

3.4 Physical and analytical data

2, 5, 7, 8-tetramethyl-N'-(Isatin)-3, 4-dihydro-6-hydroxy-2H-chromene-2-carbohydrazide (RKK-1): Yield- 74%; Melting point-238ºC; R_f value-0.7, ^{1}H NMR (DMSO, 300 MHz, ppm): δ11.17 (s, 1-H), δ7.5 (s, 1-H), δ7.48(d, 1H, *J*=7.3), δ7.31(t,1H), δ7.01(t, 1H), δ6.84 (d, 1H), δ2.54-2.60 (m, 1H), δ2.44-2.47 (m, 1H), δ2.30-2.26 (m, 1H), δ2.15 (s, 3H), δ2.05(s, 3H), δ1.96 (s, 3H), δ1.85-1.80 (m, 1H), δ1.50 (s, 3H).

2, 5, 7, 8-tetramethyl-N'-(1-methyl-Isatin)-3, 4-dihydro-6-hydroxy-2H-chromene-2-carbohydrazide (RKK-2): Yield- 72 % ; Melting point 235ºC; R_f value-0.7, ^{1}H NMR (DMSO, 300 MHz, ppm): δ13.48(s,1H), δ7.55 (s, 1H), δ7.53 (s,1H), δ7.47-7.41 (m, 1H), δ7.15–7.09 (m, 2H), δ3.17 (s, 3H), δ2.59-2.53 (m, 1H), δ2.32–2.27 (m, 1H), δ2.25 (s, 3H), δ2.09 (s, 3H), δ2.00 (s, 3H), δ1.87 (m, 1H), δ1.50 (s, 3H).

2, 5, 7, 8-tetramethyl-N'-(5-chloro-Isatin) -3, 4-dihydro-6-hydroxy-2H-chromene-2-carbohydrazide (RKK-3)*:* Yield- 87 % ; Melting point 255ºC; R_f value -0.6,^{1}H NMR (DMSO, 300 MHz, ppm): δ13.51 (s, 1H), δ11.32 (s,1H), δ7.56 (s, 1H), δ7.49-7.48 (d, 1H), δ7.41-7.37 (dd, 1H), δ6.93–6.90 (d, 1H), δ2.61–2.54 (m, 1H), δ2.35-2.27 (m, 1H), δ2.22 (s, 3H), δ2.08 (s, 3H), δ2.00 (s, 3H), δ1.92–1.85 (m, 1H), δ1.51 (s, 3H).

2, 5, 7, 8-tetramethyl-N'-(5-bromo-Isatin)-3, 4-dihydro-6-hydroxy-2H-chromene-2-carbohydrazide (RKK-4): Yield-56 % ; Melting point 260ºC; R_f value -0.4,^{1}H NMR (DMSO, 300 MHz, ppm): δ13.50 (s, 1H), δ11.32 (s, 1H), δ7.60-7.51 (m, 1H), δ7.60-7.51 (m, 1H), δ7.60-7.51 (m, 1H), δ6.88-6.86 (d, 1H), δ2.65–2.57 (m, 1H), δ2.33–2.29 (m, 1H), δ2.22 (s, 3H), δ2.08 (s, 3H), δ2.00 (s, 3H), δ1.92–1.85 (m, 1H), δ1.51 (s, 3H).

2, 5, 7, 8-tetramethyl-N'-(6-chloro-Isatin) -3, 4-dihydro-6-hydroxy-2H-chromene-2-carbohydrazide (RKK-5): Yield- 56 % ; Melting point 290ºC; R_f value -0.5, ^{1}H NMR (DMSO, 300 MHz, ppm): δ13.47 (s, 1H), δ11.34 (s, 1H), δ7.56 (s, 1H), δ7.53-7.50 (d, 1H), δ7.12-7.09 (dd, 1H), δ6.94-6.93 (d, 1H), δ2.66–2.57 (m, 1H), δ2.35–2.26 (m, 1H), δ2.22 (s, 3H), δ2.08 (s, 3H), δ2.00 (s, 3H), δ1.92–1.79 (m, 1H), δ1.51 (s, 3H).

2, 5, 7, 8-tetramethyl-N'-(5-fluoro-Isatin)-3, 4-dihydro-6-hydroxy-2H-chromene-2-carbohydrazide (RKK-6): Yield- 51% ; Melting point-289ºC; R_f value -0.4,^{1}H NMR (DMSO, 300 MHz, ppm): δ13.55(s,1H), δ11.22 (s, 1H), δ7.56 (s, 1H), δ7.35-7.31 (dd, 1H), δ7.24–7.17 (m, 1H), δ6.93-6.88 (m, 1H), δ2.61–2.49 (m, 1H), δ2.33–2.27 (m, 1H), δ2.22 (s, 3H), δ2.08 (s, 3H), δ2.00 (s, 3H), δ1.92–1.85 (m, 1H), δ1.51 (s, 3H).

2, 5, 7, 8-tetramethyl-N'-(5-chloro-1-methyl-Isatin)-3, 4-dihydro-6-hydroxy-2H-chromene-2-carbohydrazide (RKK-7): Yield- 58 % ; Melting point 256ºC ; R_f value -0.5, ^{1}H NMR (DMSO, 300 MHz, ppm): δ13.45 (s, 1H), δ7.56 (m, 2H), δ7.52 (s, 1H), δ7.52 (s, 3H), δ7.17-7.14 (dd, 1H), δ2.60 (m, 1H), δ2.33–2.29 (m, 1H), δ2.25 (s, 3H), δ2.09 (s, 3H), δ2.01 (s, 3H), δ1.91–1.86 (m, 1H), δ1.51 (s, 3H).

4. Discussion

Trimethyl hydroquinone reacts with excess methyl methacrylate, dibutyl amine, acetic acid, and para-formaldehyde to produce the substance 2-methyl ester, also referred to as trolox. The hetero Diels-Alder reaction, in which the dienophile contains a hetero atom, most frequently oxygen or nitrogen, reacts with a substituted alkene to form a substituted cyclohexane derivative, is the basic mechanism involved in the synthesis of chroman in the scheme. This further develops a potent tool for the integration of heterocyclic rings with six members. The substitution of chroman derivatives affects the biological functions, and a variety of techniques and mechanisms are available for their integration.

4.1 Reaction scheme

The synthesis of compounds consists of three steps of reaction. In the first step of the reaction, trimethyl hydroquinone and methyl-methacrylate react in the presence of para-formaldehyde, acetic acid, and dibutyl amine. The reaction proceeds *via* the hetero Diels-Alder reaction mechanism, and this reaction is well known for the synthesis of heterocyclic compounds. In this reaction, trimethyl-hydroquinone works as a diene, and methylmethacrylate acts as a dienophile (diene lover) to form the heterocyclic compound trolox methyl ester (III). The second step reaction involves Wolff-Kishner reduction. The trolox methyl ester is hydrolyzed by hydrazine hydrate to generate the tetrahedral intermediate, which can break down to form the chroman hydrazide product shown in Figure 4.The final step of scheme 1 involves the hydrolysis reaction of hydrazide with the various isatin derivatives to give the final chroman derivatives RKK-1 to RKK-7.

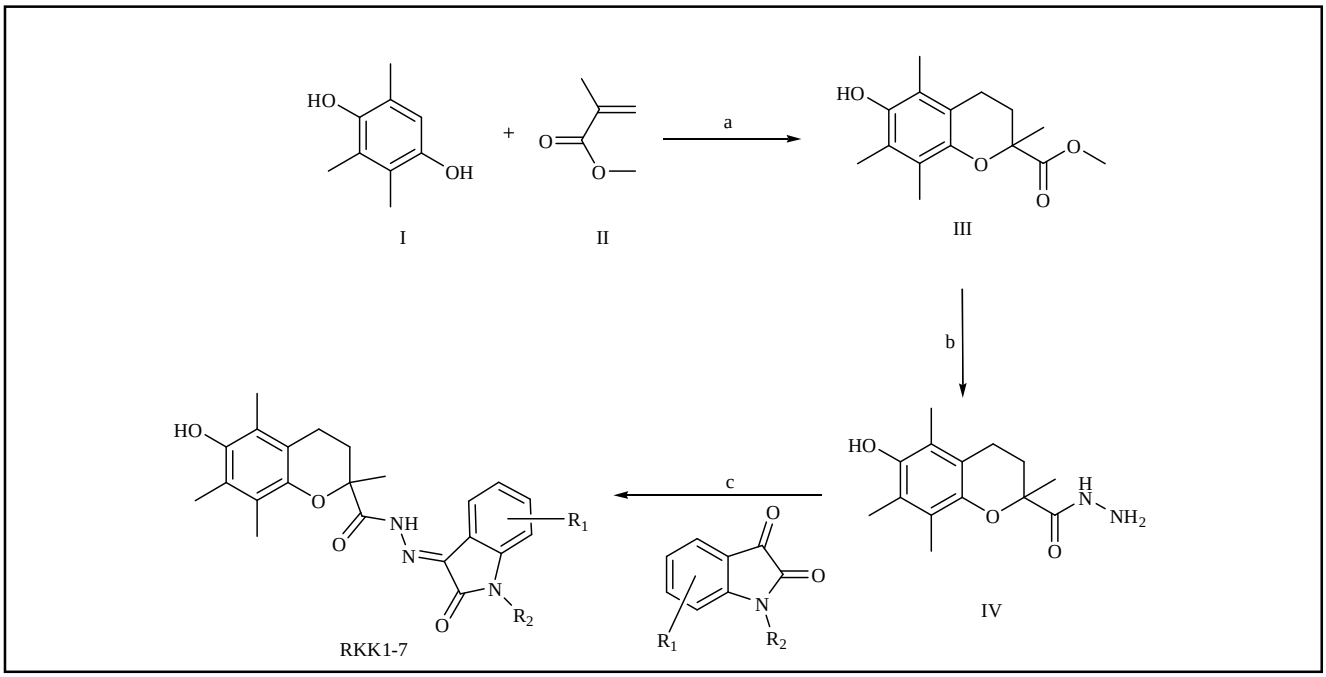


Figure3: Synthetic pathway for test compoundsRKK 1- RKK 7. (a) (HCHO)n, $[CH_3(CH_2)_3]_2NH$, CH_3COOH, reflux, 20h; (b); Hydrazine hydrate ($NH_2NH_2.H_2O$), C_2H_5OH, reflux for 10h (c) C_2H_5OH, CH_3COOH, reflux for 4-12 h.

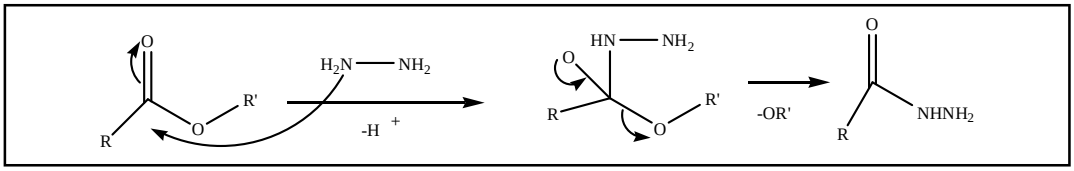


Figure 4: Formation of hydrazide.

The ^{1}H NMR spectra of each compound were used to identify it, and the chemical shifts (δ), multiplicity, and coupling constant (J) of the synthesised compounds were used to confirm the signals of protons. The hydrazide (NH) proton peak appeared as a singlet at δ 13.45-13.55 ppm, the phenolic (OH) proton peak singlet around at δ 7.52-7.56 ppm,the methyl (CH_3) proton as a singlet around (position 2a)-1.50-1.51ppm, (position-5,7,8) -2.00-2.25ppm in the 1H spectra of the synthesised compounds.

5. Conclusion

With good yields (51%-87%), the design and synthesis of the chroman isatin hybrid derivatives (RKK-1 to RKK-7) were completed. All of the synthesized compounds were tested for activity against *M. tuberculosis*, and the MABA assay revealed that compounds RKK-1 and RKK-2 had MICs of 8 µg/ml and 64 µg/ml, respectively. In order to find a new lead in the fight against tuberculosis, these compounds can be thought of as a good place to start.

Acknowledgements

The authors would like to express their gratitude towards Integral University and G.C.R.G. College of Pharmacy for providing a research facility. We are also thankful to the SAIF unit, C.D.R.I., Lucknow for their assistance in providing spectral data and anti-tubercular activity. The manuscript number provided by the Research and Development Committee isIU/R&D/2022-MCN0001400.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

References

Angelova V. T. and Valcheva V. (2017). Synthesis, antimicrobial activity and docking study of 2-aroyl-1-benzopyrano (4-3, c) pyrazole-4 (1H)-one derivatives and related hydrazide-hydrazones. Bioorg. Med. Chem., **27**(13):2996-3002.

Angelova V. T., Valcheva V., Vassilev N. G., Buyukliev R. (2017). Antimicrobial activity of novel hydrazide-hydrazone derivatives with 2H chromene and coumarin scaffolds. Bioorg. Med. Chem. Lett., **27**(2):223-227.

Alghamdi S., Rehman S. U., Shesha N. T., Faidah H., Khurram M. (2020). Promising lead compounds in the development of potential clinical drug candidate for drug-resistant tuberculosis. Molecules, **25**(23):5685.

Bardasov I. N. and Alekseeva A. U. (2015). One-pot synthesis of 4-alkyl-2-amino-4H-chromene derivatives, Het. Commu., **21**(3):0077.

Barlocco D. (2018). New chromane based derivatives as inhibitors of *Mycobacterium tuberculosis* salicylate synthase (MbtI): Preliminary biological evaluation and molecular modeling studies. Molecules, **23**(2):1506.

Bhatt, P. R., Pandya, K. B., Patel, U. D., Modi, C. M., Patel, H. B. and Javia, B. B. (2019). Antidiabetic, antioxidant and anti-inflammatory activity of medicinal plants collected from nearby area of Junagadh, Gujarat. Ann. Phytomed., **8**(2):75-84.

Caviedes L. and Delgado J. (2002). Tetrazolium microplate assay as a rapid and inexpensive colorimetric method for determination of antibiotic susceptibility of *Mycobacterium tuberculosis*. J. Clin. Microbiol., **40**(5):1873-1874.

Cordeiro R. and Kachroo M. (2020). Synthesis and biological evaluation of anti-tubercular activity of Schiff bases of 2-Amino thiazoles. Bioorg. Med. Chem. Lett., **30** (20):176-185.

Desai, S. P., Momin, Y. H., Taralekar, S. T., Dange, Y. D., Jagtap, S. R. and Khade, H. P. (2021). Evaluation of potential *in vitro* anticancer and antimicrobial activities of synthesized 5-mercapto-4-substituted 1, 2, 4 triazole derivatives. Ann. Phytomed., **10**(2):273-279.

DogamantiA.,Chiranjeevi P., Aamate V., Vagolu S., Sriram D., Balasubramanian S. and Sarasija M. (2021). Indole-fused spirochromenes as potential anti-tubercular agents: Design, synthesis and *in vitro* evaluation. Molecular Diversity, 25**:**2137-2148.

Gupta R. C., Nityanand S., Asthana O. P. and Lal J. (1996). Pharmacokinetics of centchroman in nursing women and passage into breast milk. Clin. Drug Inves., **11**(2):305-309.

Gezici, S. (2018). Original article Promising anticancer activity of lavender (Lavandulaangustifolia Mill.) essential oil through induction of both apoptosis and necrosis. Ann. Phytomed., **7**(2):38-45.

Hu Y. Q., Xu Z., Zhang S., Wu X., Ding J. W., Lv Z. S. and Feng L. S. (2017). Recent development of coumarin containing derivatives and their antitubercular activity. Eur. J. Med. Chem., **136**:122-130.

Ismail K. A. and Aziem T. A. E. (2001). Synthesis and biological evaluation of some novel 4H-benzopyran-4-one derivatives as nonsteroidal Antiestrogens. Eur. J. Med. Chem., **36**:243-253.

John A. H. (2007). Convenient preparation of 2, 7, 8-trimethyl-6-hydroxychroman-2-carboxylic acid (γ-Trolox). Synth. Commu., **38**:8-14.

Joshi N. K., Kundaria D. S. and Parmar J. M. (2012). Studies on biologically active heterocyclic analogous. I. J. C. Tech. Res., **12**(4):1503-1508.

Kanbe Y., Kim M. H. and Nishimoto M. (2006). Discovery of thiochromanand chroman derivatives as pure antiestrogens and their structure activity relationship. Bioorg. Med. Chem., **27**(14):4803-4819.

Khare P. S. and R.T. Deshmukh R. T. (2018). Design, synthesis and molecular docking studies of novel triazole chromene conjugates as antitubercular, antioxidant and antifungal agents. Chemistry Select, **2**(3):13113-13122.

Khan Y. S., Osman H. and Khan M. S. (2017). Design, characterization in-vitro antibacterial, antitubercular evaluation and structure activity relationships of new hydrazinylthiazoilyl coumarin derivatives. Med. Chem. Res., **26**(6):1139-1148.

Kumar N. and Parumasivam H. S. (2013). Synthesis of isonicotinyl hydrazone derivatives as antimycobacterial and anticancer. Med. Chem. Res., **23**(1):269-279.

Khoshneviszadeh M. and Edraki N. (2012). QSAR study of 4-aryl-4H-chromanes as new series of apoptosis inducing using different chemometric tools. Chem. Biol. Drug Des., **79**(4):442-458.

Kamdar N. R.; Haveliwala D. D.; Prashant Mistry T. and Saurabh Patel K. (2010). Synthesis and evaluation of *in vitro* antitubercular activity of some novel 4H-chromeno (2, 3-d) pyrimidine via 2-amino-4-phenyl-4H-chromene-3-carbonitriles. Med. Chem. Res., **20**(7):854-864.

Kumari, P. S.; Ranjitha, R. and Vidhya, N. (2020). Revitalizing property of banana peel extracts by antioxidant activity and antibacterial activity against acne causing Staphylococcus epidermidis. Ann. Phytomed., **9**(2):215-222.

Lal J. (2010). Clinical pharmacokinetics and interaction of centchroman-a mini review, Contraception, **81**:275-280.

Lopez G. V. and Blanco F. (2007). Second generation of α-tocopherol analogs-nitric oxide donors: Synthesis, physicochemical and biological characterization. Bioorg. Med. Chem., **15**(18):6262-6272.

Motamen S. and Quinn R. J. (2020). Analysis of approaches to anti-tubercular compounds. ACS Omega, **5**(44):28529-28540.

Mshana R. N.; Tadesse G.; Abate G. and Miorner H. (1998). Use of 3-(4, 5-dimethyl thiazole-2-yl)-2, 5-diphenyl tetrazolium bromide for rapid detection of rifampin resistant *Mycobacterium tuberculosis*. J. Clin. Microbiol., **36**:121-1214.

Nalla V.; Shaikh A.; Bapat S.; Vyas R.; Karthikeyan M.; Yogeeswari P. and Sriram D., Muthukrishnan M. (2018). Identification of potent chromone embedded (1, 2, 3)-triazole as novel anti-tubercular agents. R. Soc. Open Sci., **5**:171750.

Napoleon A. A. and Sharma V. (2017). Molecular docking and *in vitro* anti-inflammatory evaluation of novel isochromen-1-one analogues from etodolac. Res. J. Pharm. and Tech., **10**:3011-3014.

Patil R. B. and Sawant S. D. (2015). Synthesis, docking studies and evaluation of antimicrobial and *in vitro* antiproliferative activity of 5H-chromeno 4, 3-D pyrimidine-2-amine derivatives. I. J. Pharm. and Pharmacet. Sci., 7(2):0975-1491.

Pini E.; Poli G.; Tuccinardi T.; ChiarelliL.; Mori M.; Gelain A.; CostantinoL.; Villa S.; MeneghettiF.; Pires C.T.; Scodro R.B.L.; Cortez D.A. G. and Brenzan M. A. (2020). Structure activity relationship of natural and synthetic coumarin derivatives against *Mycobacterium tuberculosis*. Future Med. Chem., **12**:1533-1546.

Pancholia S. and Dhamelia T. M. (2016). Benzo [d] thiazole-2-yl (piperazine-1-yl) methanone as new antimicrobial chemotypes: Design synthesis and evaluation 3D QSAR studies, Eur. J. Med. Chem., **116**: 187-99.

Ray S.; Kamboj V.; Grover P.; Kar A. and Anand N. (1975). A process for the synthesis of 2, 2-disubstituted-3, 4-diphenylchromans. Indian Patent Spec. No. 129187.

Rawat P. and Verma S. M. (2016). Design and synthesis of chroman derivatives with dual anti-breast cancer and antiepileptic activities.Drug Des. Devel. Ther., **10**(10):2779-2788.

Sethumathi, P. P.; Manjuparkavi, K.; Lalitha, V.; Sivakumar, T.; Menaka, M.; Jayanthi, A. and Kumar, B. A. (2021). Evaluation of *in vitro* antioxidant and antimicrobial activity of polyherbal formulation of Thirikadugu-chooranam and Parangipattaichooranam. Ann. Phytomed., **10**(2):69-174.

World Health Organization Global Tuberculosis report 2021.

Waterbeemd H. van de and R. Mannhold R. (2008). In Lipophilicity in Drug Action and Toxicology. Wiley Blackwell, Vol. 4, pp:401-418.

Xu Z. Q. and Pupek K. (2006). Pyranocoumarin, a novel anti-TB Pharmacophore: Synthesis and biological evaluation against *Mycobacterium tuberculosis*. Bioorg. Med. Chem., **14**(13):4610-4626.

Yeung K. S. and Farkas M. E. (2005). A base-catalyzed, direct synthesis of 3, 5-disubstituted 1, 2, 4-triazoles from nitriles and hydrazides, Tetrahedron Lett., **46**(19):3429-3432.

Citation **R. K. Kushwaha, Kuldeep Singh, S. P. Kushwaha, D. Chandra, A. Kumar and P. Kumar (2022). Design and synthesis of chroman isatin hybrid derivatives as antitubercular agents. Ann. Phytomed., 11(2):385-390. http://dx.doi.org/10.54085/ap.2022.11.2.46.**