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An efficient protocol for the synthesis of novel 2-amino-N'-(1-(aryl-2-oxo-2Hchromen-3-yl)ethylidene) benzohydrazides act as an antimicrobial agents

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ABSTRACT

We report here the protocol for the preparation of 2-amino-N'-(1-(aryl-2-oxo-2H-chromen-3-yl)ethylidene)benzohydrazides compounds in moderate to excellent yields (46–86%) within a short reaction time (10–15 min), through a clean and efficient procedure. Additionally, the method has a wide substrate scope and provides an accessible route for the large-scale direct synthesis of 2-amino-N'-(1-(aryl-2-oxo-2H-chromen-3-yl)ethylidene)benzohydrazides. The products were assayed for their *in vitro* biological assay antimicrobial evaluation against two Gram-negative bacteria *Escherichia coli* MTCC 442*, Pseudomonas aeruginosa* MTCC 441 *and antifungal activity against Candida albicans* MTCC 227*, Aspergillus Niger* MTCC 282*, Aspergillus clavatus* MTCC 1323 at different concentrations which compared with ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin, and greseofulvin in as standard drugs which are presented.

***Keywords*:** 2-amino-N'-(1-(6-bromo-2-oxo-2H-chromen-3-yl)ethylidene)benzohydrazides, efficient procedure, antimicrobial evaluation

1. INTRODUCTION

Coumarin is used in the pharmaceutical industry as a precursor molecule in the synthesis of a number of synthetic anticoagulant dicoumarol, notably warfarin (which has a common and

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confusing brand name Coumadin) and some even more potent rodenticides that work by the same anticoagulant mechanism. Coumarin has clinical & medical value by itself, as an edema modifier i.e. anti-inflammatory activity. Coumarin and other Benzopyrones, such as 5,6-Benzopyrone, 1,2-Benzopyrone, Diosmin and others are known to stimulate macrophages to degrade extracellular albumin, allowing faster resorption of edematous fluids Coumarin is also used as a gain medium in some dye lasers. Properties, suggesting one reason for its widespread occurrence in plants, especially grasses and clovers are because of its effect of reducing the impact of grazing animals. Although the compound has a pleasant odor, it has a bitter taste and animals will avoid it. Recent studies indicate that the mediators and cellular effectors of inflammation are important constituents of the local environment of tumors [1]. Inflammation in the body's response to noxious or injurious stimuli, characterized by warmth, redness of the skin, pain, swelling and loss of function. It is a part of host defense mechanism. There are several tissue factors that are known to be involved in the inflammatory reactions such as release of histamines, bradykinin and prostaglandins [2]. Coumarin has appetite-suppressing Inflammatory diseases are becoming common in aging society throughout the world.

Coumarins (2H-1-benzopyran-2-ones) are important oxygen containing fused heterocycles used in drugs and dyes [3]. The name of coumarine originates from 'coumarou' the vernacular name of the Tonka bean (Dipteryx odorata willd, Fabaceae), from which coumarin it was isolated in 1820 [4]. They are the family of lactones containing Benzopyrone skeletal framework that have enjoyed isolation from plant as well as total synthesis in the laboratory [5].And immediately attracted the attention of perfumers on account of its pleasant and persistence odor. There are many number of naturally occurring and synthetic monomeric coumarin derivatives which are used in drugs and dyes [6].

The incorporation group as a fused component into parent Coumarin alters the property of parent Coumarin and converts it into a more useful product [7]. Coumarin is plant flavonoids widely distributed in nature. Natural coumarins are known to have antidiabetic activity [8], anabolic antioxidant and hepato protective activities [9]. Substituted Coumarins derivatives have been reported to have variety of biological activities. The potent antibiotics like Novobiocin, Coumaromycin and Chartesium are Coumarin derivatives. Recently, the interest on these compounds has been revived owing to their use as fluorescent markers in the biochemical determination of enzymes.

Coumarin derivatives can be synthesized by one of such methods as the Claisen rearrangement [10], Perkin reaction [11], Pechmann reaction [12], Witting reaction [13], as well as the Knoevnagel condensation [14]. Derivatives of Coumarins usually occur naturally as secondary metabolite present in seed, roots and leaves of many plant species [15]. These investigations have revealed their potentials as versatile biodynamic agent for example-3-heteroaryl substituted coumarin and Benzocoumarins of potential interest as pharmaceuticals and photochromic dyes [16]. Introduction of fluoro and sulfonamide moieties into Coumarin side chain hoping for an improvement of biological activity because, incorporation of fluorine to various heterocycles is known to influence the biological activity [17] and the sulfonamide moiety itself possesses important antibacterial [18] and antitumor activity [19].

The Coumarins as such are forming a large class of compounds which are extremely variable in structure, due to the various types of substitutions in their basic structure and hence can influence biological activity [20]. For example, Carbochromen is a potent specific coronary vasodilator used for many years in the treatment of angina pectoris [21].

The researchers had shown on the basis of their investigation on Coumarin compounds that these compounds are promising candidates for different types of diseases due to their wide spectrum and diverse biological properties and various effects on the different cellular systems. Coumarins have important effects in plant biochemistry and physiology, acting as antioxidants, enzyme inhibitors and precursors of toxic substances. In addition, these compounds are involved in the actions of plant growth hormones and growth regulators, the control of respiration, photosynthesis, as well as defense against infection.

Hydrazides and related compounds have attracted significant attention as useful building blocks for the assembly of various heterocyclic compounds which are found to possess antitumoral, anti-convulsant, anti-microbial, analgesic, antitubercular, and anti-inflammatory activities [22-25]. Additionally, hydrazides are also essential precursors in the synthesis of hydrazones and heterocyclic compounds [26-27]. As a result, several synthesis approaches have been developed for the construction of these hydrazides [28]. However, the problem of using the excess organic solvent or catalyst and the high temperature for the transformation remains to be solved.

2. RESULT AND DISCUSSION (MATERIALS AND METHODS)

All the starting materials, reagents, and catalysts were purchased from Aldrich or Alfa aesar and used as such we received. For thin-layer chromatography, analytical TLC plates (Alugram SIL G/UV254 and 70-230 mesh silica gel (E. M. Merck) were used). Column chromatography was performed using silica gel (Merck, 60-120 mesh size). Anhydrous solvents were purchased from allied chemicals and stored over molecular sieves. The chromatographic solvents used for isolation/purification of compounds were distilled before use. The chromatographic solvents are mentioned as volume: volume ratios. Reactions were typically run in an oven-dried screw-cap vial under an inert atmosphere.

Synthesized derivatives undergo for spectral analysis as well as characterization with ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker Avance-II Spctometer using DMSO-d6 as a solvent. The ^{1}H and ^{13}C chemical shifts are reported in parts per million relatives to tetramethylsilane using the residual solvent signal as the internal reference. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, bs = broad singlet, d = doublet, dd = double doublet, t = triplet, m = multiplet.

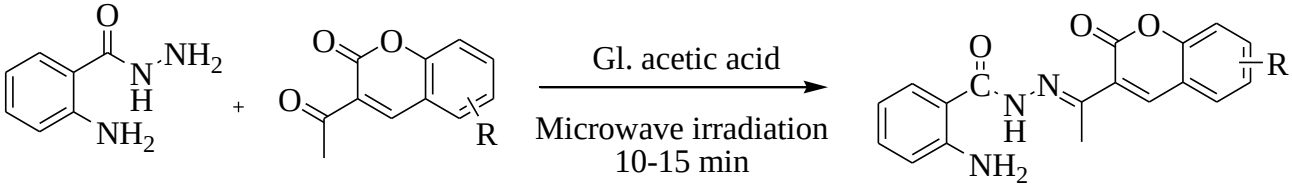
The ^{13}C NMR spectra are proton decoupled. Melting points were measured in open capillaries and are uncorrected. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). FTIR Data recorded on Shimadzu 8200 using KBr Pellet.

Herein, we report the efficient route for the synthesis of 2- amino-N'-(1-(6-bromo-2-oxo-2H-chromen-3yl)ethylidene)benz ohydrazides under the Gl. Acetic acid medium at room temprature under stirring without use of any other complex reaction conditions.

First of all, compounds were synthesized according to the previous procedure [29]. Next, benzohydrazide (4) was synthesized from salicylic acid via three steps as described in Scheme 1. Subsequently, the effect of solvents on the synthesis of 2- amino-N'-(1-(6-bromo-2-oxo-2H-chromen-3yl)ethylidene)benz ohydrazides was investigated (Table 1). The desired product was obtained in moderate to good yield under the polar solvents, while low yields were observed when non-polar solvents were employed (Table 1, entries 1–09). These results exhibited that

the polar of the solvent had a strong influence on the reaction yield. Thus, we decided to use acetic acid as a solvent/catalyst, and the desired product was afforded in excellent yield. No product was obtained in the absence of a solvent. With the optimized conditions, the scope of the acetophenones in the reaction was extended (Scheme 1). As shown in Table 4, the desired products were obtained in good to excellent yields. The substituent in the benzene ring of acetophenones was found to have little effect on the reaction rate. Substituted acetophenones bearing both electron-rich groups and electron-poor groups in the aromatic ring could effectively afford the desired products in excellent yields (>85%). When the acetophenone bearing the strong electronwithdrawing group such as NO_2 at para position, the product was obtained in lower yield. However, an excellent yield of 86% was observed when the NO_2 group at meta position was replaced by a Br group (Table 3, entry 1). It is worth noting that aromatic heterocyclic methyl ketones were successfully employed as the substrates to give the desired products with excellent yields (Table 3, entries 1-10).

The comparison of our work with previous literature is described in Table 4. The synthesis of 2-amino-N'-(1-(aryl-2- oxo-2H-chromen-3yl)ethylidene)benzohydrazides in the presence of Gl. Acetic acid afforded the desired product in excellent yield (Table 4, entry 3). The previous reports showed that synthesis of 2-amino-N'-(1-(aryl-2-oxo-2H-chromen3yl)ethylidene) benzohydrazides also delivered the expected product in good yields but those reports still suffered intrinsic drawbacks such as the requirement of long reaction time and volatile organic solvent (Table 4, entries 1–3).



1a to 1j

Scheme 1

Table 1. The effects of solvents on the synthesis of (10E)-2-amino-N'-(1-(6-bromo-2-oxo-2H-chromen-3yl)ethylidene) benzohydrazide **(1a)**

Entry[a]	Type of Solvent	Solvent	Isolated Yield (%)[b]
1	Polar protic	Ethanol	81
2		n-Butanol	65
3		Acetonitrile	46
4	Polar aprotic	DMF	83
5		DMSO	74
6		THF	48

7	Non Polar	Dichloromethane	38
8		Toluene	33
9		Hexane	0

[a] Reaction conditions: A mixture of benzohydrazide (0.5 mmol), acetophenone (0.060 g, 0.5 mmol) and 1.5 mL gl. Acetic acid was M.W. irradiated for 10 min.
[b] Yield of **1a** was recrystallized from ethanol.

Table 2. Comparision of catalyst on the synthesis of (10E)-2-amino-N'-(1-(6-bromo-2-oxo-2H-chromen-3yl)ethylidene) benzohydrazide **(1a)**

Entry[a]	Type of Catalyst	Catalyst	Isolated Yield (%)[b]
1	Metal Salts[a]	$AlCl_3$	56
2		$FeCl_3$	44
3		$ZnCl_2$	52
4	Bronsted acids[a]	H_2SO_4	83
5		HCl	78
6		CH_3COOH	86
7		CF_3COOH	85

[a] Reaction conditions: A mixture of benzohydrazide (0.5 mmol), acetophenone (0.060 g, 0.5 mmol) and 1.5 mL gl. Acetic acid was M.W. irradiated for 10 min.
[b] Yield of **1a** was recrystallized from ethanol.

Table 3. The reaction scope of methyl ketone on the synthesis of 2-amino-N'-(1-(aryl-2-oxo-2H-chromen-3-yl)ethylidene)benzohy drazides **(1a-1j)**

Entry[a]	Reaction substituent(-R)	Products	Time (min)	Isolated Yield (%)[b]
1	-6-Br	1a	10	86
2	-H	1b	15	80
3	-6-NO_2	1c	15	46
4	-6-OCH_3	1d	12	78

5	-6-CH_3	1e	10	74
6	-6-Cl	1f	10	75
7	-6-F	1g	10	68
8	-7-OCH_3	1h	15	77
9	-7-OH	1i	12	73
10	-8-OCH_3	1j	12	70

[a] Reaction conditions: A mixture of benzohydrazide (0.5 mmol), acetophenone (0.5 mmol) and 1.5 mL gl. Acetic acid was M.W. irradiated for 10 min.
[b] Yield of **1a** was recrystallized from ethanol.

Table 4. Comparision of the present method with the previously reported synthesis of 2-amino-N'-(1-(aryl-2-oxo-2H-chromen-3yl)ethylidene)benzohydrazides [30, 31] **(1a-1j)**

Entry	Catalyst	Conditions	Isolated Yield (%)[a]
1	CH_3COOH	Refluxed (EtOH), 5-9 hr	75-89
2	Catalyst free	Refluxed (EtOH), 2hr	76-88
3	CH_3COOH	M.W. irra., Solvent free, 10-15 min	46-86

[a] Yield of **1a-1j** were recrystallized from ethanol.

2. 1. Experimental

Preparation of (10E)-2-amino-N'-(1-(6-bromo-2-oxo-2H-chromen-3-yl)ethylidene) benzohy drazide 1a

A mixture of benzohydrazide (0.5 mmol), 3-acetyl-6-bromo-2H-chromen-2-one (0.5 mmol) and 1.5 mL gl. Acetic acid was M.W. at 100W irradiated for 10 min. The progress of reaction was monitored by TLC. The resulting reaction mass allowed to cool at room temperature and the solid mass obtained was filtered out, wash with hexane and recrystallise in ethanol to affording desired product with yellow solid, Yield 86%; mp 122–124 °C; ^{1}H NMR (400 MHz, DMSO) d: 2.32 (s, 3H), 6.25-6.29 (m, Ar-2H), 6.59-6.79 (m, Ar-2H), 7.21-7.23 & 7.40-7.42 (dd, Ar-2H), 7.57-7.59 & 7.76-7.78 (d,Ar-2H), 8.11 (s, Ar-1H); 8.17 (s, 2H); 10.64 (s, 1H); ^{13}C NMR (100 MHz, DMSO) d: 18.98, 106.91, 107.09, 108.34, 110.10, 113.31, 114.86, 115.30, 116.39, 128.95, 130.80, 131.02, 132.46, 136.12, 149.86, 154.70, 158.14, 159.17, 161.73, 166.14, 205.15; m/z: 400; IR (KBr, cm_1): 2964, 1691, 1626, 1537, 1485, 1261, 858, 798. Anal.Calcd for $C_{18}H_{14}BrN_3O_3$: C, 54.02; H, 3.53; N, 10.50. Found: C, 54.10; H, 3.54; N, 10.55.

Preparation of (10E)-2-amino-N'-(1-(2-oxo-2H-chromen-3-yl)ethylidene)benzohydrazide 1b

Benzohydrazide reacts with 3-acetyl-2H-chromen-2-one as described above to give 1b as pale yellow solid, Yield 80%; mp 116-118 °C; ^{1}H NMR (400 MHz, DMSO) d: 2.12 (s, 3H), 6.64-6.69 (m, Ar-2H), 6.80-6.84 (m, Ar-2H), 7.02-7.06 (m, Ar-2H), 7.11-7.13 (d,Ar-2H), 8.10 (s, Ar-1H); 8.15 (s, 2H); 10.77 (s, 1H); ^{13}C NMR (100 MHz, DMSO) d: 18.98, 108.11, 109.04, 109.34, 111.16, 114.61, 115.76, 116.00, 116.69, 127.15, 131.10, 132.06, 133.66, 137.82, 148.26, 155.40, 159.13, 160.10, 161.33, 165.47, 204.12; m/z: 321; IR (KBr, cm-1): 2961, 2333, 1770, 1620, 1529, 1469, 813, 709. Anal.Calcd for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.18; H, 4.24; N, 13.35.

Preparation of (10E)-2-amino-N'-(1-(6-nitro-2-oxo-2H-chromen-3-yl)ethylidene)benzo hydrazide 1c

Benzohydrazide reacts with 3-acetyl-6-nitro-2H-chromen-2-one as described above to give 1c as light yellow solid, Yield 46%; mp 103-105 °C; 3.78 (s, 3H), 6.32-6.79 (m, Ar-4H), 6.99-7.01 (d, Ar-1H), 7.20-7.24 (t, Ar-1H), 7.37-7.39 (d, Ar-1H), 7.54-7.66 (m,Ar-1H), 8.50 (s, Ar-1H); 11.85 (s,Ar-2H); ^{13}C NMR (100 MHz, DMSO) d: 54.45, 100.93, 101.16, 106.34, 107.05, 111.36, 112.54, 114.58, 116.45, 128.17, 131.23, 132.44, 132.73, 148.14, 150.21, 159.42, 160.67, 161.84, 162.09, 163.33, 164.74; m/z: 366; IR (KBr, cm-1): 2961, 2351, 1691, 1643, 1527, 1238, 707, 835. Anal.Calcd for $C_{18}H_{14}N_4O_5$: C, 59.02; H, 3.85; N, 15.29. Found: C, 59.05; H, 3.78; N, 15.29.

Preparation of (10E)-2-amino-N'-(1-(6-methoxy-2-oxo-2H-chromen-3-yl)ethylidene) benzohydrazide 1d

Benzohydrazide reacts with 3-acetyl-6-methoxy-2H-chromen-2-one as described above to give 1d as yellow solid, Yield 78%; mp 112-114 °C; ^{1}H NMR (400 MHz, DMSO) d: 2.10 (s, 3H), 3.37 (s, 3H), 6.60-6.64 (m, Ar-2H), 6.79-6.83 (m, Ar-2H), 7.04-7.07 (m, Ar-2H), 7.10-7.12 (d,Ar-2H), 8.11 (s, Ar-1H); 8.15 (s, 2H); 10.75 (s, 1H); ^{13}C NMR (100 MHz, DMSO) d: 17.50, 55.09, 111.00, 113.09, 116.40, 118.00, 118.90, 122.5, 123.10. 123.66, 128.31, 133.00, 133.65, 142.17, 148.40, 155.61, 159.10, 163.20 203.17; m/z: 351; IR (KBr, cm-1): 2968, 2351, 1768, 1643, 1527, 1491, 1232, 868, 711. Anal.Calcd for $C_{19}H_{17}N_3O_4$: C, 64.95; H, 4.88; N, 11.96. Found: C, 64.90; H, 4.43; N, 11.18.

Preparation of (10E)-2-amino-N'-(1-(6-methyl-2-oxo-2H-chromen-3-yl)ethylidene)benzo hydrazide 1e

Benzohydrazide reacts with 3-acetyl-6-methyl-2H-chromen-2-one as described above to give 1e as brown solid, Yield 74%, mp 107-109 °C; ^{1}H NMR (400 MHz, DMSO) d: 2.10 (s, 3H), 2.31 (s, 3H), 6.64-6.67 (m, Ar-2H), 6.80-6.83 (m, Ar-2H), 6.90-6.94 (m, Ar-2H), 7.70-7.74 (d,Ar-2H), 8.17 (s, Ar-1H); 8.19 (s, 2H); 10.86 (s, 1H); ^{13}C NMR (100 MHz, DMSO) d: 17.20, 55.11, 116.10, 116.30, 118.04, 118.90, 121.43, 122.42, 123.30. 123.66, 127.13, 128.31, 135.15, 147.23, 148.10, 155.67, 159.51, 163.00 203.87; m/z: 335; IR (KBr, cm-1): 2958, 1680, 1625, 1542, 1476, 1268, 864, 795. Anal.Calcd for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 68.15; H, 5.19; N, 12.54.

2. 2. Biological evaluation

The synthesized compounds 1a-1j were tested for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method [32-35] with two Gram-positive bacteria *Staphylococcus aureus* MTCC-96, *Streptococcus pyogenes* MTCC 443, two Gram-negative bacteria *Escherichia coli* MTCC 442, *Pseudomonas aeruginosa* MTCC 441 and three fungal strains *Candida albicans* MTCC 227, *Aspergillus Niger* MTCC 282, *Aspergillusclavatus* MTCC 1323 taking chloramphenicol, ciprofloxacin, norfloxacin, nystatin, and griseofulvin as standard drugs. The standard strains were procured from the Microbial Type Culture Collection (MTCC) and Gene Bank, Institute of Microbial Technology, Chandigarh, India. The minimal inhibitory concentration (MIC) values for all the newly synthesized compounds, defined as the lowest concentration of the compound preventing the visible growth, were determined by using microdilution broth method according to NCCLS standards [32]. All the newly synthesized compounds 1a–j showed the promising antimicrobial activity against different strains of bacterium and fungus. The compound 1c, 1d, 1e and 1j demonstrate better activity against different gram positive and gram negative bacteria as well as antifungal strain. Compound 1e emerged as the most effective antibacterial agents with a comparable MIC of Chloramphenicol and Ciprofloxacin drugs. Compound 1c also give promising antifungal activity and comparable result with MIC of standard Nystatin and Griseofulvin.

Table 5. Antibacterial and antifungal activity of **1a-1j**

Compounds	Minimum inhibition concentration (μg mL^{-1})						
	Gram-positive		Gram-negative		Fungal species		
	S. a.	***S. p.***	***E. c.***	***P. a.***	***C. a.***	***A. n.***	***A. c.***
1a	250	>1000	500	1000	>1000	500	1000
1b	500	1000	500	100	1000	>1000	1000
1c	62.5	100	250	125	100	100	100
1d	100	62.5	100	100	250	100	100
1e	62.5	50	100	100	250	250	500
1f	100	250	500	100	500	125	250
1g	500	1000	250	1000	>1000	500	>1000
1h	1000	250	500	500	>1000	500	250
1i	100	100	250	100	1000	500	500
1j	62.5	100	250	125	500	500	1000
Chloramphenicol	50	50	50	50	-	-	-

Ciprofloxacin	50	50	25	25	-	-	-
Norfloxacin	10	10	10	10	-	-	-
Nystatin	-	-	-	-	100	100	100
Griseofulvin	-	-	-	-	500	100	100

3. CONCLUSIONS

We have developed a simple, clean, and cost-effective method for the synthesis of 2-amino-N'-(1-(aryl-2-oxo-2H-chromen-3-yl)ethylidene)benzohydrazides. The as-prepared Gl. Acetic acid demonstrated remarkable potential catalyst/solvent; the desired products were obtained in excellent yield with short reaction time. The work-up simplicity, mild reaction conditions, high yields are the outstanding features of the current work. The compounds **1d** and **1e** are most potent compounds with accompanied low MIC values to the standard drugs. The results described here, merits further investigations in our laboratories using a forward chemical genetic approach for finding lead molecules as antimicrobial agents.

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