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ORIGINAL PAPER

A facile and expeditious approach for the synthesis of 2-azetidinone derivatives via a multicomponent reaction

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Abstract New organic reactions allow chemical transformations which were previously unknown. Therefore, new reactions are important contributions to progress in the field of organic synthesis. Herein, we are reporting a simple, one-pot, efficient three-component synthesis of novel 3-chloro-4-[4-(2-oxo-2*H*-chromen-4-ylmethoxy)phenyl]-1-phenylazetidin-2-one derivatives using 4-(2-oxo-2*H*-chromen-4-ylmethoxy)benzaldehydes, anilines, and chloroacetyl chloride in the presence of triethyl amine as a catalyst under different conditions. Taking into account environmental and economic considerations, the protocol presented here has the merits of simple operation, convenient work-up, being environmentally benign, and providing good yields. The synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, MS, and elemental analysis.

Keywords Multicomponent reaction · One-pot synthesis · Coumarin · 2-Azetidinones

Introduction

The increasing demand for the rapid synthesis of functional and biologically active molecules has stimulated synthetic chemists to explore and devise intelligent strategies that inevitably address the fundamental principles of efficiency and efficacy. Besides the crucial issues of chemo-, regio-, and stereoselectivity, these processes must also now consider economic factors and ecological aspects of green chemistry. Therefore, the intellectual challenge to invent concise, elegant, and conceptually novel synthetic routes has become a steadily increasing driving force in both academia and industry. In the past decade, the productive concepts of multicomponent processes have considerably stimulated the synthetic research community. Multicomponent reactions (MCRs) involving domino processes, with at least three different substrates reacting in a well-defined manner to form a single compound, have emerged as a powerful tool in organic synthesis [1]. In recent years MCRs have received considerable attention from the organic community due to their advantages over conventional multistep synthetic protocols [2]. These reactions constitute an especially attractive synthetic strategy, since they provide easy and rapid access to large libraries of organic compounds with diverse substitution patterns. In addition, MCRs are more environmentally benign and atom economic, as they avoid time-consuming and costly purification processes as well as protection–deprotection steps. They provide a powerful tool for the one-pot synthesis of diverse and complex compounds as well as small and drug-like heterocycles [3].

2-Azetidinones, commonly known as β-lactams, are well-known heterocyclic compounds among organic and medicinal chemists [4]. The activities of famous antibiotics such as penicillins, cephalosporins, thienamycin, nocardicins, aztreonam, and carbapenems are attributed to the presence of a 2-azetidinone ring in them. Azetidinones are a very important class of compounds possessing a wide range of biological activities, such as antimicrobial [5], anti-inflammatory [6], anticonvulsant [7], antibiotic [8], anticancer [9], antielastase [10], antiviral [11], antitumor [5], and anti-HCMV [12] activities.

It has also been reported that β-lactams have novel biological activities, such as cytomegalovirus protease inhibition [12], thrombin and tryptase inhibition [13],

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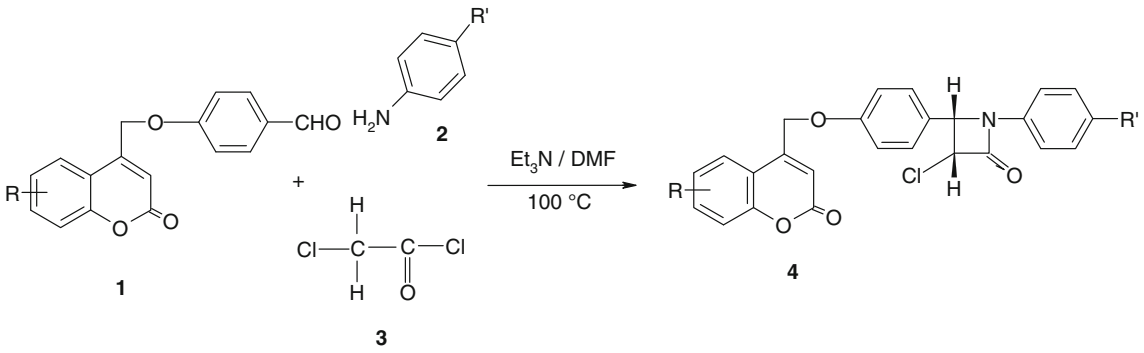


Scheme 1

cholesterol absorption inhibition [14], human leukocyte elastase (HLE) inhibition [15], and porcine pancreatic elastase (PPE) inhibition [16]. Besides their biological activities, the importance of *β*-lactams as synthetic intermediates has been widely recognized in organic synthesis [17]; for example, in the semisynthesis of taxol [18].

With the aim of developing efficient synthetic protocols, reducing laborious multiple steps and minimizing by-products, as part of our continuing interest in the development of new synthetic protocols in heterocyclic chemistry [19], this paper reports a practical, inexpensive method for the preparation of 2-azetidinone derivatives via multicomponent reactions of 4-(2-oxo-2*H*-chromen-4-yl-methoxy)benzaldehydes (**1**), anilines (**2**), and chloroacetyl chloride (**3**) under different conditions using triethylamine as catalyst (Scheme 1).

Results and discussion

In order to optimize the reaction conditions for the preparation of 3-chloro-4-[4-(6-methyl-2-oxo-2*H*-chromen-4-ylmethoxy)phenyl]-1-phenylazetidin-2-one (**4a**) using 4-(6-methyl-2-oxo-2*H*-chromen-4-ylmethoxy)benzaldehyde (**1**) and aniline (**2**) with chloroacetyl chloride (**3**) in the presence of a catalytic amount of triethylamine (1 mol%) in ethanol, the effects of solvents and temperature were studied under different reaction conditions. After stirring for 2–3 h at room temperature and monitoring with TLC, the reaction did not proceed. The mixture was then heated to reflux, and after stirring for 3.5 h TLC showed that the reaction proceeded smoothly and gave the product **4a** with a yield of 45% (Scheme 1). Based on this, different solvents were examined for the reaction at different temperatures. From Table 1, one can see that the reaction in DMF gave the best results (Table 1, entry 3), so DMF was chosen as the reaction solvent.

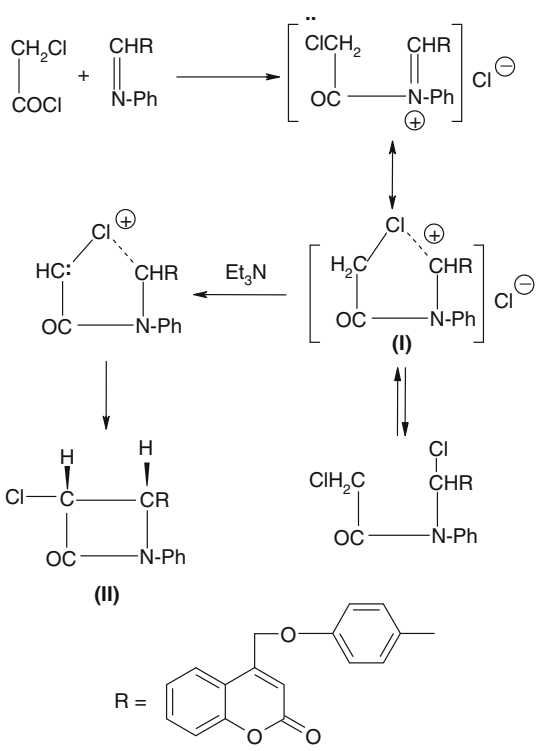
Table 1 Optimization of solvents for the synthesis of **4a**

Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	EtOH	80	3.5	45
2	Dry benzene	80	4.0	55
3	DMF	80	3.0	88
4	Dioxane	80	4.5	67
5	Dry xylene	80	3.0	56

Table 2 Temperature optimization for the synthesis of **4a** under MCR using DMF as solvent

Entry	Temperature (°C)	Time (h)	Yield (%)
1	70	5.0	56
2	80	5.0	59
3	90	4.0	70
4	100	3.0	88
5	110	2.5	72
6	120	2.5	68
7	130	2.0	72

To further optimize the reaction conditions, the same reaction was performed in DMF and at different temperatures ranging from 70 to 130 °C, increasing by 10 °C each time. The yield of product **4a** was increased and the reaction time was shortened as the temperature was raised from 70 to 100 °C (Table 2, entries 1–4). However, no significant increase in the yield of product **4a** was observed as the reaction temperature was raised from 110 to 130 °C (Table 2, entries 5–7). Therefore, 100 °C was chosen as the reaction temperature for all further reactions. After optimizing the reaction conditions, we prepared all azetidinone derivatives under same conditions. To explain the outcome of these reactions, we postulated the reaction mechanism of azetidinone formation from chloroacetyl chloride and imines. We concluded that the atom carrying a free pair of



Scheme 2

electrons would form a loose bond with carbon and generate a five-membered transition state (I). This would ease the formation of azetidinone (II) by bringing the appropriate carbon atoms C-3 and C-4 in (II) close enough to form a bond (Scheme 2) [20, 21]. The *cis* and *trans* stereochemistry of 2-azetidinones **4a**–**4t** was deduced from the coupling constants of H-3 and H-4, which were calculated to be greater than 4.0 Hz for the *cis* isomers and less than 2.5 Hz for the *trans* isomers. The coupling constants of all of the products formed were less than 2.5 Hz, so all of the products were *trans* isomers. The structures of compounds **4a**–**4t** were confirmed by IR, ^{1}H NMR, ^{13}C NMR, MS, and elemental analysis.

In the IR spectra of compound **4a**, the bands at 1,768 and 1,722 cm^{-1} correspond to the carbonyl stretching frequencies of the β-lactam ring and coumarin. In the ^{1}H NMR spectra of compound **4a**, the peak at $\delta = 5.34$ ppm is due to the >CH–Cl in the β-lactam ring; in the ^{13}C NMR spectra, a peak at 53.3 ppm was observed due to >CH–Cl and at 184.4 ppm due to cyclic >C=O in the β-lactam moiety. In the mass spectra of compound **4a**, the molecular ion peak was observed at 446 [M + 1].

Conclusions

In conclusion, we have developed a rapid and direct method that offers a simple and efficient route for one-pot, multicomponent synthesis of 2-azetidinone derivatives in good to excellent yields. This procedure offers several advantages, including mild reaction conditions; a cleaner reaction; satisfactory yields of products; an isolated procedure; easy work-up; increased safety in small-scale, high-speed synthesis; and broader substrate scope. Such advantages make it a useful and attractive protocol for the synthesis of these compounds.

Experimental

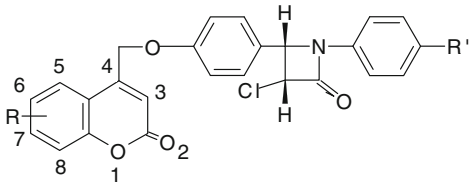
The melting points of the products were determined by an open capillary method on a Büchi apparatus. The IR spectra were recorded on a Nicolet Impact-410 FT-IR spectrophotometer using KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-300F spectrometer in $CDCl_3$ using TMS as an internal standard with a ^{1}H resonance frequency of 300 MHz and a ^{13}C resonance frequency of 75 MHz. The mass spectra were recorded on an Autospec EI-MS. The elemental analysis was carried out using a Heraus CHN rapid analyzer. All compounds gave C, H, and N analytical results that were within ±0.4% of the theoretical values. The homogeneity of the compounds was determined by TLC on 60 F_{254} aluminum silica gel (Merck), utilizing UV light (254 nm) detection and iodine vapor. Compounds **4p**–**4t** have been described previously [22].

General procedure

A solution of substituted 4-(2-oxo-2*H*-chromen-4-ylmethoxy)benzaldehyde (0.01 mol) and the appropriate aniline (0.01 mol) in 20 cm^{3} of DMF was stirred for half an hour. Then Et_3N (1 mol%) was added to the reaction mixture and it was stirred for another half an hour. Chloroacetyl chloride (0.01 mol) was then also added dropwise at room temperature. The resulting reaction mixture was vigorously stirred at 100 °C for a specific time (indicated in Table 3). After the reaction had completed (as monitored by TLC), the mixture was cooled and poured into crushed ice. The resulting precipitated solid was filtered and purified by recrystallization from DMF to afford the pure products.

3-Chloro-4-[4-(6-methyl-2-oxo-2H-chromen-4-ylmethoxy)phenyl]-1-phenylazetidin-2-one
(**4a**, $C_{26}H_{20}ClNO_4$)
Colorless shiny crystals from DMF; m.p.: 138–140 °C; IR (KBr): $\bar{\nu}$ = 3,089 (=CH–), 1,768 (>C=O of β-lactam), 1,722 (>C=O of coumarin), 1,520 (C=C), 782 (–C–Cl) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.38$ (s, 3H, C6–CH_3), 4.98 (s, 2H, CH_2–O), 5.05 (d, 1H, $J = 2.24$ Hz, H-4), 5.34 (d, 1H, $J = 2.5$ Hz, H-3), 6.65 (s, 1H, C3–H), 6.88–7.96 (m, 12H,

Table 3 Multicomponent synthesis of 2-azetidinone derivatives



Entry	Product	R	R′	Yield (%)[a]	m.p. (°C)
1	**4a**	6-CH_3	H	88	138–140
2	**4b**	7-CH_3	H	71	114–116
3	**4c**	6-Cl	H	63	118–120
4	**4d**	5,6-Benzo	H	74	198–200
5	**4e**	7,8-Benzo	H	65	232–234
6	**4f**	6-CH_3	CH_3	64	132–134
7	**4g**	7-CH_3	CH_3	72	208–210
8	**4h**	6-Cl	CH_3	82	183–185
9	**4i**	5,6-Benzo	CH_3	71	220–222
10	**4j**	7,8-Benzo	CH_3	65	110–112
11	**4k**	6-CH_3	OCH_3	64	170–172
12	**4l**	7-CH_3	OCH_3	71	98–100
13	**4m**	6-Cl	OCH_3	63	130–132
14	**4n**	5,6-Benzo	OCH_3	61	282–284
15	**4o**	7,8-Benzo	OCH_3	70	195–197
16	**4p**	6-CH_3	Cl	69	174–176
17	**4q**	7-CH_3	Cl	69	132–133
18	**4r**	6-Cl	Cl	65	175–177
19	**4s**	5,6-Benzo	Cl	60	122–124
20	**4t**	7,8-Benzo	Cl	71	180–182

All reactions were carried out at 100 °C in DMF

[a] Isolated yield

Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.0$, 53.3, 62.0, 80.8, 108.4, 115.2, 121.2, 125.2, 128.1, 134.4, 140.2, 148.4, 158.2, 162.1, 184.4 ppm; ESI-MS: $m/z = 446$ (M + 1).

3-Chloro-4-[4-(7-methyl-2-oxo-2H-chromen-4-ylmethoxy)phenyl]-1-phenylazetidin-2-one (**4b**, $C_{26}H_{20}ClNO_4$)

Colorless crystals from DMF; m.p.: 114–116 °C; IR (KBr): $\bar{\nu} = 3{,}109$ (=CH–), 1,772 (>C=O of β-lactam), 1,718 (>C=O of coumarin), 1,506 (C=C), 778 (–C–Cl) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.26$ (s, 3H, C7–CH_3), 4.67 (s, 2H, CH_2–O), 4.98 (d, 1H, $J = 2.18$ Hz, H-4), 5.40 (d, 1H, $J = 2.42$ Hz, H-3), 6.56 (s, 1H, C3–H), 6.70–8.02 (m, 12H, Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 23.4$, 56.7, 60.4, 82.0, 106.7, 114.0, 122.0, 126.8, 128.8, 132.8, 142.0, 149.0, 157.7, 160.6, 173.7 ppm; ESI-MS: $m/z = 446$ (M + 1).

3-Chloro-4-[4-(6-chloro-2-oxo-2H-chromen-4-ylmethoxy)phenyl]-1-phenylazetidin-2-one (**4c**, $C_{25}H_{17}Cl_2NO_4$)

Colorless crystals from DMF; m.p.: 118–120 °C; IR (KBr): $\bar{\nu} = 3{,}088$ (=CH–), 1,765 (>C=O of β-lactam), 1,722 (>C=O of coumarin), 1,500 (C=C), 782 (–C–Cl) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.79$ (s, 2H, CH_2–O), 5.20 (d, 1H, $J = 2.36$ Hz, H-4), 5.47 (d, 1H, $J = 2.20$ Hz, H-3), 6.40 (s, 1H, C3–H), 7.12–7.92 (m, 12H, Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 60.2$, 63.6, 79.6, 108.3, 113.2, 121.1, 123.6, 126.4, 136.6, 145.8, 150.3, 155.9, 164.4, 178.9 ppm; ESI-MS: $m/z = 466$ (M + 1).

3-Chloro-4-[4-(3-oxo-3H-benzo[f]chromen-1-ylmethoxy)phenyl]-1-phenylazetidin-2-one (**4d**, $C_{29}H_{20}ClNO_4$)

Slightly yellow crystals from DMF; m.p.: 198–200 °C; IR (KBr): $\bar{\nu} = 3{,}122$ (=CH–), 1,782 (>C=O of β-lactam), 1,730 (>C=O of coumarin), 1,521 (C=C), 792 (–C–Cl) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.57$ (s, 2H, CH_2–O), 5.08 (d, 1H, $J = 2.29$ Hz, H-4), 5.40 (d, 1H, $J = 2.47$ Hz, H-3), 6.36 (s, 1H, C3–H), 6.86–8.35 (m, 15H, Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 56.7$, 64.9, 82.1, 102.6, 110.8, 116.7, 120.0, 122.6, 126.4, 129.7, 134.0, 140.2, 149.6, 157.3, 160.1, 170.2 ppm; ESI-MS: $m/z = 482$ (M + 1).

3-Chloro-4-[4-(2-oxo-2H-benzo[h]chromen-4-ylmethoxy)phenyl]-1-phenylazetidin-2-one (**4e**, $C_{29}H_{20}ClNO_4$)

Red-colored crystals from DMF; m.p.: 232–234 °C; IR (KBr): $\bar{\nu} = 3{,}122$ (=CH–), 1,777 (>C=O of β-lactam), 1,726 (>C=O of coumarin), 1,507 (C=C), 781 (–C–Cl) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.62$ (s, 2H, CH_2–O), 5.32 (d, 1H, $J = 2.29$ Hz, H-4), 5.44 (d, 1H, $J = 2.41$ Hz, H-3), 6.20 (s, 1H, C3–H), 6.70–7.97 (m, 15H, Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 60.0$, 63.5, 80.0, 99.8, 107.2, 113.1, 122.4, 125.0, 127.7, 130.3, 135.3, 142.0, 150.8, 158.7, 163.2, 172.0 ppm; ESI-MS: $m/z = 482$ (M + 1).

3-Chloro-4-[4-(6-methyl-2-oxo-2H-chromen-4-ylmethoxy)phenyl]-1-(4-methylphenyl)azetidin-2-one (**4f**, $C_{27}H_{22}ClNO_4$)

Colorless shiny crystals from DMF; m.p.: 132–134 °C; IR (KBr): $\bar{\nu} = 3{,}089$ (=CH–), 1,768 (>C=O of β-lactam), 1,722 (>C=O of coumarin), 1,520 (C=C), 782 (–C–Cl) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.17$ (s, 3H, C6–CH_3), 2.38 (s, 3H, CH_3), 4.57 (s, 2H, CH_2–O), 5.12 (d, 1H, $J = 2.48$ Hz, H-4), 5.49 (d, 1H, $J = 2.34$ Hz, H-3), 6.55 (s, 1H, C3–H), 6.78–7.75 (m, 11H, Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 19.2$, 23.2, 59.1, 63.6, 82.5, 103.6, 110.0, 121.2, 125.2, 128.1, 134.4, 140.2, 148.4, 158.2, 162.1, 184.4 ppm; ESI-MS: $m/z = 460$ (M + 1).

3-Chloro-4-[4-(7-methyl-2-oxo-2H-chromen-4-ylmethoxy)phenyl]-1-(4-methylphenyl)azetidin-2-one
(**4g**, $C_{27}H_{22}ClNO_4$)
Colorless shiny crystals from DMF; m.p.: 208–210 °C; IR (KBr): $\bar{\nu}$ = 3,102 (=CH–), 1,772 (>C=O of β-lactam), 1,717 (>C=O of coumarin), 1,501 (C=C), 766 (–C–Cl) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.26 (s, 3H, C7–CH_3), 2.41 (s, 3H, CH_3), 4.62 (s, 2H, CH_2–O), 5.06 (d, 1H, J = 2.24 Hz, H-4), 5.51 (d, 1H, J = 2.34 Hz, H-3), 6.40 (s, 1H, C3–H), 6.68–7.56 (m, 11H, Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.0, 22.7, 60.3, 63.9, 80.8, 106.0, 112.3, 119.0, 122.2, 124.5, 125.5, 126.5, 133.0, 136.5, 138.3, 150.3, 154.5, 157.7, 160.0, 171.3 ppm; ESI-MS: *m/z* = 460 (M + 1).

3-Chloro-4-[4-(6-chloro-2-oxo-2H-chromen-4-ylmethoxy)phenyl]-1-(4-methylphenyl)azetidin-2-one
(**4h**, $C_{26}H_{19}Cl_2NO_4$)
White shiny crystals from DMF; m.p.: 183–185 °C; IR (KBr): $\bar{\nu}$ = 2,993 (=CH–), 1,768 (>C=O of β-lactam), 1,709 (>C=O of coumarin), 1,487 (C=C), 804 (–C–Cl) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.20 (s, 3H, CH_3), 4.32 (s, 2H, CH_2–O), 4.78 (d, 1H, J = 2.37 Hz, H-4), 5.37 (d, 1H, J = 2.25 Hz, H-3), 6.26 (s, 1H, C3–H), 6.82–7.68 (m, 11H, Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.9, 56.0, 61.6, 77.9, 109.1, 113.0, 120.2, 126.0, 128.5, 130.0, 134.6, 138.0, 150.0, 158.8, 163.3, 169.7 ppm; ESI-MS: *m/z* = 481 (M + 1).

3-Chloro-4-[4-(3-oxo-3H-benzo[f]chromen-1-ylmethoxy)phenyl]-1-(4-methylphenyl)azetidin-2-one
(**4i**, $C_{30}H_{22}ClNO_4$)
Yellow crystals from DMF; m.p.: 220–222 °C; IR (KBr): $\bar{\nu}$ = 3,102 (=CH–), 1,777 (>C=O of β-lactam), 1,726 (>C=O of coumarin), 1,507 (C=C), 779 (–C–Cl) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.17 (s, 3H, CH_3), 4.47 (s, 2H, CH_2–O), 5.07 (d, 1H, J = 2.46 Hz, H-4), 5.45 (d, 1H, J = 2.34 Hz, H-3), 6.42 (s, 1H, C3–H), 6.65–8.06 (m, 14H, Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.4, 52.3, 59.2, 78.6, 106.9, 114.2, 117.4, 120.0, 123.3, 127.0, 129.9, 136.2, 143.4, 148.2, 153.1, 158.7, 160.5, 165.3, 173.0 ppm; ESI-MS: *m/z* = 496 (M + 1).

3-Chloro-4-[4-(2-oxo-2H-benzo[h]chromen-4-ylmethoxy)phenyl]-1-(4-methylphenyl)azetidin-2-one
(**4j**, $C_{30}H_{22}ClNO_4$)
Reddish crystals from DMF; m.p.: 110–112 °C; IR (KBr): $\bar{\nu}$ = 3,115 (=CH–), 1,782 (>C=O of β-lactam), 1,722 (>C=O of coumarin), 1,495 (C=C), 787 (–C–Cl) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.25 (s, 3H, CH_3), 4.55 (s, 2H, CH_2–O), 5.12 (d, 1H, J = 2.27 Hz, H-4), 5.52 (d, 1H, J = 2.18 Hz, H-3), 6.30 (s, 1H, C3–H), 6.70–7.91 (m, 14H, Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0, 60.1, 64.1, 80.2, 107.0, 112.9, 120.1, 121.4, 122.8, 124.5, 127.7, 130.2, 133.2, 135.0, 138.6, 150.2, 155.3, 159.1, 160.7, 163.8, 169.6 ppm; ESI-MS: *m/z* = 496 (M + 1).

3-Chloro-1-(4-methoxyphenyl)-4-[4-(6-methyl-2-oxo-2H-chromen-4-ylmethoxy)phenyl]azetidin-2-one
(**4k**, $C_{27}H_{22}ClNO_5$)
Colorless shiny crystals from DMF; m.p.: 170–172 °C; IR (KBr): $\bar{\nu}$ = 3,089 (=CH–), 1,773 (>C=O of β-lactam), 1,716 (>C=O of coumarin), 1,479 (C=C), 779 (–C–Cl) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.09 (s, 3H, C_6–CH_3), 3.56 (s, 3H, OCH_3), 4.74 (s, 2H, CH_2–O), 5.05 (d, 1H, J = 2.19 Hz, H-4), 5.51 (d, 1H, J = 2.29 Hz, H-3), 6.37 (s, 1H, C3–H), 6.70–7.88 (m, 11H, Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3, 51.9, 60.2, 63.7, 80.8, 107.0, 111.3, 113.8, 120.7, 127.0, 128.6, 140.4, 146.9, 155.3, 158.1, 160.5, 163.0, 171.0 ppm; ESI-MS: *m/z* = 477 (M + 1).

3-Chloro-1-(4-methoxyphenyl)-4-[4-(7-methyl-2-oxo-2H-chromen-4-ylmethoxy)phenyl]azetidin-2-one
(**4l**, $C_{27}H_{22}ClNO_5$)
Colorless shiny crystals from DMF; m.p.: 98–100 °C; IR (KBr): $\bar{\nu}$ = 3,105 (=CH–), 1,766 (>C=O of β-lactam), 1,710 (>C=O of coumarin), 1,501 (C=C), 782 (–C–Cl) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.21 (s, 3H, C_7–CH_3), 3.71 (s, 3H, OCH_3), 4.53 (s, 2H, CH_2–O), 4.93 (d, 1H, J = 2.35 Hz, H-4), 5.33 (d, 1H, J = 2.12 Hz, H-3), 6.30 (s, 1H, C3–H), 6.66–7.70 (m, 11H, Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0, 47.7, 59.1, 62.0, 83.1, 105.9, 112.1, 115.2, 121.1, 122.5, 124.2, 126.3, 127.2, 128.8, 132.1, 134.7, 138.3, 150.1, 156.0, 159.0, 160.7, 162.3, 169.3 ppm; ESI-MS: *m/z* = 477 (M + 1).

3-Chloro-4-[4-(6-chloro-2-oxo-2H-chromen-4-ylmethoxy)phenyl]-1-(4-methoxyphenyl)azetidin-2-one
(**4m**, $C_{26}H_{19}Cl_2NO_5$)
Colorless shiny crystals from DMF; m.p.: 130–132 °C; IR (KBr): $\bar{\nu}$ = 3,091 (=CH–), 1,777 (>C=O of β-lactam), 1,716 (>C=O of coumarin), 1,487 (C=C), 779 (–C–Cl) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.50 (s, 3H, OCH_3), 4.61 (s, 2H, CH_2–O), 5.04 (d, 1H, J = 2.41 Hz, H-4), 5.41 (d, 1H, J = 2.50 Hz, H-3), 6.51 (s, 1H, C3–H), 6.76–7.88 (m, 11H, Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 50.3, 60.2, 63.6, 80.6, 105.9, 113.5, 116.2, 120.4, 121.9, 127.1, 128.5, 130.1, 133.0, 135.1, 145.7, 155.3, 159.2, 160.0, 163.1, 170.7 ppm; ESI-MS: *m/z* = 497 (M + 1).

3-Chloro-1-(4-methoxyphenyl)-4-[4-(3-oxo-3H-benzo[f]chromen-1-ylmethoxy)phenyl]azetidin-2-one
(**4n**, $C_{30}H_{22}ClNO_5$)
Yellow crystals from DMF; m.p.: 282–284 °C; IR (KBr): $\bar{\nu}$ = 3,118 (=CH–), 1,770 (>C=O of β-lactam), 1,731 (>C=O of coumarin), 1,515 (C=C), 792 (–C–Cl) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.41 (s, 3H, OCH_3), 4.53 (s,

2H, CH_2–O), 5.16 (d, 1H, $J = 2.48$ Hz, H-4), 5.51 (d, 1H, $J = 2.31$ Hz, H-3), 6.30 (s, 1H, C3–H), 6.85–7.91 (m, 14H, Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 53.1$, 60.0, 63.3, 80.4, 108.0, 112.7, 114.7, 121.2, 123.0, 126.6, 127.3, 128.9, 133.4, 137.0, 145.3, 150.2, 157.1, 159.7, 163.7, 168.2 ppm; ESI-MS: $m/z = 512$ (M + 1).

3-Chloro-1-(4-methoxyphenyl)-4-[4-(2-oxo-2H-benzo[h]chromen-4-ylmethoxy)phenyl]azetidin-2-one (**4o**, $C_{30}H_{22}ClNO_5$)

Slightly red-colored crystals from DMF; m.p.: 195–197 °C; IR (KBr): $\bar{\nu} = 3{,}104$ (=CH–), 1,782 (>C=O of β-lactam), 1,722 (>C=O of coumarin), 1,506 (C=C), 786 (–C–Cl) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.63$ (s, 3H, OCH_3), 4.67 (s, 2H, CH_2–O), 4.78 (d, 1H, $J = 2.13$ Hz, H-4), 5.23 (d, 1H, $J = 2.25$ Hz, H-3), 6.23 (s, 1H, C3–H), 6.76–7.83 (m, 14H, Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 47.7$, 56.3, 61.2, 82.1, 107.3, 113.0, 115.8, 118.2, 121.6, 123.4, 126.3, 127.7, 129.2, 133.7, 135.3, 148.3, 156.0, 159.1, 162.3, 170.3 ppm; ESI-MS: $m/z = 512$ (M + 1).

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