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Synthesis of Coumarin based Knoevenagel-Ugi Adducts by a sequential one pot Five-Component Reaction and their Biological evaluation as Anti-Bacterial agents

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ABSTRACT:

An efficient multicomponent synthesis of Ugi compounds comprising coumarin backbone has been achieved by employing one pot five component sequential Knoevenagel-Ugi reaction. This method offers the advantages of easy handling procedure, atom economy, mild reaction conditions and good yields of products. A molecular library was synthesized by changing the substituents on two of the independent starting materials. The synthesized compounds were also tested for anti-microbial activities and were found to be moderate to good anti-bacterial agents.

Multicomponent reactions (MCRs) are useful synthetic tools in which three or more different starting materials react to form complex molecules in a one-pot strategy with great efficiency, atom economy and low synthetic cost[1]. The development of such processes in which several bonds are formed without isolation of intermediates receives considerable attention for the preparation of structurally diverse libraries of drug-like compounds.[2-10] With regard to four-component processes, the Ugi coupling of isocyanides with carbonyl derivatives, amines and carboxylic acids is known to exhibit high efficiency for a wide range of starting components.[11-19] Most studies have related to cascades directed towards the preparation of complex hybrid heterocyclic scaffolds by means of the Ugi reaction. The Ugi four-component reaction (U-4CR) is one of the most commonly used MCRs that result in peptide-like products[20-23] and has been applied as a powerful approach to access highly functionalized hybrid heterocyclic structures. MCR's have also been reported in literature[24-26, 54] to have applications in the synthesis of hybrid heterocyclic compounds. Coumarin and its derivatives are important compounds due to their presence in naturally occurring aromatic products found in plants[27] and cinnamon flavoured foods.[28] Numerous coumarin derivatives have been synthesized and reported in literature having diverse therapeutic relevance as shown in Figure 1.

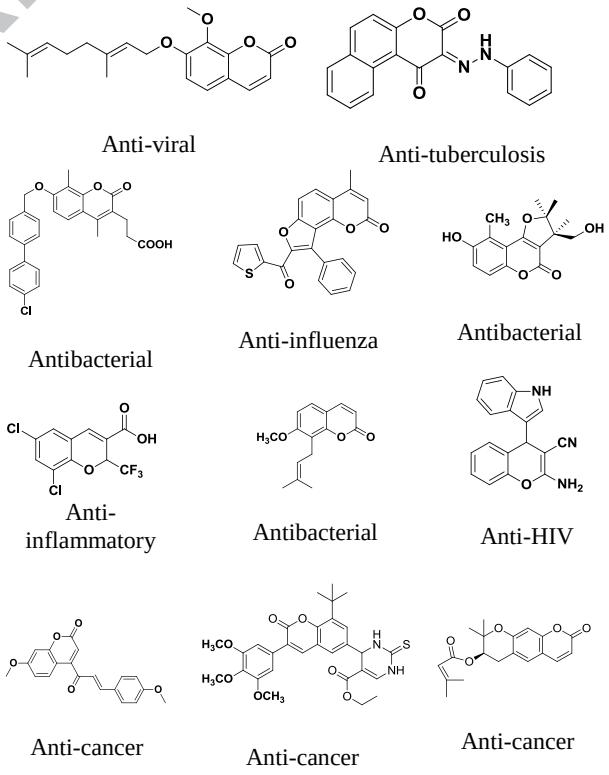
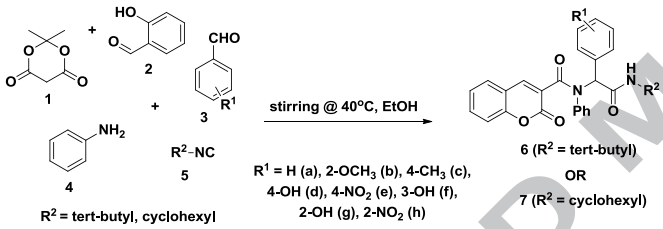


Figure 1. Therapeutically relevant coumarin derivatives

Coumarin derivatives have been reported to exhibit anticancer,[29-30] anti-influenza,[31] anti-HIV,[32] anti-alzheimer,[33-34] anti-inflammatory,[35] antituberculosis,[36] antiviral,[37] and antimicrobial activities.[38] The fluorescent properties observed in some coumarin based Ugi adducts have been used to study

proteins and nucleic acids.[39-42] It is important to note that the existence of the amide groups in coumarin-3-carboxamides improves the biological activity of these compounds.[43-46] In recent literature, various coumarin based Knoevenagel-Ugi adducts have been synthesized[47-48] and are found to be potential agents possessing one or the other biological activity[49-51] and fluorescent property[42]. In continuation to our research interest[52-53] in MCRs and synthesis of coumarin based Knoevenagel-Ugi adducts as potential antibacterial agents, we report the synthesis of coumarin-3-carboxylic acid by a reaction of salicylaldehyde and meldrum's acid in ethanol at room temperature[54] and the sequential addition of aryl amine, aromatic aldehyde and isocyanide to yield coumarin based α-acyl amino amides in a one pot five component Knoevenagel-Ugi sequential reaction. The general synthetic protocol followed for coumarin based Knoevenagel-Ugi adducts is depicted in Scheme 1.



Scheme 1. General procedure for synthesis of coumarin based Knoevenagel-Ugi adducts.

Experimental

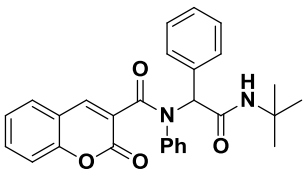
All reagents were purchased from Sigma-Aldrich, Fischer and used without further purification. Melting points were determined on a Stuart SMP30 melting point apparatus and are uncorrected. Crude products were recrystallized in mixture of EtOAc and Hexane. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d6 on a Bruker Avance II 400 spectrometer with TMS as internal standard at room temperature, the chemical shifts (δ) were expressed in ppm and *J* values were given in Hz. The following abbreviations are used to indicate the multiplicity: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). All first order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted were designated as multiplet (m). Mass spectra were recorded on Waters Micromass Q-Tof Micro spectrometer. Elemental analysis was done using Thermo Scientific (Flash 2000) CHN elemental analyzer.

General Procedure for Synthesis of Ugi adducts (coumarin based α-acyl amino amides)

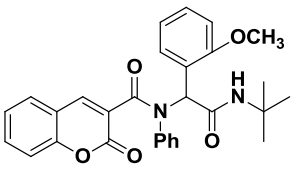
An oven-dried round bottomed flask was charged with a magnetic stir bar, salicylaldehyde (1.0 mmol, 122 mg), Meldrum's acid (1.0 mmol; 144 mg) and ethanol (5 mL). The whole mixture was then stirred vigorously at room temperature for 10 h to complete the conversion. The completion of the reaction was confirmed by TLC monitoring, showing the disappearance of starting material. Thereafter, well stirred mixture of aldehyde (1 mmol) and amine (1 mmol) in minimum volume of ethanol were sequentially added to the flask followed by the addition of isocyanide (1 mmol) and continued stirring the mixture at 40^{o}C till completion of the reaction, confirmed by TLC indicating the disappearance of starting components. Solvent was removed from crude reaction mixture under reduced pressure. Crushed ice was added and the solid product was scratched, filtered, washed thrice with cold water and dried to obtain the crude product. The crude product was then recrystallized from a mixture of EtOAc-Hexane to get the pure product. All the products were characterized by using NMR (^{1}H and ^{13}C) spectroscopy, mass spectroscopy and elemental analysis. The structures of the synthesized coumarin based Knoevenagel-Ugi adducts is shown in Figure 2.

Results & Discussions

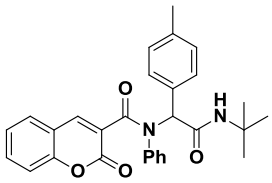
Amongst the library of the synthesized compounds **6a-6h** and **7a-7h** as shown in Figure 2, wherein different substituted aldehydes were varied while maintaining 2-oxo-2H-chromene-3-carboxylic acid (formed *in situ* by the reaction of salicylaldehyde and meldrum's acid) and aniline. The **R^{1}** as o-methoxy and m-hydroxy substituents along with cyclohexyl and tert-butyl isocyanides gave good yields of the products **6b, 6f, 7b** and **7f**. Our results also revealed that unsubstituted aryl aldehyde also gave equivalent yields of the products as in **6a** and **7a**. The optimizations of the condensation reaction for model compound **6b** in terms of time of completion of reaction and reaction solvent were also done and the results are summarized in Table 1 and Table 2 respectively.



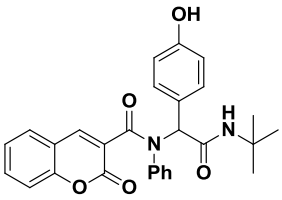
6a (86%)



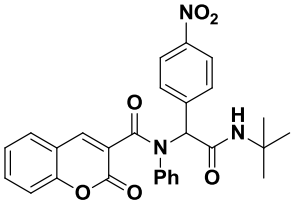
6b (92%)



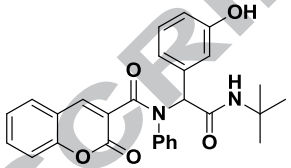
6c (88%)



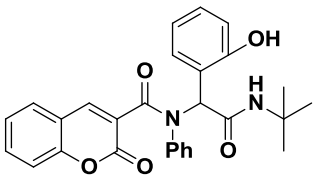
6d (86%)



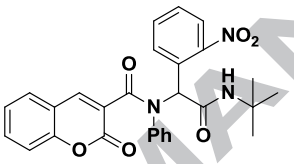
6e (85%)



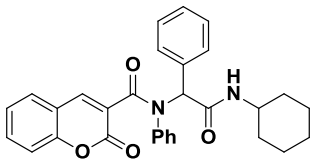
6f (89%)



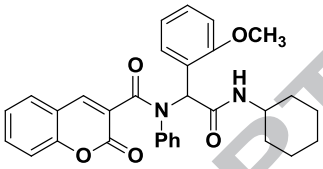
6g (81%)



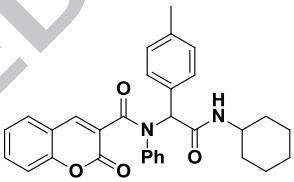
6h (84%)



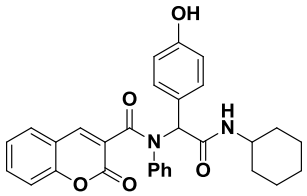
7a (87%)



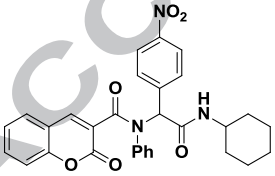
7b (90%)



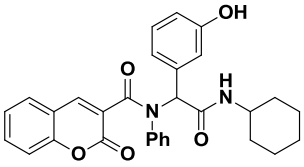
7c (88%)



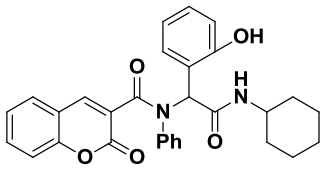
7d (87%)



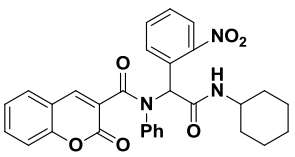
7e (85%)



7f (90%)



7g (82%)



7h (85%)

Figure 2. Structure and Isolated yields of products
Reaction Conditions: One-pot reaction; Aldehyde (1.0 mmol), Aniline (1.0 mmol), Coumarin-3-carboxylic acid (1.0 mmol), Isocyanide (1.0 mmol), EtOH (2 mL), 40^{o}C, 6-8 hours.

Table 1. Optimization of method for Ugi adduct **6b** in terms of time of completion of reaction

Entry	Time (h)	Yield %[b]
1	2	20
2	3	38
3	4	57
4	5	78
5	6	92
6	7	92

[b]Isolated Yield

Table 2. Optimization of reaction solvent for model compound **6b**

Entry	Reaction Solvent	Yield %[b]
1	Ethanol	92
2	Methanol	89
3	Water	35

[b]Isolated Yield

Using optimized reaction conditions, in the pilot experiment, salicylaldehyde was reacted with Meldrum's acid in ethanol at room temperature for 10 hours to afford coumarin-3-carboxylic acid.[51] Thereafter aniline, o-methoxy benzaldehyde and tert-butyl isocyanide were added and the mixture stirred at 40^{o}C for 6 hours. After completion of the reaction (6 h), the desired product was recrystallized in EtOAc:hexane and isolated in 92% yield. In view of the success of the above reaction, we explored the scope and limitations of this reaction by extending the procedure to different aldehydes and two different isocyanides. The reactions proceeded very efficiently at mild temperature conditions and led to the formation of a new class of the coumarin derivatives with α-acyl amino amide in good yields. Structure of the product was deduced from its ^{1}H-NMR, ^{13}C-NMR, mass spectral data and elemental analysis. The ^{1}H NMR spectrum of compound **6b** consisted of a singlet for the methyl protons of the tert-butyl entity (δ = 1.46 ppm, 9H); a singlet for protons of methoxy group (δ = 3.26 ppm, 3H); a sharp singlet for CH (δ = 6.46 ppm, 1H); a broad singlet for NH (δ = 6.50 ppm, 1H) a multiplet for aromatic protons (6.65−7.50 ppm, 13H); and a singlet for CH of coumarin ring (δ = 7.76 ppm, 1H). Also, the proton decoupled ^{13}C NMR spectrum of **6b** is completely consistent with the product structure showing peaks at δ (ppm) 28.7, 51.8, 55.1, 60.8, 110.0, 116.6, 118.1, 120.3, 122.5, 124.6, 126.2, 127.8, 128.0, 128.4, 129.6, 129.8, 131.1, 132.3, 139.0, 141.8, 153.6, 157.4, 158.2, 165.3, 168.7. The mass spectra of the compound **6b** displayed molecular ion peaks at m/z: 486 [M+1], 508 [M+Na] values. The elemental analysis showed C: 71.652 %, O: 16.761 %, H: 6.002 % and N: 5.585 % to be present in Ugi adduct **6b**.

Anti-microbial activity

All the synthesized compound were evaluated for the in vitro antimicrobial activity on both gram positive and gram negative strain bacteria. Two gram negative strains *Klebsiella pneumoniae* 43816, *Pseudomonas aeruginosa* PAO1 and two gram positive strains *Streptococcus aureus* MRSA, *Staphylococcus epidermidis* were used for screening the synthesized compounds. All the compounds were soluble in DMSO, therefore it was used as a control solvent. Cefepime was used as a standard antibiotic against all the organisms used in evaluating MIC values. For screening, the diameter of the microbial inhibition were measured for each compound (100µg/well). All the MICs were performed in triplicates (N=3) for the each test organism and the results are expressed as mean ± standard deviation for each compound. The MIC values in µM/ml of the compounds against the above mentioned organisms are presented in Table 3.

An assessment of the obtained data reveals that some of the compounds displayed good and the others showed moderate antibacterial activity when compared with the reference standard, cefepime. Among the complete library of the compounds synthesized, **7f** (R^1 = 3-OH, R^2 = cyclohexyl), **7g** (R^1 = 2-OH, R^2 = cyclohexyl) and **7h** (R^1 = 2-NO_2, R^2 = cyclohexyl) had good potency for gram negative strain *Pseudomonas aeruginosa* PAO1, while for the same class of gram negative bacteria *Klebsiella pneumoniae* 43816, **7e** (R^1 = 4-NO_2, R^2 = cyclohexyl), **7f** (R^1 = 3-OH, R^2 = cyclohexyl) and **7h** (R^1 = 2-NO_2, R^2 = cyclohexyl) showed good potency with respect to cefepime (0.027 µM/ml). For the gram positive organisms, **6c** (R^1 = 4-Me, R^2 = tert-butyl), **6g** (R^1 = 2-OH, R^2 = tert-butyl), **7e** (R^1 = 4-NO_2, R^2 = cyclohexyl), **7f** (R^1 = 3-OH, R^2 = cyclohexyl), **7g** (R^1 = 2-OH, R^2 = cyclohexyl), **7h** (R^1 = 2-NO_2, R^2 = cyclohexyl) showed good potency as antibacterial agents for *Staphylococcus epidermidis* 3382, while **6b** (R^1 = 2-OMe, R^2 = tert-butyl), **6c** (R^1 = 4-Me, R^2 = tert-butyl), **6g** (R^1 = 2-OH, R^2 = tert-butyl), **7a** (R^1 = H, R^2 =

cyclohexyl), **7e** (R^1 = 4-NO_2, R^2 = cyclohexyl), **7f** (R^1 = 3-OH, R^2 = cyclohexyl), **7g** (R^1 = 2-OH, R^2 = cyclohexyl), **7h** (R^1 = 2-NO_2, R^2 = cyclohexyl) had good potency for *Streptococcus aureus* MRSA in comparison to cefepime (0.008 μM/ml).

Table 3. Antimicrobial Evaluation* of synthesized coumarin based Knoevenagel-Ugi adducts

	***P. aeruginosa* PAO1**	***K. pneumoniae* 43816**	***S. epidermidis* 3382**	***S. aureus* MRSA**
6a	0.458±0.033	0.734±0.044	0.458±0.033	0.334±0.026
6b	0.428±0.031	0.428±0.031	0.107±0.012	0.039±0.004
6c	0.356±0.030	0.445±0.032	0.028±0.006	0.020±0.004
6d	0.221±0.021	0.354±0.025	0.885±0.060	0.649±0.053
6e	0.834±0.056	0.834±0.056	0.417±0.030	0.305±0.024
6f	0.708±0.043	0.708±0.043	0.354±0.027	0.324±0.027
6g	0.442±0.032	0.619±0.042	0.055±0.008	0.041±0.005
6h	0.417±0.030	0.208±0.020	0.104±0.012	0.152±0.020
7a	0.867±0.058	0.346±0.027	0.108±0.012	0.039±0.008
7b	0.203±0.019	0.203±0.019	0.101±0.011	0.108±0.015
7c	0.842±0.057	0.842±0.057	0.421±0.030	0.308±0.024
7d	0.419±0.030	0.419±0.030	0.104±0.012	0.153±0.018
7e	0.198±0.019	0.158±0.021	0.025±0.006	0.018±0.004
7f	0.104±0.012	0.053±0.007	0.041±0.014	0.019±0.004
7g	0.104±0.012	0.209±0.020	0.052±0.007	0.019±0.004
7h	0.049±0.007	0.099±0.011	0.049±0.007	0.036±0.004
Cefe-pime	0.027±0.008	0.027±0.008	0.008±0.0003	0.008±0.0003

*DMSO was used as control solvent and Cefepime as standard antibiotic, MIC values are represented in μM/ml.

The study of structure-activity relationship (SAR studies) of the potencies indicate that the compounds containing cyclohexyl ring showed overall better antibacterial activity compared to the compounds containing tert-butyl group. Synthesized Ugi adducts containing p-methyl, m-hydroxy, o-nitro, o-hydroxy and p-nitro groups on phenyl ring along with unsubstituted phenyl ring were found to possess good antimicrobial activity in comparison to other coumarin based Ugi adducts. In case of *Pseudomonas aeruginosa* PAO1, the compounds containing o-nitro, o-hydroxy and m-hydroxy groups on phenyl ring showed comparable results in inhibiting bacterial growth. For *Klebsiella pneumoniae* 43816, compounds having o-nitro, p-nitro and m-hydroxy substituted phenyl ring showed good antibacterial activity. Coumarin based Knoevenagel-Ugi adducts having p-methyl and o-hydroxy substituted phenyl ring with tert-butyl group and p-nitro, m-hydroxy, o-hydroxy and o-nitro substituted phenyl ring with cyclohexyl group were found to be inhibitory for the growth of *Staphylococcus epidermidis* 3382. In case of *Streptococcus aureus* MRSA, compounds containing o-methoxy, p-methyl, o-hydroxy substituted phenyl ring with tert-butyl group and o-hydroxy, p-nitro, m-hydroxy, o-nitro substituted phenyl ring and unsubstituted phenyl ring with cyclohexyl group showed good inhibitory results.

Conclusions

In conclusion, we have synthesized bioactive molecules by incorporating the coumarin nucleus via a one-pot five component sequential Knoevenagel-Ugi approach, which is green, efficient in terms of atom economy and avoidance of multistep synthesis. This protocol has several advantages such as simple experimental procedure, mild reaction conditions at almost RT conditions with less side products, simple post - reaction work up and easy extraction of pure products in good yields. The functionalized molecules are potential candidates of medicinal importance as exhibited by their antibacterial activity. The synthesized compounds showed moderate to good results in terms of anti-bacterial activity for both gram positive and gram-negative strains.

Acknowledgements

The authors are thankful to Punjab Engineering College (Deemed to be University), Chandigarh for necessary facilities and RSIC-CIL, Panjab University, Chandigarh for spectroscopic analysis.

Supplementary Data

Supplementary data (supplementary data including relevant preparation procedures for all compounds, characterization data of all compounds, ^{1}H/ ^{13}C NMR and MS spectra for model compounds) associated with this article can be found.

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HIGHLIGHTS

- Synthesized coumarin based adducts via sequential Knoevenagel-Ugi approach.

- The compounds were tested for their anti-bacterial activity and showed moderate to good anti-bacterial properties.
- Compounds are active against both gram positive and gram negative bacterial strains.
- Methodology adopted offers easy handling procedure, atom economy and mild reaction conditions.
- A simple one-pot sequential multi component, uncatalyzed strategy gave products in high yield and purity.

Synthesis of Coumarin based Knoevenagel-Ugi Adducts by a sequential one pot Five-Component Reaction and their Biological evaluation as Anti-Bacterial agents

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GRAPHICAL ABSTRACT