Recyclization of 2-Imino-2*H*-1-benzopyrans with Nucleophilic Reagents – Reaction of 2-Iminocoumarin-3-carboxamides with 2-Aminothiophene-3-carboxamides

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Abstract: In the course of our research on the synthesis of coumarins, the interaction of 2-iminocoumarin-3-carboxamides with a series of 2-aminothiophene-3-carboxamides was studied. It was established that the initial products – 2-substituted coumarin-3-carboxamides – can undergo rearrangement to 2-(coumarin-3-yl)thieno[2,3-*d*]pyrimidin-4-ones by refluxing in DMF.

Key words: cyclizations, heterocycles, lactones, Gewald reaction, coumarins

2-Hetarylthieno[2,3-*d*]pyrimidines have been reported to exhibit a range of biological activities: anti-inflammatory, anti-anginal, anti-allergenic[1–4,7,9,11] and anti-cancer activity;[5] some of them can be useful as selective 5-HT3 and 5-HT4 receptor ligands.[6] Several compounds of this class showed significant analgesic and CNS depressant activity[8] and some exhibited anticonvulsant activity in mice against the convulsant corazole;[10] compounds with thrombocyte aggregation inhibiting activity are also known.[12] Some of the compounds were patented as useful for treating mammals suffering from discords related to gonadotropin releasing hormone,[13] and some as ALK-5 receptor ligands for the treatment of kidney fibrosis,[14] PDE7 inhibitors,[15] and c-GMP-specific phosphodiesterase inhibitors.[16] Among the 2,4-aminothieno[2,3-*d*]pyrimidines substances with bacteriostatic activity related to *Staphylococcus aureus*, *Streptococcus faecum* and *Lactobacillus casei* have been found.[17,18] Bactericidal and trichomonacidal properties of some 4-amino-2-(5-nitro-2-furyl)thieno[2,3-*d*]pyrimidines were determined.[19]

It can be expected that modification of the thieno[2,3-*d*]pyrimidine ring system with the naturally occurring and undoubtedly pharmacologically active coumarin moiety will increase the potential biological activity of such compounds.

The simplest and most elegant method for the synthesis of 3-hetaryl-substituted coumarins is the Knoevenagel condensation of salicylic aldehydes and hetaryl acetates.[20] However, this method is difficult to apply to the synthesis of 2-(coumarin-3-yl)thieno[2,3-*d*]pyrimidin-4-ones, because the starting thieno[2,3-*d*]pyrimidin-4-one-2-acetic acid derivatives require complex synthetic procedures.[21]

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In previous papers[22,23] we described a simpler method for the synthesis of substituted 2-(coumarin-3-yl)-3,4,5,6,7,8-hexahydrobenzothieno[2,3-*d*]pyrimidin-4-ones by rearrangement of 2-substituted coumarin-3-carboxamides, which can also be applied to the synthesis of other 3-hetarylcoumarins.[24]

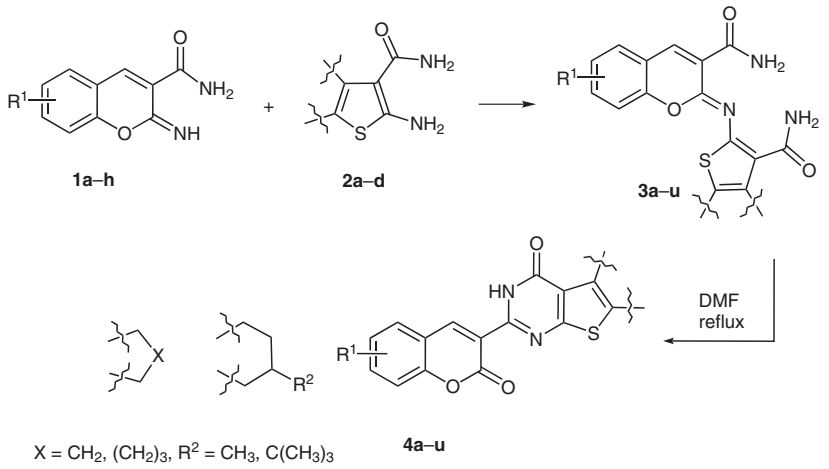
As an extension of our work related to the recyclization of 2-imino-2*H*-1-benzopyrans by nucleophilic reagents we investigated the scope of this approach for the synthesis of a range of 2-(coumarin-3-yl)thieno[2,3-*d*]pyrimidin-4-ones.

In order to obtain a series of novel 2-(coumarin-3-yl)thieno[2,3-*d*]pyrimidin-4-ones **4** we studied the interaction of 2-iminocoumarin-3-carboxamides **1a–h** with different 2-aminothiophene-3-carboxamides **2a–d**, which were obtained from cyclopentanone, cycloheptanone, and 4-substituted cyclohexanones according to the Gewald procedure (Scheme 1).[25]

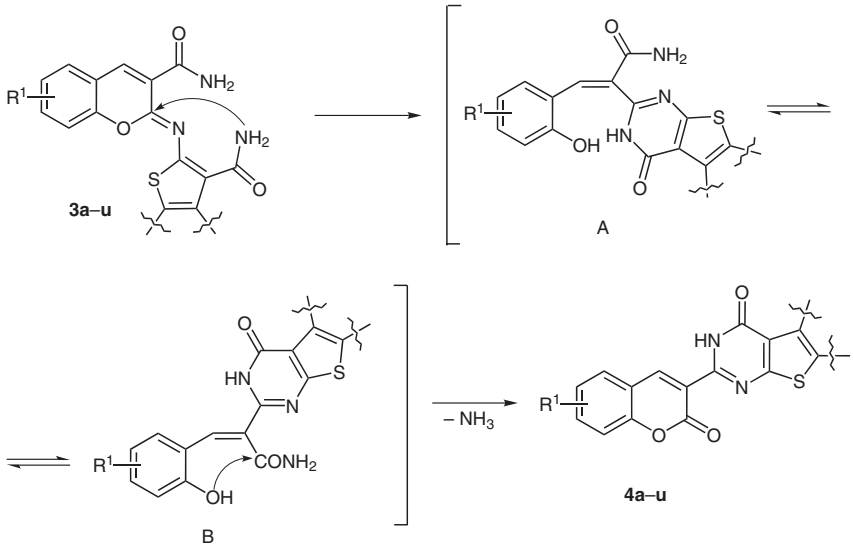
Under these conditions (reflux in DMF) it appears the reaction pathway follows the recyclization transformations recently reported.[23] Intermolecular nucleophilic attack of the thiophene-3-carboxamide NH_2 group on the carbon atom in the 2-position of the iminolactone ring is accomplished by ring opening and formation of thieno[2,3-*d*]pyrimidin-4-one condensed system. After a further *cis–trans* isomerization of intermediate **A** to intermediate **B**, the most thermodynamically stable product **4** is formed, as a result of coumarin ring closure with cleavage of ammonia (Scheme 2).

As determined in the course of the experiment, the synthesis of 2-(3-carbamoyl-2-thienylimino)coumarin-3-carboxamides **3a–u**, can be easily performed by heating the starting reagents in glacial acetic acid for five hours. The products **3**, separated as orange-red crystals, which were slightly soluble in DMF or DMSO at ambient temperature.

We encountered some difficulties with the second step of the synthesis of some 2-(R^1-coumarin-3-yl)thieno[2,3-*d*]pyrimidin-4-ones **4** via recyclization of **3**. The reaction conditions had to be changed because all our attempts to obtain compounds **4a** and **4b** from the corresponding 2-substituted coumarin-3-carboxamides using previously described methods failed. Decomposition of the products was observed when nitrobenzene is used as a solvent; refluxing the starting 2-(3-carbamoyl-2-thienylimino)cou-



Scheme 1 Synthesis of 2-(R[1]-coumarin-3-yl)thieno[2,3-*d*]pyrimidin-4-ones **4** by recyclization



Scheme 2 The suggested mechanism for the rearrangement of 2-(3-carbamoyl-2-thienylimino)coumarin-3-carboxamides **3** into 2-(coumarin-3-yl)thieno[2,3-*d*]pyrimidin-4-ones **4**

marin-3-carboxamides **3** in glacial acetic acid for 10–12 hours resulted only in the starting material.

In view of this, we propose alternative reaction conditions, with DMF as solvent. In our opinion utilization of a solvent that promotes the iminolactone ring opening[26] facilitates the reaction. As a result, **4a**–**u** were obtained in 48–82% yield after refluxing **3a**–**u** in DMF for three to five hours. The reaction was monitored by TLC (EtOAc–

Table 1 Analytical Data of **3a** and **3b**

					^{1}H NMR		
Compd	R^1	X	Yield (%)	Mp (°C)	H_{Ar}	H_{Alk}	$CONH_2$
3a	H	CH_2	75	>300	8.08 (s, 1 H, 4-H), 7.73 (d, *J* = 8.3 Hz, 1 H, 5-H), 7.57 (m, 2 H, 7-H, $CONH_2$), 7.46 (d, *J* = 9.0 Hz, 1 H, 8-H), 7.33 (t, *J* = 8.3 Hz, 1 H, 6-H)	2.25 (m, 2 H, $CH_2CH_2CH_2$), 2.92 (t, *J* = 7.6 Hz, 4 H, $CH_2CH_2CH_2$)	8.53 (br s, 1 H), 8.04 (br s, 1 H), 7.03 (br s, 1 H)
3b	8-OMe	CH_2	82	>300	8.04 (m, 2 H, 4-H, $CONH_2$), 7.28 (m, 3 H, 5-H, 6-H, 7-H)	2.27 (m, 2 H, $CH_2CH_2CH_2$), 2.88 (t, *J* = 7.1 Hz, 4 H, $CH_2CH_2CH_2$)	8.54 (br s, 1 H), 7.58 (br s, 1 H), 7.02 (br s, 1 H)

Table 2 Structure and Data of Products **4a–u**[a]

Compd	R^1	R^2	X	Yield (%)	Mp (°C)	IR (C=O, cm^{-1})
4a	H	–	CH_2	56	>300	1705, 1648
4b	8-OMe	–	CH_2	48	>300	1678
4c	H	CH_3	–	55	235–237	1716, 1692
4d	6-Cl	CH_3	–	72	292–293	1716, 1688
4e	8-OEt	CH_3	–	65	279–281	1704, 1684
4f	8-OMe	CH_3	–	67	277–278	1712, 1684
4g	7-OMe	CH_3	–	76	>300	1696, 1684
4h[a]	6-NO_2	CH_3	–	82	>300	1720, 1680
4i	6-Br	CH_3	–	78	>300	1716, 1688
4j	7-NEt_2	CH_3	–	53	>300	1716, 1672
4k	8-OH	CH_3	–	51	>300	1700, 1658
4l	H	$C(CH_3)_3$	–	49	256–257	1712, 1684
4m	6-Cl	$C(CH_3)_3$	–	64	>300	1716, 1696
4n	8-OEt	$C(CH_3)_3$	–	69	277–279	1680
4o	8-OMe	$C(CH_3)_3$	–	75	300–302	1684
4p	7-OMe	$C(CH_3)_3$	–	54	>300	1700, 1684
4q[a]	6-NO_2	$C(CH_3)_3$	–	73	>300	1724, 1668
4r	6-Br	$C(CH_3)_3$	–	78	>300	1716, 1696
4s	7-NEt_2	$C(CH_3)_3$	–	43	>300	1672
4t	6-Cl	–	$(CH_2)_3$	57	267–269	1708, 1680
4u	6-Br	–	$(CH_2)_3$	64	284–286	1708, 1676

[a] NO_2 was observed at 1348 cm^{-1}.

hexane 1:2) and by the release of ammonia, no additional crystallization was required for the precipitated products.

It should be noted that derivatives **3a** and 3**b** appeared to be the most stable in highly polar organic solvents. Their unusual stability allowed us to measure the ^{1}H NMR spectra of these substances in DMSO (Table 1). The ^{1}H NMR spectra of the other compounds of this class **3c–u** showed signals corresponding to a mixture of products, which probably results from the iminolactone ring opening and product isomerization as reported by O'Callaghan and coworkers.[26]

The IR spectra of all compounds exhibited strong absorption bands in the range 1720–1668 cm^{-1} (C=O), while compounds **4f** and **4n** exhibited a characteristic band at 1348 cm^{-1} (NO_2) (Table 2). The ^{1}H NMR spectra of compounds **4** revealed the coumarin protons at 7.42–9.10 ppm, a broad signal corresponding to the proton at position 3 of the thieno[2,3-*d*]pyrimidin-4-one ring system, and signals corresponding to the aliphatic protons were also observed. In the case of methoxy-substituted coumarins the singlet signal at 3.89–3.95 ppm was observed, while ethoxy-substituted coumarins exhibited both a characteristic triplet at 1.33–1.37 ppm and quartet at 4.13–4.18 ppm (Table 3).

The proposed method for the synthesis of 2-(R^1-coumarin-3-yl)thieno[2,3-*d*]pyrimidin-4-ones allowed us to expand the scope of the recyclization approach for the synthesis of 3-heterylcoumarins. A range of 2-aminothiophene-3-carboxamides was condensed with cycloaliphatic systems to furnish 2-(R^1-coumarin-3-yl)thieno[2,3-*d*]pyrimidin-4-ones **4** via recyclization in DMF.

Table 3 Analytical Data of **4a–u**

Compd	4-H (1 H, s)	H_{Ar}	NH (1 H, br s)	H_{Alk}	UV-VIS [λ_{max} (cm^{-1}), log ε ($Lmol^{-1}cm^{-1}$)]
4a	9.03	8.02 (d, *J* = 7.6 Hz, 1 H, 5-H), 7.76 (t, *J* = 7.3 Hz, 1 H, 7-H), 7.50 (m, 2 H, 8-H, 6-H)	12.08	2.29 (m, 2 H), 2.92 (t, *J* = 8.8 Hz, 4 H)	38680 (3.98) 33560 (4.08) 24440 (4.04)
4b	8.95	7.45 (m, 3 H, 5-H, 6-H, 7-H)	11.98	2.32 (m, 2 H), 2.89 (t, *J* = 8.8 Hz, 4 H), 3.95 (s, 3 H, OCH_3)	38940 (3.99) 32460 (4.08) 24280 (4.03)
4c	9.02	8.02 (d, *J* = 8.4 Hz, 1 H, 5-H), 7.74 (t, *J* = 8.3 Hz, 1 H, 7-H), 7.47 (m, 2 H, 8-H, 6-H)	11.89	0.97 (d, *J* = 7.2 Hz, 3 H, CH_3), 1.35 (m, 1 H, C*H*CH_3), 1.85 [2 H, m, $CH_2CH_2CH(CH_3)CH_2$], 2.60 [m, 4 H, $CH_2CH_2CH(CH_3)CH_2$]	39000 (4.16) 33240 (4.30) 24460 (4.27)
4d	8.96	8.12 (d, *J* = 2.7 Hz, 1 H, 5-H), 7.78 (dd, *J* = 8.9, 2.7 Hz, 1 H, 7-H), 7.57 (d *J* = 8.9 Hz, 1 H, 8-H)	11.95	0.97 (d, *J* = 8.0 Hz, 3 H, CH_3), 1.35 (m, 1 H, C*H*CH_3), 1.85 [m, 2 H, $CH_2CH_2CH(CH_3)CH_2$], 2.60 [m, 4 H, $CH_2CH_2CH(CH_3)CH_2$]	38360 (4.52) 33960 (4.60) 24060 (4.57)
4e	8.95	7.43 (m, 3 H, 5-H, 6-H, 7-H)	11.92	0.97 (d, *J* = 7.3 Hz, 3 H, CH_3), 1.35 (m, 1 H, C*H*CH_3), 1.85 [m, 2 H, $CH_2CH_2CH(CH_3)CH_2$], 2.60 [m, 4 H, $CH_2CH_2CH(CH_3)CH_2$], 1.37 (3 H, t, *J* = 8.1 Hz, OCH_2CH_3), 4.18 (q, *J* = 8.1 Hz, 2 H, OCH_2CH_3)	38920 (3.85) 32500 (3.93) 24500 (3.88)
4f	8.93	7.44 (m, 3 H, 5-H, 6-H, 7-H)	11.92	0.97 (d, *J* = 8.2 Hz, 3 H, CH_3), 1.35 (m, 1 H, $CHCH_3$), 1.85 [m, 2 H, $CH_2CH_2CH(CH_3)CH_2$], 2.60 [m, 4 H, $CH_2CH_2CH(CH_3)CH_2$], 3.89 (s, 3 H, OCH_3)	39100 (4.38) 32540 (4.56) 31460 (4.39) 24520 (4.39)
4g	9.03	7.92 (d, *J* = 8.6 Hz, 1 H, 5-H), 7.12 (d, *J* = 2.1 Hz, 1 H, 8-H), 7.02 (dd, *J* = 8.6, 2.1 Hz, 1 H, 6-H)	11.89	0.97 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.35 (m, 1 H, C*H*CH_3), 1.85 [m, 2 H, $CH_2CH_2CH(CH_3)CH_2$], 2.60 [m, 4 H, $CH_2CH_2CH(CH_3)CH_2$], 3.92 (s, 3 H, OCH_3)	38440 (3.80) 31680 (3.78) 29060 (3.79) 24400 (4.00)
4h	9.08	8.97 (d, *J* = 2.9 Hz, 1 H, 5-H), 8.49 (dd, *J* = 9.1, 2.9 Hz, 1 H, 7-H), 7.73 (d, *J* = 9.1 Hz, 1 H, 8-H)	11.98	0.97 (d, *J* = 7.6 Hz, 3 H, CH_3), 1.35 (m, 1 H, C*H*CH_3), 1.85 [m, 2 H, $CH_2CH_2CH(CH_3)CH_2$], 2.6 [m, 4 H, $CH_2CH_2CH(CH_3)CH_2$]	43420 (4.51) 38200 (4.53) 23860 (4.24)
4i	8.94	8.26 (d, *J* = 3.3 Hz, 1 H, 5-H), 7.89 (dd, *J* = 9.2, 3.3 Hz, 1 H, 7-H), 7.51 (d, *J* = 9.2 Hz, 1 H, 8-H)	11.98	0.97 (d, *J* = 7.1 Hz, 3 H, CH_3), 1.35 (m, 1 H, C*H*CH_3), 1.85 [m, 2 H, $CH_2CH_2CH(CH_3)CH_2$], 2.6 [m, 4 H, $CH_2CH_2CH(CH_3)CH_2$]	38420 (4.37) 33860 (4.45) 24060 (4.41)
4j	8.92	7.76 (d, *J* = 9.1 Hz, 1 H, 5-H), 6.85 (dd, *J* = 9.1, 3.0 Hz, 1 H, 6-H), 6.67 (d, *J* = 3.0 Hz, 1 H, 8-H)	11.85	0.97 (d, *J* = 7.2 Hz, 3 H, CH_3), 1.35 (m, 1 H, $CHCH_3$), 1.85 [m, 2 H, $CH_2CH_2CH(CH_3)CH_2$], 2.60 [m, 4 H, $CH_2CH_2CH(CH_3)CH_2$], 1.25 [t, *J* = 6.3 Hz, 6 H, $N(CH_2CH_3)_2$,], 3.47 [q, *J* = 6.3 Hz, 4 H, $N(CH_2CH_3)_2$]	39760 (3.81) 32060 (3.66) 21960 (4.35)
4k	8.92	7.45 (m, 3 H, 5-H, 6-H, 7-H)	10.50	0.97 (d, *J* = 7.2 Hz, 3 H, CH_3), 1.39 (m, 1 H, C*H*CH_3), 1.87 [m, 2 H, $CH_2CH_2CH(CH_3)CH_2$], 2.60 [m, 4 H, $CH_2CH_2CH(CH_3)CH_2$]	38700 (4.29) 32140 (4.33) 24560 (4.28)
4l	9.01	8.01 (dd, 1 H, 5-H, *J* = 7.4, 1.3 Hz), 7.76 (td, *J* = 7.4, 1.6 Hz, 1 H, 7-H), 7.50 (m, 2 H, 8-H, 6-H)	11.98	0.93 [s, 9 H, $C(CH_3)_3$], 2.2 [m, 7 H, $CH_2CH_2CH(CCH_3)_3CH_2$]	38580 (4.12) 33180 (4.26) 24460 (4.25)

Table 3 Analytical Data of **4a–u** (continued)

Compd	4-H (1 H, s)	H_{Ar}	NH (1 H, br s)	H_{Alk}	UV-VIS [λ_{max} (cm^{-1}), log ε ($Lmol^{-1}cm^{-1}$)]
4m	8.94	8.11 (d, *J* = 2.6 Hz, 1 H, 5-H), 7.76 (dd, *J* = 9.2, 2.6 Hz, 1 H, 7-H), 7.56 (d, *J* = 9.2 Hz, 1 H, 8-H)	11.89	0.92 [s, 9 H, $C(CH_3)_3$], 2.20 [m, 7 H, $CH_2CH_2CH(CCH_3)_3CH_2$]	38460 (4.07) 33960 (4.14) 24040 (4.10)
4n	8.92	7.42 (m, 3 H, 5-H, 6-H, 7-H)	11.85	0.92 [s, 9 H, $C(CH_3)_3$], 2.20 [m, 7 H, $CH_2CH_2CHC(CH_3)_3CH_2$], 1.33 (t, *J* = 7.3 Hz, 3 H, OCH_2CH_3), 4.13 (q, *J* = 7.3 Hz, 2 H, OCH_2CH_3)	38780 (4.13) 32480 (4.20) 24480 (4.17)
4o	8.92	7.43 (m, 3 H, 5-H, 6-H, 7-H)	11.92	0.92 [s, 9 H, $C(CH_3)_3$], 2.2 [m, 7 H, $CH_2CH_2CH(CCH_3)_3CH_2$], 3.89 (s, 3 H, OCH_3)	39080 (4.12) 32520 (4.18) 24460 (4.13)
4p	9.02	7.94 (d, *J* = 9.2 Hz, 1 H, 5-H), 7.15 (d, *J* = 1.9 Hz, 1 H, 8-H), 7.06 (dd, *J* = 9.2, 1.9 Hz, 1 H, 6-H)	11.70	0.92 [9 H, s, $C(CH_3)_3$], 2.2 [m, 7 H, $CH_2CH_2CH(CCH_3)_3CH_2$] 3.89 (s, 3 H, OCH_3)	38400 (4.10) 31720 (4.10) 29040 (4.12) 24340 (4.35)
4q	9.10	8.97 (s, 1 H, 5-H), 8.49 (d, *J* = 10.0 Hz, 1 H, 7-H), 7.73 (d, *J* = 10.0 Hz, 1 H, 8-H)	11.92	0.88 [s, 9 H, $C(CH_3)_3$], 2.20 [m, 7 H, $CH_2CH_2CH(CCH_3)_3CH_2$]	43340 (4.39) 38160 (4.42) 23800 (4.15)
4r	8.93	8.24 (d, *J* = 2.8 Hz, 1 H, 5-H), 7.89 (1 H, dd, *J* = 9.8, 2.8 Hz, 7-H), 7.51 (d, *J* = 9.8 Hz, 1 H, 8-H)	11.89	0.88 [9 H, s, $C(CH_3)_3$], 2.20 [7 H, m, $CH_2CH_2CH(CCH_3)_3CH_2$]	38480 (4.29) 33860 (4.35) 23980 (4.30)
4s	8.96	7.74 (d, *J* = 8.8 Hz, 1 H, 5-H), 6.82 (d, *J* = 8.8 Hz, 1 H, 6-H), 6.63 (s, 1 H, 8-H)	11.83	0.88 [s, 9 H, $C(CH_3)_3$], 2.20 [m, 7 H, $CH_2CH_2CH(CH_3)_3CH_2$], 1.12 [t, *J* = 7.8 Hz, 6 H, $N(CH_2CH_3)_2$], 3.47 [q, *J* = 7.8 Hz, 4 H, $N(CH_2CH_3)_2$]	39680 (3.83) 31960 (3.68) 22000 (4.41)
4t	8.93	8.12 (d, *J* = 2.1 Hz, 1 H, 5-H), 7.77 (dd, *J* = 8.6, 2.1 Hz, 1 H, 7-H), 7.57 (d, *J* = 8.6 Hz, 1 H, 8-H)	11.70	1.70 (m, 6 H), 2.80 (m, 2 H), 3.12 (m in H_2O, 2 H)	38060 (4.27) 33980 (4.32) 23980 (4.28)
4u	8.92	8.28 (d, *J* = 2.2 Hz, 1 H, 5-H), 7.92 (dd, *J* = 8.2, 2.2 Hz, 1 H, 7-H), 7.51 (d, *J* = 8.2 Hz, 1 H, 8-H)	–	1.70 (m, 6 H), 2.90 (m, 2 H), 3.10 (m in H_2O, 2 H)	38040 (4.23) 33860 (4.29) 23960 (4.22)

[a] Elemental analysis: C ± 0.19, H ± 0.02, N ± 0.02.

Mps were measured with a Buchi B-520 melting point apparatus and were not corrected. IR spectra were recorded on a Specord M-80 spectrometer in KBr. ^{1}H NMR spectra were recorded on a Varian WXR-400 (200 MHz) spectrometer in DMSO-d_6 using TMS as the internal. UV-VIS absorption spectra were registered on a Specord M-40 spectrophotometer in 1,4-dioxane. 2-Aminothiophene-3-carboxamides 2a–d and 2-iminocoumarin-3-carboxamides 1a–h were prepared according to reported methods.[25–28]

Synthesis of 4a–u; General Procedure

To a warm solution of 2-aminothiophene-3-carboxamide **2** (2 mmol) in glacial AcOH (20 mL) 2-iminocoumarin-3-carboxamide **1** (2 mmol) was added. The mixture was stirred and heated for 5 h. The resulting crystals of **3** were filtered off, thoroughly washed with *i*-PrOH, and dried. The obtained product **3** (1.5 mmol) was refluxed in DMF (10 mL) for 3 h and then cooled. The precipitate formed was filtered off and washed with *i*-PrOH to give **4** in satisfactory yields (Table 2).

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