

Solution-phase Synthesis of a Combinatorial Library of 3-[4-(Coumarin-3-yl)-1,3-thiazol-2-ylcarbamoyl]propanoic acid Amides

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Abstract: The parallel solution-phase synthesis of a new combinatorial library of 3-[4-(R1-coumarin-3-yl)-1,3-thiazol-2-ylcarbamoyl]propanoic acid amides **9** has been developed. The synthesis involves two steps: 1) the synthesis of core building blocks – 3-[4-(coumarin-3-yl)-1,3-thiazol-2-ylcarbamoyl]propanoic acids, **6** – by the reaction of 3-(ω -bromacetyl)coumarins **1** with 3-amino(thioxo)methylcarbamoylpropanoic acid (**5**); 2) the synthesis of the corresponding 3-[4-(coumarin-3-yl)-1,3-thiazol-2-ylcarbamoyl]propanoic acid amides **9** using 1,1'-carbonyldimidazole as a coupling reagent. The advantages of the method compared to existing ones are discussed.

Keywords: Coumarin derivatives, 2-aminothiazole derivatives, dicarboxylic acids, combinatorial synthesis.

Introduction

2-Aminothiazole derivatives are widely used as pharmaceuticals. For example, Talipexol [1] and Pramipexole [2] with a 2-aminothiazole moiety are used as antiparkinsonian drugs and dopamine agonists; Tigemonam [3] is an antibacterial drug and Amthamine [4] is known as an antiasthmatic one. It is also known that heterocyclic compounds with free amino groups may exhibit teratogenic and mutagenic properties because of their ability to form non-covalent complexes with DNA [5,6]. That is

why 2-aminothiazole derivatives with an acylated amino group may be of interest as potentially less toxic drugs with a wide variety of pharmacological activities.

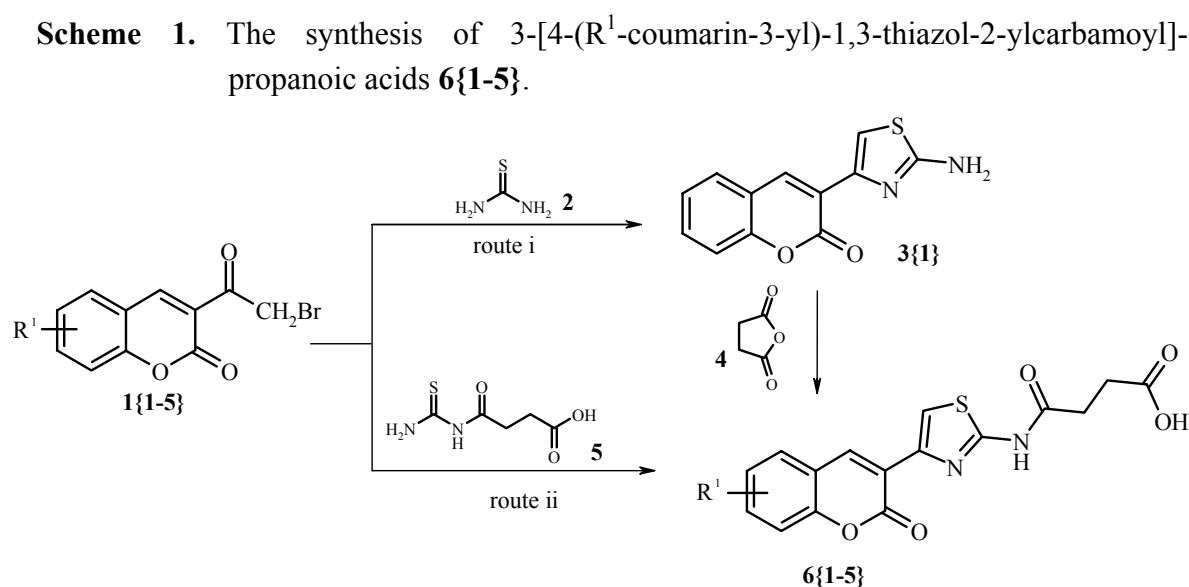
A number of publications have described the synthesis of 2-aminothiazoles, N-acylated with aliphatic [7 – 11], aromatic [7, 8, 10] and dicarboxylic acids [10, 12 – 17]. The importance of such derivatives is due to their biological properties; for example, some of them show significant bacteriostatic [7], tuberculostatic [8], hypoglycemic, anti-inflammatory, diuretic and fungicidal activities [10], and some of them are useful for treating of asthma [14].

However, there are only a few publications describing syntheses of 3-(*N*-acyl-2-amino-1,3-thiazol-4-yl)coumarin derivatives. These papers described syntheses of *N*-acetyl-*N*-allylamino-4-thiazolyl-coumarins [18], *N*-chloroacetamido derivatives [19], and *N*-benzoyl derivatives, which displayed significant analgesic and anti-inflammatory activity [20]. Some derivatives of *N*-[4-(*R*-coumarin-3-yl)-2-thiazolyl]oxamates possess anti-allergic, antianaphylactic and antiarthritic activity [21]. 2-Amino-4-(coumarin-3-yl)thiazoles were also acylated with the cycloaddition product of methacrylic acid and anthracene [22]. These compounds are glucocorticoid receptor modulators which are useful in treating diabetes, inflammatory and immune diseases.

In spite of the above mentioned activities of the corresponding oxamates, their succinic analogues have not been synthesized, though they may possess a great pharmacological potential. The aim of this work was to develop a method and detailed procedures suitable for solution-phase parallel synthesis of a library of 3-[4-(*R*¹-coumarin-3-yl)-1,3-thiazol-2-ylcarbamoyl]propanoic acid amides.

Results and Discussion

Different substituted 3-(ω -bromoacetyl)-*R*¹-coumarins **1{1-5}** [23] were used as starting compounds for the library synthesis. The synthesis of the core building blocks, 3-[4-(*R*¹-coumarin-3-yl)-1,3-thiazol-2-ylcarbamoyl]propanoic acids **6{1-5}**, has been carried out by two methods (Scheme 1).



According to the first pathway (route i, Scheme 1), 2-amino-4-(coumarin-3-yl)thiazole **3{1}** was obtained by reaction of 3-(ω -bromoacetyl)coumarine **1{1}** with thiourea (**2**), then it was directly

acylated with succinic anhydride (**4**). Generally heterocyclic amines are acylated by succinic anhydride in ethyl acetate [16], acetone [13], benzene [13] or glacial acetic acid media. We performed this synthesis both in benzene and glacial acetic acid, obtaining **6{1}** in yields of 48 and 52 %, respectively.

The second pathway (route ii, Scheme 1) involves synthesis of the intermediate 3-amino(thioxo)-methylcarbamoylpropanoic acid (**5**), by the acylation of thiourea (**2**) with succinic anhydride (**4**) [24]. Then the reaction of **5** in boiling ethanol or acetic acid for 10 – 25 minutes with 3-(ω -bromoacetyl)-R¹-coumarins **1{1-5}** yielded 3-[4-(R¹-coumarin-3-yl)-1,3-thiazol-2-ylcarbamoyl]propanoic acids **6{1-5}**. In this case the reaction was carried out in solution to facilitate the interaction. The product **6{1}** obtained by both methods found to be identical by m.p. and ¹H-NMR. However, the second route afforded compound **6{1}** in better yield and purity, and it was thus used to prepare compounds **6{2-5}** (Tables 1 and 2). Consequently the use of 3-amino(thioxo)methylcarbamoylpropanoic acid (**5**) (route ii, Scheme 1) for the synthesis of core building blocks, 3-[4-(R¹-coumarin-3-yl)-1,3-thiazol-2-ylcarbamoyl]propanoic acids **6**, has been found to be the preferable approach.

Table 1. Physico-chemical data of 3-[4-(R¹-coumarin-3-yl)-1,3-thiazol-2-ylcarbamoyl]propanoic acids

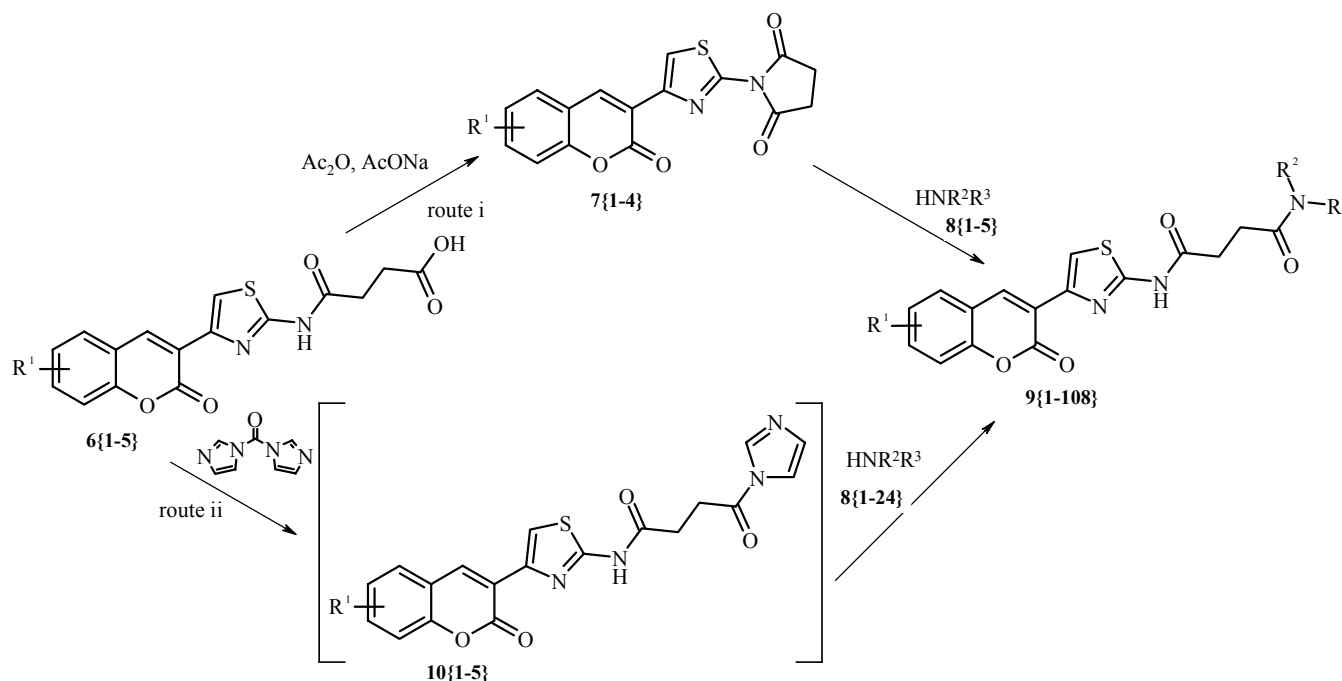
Code	R ¹	Yield, % (route ii)	Time of reaction	M.p. °C
6{1}	H	72	10 min	260-61
6{2}	8-OCH ₃	83	15 min	>300
6{3}	6-Cl	85	25 min	276-78
6{4}	7-OCH ₃	78	15 min	215-16
6{5}	8-OCH ₂ CH ₃	76	15 min	255-56

Table 2. IR and ¹H-NMR spectra of 3-[4-(R¹-coumarin-3-yl)-1,3-thiazol-2-ylcarbamoyl]propanoic acids

Code	IR-spectra			¹ H-NMR -spectra			
	ν N-H ν C-H	ν C=O ν C=N ν C=C	Coumarin ring, R ¹	s, 1H, H-4	s, 1H, H-5, thiazole	-CH ₂ CH ₂ -	NH, OH
6{1}	3455, 3412, 3142, 2980	1721, 1684, 1608, 1574	7.37 (t, 1H, H-6), 7.45 (d, 1H, H-8), 7.63 (t, 1H, H-7), 7.82 (d, 1H, H-5)	8.56	7.95	2.52 (t, 2H), 2.64 (t, 2H)	12.17 (s, 1H), 12.34 (s, 1H)
6{2}	3445, 3140, 2966	1723, 1686 1579	3.92 (s, 3H, OCH ₃), 7.33 (m, 3H, Ar)	8.54	7.96	2.50 (t, 2H), 2.67 (t, 2H)	12.15 (s, 1H), 12.33 (s, 1H)
6{3}	3447, 3134, 3050, 2828	1706, 1688 1560	7.45 (d, 1H, H-8), 7.63 (dd, 1H, H-7), 7.95 (d, 1H, H-5)	8.47	7.94	2.57 (t, 2H), 2.69 (t, 2H)	12.22 (s, 1H), 12.33 (s, 1H)
6{4}	3420, 3300, 3063, 2891	1708, 1671, 1612, 1555	3.87 (s, 3H, OCH ₃), 6.97 (dd, 1H, H-6), 7.06 (s, 1H, H-8), 7.72 (d, 1H, H-5)	8.51	7.87	2.50 (t, 2H), 2.64 (t, 2H)	12.15 (s, 1H), 12.33 (s, 1H)
6{5}	3441, 3151, 2985, 2893	1726, 1687, 1578	1.33 (t, 3H, OCH ₂ CH ₃), 4.15 (q, 2H, OCH ₂ CH ₃), 7.32 (m, 3H, Ar)	8.54	7.97	2.53 (t, 2H), 2.64 (t, 2H)	12.15 (s, 1H), 12.33 (s, 1H)

For the synthesis of amides of 3-[4-(R¹-coumarin-3-yl)-1,3-thiazol-2-ylcarbamoyl]propanoic acids **9** several approaches were also developed (Scheme 2).

Scheme 2. The synthesis of 3-[4-(R¹-coumarin-3-yl)-1,3-thiazol-2-ylcarbamoyl]propanoic acid amides **12**



Earlier we had reported the synthesis of some amides of 3-[4-(coumarin-3-yl)-1,3-thiazol-2-ylcarbamoyl]propanoic acid starting from the methyl ester of **6{1}** [25]. However, this method gave poor yields of the products (27 – 42%), due to the possibility of re-amidation as a side reaction and formation of succinic acid diamide as a by-product.

We have more successfully applied another two methods: one of them (route i, Scheme 2) involves utilization of 3-[4-(R¹-coumarin-3-yl)-1,3-thiazolyl-2-N-pyrrolidin-2,5-diones **7** as key intermediates for synthesis of **9{1-3}** [26] and the other one is the method using 1,1'-carbonyldimidazole as a coupling reagent (route ii, Scheme 2).

In accordance with the first method (route i, Scheme 2) the initial step is the synthesis of 3-[4-(R¹-coumarin-3-yl)-1,3-thiazolyl-2-N-pyrrolidin-2,5-diones **7{1-4}** (59 – 96%), which was performed by heating the corresponding acids **6** in acetic anhydride in the presence of sodium acetate. The pyrrolidindiones **7** were then treated in dioxane for 1-3 hours with a series of primary amines to form the corresponding amides **9{2, 3, 10, 14, 18, 22, 23, 26}**. However, the heterogeneous conditions of this procedure and steric difficulties make this method unsuitable for the synthesis of the combinatorial library.

According to the second method *N*¹-[4-(R¹-coumarin-3-yl)-1,3-thiazol-2-yl]-4-(1*H*-1-imidazolyl)oxobutanamides **10{1-5}**, which were generated *in situ* using 1,1'-carbonyldimidazole, were directly treated with corresponding amines **8{1-24}**. The reaction was carried out at 80°C using a 10% excess of amine. This method provided high yields of amides **9** and appeared to be suitable for application to solution-phase parallel synthesis methods.

Using this method the combinatorial library of 108 amides of 3-[4-(R¹-coumarin-3-yl)-1,3-thiazol-2-ylcarbamoyl]propanoic acid **9** has been accomplished. For illustration purposes 37 arbitrary compounds synthesized **9**{**1-37**} and their physico-chemical data are listed in the Table 3.

The structures of the compounds **6** and **9** have been confirmed by elemental analysis, ¹H-NMR and IR spectra. (Tables 2, 3 and 4). The ¹H-NMR spectra of the compounds **6**{**1-5**} showed a broad signal for the OH proton at δ 12.33 – 12.34 ppm and a NH signal at 12.15 – 12.22 ppm, whereas the corresponding amides **9** were characterised by two broad NH signals at 7.53 – 8.47 ppm and 12.30 – 12.41 ppm in the case of primary amides and only one signal at 11.95 – 12.25 ppm in the case of secondary amides. The protons of the succinic acid moiety showed two triplets at 2.52 (2H) and 2.64 (2H) for the most of compounds **9** but in the case of the morpholinyl and *N*-methylpiperazinyl amides (**9**{**5**}, **9**{**12**} and **9**{**37**}) their signals are observed as singlet (4H) protons at 2.59 for **9**{**5**}, **9**{**12**} and at 2.65 ppm for **9**{**37**}. The IR spectra of all compounds exhibited strong absorption bands 1726 – 1684 cm⁻¹ (νC=O) and a broad band at 3445 – 3420 cm⁻¹ (νO–H) in the case of 3-[4-(R¹-coumarin-3-yl)-1,3-thiazol-2-ylcarbamoyl]propanoic acids **6**; amides **9** have NH bands at 3448 – 3176 cm⁻¹.

Conclusions

Two alternative approaches for synthesis of 3-[4-(R¹-coumarin-3-yl)-1,3-thiazol-2-ylcarbamoyl]propanoic acids **6** have been compared. In the first pathway (route i) 3-(2-amino-1,3-thiazol-4-yl)-coumarine **3**{**1**} was directly acylated with succinic anhydride (**4**) in benzene or in glacial acetic acid medium, in the second method (route ii) we used the Hantsch reaction between 3-(ω-bromacetyl)oumarins **1**{**1-5**} and 3-amino(thioxo)methylcarbamoylpropanoic acid (**5**). However, the second route has been found to afford the targets **6** in better yields and purity. The choice of the synthetic method for a new combinatorial library of 3-[4-(R¹-coumarin-3-yl)-1,3-thiazol-2-ylcarbamoyl]propanoic acid amides **9** by the solution-phase parallel synthesis method has been established. Using this method the combinatorial library of 108 amides of 3-[4-(R¹-coumarin-3-yl)-1,3-thiazol-2-ylcarbamoyl]propanoic acid **9** has been accomplished.

Table 3. Physico-chemical data of 3-[4-(R¹-coumarin-3-yl)-1,3-thiazol-2-ylcarbamoyl]propanoic acids amides

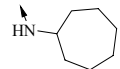
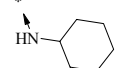
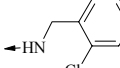
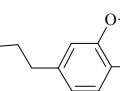
Code	Structure R ¹ = H	Molecular formula, M.w.	M.p., °C	Yield, %	N, %, calc/ found	IR-spectral data		
						ν N-H	ν C=O	ν C=N ν C=C
9 { 1 }		C ₂₃ H ₂₅ N ₃ O ₄ S 439.54	262-63	77	9.56 9.60	3320	1696	1642 1604 1538
9 { 2 }		C ₂₂ H ₂₃ N ₃ O ₄ S 425.51	278-80	85	9.88 9.85	3316 3292	1696	1644 1604 1537
9 { 3 }		C ₂₃ H ₁₈ ClN ₃ O ₄ S 467.93	244-46	65	8.98 9.01	3317 3292	1696	1643 1604 1538
9 { 4 }		C ₂₆ H ₂₅ N ₃ O ₆ S 507.57	228-30	73	8.28 8.30	3344	1719 1686	1641 1605 1547

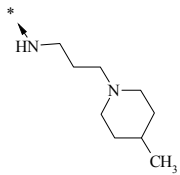
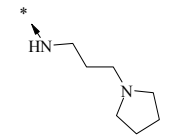
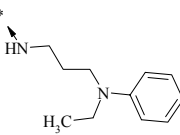
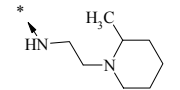
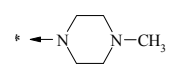
Table 3. Cont.

Code	Structure R ¹ = H	Molecular formula, M.w.	M.p., °C	Yield, %	N, %, calc/ found	IR-spectral data		
						ν N-H	ν C=O	ν C=N ν C=C
9{5}		C ₂₀ H ₁₉ N ₃ O ₅ S 413.46	273-75	60	10.16 10.15	3176	1719	1627 1648 1527
9{6}		C ₂₅ H ₂₁ N ₃ O ₄ S 459.53	259-61	78	9.14 9.15	3423 3256	1711	1616 1546
9{7}		C ₂₈ H ₂₈ N ₄ O ₄ S 516.62	243-45	92	11.15 11.14	3407 3314 3295	1695	1641 1544
9{8}		C ₂₃ H ₂₆ N ₄ O ₅ S 470.55	239-41	90	11.91 11.88	3407 3340 3244	1699	1656 1553
9{9}		C ₂₆ H ₃₂ N ₄ O ₅ S 512.63	182-84	65	10.93 10.94	3254	1728	1640 1605 1549
9{10}	R1= 8-OCH₃ 	C ₂₅ H ₂₁ N ₃ O ₇ S 507.53	253-55	73	8.28 8.31	3255	1720	1647 1604 1577
9{11}		C ₂₃ H ₂₅ N ₃ O ₄ S 439.54	252-53	89	7.82 7.82	3344	1710	1634 1607 1577
9{12}		C ₂₁ H ₂₁ N ₃ O ₆ S 443.48	272-73	63	9.48 9.50	3245	1720	1628 1691 1573
9{13}		C ₂₆ H ₂₅ N ₃ O ₅ S 491.57	252-54	76	8.55 8.54	3408 3294	1700	1642 1545
9{14}		C ₂₅ H ₂₂ ClN ₃ O ₅ S 511.99	275-77	72	8.21 8.23	3292	1700	1647 1572 1548
9{15}		C ₂₄ H ₂₇ N ₃ O ₅ S 469.56	257-59	58	8.95 8.97	3430 3301	1688	1637 1545
9{16}		C ₂₃ H ₂₄ N ₄ O ₆ S 484.53	306-08	47	11.24 11.27	3448 3252 3223	1726	1656 1624 1550
9{17}		C ₂₂ H ₁₉ N ₃ O ₆ S 453.48	281-82	63	9.27 8.28	3355 3236	1719	1650 1571 1547
9{18}		C ₂₄ H ₂₀ ClN ₃ O ₅ S 497.96	282-83	68	8.44 8.43	3426 3293	1700	1639 1575 1545
9{19}		C ₂₆ H ₂₃ N ₃ O ₅ S 489.55	259-60	73	8.58 8.58	3408 3236	1721	1627 1688 1544

Table 3. Cont.

Code	Structure R ¹ = H	Molecular formula, M.w.	M.p., °C	Yield, %	N, %, calc/ found	IR-spectral data		
						ν N-H	ν C=O	ν C=N ν C=C
9{20}		C ₂₂ H ₁₈ ClN ₃ O ₅ S 471.92	274-75	83	8.90 8.94	3407 3334 3244	1704	1649 1547
9{21}		C ₂₈ H ₂₇ ClN ₄ O ₄ S 551.07	259-60	87	10.17 10.18	3448 3255	1736	1666 1556
9{22}		C ₂₄ H ₁₉ Cl ₂ N ₃ O ₄ S 516.41	246-47	76	8.14 8.15	3360	1726	1657 1640 1557 1534
9{23}		C ₂₃ H ₂₄ ClN ₃ O ₄ S 473.98	255-56	69	8.87 8.91	3252	1734	1657 1632 1556 1547
9{24}		C ₂₃ H ₂₅ ClN ₄ O ₄ S 489.00	229-30	56	11.46 11.45	3366 3348 3238	1704	1659 1552
9{25}		C ₂₆ H ₂₄ ClN ₃ O ₆ S 542.01	243-45	74	7.75 7.74	3360 3179	1729	1655
9{26}	R1= 7-OCH₃ 	C ₂₃ H ₂₅ N ₃ O ₅ S 455.54	270-72	66	9.22 9.22	3292 3228	1708	1644 1612 1564 1540
9{27}		C ₂₅ H ₂₂ ClN ₃ O ₅ S 511.99	249-50	72	8.21 8.25	3324 3288 3256	1716	1664 1648 1552
9{28}		C ₂₅ H ₃₀ N ₄ O ₅ S 498.61	196-98	56	11.24 11.21	3360 3248	1716	1648 1620 1560
9{29}		C ₂₂ H ₁₉ N ₃ O ₆ S 453.48	307-08	63	9.27 9.31	3360 3232	1716	1648 1616 1548 1540
9{30}		C ₂₃ H ₂₁ N ₃ O ₆ S 467.50	277-79	82	8.99 8.98	3364 3236	1724	1648 1616 1688 1548
9{31}		C ₂₂ H ₂₃ N ₃ O ₅ S 441.51	267-68	66	9.52 9.50	3228	1708	1648 1620 1684 1540
9{32}	R1=8-OCH₂CH₃ 	C ₂₈ H ₂₇ N ₃ O ₅ S 517.61	301-02	79	8.12 8.16	3308	1720	1616 1604 1540

Table 3. Cont.

Code	Structure R ¹ = H	Molecular formula, M.w.	M.p., °C	Yield, %	N, %, calc/ found	IR-spectral data		
						ν N-H	ν C=O	ν C=N ν C=C
9{33}		C ₂₇ H ₃₄ N ₄ O ₅ S 526.66	210-12	71	10.64 10.65	3280	1708 1684	1616 1604 1544
9{34}		C ₂₅ H ₃₀ N ₄ O ₅ S 498.61	208-10	53	11.24 11.28	3332 3280	1708 1684	1648 1616 1604 1572 1544
9{35}		C ₂₉ H ₃₂ N ₄ O ₅ S 548.67	230-32	87	10.21 10.23	3356	1720 1688	1644 1604 1552
9{36}		C ₂₆ H ₃₂ N ₄ O ₅ S 512.63	213-15	62	10.93 10.95	3304	1720 1700	1652 1604 1572 1544
9{37}		C ₂₃ H ₂₆ N ₄ O ₅ S 470.55	259-61	56	11.91 11.96	3439 3258	1718 1695	1624 1557

Experimental

General

The melting points were measured with a Buchi B-520 melting point apparatus and are not corrected. IR spectra were recorded on Specord M80 spectrometers in KBr. ¹H-NMR spectra were recorded on Varian WXR-400 (200 MHz) and Bruker DRX-500 (500 MHz) spectrometers in DMSO-*D*₆ or CDCl₃ using TMS as an internal standard (chemical shifts are reported in ppm). 3-(ω-Bromacetyl)-R¹-coumarins **1{1-5}** were prepared according to a reported method [23].

3-(2-Amino-1,3-thiazol-4-yl)coumarin (3{1}). Thiourea (**2**, 0.38 g, 5 mmol) was added to the solution of 3-(ω-bromacetyl)coumarin (**1**, 1.34 g, 5 mmol) in boiling ethanol (20 mL). The mixture was refluxed for 1 hour, then cooled and neutralized with aqueous ammonia. The precipitate was filtered off, washed with ethanol and used directly without crystallization or other purification. Yield 84%, m.p. 225-226°C.

3-Amino(thioxo)methylcarbamoylpropanoic acid (5). Thiourea (**2**, 3.8 g, 50 mmol) and succinic anhydride (**4**, 5.0 g, 50 mmol) were well mixed, then this mixture was placed in a 25 mL round-bottomed flask equipped with a magnetic stirrer and heated in an oil bath at 150°C for 10 minutes; without any other additional solvent. Then the reaction mixture had cooled, the flask was broken and

the resulting product was crystallized from 10 % acetic acid to form yellow crystals of the title compound. Yield 80%, m.p.210-211°C [24].

General method for synthesis of 3-[4-(R¹-coumarin-3-yl)-1,3-thiazol-2-ylcarbamoyl]propanoic acids (**6{1-5}**).

Route i

A mixture of 3-(2-amino-1,3-thiazol-4-yl)coumarin (**3{1}**, 2.44 g, 10 mmol) and dihydrofuran-2,5-dione (**4**, 1.0 g, 10 mmol) was heated in benzene (25 mL) with the addition of glacial acetic acid (1.5 mL) (Method A) or in glacial acetic acid (30 mL) (Method B). The reaction mixture was refluxed for 2 – 3 h and then cooled. The solid formed was filtered off, dried and recrystallized from dioxane. Yield 48%, m.p. 260-261°C.

Route ii

3-Amino(thioxo)methylcarbamoylpropanoic acid (**5**, 1.76 g, 10 mmol) was added to the solution of the corresponding 3-(ω-bromacetyl)-R¹-coumarin **4** (10 mmol) in glacial acetic acid (30 mL) or ethanol (30 mL). The reaction mixture was heated under a condenser for 15 – 20 minutes, then cooled and diluted with water. The precipitate formed was filtered off, washed with water and crystallized from glacial acetic acid. Yield 72%, m.p.=260-261°C.

3-[4-(R¹-coumarin-3-yl)-1,3-thiazolyl-2-N-pyrrolidin-2,5-diones (**7{1-4}**) were prepared according to the reported method [26].

*Synthesis of 3-[4-(R¹-coumarin-3-yl)-1,3-thiazol-2-ylcarbamoyl]propanoic acid amides **9{2, 3, 10, 14, 18, 22, 23, 26}** (Route i)*

To a suspension of the corresponding 3-[4-(R¹-coumarin-3-yl)-1,3-thiazolyl-2-N-pyrrolidin-2,5-dione **7** (10 mmol) in anhydrous dioxane (30 mL) an appropriate primary amine **8** (15 mmol) was added. The reaction mixture was refluxed for 1 – 3 h. After cooling the mixture was poured into cold water (50 mL) to form a precipitate of the corresponding amide. Solids were filtered off and purified by crystallization from a DMF – ethanol mixture.

*Synthesis of 3-[4-(R¹-coumarin-3-yl)-1,3-thiazol-2-ylcarbamoyl]propanoic acid amides **9{1-108}** (Route ii)*

A solution of 1,1'-carbonyldiimidazole (**7**, 27 mmol) in anhydrous dioxane (120 mL) was added to the stirred suspension of the corresponding 3-[4-(R¹-coumarin-3-yl)-1,3-thiazol-2-ylcarbamoyl]-propanoic acid **6** (24 mmol) in anhydrous dioxane (240 mL) at 90°C. The mixture was stirred at reflux for 2 h, then the solution was cooled and dispensed into 24 combinatorial vials (15 mL per vial). The appropriate primary or secondary amine **8{1-24}** (1.1 mmol) was then added to these aliquots by injection and the resulting mixtures were heated at 80°C for 12 hours. After cooling each portion was poured into cold water (50 mL) to form the precipitate of the corresponding amide. The solids separated were filtered off and purified by crystallization from a DMF – 2-propanol mixture.

Table 4. ¹H-NMR -spectra of 3-[4-(R¹-coumarin-3-yl)-1,3-thiazol-2-ylcarbamoyl]propanoic acids amides

Code	Coumarin ring, R ¹	s, 1H, H-4	s, 1H, H-5- thiazole	-CH ₂ CH ₂ -	NH	R2, R3
9{1}	7.37 (t, 1H, H-6), 7.47 (d, 1H, H-8), 7.63 (t, 1H, H-7), 7.83 (d, 1H, H-5)	8.55	7.65	2.38 (t, 2H), 2.65 (t, 2H)	7.81 (br.d, 1H), 12.30 (s, 1H)	1.30 – 1.65 (m, 12H), 3.68 (s, 1H)
9{2}	7.38 (t, 1H, H-6), 7.44 (d, 1H, H-8), 7.63 (t, 1H, H-7), 7.83 (d, 1H, H-5)	8.52	7.96	2.38 (t, 2H), 2.65 (t, 2H)	7.73 (br.d, 1H), 12.41 (s, 1H)	1.10 (m, 5H), 1.60 (m, 5H), 3.48 (s, 1H)
9{3}	7.35 (t, 1H, H-6), 7.43 (d, 1H, H-8), 7.63 (t, 1H, H-7), 7.83 (d, 1H, H-5)	8.56	7.77	2.38 (t, 2H), 2.65 (t, 2H)	8.44 (br.d, 1H), 12.18 (s, 1H)	4.32 (d, 2H, CH ₂), 7.30 (m, 4H, Ar)
9{4}	7.35 (t, 1H, H-6), 7.46 (d, 1H, H-8), 7.62 (t, 1H, H-7), 7.82 (d, 1H, H-5)	8.51	7.99	2.52 (t, 2H), 2.78 (t, 2H)	7.99 (br.t, 1H), 12.30 (s, 1H)	2.60 (t, 2H, CH ₂ CH ₂), 3.20 (q, 2H, CH ₂ CH ₂), 3.70 (s, 6H, 2OCH ₃), 6.40 (d, 1H), 6.65 (d, 2H)
9{5}	7.36 (t, 1H, H-6), 7.42 (d, 1H, H-8), 7.60 (t, 1H, H-7), 7.79 (d, 1H, H-5)	8.55	7.95	2.65 (s, 4H)	12.1 (s, 1H)	3.47 (br.d, 8H, 4CH ₂)
9{6}	7.39 (t, 1H, H-6), 7.46 (d, 1H, H-8), 7.64 (t, 1H, H-7), 7.83 (d, 1H, H-5)	8.58	7.98	2.72 (m, 4H)	12.18 (s, 1H)	2.89 (d, 2H, CH ₂), 3.69 (d, 2H, CH ₂), 4.62 (d, 2H, CH ₂), 7.18 (m, 4H, Ar)
9{7}	7.37 (t, 1H, H-6), 7.44 (d, 1H, H-8), 7.63 (t, 1H, H-7), 7.82 (d, 1H, H-5)	8.62	7.96	2.40 (t, 2H), 2.65 (m, 2H)	7.25 (m, 1H), 12.23 (s, 1H)	1.33 (t, 2H, CH ₂), 1.62 (d, 2H, CH ₂), 1.95 (t, 2H, CH ₂), 2.65 (m, 2H, CH ₂), 3.37 (s, 2H, CH ₂ Ar), 3.50 (m, 1H, CH), 7.25 (m, 5H Ar)
9{8}	7.37 (t, 1H, H-6), 7.43 (d, 1H, H-8), 7.63 (t, 1H, H-7), 7.79 (d, 1H, H-5)	8.54	7.94	2.43 (t, 2H), 2.68 (t, 2H)	7.69 (m, 1H), 12.12 (s, 1H)	1.53 (m, 2H, CH ₂), 2.26 (m, 6H, 3CH ₂), 3.07 (q, 2H, CH ₂), 3.55 (m, 4H, 2CH ₂)
9{9}	3.80 (s, 3H, OCH ₃), 7.65 (m, 3H)	8.55	7.99	2.38 (t, 2H), 2.65 (t, 2H)	7.87 (t, 1H)	0.60 (t, 3H, CH ₃), 1.07 (dt, 2H, CH ₂), 1.40 (m, 1H, CH), 1.45 (m, 4H, 2CH ₂), 1.75 (t, 2H, CH ₂), 2.70 (m, 4H 2CH ₂), 3.05 (q, 2H, CH ₂)
9{10}	3.85 (s, 3H, OCH ₃), 7.32 (m, 3H)	8.52	7.99	2.40 (t, 2H), 2.60 (t, 2H)	8.35 (t, 1H), 12.32 (s, 1H)	4.15 (d, 2H, CH ₂), 5.95 (s, 1H, OCH ₂ O), 6.37 (d, 1H), 6.51 (d, 2H)
9{11}	3.91 (s, 3H, OCH ₃), 7.32 (m, 3H)	8.52	7.95	2.40 (t, 2H), 2.63 (t, 2H)	7.90 (br.t, 1H), 12.24 (s, 1H)	2.65 (t, 2H, CH ₂), 3.15 (q, 2H, CH ₂), 3.66 (s, 3H, OCH ₃), 3.71 (s, 3H, OCH ₃), 6.20 (d, 1H), 6.78 (d, 2H)
9{12}	3.89 (s, 3H, OCH ₃), 7.28 (m, 3H)	8.49	7.92	2.65 (s, 4H)	12.20 (s, 1H)	3.45 (br.d, 8H, 4CH ₂)
9{13}	3.94 (s, 3H, OCH ₃), 7.31 (m, 3H)	8.54	7.96	2.39 (t, 2H), 2.65 (t, 2H)	7.89 (m, 1H), 12.22 (s, 1H)	2.65 (m, 2H, CH ₂), 3.15 (s, 2H, CH ₂), 7.06 (s, 4H)
9{14}	3.92 (s, 3H, OCH ₃), 7.27 (m, 3H)	8.52	7.94	2.35 (t, 2H), 2.62 (t, 2H)	7.97 (br.t, 1H), 12.19 (s, 1H)	2.78 (t, 2H, CH ₂), 3.20 (s, 2H, CH ₂), 7.27 (m, 4H)
9{15}	3.94 (s, 3H, OCH ₃), 7.30 (m, 3H)	8.53	7.96	2.39 (t, 2H), 2.65 (m, 2H)	7.53 (br.d, 1H), 12.25 (s, 1H)	0.80 (d, 3H, CH ₃), 1.40 (m, 8H, 4CH ₂), 1.73 (m, 2H, 2CH)

Table 4. Cont.

Code	Coumarin ring, R ¹	s, 1H, H-4	s, 1H, H-5- thiazole	-CH ₂ CH ₂ -	NH	R2, R3
9{16}	3.87 (s, 3H, OCH ₃), 7.25 (m, 3H)	8.49	7.93	2.59 (s, 4H)	12.12 (s, 1H)	1.40 (m, 4H, 2CH ₂), 2.23 (t, 2H, CH ₂), 2.99 (t, 2H, CH ₂), 4.23 (d, 1H, CH), 6.72 (s, 1H, NH), 7.20 (s, 1H, NH)
9{17}	3.87 (s, 3H, OCH ₃), 7.27 (m, 3H)	8.49	7.93	2.46 (t, 2H), 2.67 (t, 2H)	8.34 (br.t, 1H), 12.18 (s, 1H)	4.23 (d, 2H, CH ₂), 6.22 (d, 1H), 6.39 (t, 1H), 7.52 (d, 1H)
9{18}	3.88 (s, 3H, OCH ₃), 7.30 (m, 3H)	8.49	7.97	2.55 (t, 2H), 2.73 (t, 2H)	8.47 (br.t, 1H), 12.42 (s, 1H)	4.29 (d, 2H, CH ₂), 7.30 (m, 4H)
9{19}	3.92 (s, 3H, OCH ₃), 7.23 (m, 3H)	8.53	7.94	2.63 (m, 4H)	12.18 (s, 1H)	2.87 (d, 2H, CH ₂), 3.68 (d, 2H, CH ₂), 4.62 (d, 2H, CH ₂), 7.12 (m, 4H)
9{20}	7.44 (d, 1H, H-8), 7.71 (dd, 1H, H-7), 7.94 (d, 1H, H-5)	8.49	7.99	2.42 (t, 2H), 2.65 (t, 2H)	8.24 (br.t, 1H), 12.21 (s, 1H)	2.12 (s, 3H, CH ₃), 4.15 (d, 2H, CH ₂), 5.93 (d, 1H), 6.07 (d, 1H)
9{21}	7.39 (d, 1H, H-8), 7.53 (dd, 1H, H-7), 7.89 (d, 1H, H-5)	8.52	7.99	2.45 (t, 2H), 2.67 (t, 2H)	7.62 (br.d, 1H), 12.18 (s, 1H)	1.44 (m, 2H, CH ₂), 1.72 (m, 2H, CH ₂), 2.04 (m, 2H, CH ₂), 2.75 (m, 2H, CH ₂), 3.55 (m, 1H, CH), 7.18 (q, 1H), 7.26 (d, 4H)
9{22}	7.45 (d, 1H, H-8), 7.61 (dd, 1H, H-7), 7.94 (d, 1H, H-5)	8.47	7.98	2.35 (t, 2H), 2.63 (t, 2H)	7.97 (m, 1H), 12.22 (s, 1H)	2.79 (t, 2H, CH ₂), 3.20 (s, 2H CH ₂), 7.28 (m, 4H)
9{23}	7.44 (d, 1H, H-8), 7.62 (dd, 1H, H-7), 7.93 (d, 1H, H-5)	8.49	7.93	2.39 (t, 2H), 2.65 (t, 2H)	7.62 (d, 1H), 12.05 (s, 1H)	1.39 (m, 10H, 5CH ₂), 1.72 (m, 2H, CH ₂), 3.68 (m, 1H, CH)
9{24}	7.45 (d, 1H, H-8), 7.62 (dd, 1H, H-7), 7.95 (d, 1H, H-5)	8.48	7.98	2.33 (m, 2H), 2.67 (t, 2H)	7.30 (br.t, 1H)	1.25 (m, 2H, CH ₂), 1.49 (m, 2H, CH ₂), 1.63 (m, 4H, 2CH ₂), 2.32 (m, 6H, 3CH ₂), 3.05 (q, 2H, CH ₂)
9{25}	7.46 (d, 1H, H-8), 7.65 (dd, 1H, H-7), 7.94 (d, 1H, H-5)	8.50	7.99	2.43 (m, 2H), 2.63 (m, 2H)	7.84 (br.t, 1H), 12.12 (s, 1H)	2.65 (m, 2H, CH ₂), 3.22 (m, 2H, CH ₂), 3.71 (s, 6H, 2OCH ₃), 6.70 (m, 3H)
9{26}	3.92 (s, 3H, OCH ₃), 6.97 (dd, 1H, H-6), 7.03 (s, 1H, H-8), 7.72 (d, 1H, H-5)	8.51	7.84	2.38 (m, 2H), 2.65 (t, 2H)	7.62 (br.d, 1H), 12.01 (s, 1H)	1.10 (m, 5H), 3.48 (s, 1H), 1.60 (m, 5H)
9{27}	3.89 (s, 3H, OCH ₃), 6.97 (dd, 1H, H-6), 7.03 (s, 1H, H-8), 7.72 (d, 1H, H-5)	8.51	7.84	2.38 (m, 2H), 2.65 (t, 2H)	7.87 (br.t, 1H), 12.09 (s, 1H)	2.83 (t, 2H, CH ₂), 3.28 (q, 2H, CH ₂), 7.28 (m, 4H)
9{28}	3.87 (s, 3H, OCH ₃), 6.97 (dd, 1H, H-6), 7.03 (s, 1H, H-8), 7.72 (d, 1H, H-5)	8.51	7.84	2.38 (m, 2H), 2.65 (m, 2H)	7.60 (br.t, 1H), 12.05 (s, 1H)	0.96 (d, 3H, CH ₃), 1.15 - 3.05 (m, 13H)
9{29}	3.87 (s, 3H, OCH ₃), 6.97 (dd, 1H, H-6), 7.03 (s, 1H, H-8), 7.72 (d, 1H, H-5)	8.49	7.84	2.38 (m, 2H), 2.65 (m, 2H)	8.23 (br.t, 1H), 11.99 (s, 1H)	4.24 (d, 2H, CH ₂), 6.21 (d, 1H), 6.39 (t, 1H), 7.49 (d, 1H)
9{30}	3.85 (s, 3H, OCH ₃), 6.97 (d, 1H, H-6), 7.03 (s, 1H, H-8), 7.72 (d, 1H, H-5)	8.49	7.84	2.38 (m, 2H), 2.65 (m, 2H)	8.16 (br.t, 1H), 12.09 (s, 1H)	2.09 (s, 3H, CH ₃), 4.15 (d, 2H, CH ₂), 5.93 (d, 1H), 6.07 (d, 1H)
9{31}	3.87 (s, 3H, OCH ₃), 6.97 (dd, 1H, H-6), 7.03 (s, 1H, H-8), 7.72 (d, 1H, H-5)	8.52	7.85	2.38 (t, 2H), 2.65 (t, 2H)	7.64 (br.d, 1H), 12.05 (s, 1H)	1.50 (m, 8H, 4CH ₂), 3.97 (m, 1H, CH)

Table 4. Cont.

Code	Coumarin ring, R ¹	s, 1H, H-4	s, 1H, H-5- thiazole	-CH ₂ CH ₂ -	NH	R2, R3
9{32}	1.35 (t, 3H, OCH ₂ CH ₃), 4.18 (q, 2H, OCH ₂ CH ₃), 7.28 (m, 3H, Ar)	8.53	7.92	2.48 (m, 2H), 2.72 (m, 2H)	8.11 (br.d, 1H), 12.12 (s, 1H)	1.70 (m, 4H, 2CH ₂), 2.60 (m, 2H, CH ₂), 4.95 (s, 1H, CH), 7.08 (m, 4H)
9{33}	1.35 (t, 3H, OCH ₂ CH ₃), 4.19 (q, 2H, OCH ₂ CH ₃), 7.28 (m, 3H, Ar),	8.52	7.96	2.38 (t, 2H), 2.65 (t, 2H)	7.72 (br.t, 1H), 12.04 (s, 1H),	0.64 (t, 3H, CH ₃), 1.07 (dt, 2H, CH ₂), 1.40 (m, 1H, CH), 1.45 (m, 4H, 2CH ₂), 1.75 (t, 2H, CH ₂), 2.70 (m, 4H, 2CH ₂), 3.05 (q, 2H, CH ₂)
9{34}	1.40 (t, 3H, OCH ₂ CH ₃), 4.19 (q, 2H, OCH ₂ CH ₃), 7.28 (m, 3H, Ar)	8.52	7.94	2.33 (m, 2H), 2.65 (t, 2H)	7.69 (br.t, 1H), 12.05 (s, 1H)	1.63 (m, 8H, 4CH ₂), 2.32 (m, 4H, 2CH ₂), 3.05 (q, 2H, CH ₂)
9{35}	1.35 (t, 3H, OCH ₂ CH ₃), 4.19 (q, 2H, OCH ₂ CH ₃), 7.31 (m, 3H, Ar), 8.52 (s, 1H, H-4)		7.96	2.39 (m, 2H), 2.65 (t, 2H)	7.64 (br.t, 1H), 12.11 (s, 1H)	1.02 (t, 3H, CH ₃), 1.63 (m, 2H, CH ₂), 3.05 (d, 2H, CH ₂), 3.20 (d, 2H, CH ₂), 3.25 (q, 2H, CH ₂), 6.53 (t, 2H), 6.63 (d, 2H), 7.11 (t, 2H)
9{36}	1.35 (t, 3H, OCH ₂ CH ₃), 4.19 (q, 2H, OCH ₂ CH ₃), 7.34 (m, 3H, Ar), 8.52 (s, 1H, H-4)		7.96	2.39 (m, 2H), 2.65 (t, 2H)	7.62 (br.t, 1H), 12.09 (s, 1H)	0.96 (d, 3H, CH ₃), 1.15 (m, 2H, CH ₂), 1.50 (m, 4H, 2CH ₂), 2.22 (m, 2H, CH ₂), 2.68 (m, 2H, CH ₂), 3.05 (m, 3H, CH ₂ + CH)
9{37}	1.39 (t, 3H, OCH ₂ CH ₃), 4.19 (q, 2H, OCH ₂ CH ₃), 7.34 (m, 3H, Ar), 8.51 (s, 1H, H-4)		7.92	2.65 (s, 4H)	11.95 (s, 1H),	2.09 (s, 4H, CH ₂), 2.25 (s, 4H, 2CH ₂), 3.39 (s, 4H, CH ₂)

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