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Aqua mediated synthesis of substituted 2-amino-4*H*-chromenes and in vitro study as antibacterial agents

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Abstract—A simple, clean, environmentally benign route to the synthesis of 2-amino-chromenes is described using K_2CO_3 as a green catalyst in water under microwave irradiation. This implies a convenient route avoiding the usage of hazardous organic solvents and organic bases. This technique requires only water in both the reaction step and workup, thus rendering the whole procedure into a truly ecofriendly green protocol. All the synthesized compounds were shown to possess antibacterial activity as tested in vitro against standard strains of *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus.*

1. Introduction

The environment calls on the entire research edifice to define long-term strategic goals for clean chemistry and to reduce the amount of pollutants produced including organic solvents whose recovery is mandated by evermore strict laws. To reduce the dependence on ecologically unsafe chemicals, it is most advantageous to carry out reactions in aqueous media. Water is the cheapest abundantly available solvent. Indeed, water is recognized as an attractive medium for many organic reactions. Reactions in aqueous media are generally environmentally safe, devoid of any carcinogenic effects, simple to handle, comparatively cheaper to operate, and especially important in industry.[1,2] Further, coupling of this solvent-free synthesis with microwave irradiation (MWI) has associated benefits of shorter reaction times, uniform heating, higher yields, enhanced selectivity, and associated ease of manipulation.[3,4]

2-Amino-chromenes represent an important class of compounds being the main components of many natural occurring products and are widely employed as cosmetics, pigments,[5] and potential biodegradable agrochemicals.[6] Fused chromenes are biologically active compounds with a wide spectrum of activities viz. antimicrobial,[7] antiviral,[8,10] mutagenicity,[9] antiproliferative,[11] sex pheromone,[12] antitumor,[13] and central nervous system activity.[14] Thus, in view of the diverse therapeutic activity of chromenes and in continuation to our ongoing endeavour[15–17] aimed at developing new selective and environmentally benign methodologies using MWI, we report herein the synthesis of substituted 2-amino-4*H*-chromene and benzo[*e*]chromene derivatives and their in vitro antibacterial profile against gram negative and gram positive standard strains of bacteria using Broth Microdilution MIC method.[18]

2. Results and discussion

2-Amino-chromenes are generally prepared by refluxing malononitrile, aldehyde, and activated phenol in the presence of hazardous organic bases like piperdine in organic solvents like ethanol and acetonitrile for several hours.[19] A literature survey revealed that several modified procedures using CTACI,[20] TEBA,[21] and γ alumina[22] as catalyst have been recently reported but all these methods require long refluxing hours. To study the role of base used and to make the classical method a clean, efficient, economical, and green method utilizing MWI under solvent-free conditions, the reaction was

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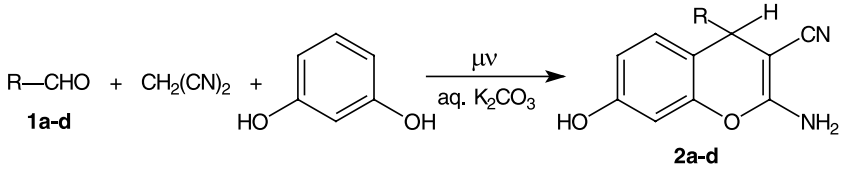
attempted in K_2CO_3. As a test case, a saturated solution of K_2CO_3 in water was added to the reaction mixture containing equimolar amount of aldehyde **1a–d**, malononitrile, and resorcinol (Scheme 1), and was subjected to MWI at low power (560 W). On completion of reaction as monitored by TLC, the reaction mixture was cooled and the solid obtained was triturated with few milliliters of water to give the required product **2a–d** in excellent yields within just few minutes of MWI. To extend the scope of this reaction and its utility as a new synthetic approach to substituted 2-amino-4*H*-chromene, we also studied the synthesis of substituted 2-amino-benzo[*e*]chromene derivatives (Scheme 2) by the condensation reaction of aldehyde **1a–d**, malononitrile, and β-naphthol in aqueous K_2CO_3. Excellent yield of products were obtained within few minutes of MWI (Table 1). Furthermore, the use of several heterocyclic aldehydes led to the synthesis of novel 4*H*-chromene derivatives. The structure of the products was confirmed on the basis of spectroscopic and analytical data (Table 2). To assess the efficiency of MWI in inducing these reactions, the reaction of activated phenols with aldehyde and malononitrile with classical heating under comparable reaction conditions (time and temperature) was also studied. However, in this case, the reaction gave impure product even after long hours of heating and in certain cases led to charring.

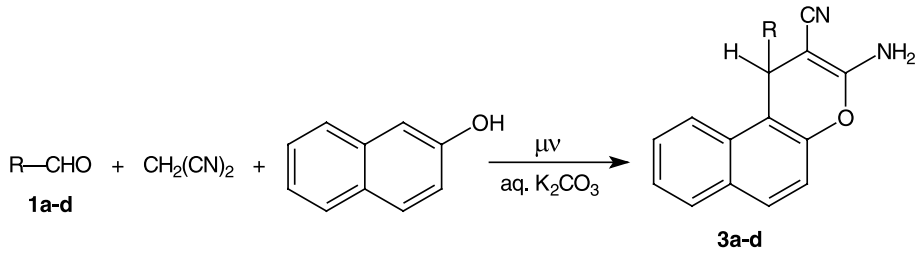
All the synthesized compounds **2a–d** and **3a–d** were dissolved in dimethylformamide (DMF) and tested for their antibacterial activity at concentrations of 0.5, 1.0, 2.0, 4.0, 8.0, 16.0, 32.0, 64.0, and 128.0 μg/ml using Broth Microdilution MIC method. All the compounds showed antibacterial activity against standard reference strains of *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853), and *Staphylococcus aureus* (ATCC 25923), and their MICs ranged between 64 and 128 μg/ml. Ampicillin was used as the standard drug (Table 3).

3. Conclusion

Thus, an easier, practically convenient, and ecofriendly green synthesis of substituted 2-amino-4*H*-chromene and benzo[*e*]chromene derivatives has been developed that avoids the use of harsh and highly environment contaminating conditions, viz., classical heating, use of expensive and toxic reagents, solvents, and catalyst. Moreover, it offers benefits like elimination of solvent,



Scheme 1. Synthesis of substituted 2-amino-4*H*-chromene derivatives in aqueous medium.



Scheme 2. Synthesis of substituted 2-amino-4*H*-benzo[*e*]chromene derivatives in aqueous medium.

Table 1. Reaction times and yields for compounds **2a–d** and **3a–d**

Compound	R	Melting point, mp (°C)	Time (min)[a]	Yield (%)
2a	Phenyl	232–234[b]	2.8	91
2b	Piperonyl	164–165[b]	2.5	92
2c	Indolyl	207–209	3.5	90
2d	2-Chloro-3-quinolyl	185–187	1.9	88
3a	Phenyl	278–279[b]	3.2	90
3b	Piperonyl	188–190[b]	2.9	93
3c	Indolyl	218–220	3.3	89
3d	2-Chloro-3-quinolyl	296–298	2.0	87

[a] Microwave heating (560 W, 2450 MHz, 95–105 °C, 30 s).
[b] See Ref. 24.

Table 2. Analytical and spectroscopic data of compounds **2a–d** and **3a–d**

Compound	IR (ν_{max} values in cm^{-1})	NMR (δ values in ppm) ($CDCl_3$, DMSO-d_6, 300 MHz)	Elemental analysis (%), found (calcd.)		
			C	H	N
2a	3420 (NH_2), 3210 (OH), 2193 (C≡N), 1677 (C=C, vinylnitrile), 1595 (C=C, aromatic)	4.32 (s, 1H, H-4), 6.78 (br s, 2H, NH_2), 7.02 (s, 1H, OH), 7.47–7.86 (m, 8H, ArH)	72.56 (72.72)	4.50 (4.54)	10.54 (10.60)
2b	3385 (NH_2), 3215 (OH), 2254 (C≡N), 1674 (C=C, vinylnitrile), 1585 (C=C, aromatic)	4.41 (s, 1H, H-4), 5.90 (s, 2H, OCH_2), 6.84 (br s, 2H, NH_2), 7.12 (s, 1H, OH), 7.32–7.75 (m, 6H, ArH)	66.58 (66.62)	3.81 (3.89)	9.01 (9.09)
2c	3354 (NH_2), 3205 (OH), 2212 (C≡N), 1655 (C=C, vinylnitrile), 1570 (C=C, aromatic)	4.52 (s, 1H, H-4), 6.89 (br s, 2H, NH_2), 7.14 (s, 1H, OH), 7.31–7.85 (m, 8H, ArH), 10.1 (s, 1H, NH indole)	71.21 (71.28)	4.22 (4.29)	13.78 (13.86)
2d	3343 (NH_2), 3212 (OH), 2205 (C≡N), 1664 (C=C, vinylnitrile), 1545 (C=C, aromatic)	5.35 (s, 1H, H-4), 6.92 (br s, 2H, NH_2), 7.08 (s, 1H, OH), 7.45–7.96 (m, 8H, ArH)	65.28 (65.23)	3.48 (3.43)	12.10 (12.01)
3a	3435 (NH_2), 3208 (OH), 2185 (C≡N), 1669 (C=C, vinylnitrile), 1560 (C=C, aromatic)	5.24 (s, 1H, H-4), 7.11 (br s, 2H, NH_2), 7.25–7.81 (m, 11H, ArH)	80.58 (80.53)	4.61 (4.69)	9.32 (9.39)
3b	3412 (NH_2), 3210 (OH), 2178 (C≡N), 1635 (C=C, vinylnitrile), 1545 (C=C, aromatic)	5.16 (s, 1H, H-4), 6.13 (s, 2H, OCH_2), 6.98 (br s, 2H, NH_2), 7.30–7.64 (m, 9H, ArH)	73.60 (73.68)	4.01 (4.09)	8.12 (8.18)
3c	3420 (NH_2), 3215 (OH), 2155 (C≡N), 1648 (C=C, vinylnitrile), 1538 (C=C, aromatic)	3.82 (s, 1H, H-4), 7.01 (br s, 2H, NH_2), 7.40–7.81 (m, 11H, ArH), 10.3 (s, 1H, NH, indole)	78.38 (78.33)	4.40 (4.45)	12.38 (12.46)
3d	3415 (NH_2), 3225 (OH), 2168 (C≡N), 1654 (C=C, vinylnitrile), 1560 (C=C, aromatic)	3.90 (s, 1H, H-4), 7.11 (br s, 2H, NH_2), 7.32–7.76 (m, 11H, ArH)	71.89 (71.96)	3.69 (3.65)	10.3 (10.9)

simplification of the work up, procedures, facility of scale up, and savings in energy consumption, and in addition giving higher yields of products and enhancement in reaction rate. Further, the use of water as a green solvent combined with the exploitation of the multicomponent strategy open to this process, suggests good prospects for its industrial applicability. All the compounds synthesized were shown to have antibacterial activity against standard strains of gram negative and gram positive bacteria.

4. Experimental

Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR-1710 spectrophotometer using KBr pellets. ^{1}H NMR spectra were recorded on a Bruker Avance 300 Spectrospin (300 MHz) instrument using TMS as an internal standard and $CDCl_3$/DMSO as a solvent. Microwave irradiation was carried out in a Kenstar Microwave Oven, Model No. OM 9925E (2450 MHz, 800 W). The reaction was monitored by TLC, using silica gel coated Al plates (Merck). The reaction temperature was measured through AZ, Mini Gun Type Non-Contact IR Thermometer (Model No. 8868). 2-Chloro-3-quinoline aldehyde was prepared according to literature method.[23]

4.1. General procedure for the synthesis of 2-amino-3-cyano-7-hydroxy-4-substituted-4*H*-chromene derivatives (2a–d)

Equimolar amounts of neat reactants, aldehyde (**1a–d**), malononitrile, and resorcinol were taken in an Erlenmeyer flask, and 10 ml saturated solution of K_2CO_3 in water was added to it. The reaction mixture was subjected to MWI for a specific time (Table 1) at low power (560 W). The progress of the reaction was monitored by TLC examination at an interval of every 30 s. On completion of reaction, the reaction mixture was cooled and was triturated with 2–3 ml of ice cold water to get the solid product **2a–d**, leaving behind K_2CO_3 dissolved in water. The product obtained was filtered, washed with cold water, dried, and recrystallized from ethanol.

4.2. General procedure for the synthesis of 2-amino-3-cyano-4-substituted-4*H*-benzo[*e*]chromene derivatives (3a–d)

An equimolar mixture of aldehyde (**1a–d**), malononitrile, and β-naphthol in 10 ml saturated solution of 10 ml K_2CO_3 was taken in an Erlenmeyer flask and subjected to MWI. On completion of reaction as monitored by TLC examination at an interval of 30 s, the reaction mixture was cooled and triturated with few milliliters of water and the product was recrystallized from ethanol.

4.3. Antibacterial activity

Screening of all the synthesized compounds for their antibacterial activity was performed by employing Broth Microdilution MIC method. Using sterile microtiter

Table 3. Antibacterial activity of different compounds (**2a–d** and **3a–d**) and ampicillin by Broth Microdilution MIC method

Concentration used (μg/ml)	Antibacterial activity against standard strains—Compounds																										
	2a			**2b**			**2c**			**2d**			**3a**			**3b**			**3c**			**3d**			Ampicillin		
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
0.5	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
1.0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
2.0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
4.0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
8.0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–
16.0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–
32.0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–
64.0	+	+	+	+	–	+	+	–	+	–	–	+	+	–	+	+	–	+	+	–	+	+	–	–	–	–	–
128.0	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

1, *E. coli* (ATCC 25922); 2, *P. aeruginosa* (ATCC 27853); 3, *S. aureus* (ATCC 25923); +, resistant; −, susceptible.

plates, 0.1 ml of Mueller Hinton Broth was added to each of the 96 wells. Doubling dilutions of each compound were made in the wells, thus a plate contained 0.5–128 μg/ml dilutions of eight different compounds and of ampicillin. In each plate, one well was kept as positive control (broth + inoculum) and another one as negative control (broth only). The inoculum was adjusted to a turbidity equivalent to McFarland 0.5 turbidity standard. The inoculum was suitably diluted so as to get a final concentration of approximately 5×10^5 cfu/ml of bacteria in each well. Each well was inoculated with 0.01 ml of the prepared inoculum using a multichannel micropipette and the plates were incubated overnight at 37 °C. The MICs of these compounds and ampicillin were determined by using the standard protocol of NCCLS Broth Microdilution MIC method.[18]

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