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DESIGN, SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY STUDIES ON COUMARIN CARBOHYDRAZIDE CONTAINING QUINOLINE DERIVATIVES

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ABSTRACT

Ten new 2-oxo-N[1]-[(E)-quinolin-3-ylmethylidene]-2H-chromene-3-carbo hydrazones (NS 1-10) were synthesized by the reaction of substituted the 2-oxo-2H-chromene-3-carbohydrazide in N, N-dimethyl form amide various 2-Chloro,2-hydr oxy,2-thione-3-formyl quinolines and tetrazolo[1,5-a]quinoline-4-carbaldehyde in presence of catalytic amount of glacial acetic acid. Newly synthesized compounds were characterized by spectroscopic and physical methods. All the synthesized com pounds were screened for antimicrobial by standard methods. Results of the activities reveal that, some compounds exhibited moderate to good anti-microbial activities.

KEYWORDS

Coumarin carbohydrazide, Quinoline derivatives and Biological activity studies.

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INTRODUCTION

Coumarin (Figure No.1) name was given by "HANTZSCH AND ZURCHER" to the class of compound which contains benzene ring fused to pyran ring in 1871. Coumarin is simple oxygen containing heterocyclic (Benzo-2-pyrone) ring. Coumarin analogues are present in several important groups of natural products[1].

Coumarin and its derivatives are biologically active compounds and are widely distributed in nature. The coumarin heterocyclic ring is common feature of various bioactive compounds like calanolides, lipid

lowering agent. Coumarin and its derivatives exhibit several biological and pharmacological properties such as anticoagulants, anti-fungal, anti-bacterial, insecticidal, anthelminths, hypnotics, phytoalexins, HIV protease inhibitors, CNS depressants, anti-tumors agent, anti-tubercular, anti-inflammatory, anti-oxidant, anti-viral, analgesic, anti-leshmanial, and ACE inhibitor[2-4].

Coumarins also act as intermediates for the synthesis of various biologically active molecules such as coumarones, chromenes, fluorocoumarins and bromocoumarins.

Many methods for synthesis of coumarins have been reported including Perkin reaction, Knoevenegel reaction, Reformestsky reaction, Witting reaction and Pechmann condensations. Substituted 2-oxo-2H-chromene-3-carbohydrazide (Figure No.2) are versatile molecules as they have widely used for the synthesis of various hetrocycles such as thiadiazole, imidazolinones, thiosemicarbazones, aryl hydrazones, thiazolidinones, 1,3,4-oxadizoles and triazolo thiazolidinones which are obtained when these 2-oxo-2H-chromene-3-carbohydrazides react with aldehydes possess multiple biological activities like anti-tubercular, anti-cancer, anti-viral, anti-amoebic, herbicidal, anti-oxidant, anti-inflammatory and anti-microbial activities. Diverse biological activities of Substituted 2-oxo-2H-chromene-3-carbohydrazide are probably by virtue of toxophoric –N-C=O grouping[5-6].

As part of a program of medicinal chemistry under-taken a few years ago, we are pursuing investigations on the synthesis and reactivity of heterocycles containing nitrogen. Recently we were confronted with the preparation of quinoline derivatives.

Quinoline (Figure No.3) and their derivatives occur in numerous natural products. Many quinolines display interesting physiological activities and have found important applications as pharmaceuticals (e.g.norfloxacin and ciprofloxacin). Moreover fused quinolines are known to bind DNA with high affinity, inhibit DNA topoisomerase and display cytotoxic and antitumor activities anticonvulsant, antidepressant, antimalarial and antihistaminic activities[6-8].

The vilsmerier-Haack reagent has been proved to be a versatile reagent capable of executing a large variety of synthetic transformations. It finds application in formylation cyclohaloaddition, cyclisation and ring annulations. Recently, its potentiality was explored in the synthesis of 4-(N,N-dimethylaminomethylene)-2-alkyl/aryl-2-oxazolin-5-ones from N-acylderivatives of alpha-amino acid esters and alpha-aminoacetanilides. To develop novel quinoline based fused hetrocyclic systems quinoline nucleus with different substituents at 2- and 3-positions was required which afforded a versatile synthon for further heteroannulations (Figure No.4)[9-11].

Hence, in the present work we have attempted to combine the 2-oxo-2H-chromene-3-carbohydrazide with various substituted 2-Chloro, 2-hydroxy, 2-thione 3-formyl quinolines, and tetrazolo[1,5-a]quinoline-4-carbaldehyde to get some new novel 2-oxo-N^1-[(E**)**-quinolin-3- ylmethylidene]-2H-chromene-3-carbohydrazides (NS1-10) and screened for their possible anti-bacterial activity[11-13].

Experimental

Synthesis of 2-chloroquinoline-3-carboladehyde (3a-d)

The procedure is as per literature survey Pramod *et al*, Similarly, 2-chloro-3-formyl-6-methylquinoline M.P.123^{0}C, yield 80%; 2-chloro-3-formyl-8-methyl quinoline M.P.137 ^{0}c, yield 77% and 2-chloro-3-formyl-7-methyl quinoline M.P.146^{0}c, yield 86% were prepared from respective acetanilides following the procedure as prescribed by Meth-Cohn et al.

Synthesis of 2-Hydroxy-3-Formylquinoline-3-carbaldehyde (4a-d)

In dry round- bottomed flask containing a mixture of 2-chloro-3-formylquinoline-3-carbaldehyde (0.01mol, 1.9gm) and aqueous hydrochloric acid (35ml, 4M) was heated under reflux for 2hrs and then allowed to cool to room temperature. Then the

reaction mixture was poured on to crushed ice, when 2-Hydroxy-3-formyl quinoline separated as a yellow solid. It was filtered washed with water and dried. It was recrystalised from aqueous acetic acid into yellow silky needles M.P.295-297 ^{0}C, yield 70 %.

Similarly, 2-Hydroxy-3-formyl-6-methyl quinoline M.P.274-276 ^{0}C, yield 66%; 2-Hydroxy-3-formyl-8-methyl quinoline M.P.283-285 ^{0}C, yield 70% and 2-Hydroxy-3-formyl-7-methyl quinoline M.P.326-328 ^{0}C, yield 78 % are prepared by adopting the procedure given above.

Synthesis of 2-thiones- 3-formylquinoline (5a)

In dry-round bottom flask, to a solution of 2-chloro-3-formyl quinoline (0.001mol 0.191gm) and dry DMF (5ml) were added and sodium sulphide (0.015mol,0.114gm fused flakes) was added and stirred for 1-2hrs at room temperature after completion of the reaction mixture (monitored by TLC) was poured in to ice cold water (ca.15ml) and made acidic with acetic acid. The product was filtered off washed well with water, dried and was pure enough for further use. M.P. 287-288^{0}C, yield 84%.

Synthesis of Tetrazolo[1,5-a]quinoline-4-carbaldehyde (6a)

In dry round-bottomed flask, to a solution of 2-chloroquinoline-3-carbaldehyde (0.001mol 0.191gm) taken in absolute ethanol (5ml) p-toulene sulphonic acid (0.001mol 0.190gm) and sodiumazide (0.0015mol, 0.0975gm) were added and reaction mixture was heated under reflux for 65hrs at 125-135^{0}C. After completion of the reaction (monitored by TLC) the reaction mixture was poured into ice cold water (100ml) and the resulting precipitate was filtered, dried and recrystalized from dimethylformamide as whitish light yellow needle shaped crystals M.P. 240-242^0 C, yield76%.

Synthesis of ethyl-2-oxo-2H-chromene-3-carboxylate

In dry round-bottomed flask, containing solution of Salicyaldehyde (0.01 mol, 1.22 gm) and diethylmalonate (1.6 g, 0.01 mol) were dissolved in ethanol (15 ml) to give clear solution. Piperidine (2 ml) was added and the mixture was refluxed for 10hr's. The content was concentrated to small volume. The product ethyl-2-oxo-2H-chromene-3-carboxylate was poured onto crushed ice, filtered out and recrystallized from ethanol to give white shiny crystals, TLC pure (chloroform : methanol, 9ml:1ml,v/v). M.p.120-122^{0}C; yield: 90%.

Synthesis of 2-oxo-2H-chromene-3-carbohydrazide

In dry round-bottomed flask, containing solution of ethyl-2-oxo-2H-chromene-3-carboxylate (0.01 mol, 2.18 gm) and hydrazine hydrate 99% (0.01mol,0.5 gm) were dissolved in ethanol (50 ml) to give clear solution and refluxed for 13hr's. The content was concentrated to half of the volume and allowed to cool. The solid mass of 2-oxo-2H-chromene-3-carbohydrazide which separated out on cooling was retained by filtering and washed with small amount of ice cooled ethanol (90%). M.p.136-138^{0}C; yield: 87%.

Synthesis of N'-[(E)-(2-chloroquinolin-3-yl)methylidene]-2-oxo-2H-chromene-3 carbohydrazide(NS-1)

In dry round-bottomed flask, mixture of 2-chloro-3 formylquinoline (0.01mol,1.91gm) 2-oxo-2H-chromene-3-carbohydrazide (0.01mol, 2.04g) N,N-Dimethyl formamide (20ml) and catalytic amount of glacial acetic acid(1-2drops) were added and the reaction mixture was refluxed for 16- 18hr's. After completion of reaction (monitored by TLC), the reaction mixture was poured onto ice cold water (50ml) and resulting precipitate was filtered, washed with Petroleum ether, dried and recrystalised from aqueous alcohol to give N'-[(E)-(2-chloroquinolin-3-yl)methylidene]-2-oxo-2H-chromene-3-carbohydrazide.

Similarly, *N*'-[(*E*)-(2-chloro-6-methylquinolin-3-yl)methylidene]-2-oxo-2*H*-chromene-3 carbohydrazide (NS - 2),N'- [(E) - (2-chloro-8-methylquinolin-3-yl) methylidene]- 2- oxo - 2H-chromene - 3-carbohydrazide(NS-3) and N'- [(E)-(2- chloro- 7-methyl quinolin-3-yl) methylidene]-2-oxo-2H-chromene-3-carbohydrazide (NS-4) were

prepared by adopting the procedure given above and physical data of thus synthesized compounds is given in Table No.1.

Synthesis of N'-[(E)-(2-hydroxyquinolin-3-yl) methylidene]-2-oxo-2H-chromene-3-carbohydrazide (NS-5)

In dry round-bottomed flask, mixture of 2-hydroxy-3-formyl quinoline (0.01mol, 1.73gm) 2-oxo-2H-chromene-3-carbohydrazide (0.01mol, 2.04gm) N,N-Dimethyl formamide (20ml) and catalytic amount of glacial acetic acid (1-2drops) were added and the reaction mixture was refluxed for 17-20hr's. After completion of reaction (monitored by TLC), the reaction mixture was poured onto ice cold water (50ml) and resulting precipitate was filtered, washed with Petroleum ether, dried and recrystalised from aqueous alcohol to give N'-[(E)-(2-hydroxyquinolin-3-yl)methylidene]-2-oxo-2H-chromene-3-carbohydrazide. Similarly, *N*'-[(*E*)-(2-hydroxy-6-methylquinolin-3-yl) methylidene]-2-oxo-2*H*-chromene-3-carbohydrazide (NS-6), N'-[(E)-(2-hydroxy-8-methylquinolin-3-yl)methylidene]-2-oxo-2H-chromene-3-carbohydrazide (NS-7), and N'-[(E)-(2-hydroxy-7 methylquinolin-3-yl) methylidene]-2-oxo-2H-chromene-3 carbohydrazide(NS-8) were prepared adopting the procedure given above and physical data of thus synthesized compounds is given in Table No.1.

Synthesis of (2-oxo-N'-[(E)-(2-sulfanylquinolin-3-yl) methylidene]-2H-chromene-3-carbohydrazide (NS-9)

In dry round-bottomed flask, mixture of 2-thione-3-formyl quinoline (0.01mol,1.89gm) 2-oxo-2H-chromene-3-carbohydrazide (0.01mol,2.04gm) N,N-Dimethyl formamide (20ml) and catalytic amount of glacial acetic acid (1-2drops) were added and the reaction mixture was refluxed for 16hr's. After completion of reaction (monitored by TLC), the reaction mixture was poured onto ice cold water (50ml) and resulting precipitate was filtered, washed with Petroleum ether, dried and recrystalised from aqueous alcohol to give (2-oxo-N'-[(E)-(2-sulfanylquinolin-3-yl)methylidene]-2H-chromene-3-carbohydrazide and physical data of thus synthesized compound is given in Table No.1.

Synthesis of 2 - oxo - N' - [(E) - tetrazolo [1, 5 - a] quinoline -4-ylmethylidene] - 2H - chromenes - 3 - carbohydrazide (NS10)

In dry round-bottomed flask, mixture of tetrazolo[1,5-a]quinoline-4-carbaldehyde (0.01mol, 1.98gm) 2-oxo-2H-chromene-3-carbohydrazide (0.01mol, 2.04gm) N,N-Dimethyl formamide (20ml) and catalytic amount of glacial acetic acid(1-2drops) were added and the reaction mixture was refluxed for 21hr's. After completion of reaction (monitored by TLC), the reaction mixture was poured onto ice cold water (50ml) and resulting precipitate was filtered, washed with Petroleum ether, dried and recrystalised from aqueous alcohol to give 2-oxo-N'-[(E)-tetrazolo[1,5-a]quinolin-4-ylmethylidene]-2H-chromene-3-carbohydrazide and physical data of thus synthesized compound is given in Table No.1.

Biological activity

Method

In vitro antibacterial activity of all synthesized compounds was evaluated against four strains of microorganisms namely *Staphylococcus aureus* (MTCC 96, Gm+ve), *Staphylococcus pyrogenus* (MTCC 442, Gm+ve), *Pseudomonas aeruginosa* (MTCC 1688, Gm–ve) *and Escherichia coli* (MTCC 443, Gm–ve) by MIC (Broth dilution method). Mueller Hinton broth was used as nutrient medium to grow and dilute the drug suspension for the test bacteria. Here DMSO was used as diluents / vehicle to get desired concentration of drugs to test upon standard bacterial strains. This method depends upon the minimum concentration of drugs which inhibits the growth of microbial culture in a serial dilution solution of antibacterial in a fluid medium that is favorable to its rapid growth in the absence of the antibacterial agent. In this method minimal inhibitory concentration (MIC) of the lowest concentration of an antibacterial agent that inhibits the growth of test organism can be detected.

Antibacterial activity

The antibacterial activity of the synthesized compounds NS1-10 was determined invitro using MIC (Broth Dilution Method) against four pathogenic microorganisms viz., *Escherichia coli* (Gm–ve), *Pseudomonas aeruginosa* (Gm–ve) and *Staphylococcus aureus* (Gm+ve), *Staphylococcus pyrogenus* (Gm+ve) at various conc between 6.125 μg/ml to 1000 μg/ml. Out of tested compounds NS-6 exhibited high potent activity against *S. aureus* at MIC of 62.5 μg/ml respectively , NS-10 exhibited high potent activity against *S. pyogenus* at MIC of 125 μg/ml respectively NS-5 showed equipotent activity against *P. aeruginosa* at MIC of 100 μg/ml respectively.

NS-2, NS-8 and NS-9 showed equipotent activity against *S. aureus* at MIC of 62.5 μg/ml respectively. NS-3, NS-4 and NS-6 showed equipotent activity against *S. pyogenus* at MIC of 125 μg/ml respectively (Table No.2 and 3). Whereas, the rest of the synthesized compounds exhibited mild to moderate activity against all strains of tested organisms when compared to reference standard ampicillin at 100 μg/ml.

This indicates relationship between the structure and antibacterial activity of the compounds. Further research is required to get the clear idea about relationship between antibacterial activity and structure of the compounds (Figure No.5).

Table No.1: Physical data of thus synthesized compound

S.No	Compound Code	M.P°C	% Yield	Mol. Form	M. Wt.	Calculated %		
						C	H	N
1	NS-1	288-290	70	$C_{20}H_{12}ClN_3O_3$	377	63.59	3.20	11.12
2	NS-2	300-303	65	$C_{21}H_{14}ClN_3O_3$	391	64.37	3.60	10.72
3	NS-3	268-270	74	$C_{21}H_{14}ClN_3O_3$	391	64.37	3.60	10.78
4	NS-4	260-262	61	$C_{21}H_{14}ClN_3O_3$	391	64.37	3.60	10.72
5	NS-5	306-308	65	$C_{20}H_{13}N_3O_4$	359	66.85	3.65	11.69
6	NS-6	320-322	69	$C_{21}H_{15}N_3O_4$	373	67.56	4.05	11.25
7	NS-7	270-272	70	$C_{21}H_{15}N_3O_4$	373	67.56	4.05	11.25
8	NS-8	310-312	71	$C_{21}H_{15}N_3O_4$	373	67.56	4.05	11.25
9	NS-9	266-268	65	$C_{20}H_{13}N_3O_3S$	375	67.56	3.49	11.19
10	NS-10	267-269	74	$C_{20}H_{12}N_6O_3$	384	62.50	3.15	21.49

Table No.2: Thin Layer Chromatography

S.No	Compound Code	R_f Value*
1	NS-1	0.73
2	NS-2	0.79
3	NS-3	0.78
4	NS-4	0.74
5	NS-5	0.65
6	NS-6	0.61
7	NS-7	0.52
8	NS-8	0.67
9	NS-9	0.70
10	NS-10	0.52

* Solvent system: Chloroform: Methanol, Ratio = 9: 1

Table No.3: IR, ^{1}HNMR and Mass spectral characteristic analytical data of 2-oxo-N^1-[(E)-quinolin-3-ylmethylidene]-2H-chromene-3-carbohydrazides

S.No	Compd. Code	N-H cm^{-1}	C=O cm^{-1}	C=C cm^{-1}	CH=N cm^{-1}	C=Cl cm^{-1}	C-S cm^{-1}	^{1}HNMR (in δ ppm) and Mass spectral data
1	NS-1	3178	1652	1487	1652	782	-	δ 6.7- 8.0 (m, 9 Ar-H+NH+CH), δ 8.7 (s, 1Ar-H). m/z 377 (M^+), 376(M+2).
2	NS-2	3167	1653	1488	1653	749	-	δ 2.6 (s, 3H, CH_3), δ 6.7- 8.0 (m, 8 Ar-H+NH+CH), δ 8.7 (s, 1Ar-H).
3	NS-3	3179	1650	1488	1650	753	-	δ 2.6 (s, 3H, CH_3), δ 6.7- 7.9 (m, 8 Ar-H+NH+CH), δ 8.8 (s, 1Ar-H).
4	NS-4	3177	1651	1487	1651	752	-	δ 2.4 (s, 3H, CH_3), δ 6.8- 7.8 (m, 8 Ar-H+NH+CH), δ 8.7 (s, 1Ar-H).

5	NS-5	3168	1653	1487	1653	-	-	δ 6.8- 8.1 (m, 9 Ar-H+NH+CH), δ 9.1 (s, 1Ar-H) δ 11.9 (s, 1 Ar-OH). m/z 354.
6	NS-6	3156	1661	1487	1661	-	-	δ 2.4 (s, 3H, CH_3), δ 6.8- 7.9 (m, 8 Ar H+NH+CH), δ 8.9 (s, 1Ar-H), δ 11.7 (s, 1 Ar-OH).
7	NS-7	3177	1650	1488	1650	-	-	δ 2.8 (s, 3H, CH_3), δ 6.7- 7.9 (m, 8 Ar-H+NH+CH), δ 8.7 (s, 1Ar-H), δ 11.3 (s, 1 Ar-OH).
8	NS-8	3176	1651	1488	1651	-	-	δ 2.4 (s, 3H, CH_3), δ 6.7- 7.5 (m, 8 Ar-H+NH+CH), δ 8.9 (s, 1Ar-H), δ 11.2 (s, 1 Ar-OH). m/z 377.
9	NS-9	3144	1683	1488	-	-	684	δ 6.7- 7.9 (m, 9 Ar-H+NH+CH), δ 8.9 (s, 1Ar-H), δ 13.8 (s, 1 Ar-SH).
10	NS-10	3167	1649	1486	1649	-	-	δ 6.7- 7.9 (m, 9 Ar-H+NH+CH), δ 8.8 (s, 1Ar-H). m/z 380.

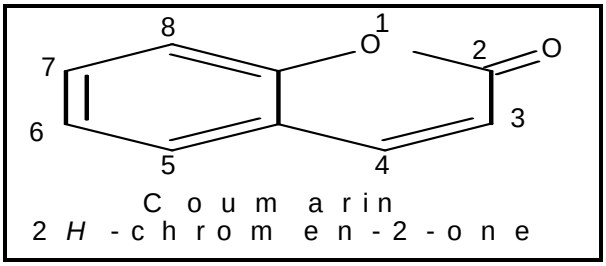


Figure No.1: Structure of Coumarin

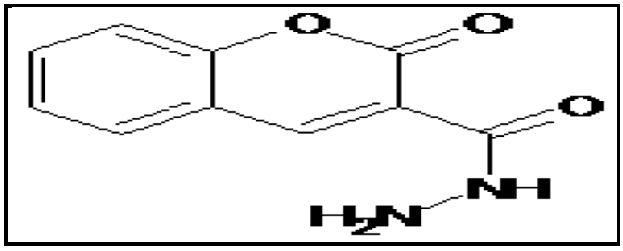


Figure No.2: 2-oxo-2H-chromene-3-carbohydrazide

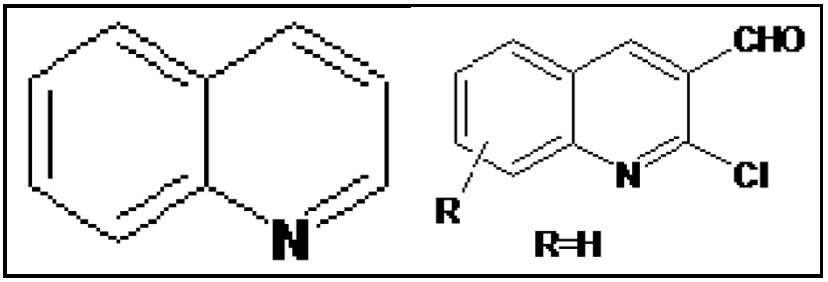


Figure No.3: Quinoline **Figure No.4: 2-Chloro-3-formyl quinoline**

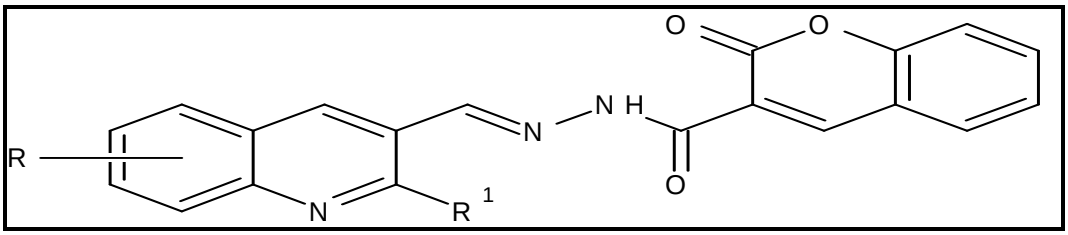
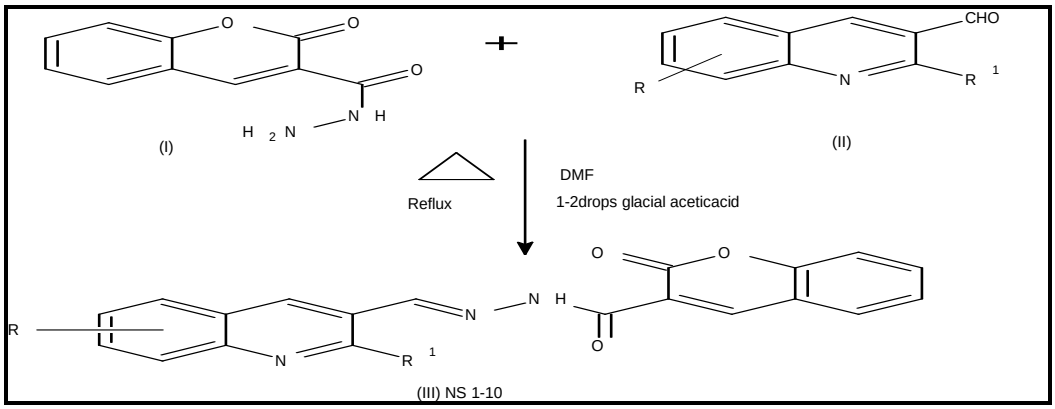


Figure No. 5: 2-oxo-N[1]-[(E)-quinolin-3-ylmethylidene]-2H-chromene-3-carbohydrazide

Scheme – I



Compounds	R	R	R	R	R^1
NS (1-4)	H	6-CH_3	8-CH_3	7-CH_3	Cl
NS (5-8)	H	6-CH_3	8-CH_3	7-CH_3	OH
NS (9)	H	-	-	-	SH
NS(10)	H	-	-	-	N_3

CONCLUSION

Ten new 2-oxo-N[1]-[(E)-quinolin-3-ylmethylidene]-2H-chromene-3-carbohydrazide were synthesized. Analytical and spectral data were used to characterize few synthesized compounds.

All synthesized compounds were screened for antibacterial and antifungal activities. Some of the tested compounds exhibited moderate to potent antibacterial activity against Gm $^{+}$ve organisms like *S. pyogenus* and *S. aureus* and Gm $^{-}$ve organism's *P. aeruginosa* and *E. coli*. Few of the tested compounds exhibited significant and equipotent antifungal activity against *Candida albicans*, but none of the synthesized compounds shown significant antifungal activity against *A. Niger* and *A. clavatus.*

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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