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Synthesis and Photophysical Properties of 1,4-Dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-ones, and Derivatives Containing Tethered 1,2,3-Triazoles, from 4-Aminocoumarins

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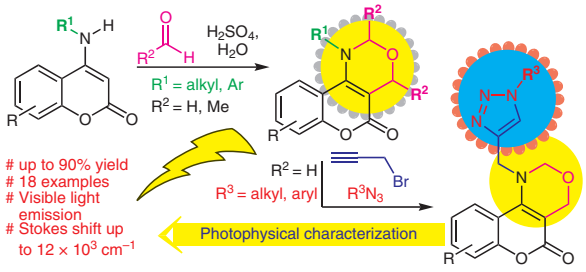

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Abstract A facile protocol for the unprecedented one-pot H_2SO_4-mediated hydroxymethylation/cyclative *N*,*O*-acetalization of 4-aminocoumarins to 1,4-dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-ones, in moderate to good yields, was developed and optimized. The scope and limitations of the transformation, which takes place in water or water/THF mixtures, were also studied. The nitrogen atom of the resulting tricycles was used to tether alkyl, aryl and 1,2,3-triazolylmethyl moieties, employing a two-step click chemistry approach for the latter. The photophysical properties of the heterocycles, as well as of their 1,2,3-triazole derivatives, were also examined. The *N*-aryl derivatives exhibited high quantum yields of fluorescence (up to $\Phi_f = 0.69$) and very large Stokes shifts (up to 201 nm).

Key words 4-aminocoumarins, tethered triazoles, 1,3-oxazines, cyclization reaction, photophysical properties

The coumarin core is a privileged scaffold. Decoration of this heterocycle proved to be an effective strategy toward the development of new bioactive compounds[1] and technologically relevant materials. The interest in the latter is related to their photophysical properties, especially strong fluorescence, which are at the heart of various applications, such as optical chromophores, sensitive fluorescent probes[2] and laser dyes,[3] among others.

On the other hand, oxazines are six-membered heterocycles which contain one atom each of nitrogen and oxygen. There are several isomeric oxazines, and their dihydro and tetrahydro forms are also known. The different approaches toward their synthesis have been recently reviewed.[4]

Several natural products are 1,3-oxazine derivatives (Figure 1). Representative structures are terresoxazine (**A**),[5a] maltoxazine (**B**)[5b,c] and brevioxime (**C**).[5d,e] Many 1,3-

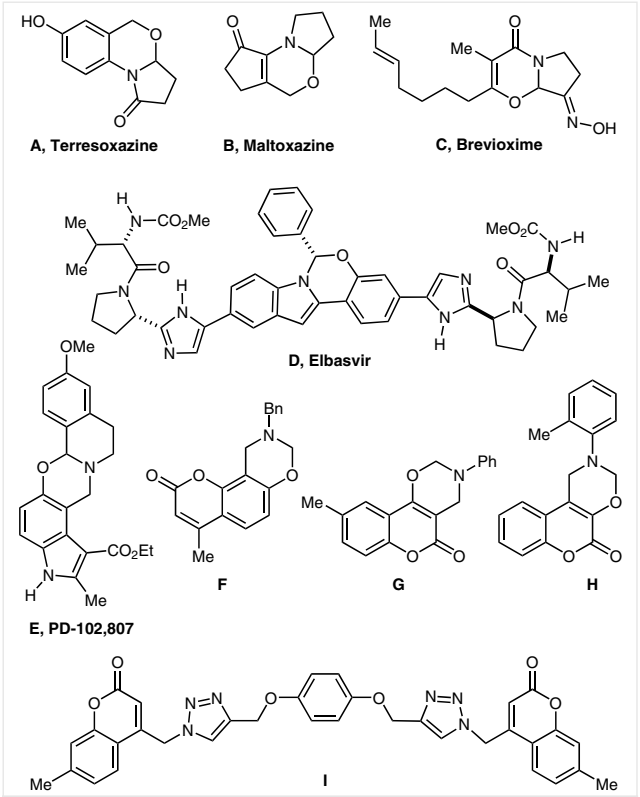

Figure 1 Selected examples of relevant heterocycles, natural products and pharmacologically active compounds, displaying the coumarin, 1,3-oxazine and 1,2,3-triazole motifs

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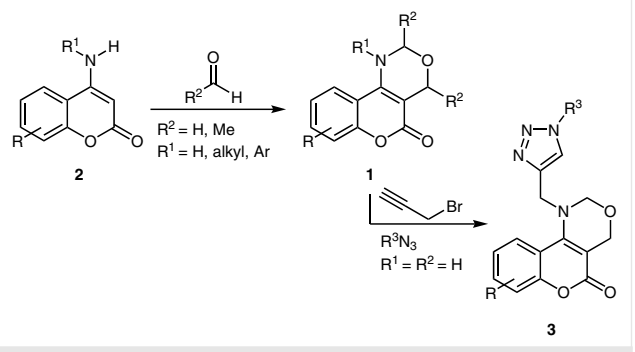
oxazines are interestingly bioactive,[6,7] and the heterocyclic motif is present in various active pharmaceutical ingredients, such as the antiviral agent elbasvir (**D**)[8] and PD-102,807 (**E**), a selective antagonist for the muscarinic acetylcholine receptor M4.[9a,b] In addition, this scaffold has recently gained interest due to the photophysical properties of some of its derivatives.[9c,d]

Coumarins fused to 1,3-oxazines have been reported. Essentially all of them have been synthesized by sequential aminomethylation of 7-hydroxy- (**F**),[6a,10] 4-hydroxy- (**G**)[11] and 3-hydroxy- (**H**)[12a] coumarins, followed by *N*,*O*-acetalization. 1,3-Oxazines resulting from other hydroxycoumarins have also been described.[12b–d]

Triazoles are five-membered heterocycles with three nitrogen atoms, being found in antifungals (ravuconazole, fluconazole),[13a] antibiotics (tazobactam, cefatrizine)[13b] and antiepileptics (rufinamide),[13c] among others. The 1,2,3-regioisomer has gained biological significance,[14] coumarins with an attached triazole motif have been tested as anticancer, antibacterial and antitubercular (**I**) agents.[15] 1,2,3-Triazoles have also elicited interest for the photophysical properties of their derivatives.[16]

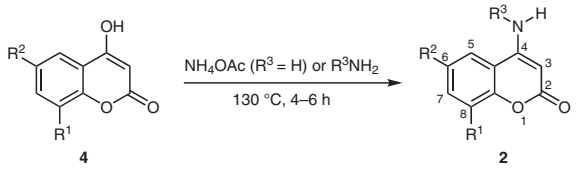
Recently, we have focused our attention on the synthesis and evaluation of polysubstituted coumarins.[17] In pursuit of such an interest, herein we report the synthesis of the unprecedented 1,4-dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-ones **1** from 4-aminocoumarins **2**, through a convenient one-pot hydroxymethylation/*N*,*O*-acetalization sequence in aqueous medium, as well as their *N*-functionalization with alkyl, aryl and tethered 1,2,3-triazolylmethyl (**3**) moieties (Scheme 1). Considering the scarcity of information on the photophysical properties of 4-aminocoumarin derivatives,[18] photophysical characteristics of the synthetic heterocycles are also discussed.



Scheme 1 Proposed synthetic approach toward 1,4-dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-ones **1** and 1,2,3-triazolylmethyl-substituted derivatives **3**

The starting 4-aminocoumarins **2a–l** were conveniently and uneventfully synthesized in 57–82% yield (Table 1), as reported by Saha and co-workers,[19a] from the readily available 4-hydroxycoumarins **4a–c**, by heating for 4–6 hours with NH_4OAc and different primary amines.

Table 1 Synthesis of the Starting 4-Aminocoumarins **2a–l**



Entry	Coumarin	R^1	R^2	R^3	Product	Yield (%)
1	**4a**	H	H	H	**2a**	62
2	**4b**	Me	H	H	**2b**	75
3	**4c**	H	Cl	H	**2c**	82
4	**4a**	H	H	Ph	**2d**	79
5	**4b**	Me	H	Ph	**2e**	80
6	**4c**	H	Cl	Ph	**2f**	78
7	**4a**	H	H	4-MeC_6H_4	**2g**	57
8	**4a**	H	H	4-FC_6H_4	**2h**	77
9	**4a**	H	H	4-ClC_6H_4	**2i**	80
10	**4a**	H	H	Bn	**2j**	69
11	**4a**	H	H	$PhCH_2CH_2$	**2k**	70
12	**4a**	H	H	*n*-Bu	**2l**	73

Next, the installation of the 1,3-oxazine moiety was undertaken. We reasoned that the proposed framework should be accessible if we could manage to control the unprecedented 3-hydroxymethylation of the starting 4-aminocoumarins,[19b] and couple this transformation with an *N*,*O*-acetalization of the resulting γ-amino alcohols. Since formaldehyde is the most suitable reagent for both reactions, it was hoped that ideally both transformations could be performed as a one-pot process.

Surprisingly, however, we found out that only a handful of scattered articles report the access to 1,3-oxazines from enamino derivatives of 1,3-dicarbonyl compounds.[20] Further, it was apparent that the transformation has not been carried out previously with enamines resulting from 3-keto lactones. In addition, due to the reactivity of the resulting product, the 3-hydroxymethylation of coumarins is also a highly uncommon transformation, which may result in over-reaction.[21]

With this background in mind, we initially undertook optimization of the synthesis of oxazine derivative **1a**, by reaction between 4-aminocoumarin (**2a**) and formaldehyde. First, the reaction was studied under Lewis acid promotion (Table 2) and consumption of the starting material was monitored by TLC, where the product was luminescent when irradiated with UV light. However, in dioxane, only traces of product were detected when the reaction was driven by 1 equivalent of $BF_3{\cdot}OEt_2$ (entry 1). Changing the promoter to $SnCl_4$ gave a 42% yield of **1a** after 3 hours at 60 °C (entry 2), which increased to 71% upon using THF as solvent over 1.5 hours (entry 3). On the other hand,

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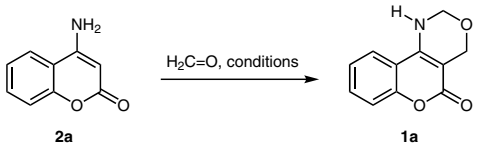
$FeCl_3·6H_2O$ resulted in a 76% yield of **1a** when THF was employed as solvent (entry 4), but a meagre performance was attained (34% yield) when the reaction was executed in water (entry 5).

Table 2 Optimization of the Synthesis of 1,4-Dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-one (**1a**)[a]



2a **1a**

Entry	Promoter (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	$BF_3·OEt_2$ (1)	dioxane	60	3	traces
2	$SnCl_4$ (1)	dioxane	60	3	42
3	$SnCl_4$ (1)	THF	60	1.5	71
4	$FeCl_3·6H_2O$ (1)	THF	60	4	76
5	$FeCl_3·6H_2O$ (1)	H_2O	60	2	34
6	H_3BO_3 (1)	dioxane	60	4	–
7	TsOH (1)	dioxane	60	16	traces
8	TFA (1)	dioxane	60	2	61
9	TFA (1)	THF	60	2	56
10	HCl (12)	dioxane	60	1.5	21
11	HCl (12)	THF	60	3	35
12	HCl (12)	H_2O	60	2	44
13	HCl (12)	H_2O	60	3.5	70
14	H_2SO_4 (12)	H_2O	60	0.5	77
15	H_2SO_4 (12)	THF	60	3.5	47
16	H_2SO_4 (4)	H_2O	60	2	61
17	H_2SO_4 (8)	H_2O	60	3.5	47
18	H_2SO_4 (12)	H_2O	r.t.	0.5	63
19	H_2SO_4 (1)	H_2O	60	0.5	60[c]

[a] Reaction conditions, unless otherwise stated: **2a** (0.5 mmol), 37% formaldehyde solution (2 mL), promoter (1 equiv), open system.
[b] After purification by column chromatography.
[c] 37% formaldehyde solution (1 mL).

With the aim of still improving the yield, the performance of protic acids was tested. However, essentially no product was observed when H_3BO_3 or TsOH in dioxane was used (entries 6 and 7). Interestingly, however, yields of 61% and 56% were achieved with TFA when the solvents were dioxane and THF (entries 8 and 9), respectively. The use of 3 M HCl in different media (entries 10–13) revealed that the best performance (70% yield) was reached in water (60 °C, 3.5 h), at the expense of using 12 equivalents of the promoter.

On the other hand, tests with 3 M H_2SO_4 were also carried out (entries 14–19) to assess the most suitable amounts of acid and formaldehyde required, as well as the ideal temperature for the synthesis. Here, the best performance was attained in water with 12 equivalents of the acid, after warming the reaction at 60 °C for 0.5 hours (77% yield, entry 14). Although the transformation exhibited a result similar to that of entry 4, the shorter reaction time combined with the use of a convenient mineral acid in water were considered highly convenient conditions and the best choice. Diminishing the amount of H_2SO_4 led to reduced yields, even after longer reaction times. In addition, carrying out the reaction at room temperature was also less efficient.

After establishing the optimal reaction conditions to access the dihydro-1,3-oxazine system, the substrate scope for the synthesis of heterocycles **1** was investigated, extending the study to the starting aminocoumarins **2b–l**. Introduction of an additional point of variation through the installation of an additional substituent on the nitrogen atom (**2d–l**) proved to be important, since it ultimately afforded more stable heterocycles.

In general, the optimized protocol proved to be effective (Table 3) with formaldehyde at 60 °C (entries 1–11), furnishing moderate to good yields of product (34–85%) in reaction times ranging from 0.5 to 18 hours. Not unexpectedly, the reactions of the primary amines **2a–c** were comparatively speedier (entries 1–3), whereas among the secondary amines, in general, those bearing alkyl or benzyl substituents (entries 10–17) reacted faster than their aromatic counterparts (entries 4–9). Interestingly, while the use of TFA as promoter (Table 2, entries 8 and 9) proved to offer suboptimal results during the optimization stage, it was superior to H_2SO_4 in the case of coumarins **2e** and **2f** (Table 3, entries 5 and 6).

In addition, it was found that, under the standard conditions, benzylamine **2j** gave only a 16% yield of **1j** after 5 hours (entry 10); however, the yield increased to 44–49% (0.5–1 h) when THF was added as cosolvent (entries 11 and 12). The transformation was also successful at room temperature (entry 13), proceeding in 3.5 hours and 47% yield. Analogously, compound **1k** was obtained in 56% yield after 4 hours (entry 14).

A similar observation was made with 4-aminocoumarin **2l** (entries 15–17), which gave only a 13% yield of **1l** when the reaction was executed in water. In this case, addition of THF improved the performance to 25% yield, while running the reaction at room temperature resulted in a 39% yield of **1l**.

When the reaction protocol was applied to other aldehydes (entries 18–20), the most reactive acetaldehyde (entry 18) furnished the expected heterocycle **1m** (90% yield after 1 h), whereas the less reactive benzaldehyde and butanal gave no reaction at all (entries 19 and 20).

Although the intimate details of the constructive mechanism for the dihydro-1,3-oxazine ring system of the 1,3-oxazino[5,4-*c*]coumarins remain unclear, a mechanistic picture for the reaction can be advanced, based on literature proposals for similar transformations.[22]

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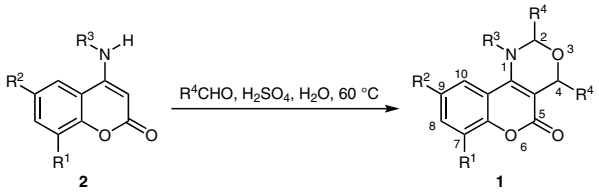
Table 3 Scope of the Synthesis of 1,4-Dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-ones **1**



2 **1**

Entry	Coumarin	R^1	R^2	R^3	R^4	Time (h)	Product	Yield (%)[a]
1	**2a**	H	H	H	H	0.5	**1a**	77 (61)[b]
2	**2b**	Me	H	H	H	0.5	**1b**	85
3	**2c**	H	Cl	H	H	0.5	**1c**	41
4	**2d**	H	H	Ph	H	16	**1d**	79
5	**2e**	Me	H	Ph	H	16	**1e**	34 (78)[b]
6	**2f**	H	Cl	Ph	H	16	**1f**	38 (76)[b]
7	**2g**	H	H	4-MeC_6H_4	H	1.5	**1g**	–[c]
8	**2h**	H	H	4-FC_6H_4	H	16	**1h**	82
9	**2i**	H	H	4-ClC_6H_4	H	18	**1i**	40
10	**2j**	H	H	Bn	H	5	**1j**	16
11	**2j**	H	H	Bn	H	0.5	**1j**	49[d]
12	**2j**	H	H	Bn	H	1	**1j**	44[e]
13	**2j**	H	H	Bn	H	3.5	**1j**	47[d,f]
14	**2k**	H	H	$PhCH_2CH_2$	H	4	**1k**	56
15	**2l**	H	H	*n*-Bu	H	3	**1l**	13
16	**2l**	H	H	*n*-Bu	H	1	**1l**	25[e]
17	**2l**	H	H	*n*-Bu	H	1	**1l**	39[e,f]
18	**2a**	H	H	H	Me	1	**1m**	90
19	**2a**	H	H	H	Ph	24	**1n**	–
20	**2a**	H	H	H	*n*-Pr	24	**1o**	–

[a] Isolated yield after column chromatography.
[b] TFA used as acid catalyst.
[c] The product was detected by EI-MS, but extensive decomposition took place during the chromatographic purification.
[d] THF added.
[e] THF added after 30 min of reaction.
[f] Reaction carried out at room temperature.

In the first stage, a hydroxymethylation of **2a** can be suggested (Scheme 2), where the double bond of coumarin **2a** may perform a nucleophilic attack at the electrophilic center of the aldehyde, to give iminium intermediate ***A***, under assistance by the lone electron pair of the nitrogen. Subsequent removal of the proton attached to C-3 would regenerate the coumarin unsaturation (***B***) and the acid medium.

In the next step, hydroxymethyl enamine intermediate ***B*** may undergo an acid-catalyzed *N*,*O*-acetalization. Thus, the electrophilic center of the aldehyde would be attacked again, by the free electron pair of the amine, resulting in bis-hydroxymethyl intermediate ***C***. A prototropic rearrangement would then take place, to afford protonated intermediate ***D*** which, in the next step, could undergo dehydration to furnish Mannich base ***E***. Then, the thus-formed iminium ion could be attacked by the neighboring alcohol in a fashion reminiscent of the Prins reaction, to give protonated intermediate ***F***. Final deprotonation of the latter should result in dihydro-1,3-oxazine derivative **1a**.

A quite similar mechanism could account for analogous transformations, such as the gold-catalyzed mechanochemical synthesis of tetrahydropyrimidines and octahydroquinazolines from enaminone derivatives of 1,3-dicarbonyl precursors.[23]

The photophysical properties of the synthesized heterocycles were next examined, commencing with an analysis of their UV spectra (Figure 2), measured between 250 and 400 nm, on 10^{-4} M DMSO solutions. The coumarin ring oxygen atom has an sp^2 hybridization, being part of the π-sys-

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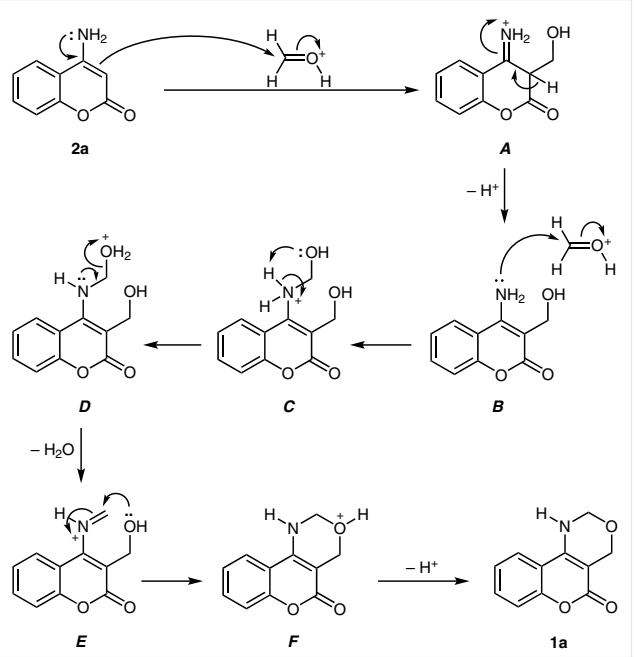
Table 4 Photophysical Data of 1,4-Dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-ones **1**

Entry	Compound	λ_{max}, nm (ε, $mol^{-1}·cm^{-1}$)[a]	λ_{em}, nm (Φ_f)[b]	$E_{0\text{-}0}$ (eV)[c]	Stokes shift (nm, 10^3 cm^{-1})[d]
1	**1a**	279 (2529), 314 (3693)	380 (0.48)	3.594	66, 5.5
2	**1b**	279 (2521), 316 (3696)	379 (0.30)	3.583	63, 5.3
3	**1c**	306 (6019), 324 (6347)	395 (0.42)	3.492	71, 5.5
4	**1d**	280 (2428), 314 (3590)	502 (0.32)	2.870	188, 11.9
5	**1e**	287 (4151), 315 (4521)	495 (0.37)	2.837	180, 11.5
6	**1f**	268 (sh),[e] 322 (4507)	523 (0.69)	2.883	201, 11.9
7	**1h**	280 (6578), 313 (8530)	501 (0.47)	2.871	188, 12.0
8	**1i**	281 (3575), 314 (4940)	492 (0.68)	2.890	178, 11.5
9	**1j**	265 (3836), 303 (5022)	416 (0.59)	3.492	113, 9.0
10	**1k**	257 (3878), 306 (4737)	428 (0.66)	3.483	122, 9.3
11	**1l**	260 (4607), 305 (5546)	426 (0.52)	3.454	121, 9.3
12	**1m**	296 (3448), 315 (3664)	377 (0.25)	3.647	62, 5.2

[a] In DMSO solution at a concentration of 10^{-4} M; the position of the first maximum (~255 nm) is not listed.
[b] In DMSO solution at a concentration of 10^{-6} M, employing 9,10-diphenylanthracene (DPA) as standard (Φ_f = 0.65) in $CHCl_3$.
[c] $E_{0\text{-}0} = 1240/\lambda$.
[d] $\Delta\lambda = \lambda_{em} - \lambda_{max}$, in nm, or $\Delta\tilde{\nu} = 10^7 \cdot (1/\lambda_{max} - 1/\lambda_{em})$, in cm^{-1}.
[e] sh = shoulder.



Scheme 2 Plausible mechanism of the H_2SO_4-promoted cyclization of 4-aminocoumarin (**2a**) with formaldehyde to afford 1,4-dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-one (**1a**)

tem of the molecule, and the UV spectra of the heterocycles may show π→π* and *n*→π* transitions, where one of the latter relates to the C=O chromophore. It was observed (Figure 2A) that the compounds exhibit spectra with a similar general shape, and 2–3 distinguishable maxima, around 255 nm, at approximately 285 ± 20 nm and at 315 ± 10 nm.[24]

Most probably, any *n*→π* transition which also takes place (ε <100) is submerged under the comparatively stronger π→π* transitions (ε >2400). The band around 255 nm may be caused by π→π* transitions in the isocyclic ring; the remaining bands seem to correspond to characteristic transitions between molecular orbitals of the whole coumarin ring system.[24a] The lower-energy band has been assigned to the HOMO→LUMO transition, whereas it has been proposed that the 285 nm band corresponds to the HOMO-1→LUMO transition.[24b]

In the less-functionalized compounds **1a**,**b**, the first maximum was hardly visible (Table 4, entries 1 and 2), being more evident in **1c** and **1m** (entries 3 and 12). Compounds **1j–l**, bearing nitrogen substituents unable to conjugate with the nitrogen (*n*-Bu, Bn, $PhCH_2CH_2$), displayed broad maxima (entries 9–11) around 268 nm, whereas 9-chloro derivatives **1c** and **1f** showed the most hypsochromic peaks of the series, at 324 and 322 nm, respectively (entries 3 and 6). Bathochromic and hyperchromic effects were detected on the second and third maxima of the *N*-aryl-substituted derivatives **1e**, **1f**, **1h** and **1i**, related to the substituent electron-withdrawing ability (entries 5–8). Notably, fluorinated derivative **1h** (entry 7) exhibited a markedly higher absorption in the studied range, with ε = 8530 (λ_{max} = 313 nm). However, all compounds displayed very low absorption at 375 nm and were essentially transparent in the visible region.

The fluorescence measurements were made on 10^{-6} M DMSO solutions, where other coumarin derivatives have afforded higher fluorescence intensity than in other solvents.[18a] It was detected that the emission maxima (λ_{em}) and fluorescence quantum yields (Φ_f) depend on the cou-

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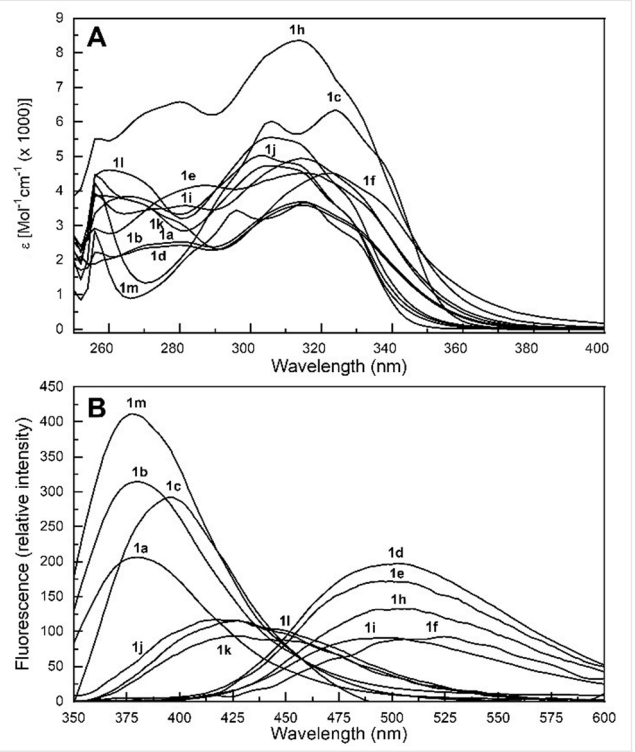


Figure 2 (A) Excitation spectra of 1,4-dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-ones **1a–f**,**h–m** in DMSO at a concentration of 10^{-4} M. (B) Emission spectra of the heterocycles, in DMSO at a concentration of 10^{-6} M.

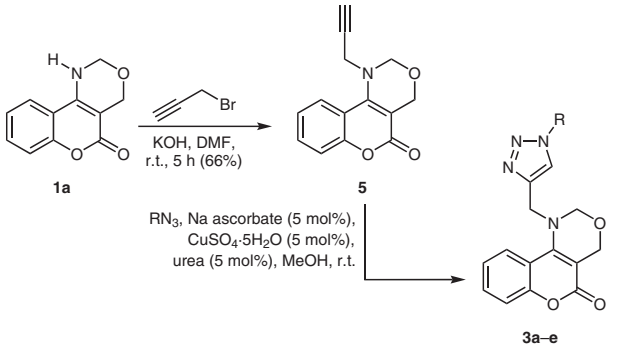
marin substituents. Excitation of the lowest-energy absorption band at its maximum resulted in λ_{em} around 385 ± 10 nm (Figure 2B) in the case of the *N*-unsubstituted compounds **1a–c** and **1m** (Table 4, entries 1–3 and 12), where a comparatively small Stokes shift (62–71 nm; equivalent to 5.2–5.5 × 10^3 cm^{-1}) was observed. This parameter indicates the extent of the red shift of the fluorescence maximum (λ_{em}) compared to the corresponding absorption peak (λ_{max}). Their Φ_f values were in the range 0.25–0.48, being lower among the compounds bearing methyl substituents on the homocyclic (**1b**) and oxazine (**1m**) rings.

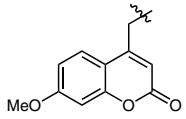
Installation of a nitrogen substituent caused a noticeable red shift in the emission maxima. The heterocycles **1j–l** (entries 9–11) bearing non-conjugating substituents (λ_{em} = 422 ± 6 nm), displayed a small shift (~35 nm) and a slight increase in their Stokes shift (117 ± 4 nm; equivalent to 9.0–9.3 × 10^3 cm^{-1}). These compounds also displayed higher Φ_f values (0.52–0.66) than their *N*-unsubstituted congeners (entries 1–3 and 12). On the other hand, the *N*-aryl-substituted compounds **1d–f**,**h**,**i** (entries 4–8) possessed emission maxima around 500 nm and larger Stokes shifts (180–200 nm). This results in lower $E_{0\text{-}0}$ values (2.83–2.89 eV), meaning that their normalized excitation and emission spectra cross each other at longer wavelengths. While the *N*-phenyl-substituted derivative **1d** exhibited the highest intensity, its 9-chloro congener **1f** displayed the most-red-shifted emission (λ_{em} = 523 nm) and the highest quantum efficiency (Φ_f = 0.69), comparable with that of **1i** (entry 8).

Some multicolor imaging microscopy methods require fluorophores with large Stokes shifts, to reduce the number of detection channels and simplify the experimental imaging scheme. These fluorophores, among them coumarins, are still rare.[25] The *N*-aryl-substituted 1,4-dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-one motif is a compact fluorophore with a large Stokes shift and many potential diversification points. It may be considered as a starting scaffold, suitable for further modification toward enlarging the list of chemical probes for microscopy and similar fields.

Next, further functionalization of the rather unstable tricyclic compounds was conveniently achieved in two steps by means of a click reaction,[26] affording more stable heterocycles. Thus, compound **1a** was first submitted to an *N*-alkylation with propargyl bromide in DMF for 5 hours, using KOH as base,[27] to obtain **5** in 66% yield (Table 5). Then, the latter was subjected to catalytic azide–alkyne cycloaddition with different alkyl and aryl azides in the presence of sodium ascorbate and $CuSO_4$ as the catalyst system[26c] for 3–5 hours, which afforded the expected 1,4-disubstituted 1,2,3-triazoles **3a–e** in good to excellent overall yields. The azides required for the click cycloaddition reaction were

Table 5 Triazolization of 1,4-Dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-one (**1a**)



Entry	R	Time (h)	Product	Yield (%)[a]
1	Bn	4	**3a**	96
2	Ph	4	**3b**	68
3	4-MeC_6H_4	3	**3c**	69
4	4-ClC_6H_4	5	**3d**	65
5		5	**3e**	84

[a] Isolated yield after column chromatography.

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conveniently obtained by diazotization–azidation of the corresponding anilines in the case of the aromatic compounds, while nucleophilic substitution of the corresponding alkyl halides with azide ion was used to access the remaining counterparts.[28]

The excitation spectra of alkyne precursor **5** and the resulting 1,2,3-triazole derivatives **3a–e** (Figure 3) were acquired in DMSO solutions, as done before. In general, the spectra were reminiscent of that of the structurally similar compound **1j** (Figure 3A). The heterocycles displayed a sharp peak at 263 ± 5 nm (Table 6) and a twin peak around 302 and 314 nm (entries 1–5), except for the coumarin derivative **3e** (entry 6). All of these compounds were essentially UV transparent beyond 350 nm.

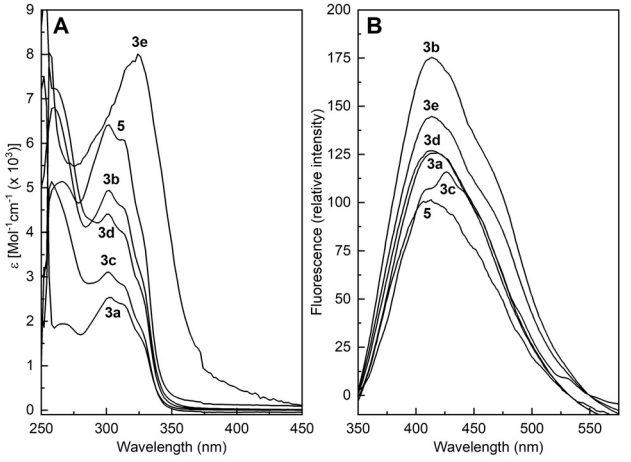

Figure 3 (A) Excitation spectra of alkyne **5** and 1,2,3-triazole derivatives **3a–e** of 1,4-dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-one in DMSO, in the range 250–450 nm. (B) Emission spectra of the compounds in DMSO, in the range 350–580 nm.

On the other hand, the emission spectra of **3a–e** (Figure 3B) were similar in shape, also resembling the emission spectrum of **1j** and displaying a single maximum at 413 ± 2 nm except for compound **3c** (lambda em= 426 nm). Their Φ_f values, in the range 0.41–0.66, and the Stokes shifts (89–112 nm; equivalent to 6.7–8.4 × 10^3 cm^{-1}) were also similar to those exhibited by **1j**.

All products were characterized by NMR spectroscopy and high-resolution mass spectrometry. In the ^{1}H NMR spectra, H-2 was observed as a singlet in the δ 4.55 ppm region, whereas H-4 appeared as broad doublet around δ 4.85 ppm. The latter experienced a small deshielding (~0.2 ppm) and became a singlet in the *N*-aryl derivatives (**1d–f**,**h**,**i**), and suffered a similar shielding effect in the case of the non-conjugating alkyl (**1k**, **1l**), benzyl (**1j**) and 1,2,3-tetrazole (**3a–e**) derivatives.

On the other hand, in the ^{13}C NMR spectra, the diagnostic C-2 resonance was observed at ~92 ppm in the *N*-unsubstituted tricycles (**1a–c**), being more shielded (~82 ppm) in the *N*-aryl derivatives (**1d–f**,**h**,**i**) and even slightly more shielded (~78 ppm) in the heterocycles bearing non-conjugating substituents (**1j–l** and **3a–e**). A characteristic and highly deshielded singlet (δ 8.35–9.0 ppm) confirmed the presence of the 1,2,3-tetrazole moiety in **3a–e**.

In summary, we have developed and optimized a facile and convenient H_2SO_4-mediated one-pot approach to the synthesis of fused coumarin and 1,3-oxazine heterocycles. The reaction takes place in moderate to good yields, from 4-aminocoumarins in water or water/THF mixtures, providing a direct and useful entry to the virtually unexplored 1,4-dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-ones. The use of amines for the preparation of the 4-aminocoumarin precursors yields *N*-substituted tricycles. On the other hand, *N*-alkylation of the oxazine moiety with a propargyl halide, followed by copper-catalyzed azide–alkyne cycloaddition, enabled the installation of a tethered 1,2,3-triazole moiety.

The photophysical characteristics of the heterocycles were studied, with the observation that *N*-alkylation of the oxazine moiety (alkyl, benzyl, 1,2,3-triazolylmethyl) caused a small red shift (~35 nm) of the fluorescence spectra, which displayed emission peaks around 419 ± 10 nm, whereas the *N*-phenyl derivatives exhibited fluorescence peaks in the green region (~500 nm) and Stokes shifts up to

Table 6 Photophysical Data of Compound **5** and the 1,2,3-Triazole Derivatives **3a–e** of 1,4-Dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-one

Entry	Compound	λ_{max}, nm (ε, $mol^{-1}\cdot cm^{-1}$)[a]	λ_{em}, nm (Φ_f)[b]	$E_{0\text{-}0}$ (eV)[c]	Stokes shift (nm, 10^3 cm^{-1})[d]
1	**5**	266 (5151), 301 (6417), 314 (6045)	411 (0.63)	3.483	97, 7.5
2	**3a**	268 (1940), 302 (2519), 314 (2368)	415 (0.64)	3.594	101, 7.8
3	**3b**	260 (6803), 302 (4942), 314 (4551)	413 (0.41)	3.604	99, 7.6
4	**3c**	258 (5135), 301 (3111), 314 (2793)	426 (0.61)	3.604	112, 8.4
5	**3d**	262 (7181), 301 (4406), 314 (3951)	411 (0.66)	3.615	97, 7.5
6	**3e**	<250, 324 (7987)	413 (0.50)	3.406	89, 6.7

[a] In DMSO solution at a concentration of 10^{-4} M.
[b] In DMSO solution at a concentration of 10^{-6} M, employing DPA as standard (Φ_f = 0.65) in $CHCl_3$.
[c] $E_{0\text{-}0} = 1240/\lambda$.
[d] $\Delta\lambda = \lambda_{em} - \lambda_{max}$, in nm, or $\Delta\tilde{\nu} = 10^7 \cdot (1/\lambda_{max} - 1/\lambda_{em})$, in cm^{-1}.

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200 nm (equivalent, in wavenumber units, to **1d**: 11.9/**1h**: 12×10^3 cm^{-1}). The large Stokes shifts (up to 12×10^3 cm^{-1}), coupled with Φ_f values in the range 0.25–0.69, with most compounds being over 0.5, turn these compounds into potential scaffolds toward the design of organic dyes useful for biological imaging.

The reagents for synthesis were obtained commercially. Solvents were purified and dried according to usual procedures.[29] All other reagents were used as received, without further purification. The progress of reactions was monitored by TLC on silica gel plates. For detection of the spots, the plates were exposed to UV light (254 and 365 nm), I_2 or H_2SO_4/vanillin solution. Chromatographic purifications were performed by column chromatography employing silica gel (230–400 mesh, 40–63 μm), and eluting with hexane–EtOAc mixtures of increasing polarity. Melting points were taken on an MQAPF-301 melting point apparatus and are reported uncorrected. ^1H and ^{13}C NMR spectra were recorded on Bruker 400 and 600 (for compound 1m) MHz NMR spectrometers, with the samples dissolved in DMSO-d_6. Chemical shifts are given in ppm downfield from the signal of TMS, used as internal standard, and coupling constants (*J*) are expressed in hertz (Hz). Electron-impact low-resolution mass spectra (EI-MS) were obtained on a Shimadzu QP2010 gas chromatograph coupled to a mass spectrometer. The relative intensity of the signals is given. High-resolution mass spectral data were obtained on an LTQ Orbitrap Discovery mass spectrometer (Thermo Fisher Scientific), using sodium formate as reference. UV–vis absorption spectra were acquired on a Shimadzu UV-2600 spectrophotometer and fluorescence spectra were obtained with a Varian Cary 50 fluorescence spectrophotometer. The emission slit was set at 2.0 mm.

Photophysical Determinations

UV–vis absorption spectra were measured at 1.0 nm intervals, with the samples dissolved in DMSO at a concentration of 10^{-4} M, in a 10 mm optical path length quartz cuvette. Fluorescence spectra and fluorescence quantum yields were measured on 10^{-6} M DMSO solutions of the compounds, in a 10 mm optical path length quartz cuvette. Excitation was performed at the lowest-energy electronic transition of each derivative and the spectra were corrected according to the manufacturer's instructions. The fluorescence quantum yields (Φ_f) were measured by comparison with the corrected fluorescence spectrum of 9,10-diphenylanthracene (DPA) in $CHCl_3$ (Φ_f = 0.65, λ_{ex} = 366 nm),[17a,30] using the standard equation:

$$\Phi_f^{spl} = \Phi_f^{ref} \cdot I_f^{spl} \cdot A^{ref} \cdot \eta^{spl} / (I_f^{ref} \cdot A^{spl} \cdot \eta^{ref})$$

where Φ_f, I_f, *A*, and η are the fluorescence quantum yield, integrated fluorescence intensity under the emission band of the fluorophore, optical density at the excitation wavelength, and refractive index of the studied solvents, respectively, for the sample (spl) and the reference (ref).

1,4-Dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-ones 1; General Procedure

A stirred solution of 37% formaldehyde in water (2 mL, 24.67 mmol) was successively treated with 3 M H_2SO_4 (2 mL) and a 4-aminocoumarin **2** (0.5 mmol). The reaction was heated at 60°C and further stirred until judged complete by TLC, when the mixture was treated with saturated $NaHCO_3$ solution to neutralize the acid and EtOAc (4 × 15 mL) to extract the product. The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure, and the residue was purified by silica gel column chromatography.

1,4-Dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-one (1a)

Yellowish solid; yield: 77% (78 mg); mp 211–213 °C.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.29 (s, 1 H), 7.85 (dd, *J* = 7.9, 1.3 Hz, 1 H), 7.62–7.56 (m, 1 H), 7.38–7.30 (m, 2 H), 4.85 (d, *J* = 3.4 Hz, 2 H), 4.52 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.9, 152.4, 147.7, 131.7, 123.7, 122.0, 116.9, 113.7, 92.0, 72.9, 63.2.

EI-MS: *m*/*z* (%) = 203 (M^+, 50), 174 (100), 146 (58), 118 (47), 91 (94), 63 (95).

HRMS (ESI-Orbitrap): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{10}NO_3$: 204.0661; found: 204.0670.

7-Methyl-1,4-dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-one (1b)

Brownish solid; yield: 85% (92.3 mg); mp 204–206 °C.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.24 (s, 1 H), 7.70–7.65 (m, 1 H), 7.48–7.43 (m, 1 H), 7.23 (t, *J* = 8.1 Hz, 1 H), 4.83 (d, *J* = 3.5 Hz, 2 H), 4.52 (s, 2 H), 2.36 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.5, 150.5, 147.7, 132.3, 125.4, 122.8, 119.3, 113.3, 91.9, 72.8, 62.9, 14.9.

EI-MS: *m*/*z* (%) = 217 (M^+, 64), 188 (100), 160 (30), 132 (31), 104 (29), 77 (50).

HRMS (ESI-Orbitrap): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{12}NO_3$: 218.0812; found: 218.0812.

9-Chloro-1,4-dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-one (1c)

Yellowish solid; yield: 41% (48.4 mg); mp 255–257 °C.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.45 (s, 1 H), 8.03–8.00 (m, 1 H), 7.63–7.59 (m, 1 H), 7.38–7.34 (m, 1 H), 4.84 (s, 2 H), 4.51 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.5, 151.0, 146.7, 131.4, 127.9, 121.7, 119.0, 115.1, 92.7, 72.9, 63.1.

EI-MS: *m*/*z* (%) = 239 ($[M + 2]^+$, 17), 237 (M^+, 50), 210 (33), 208 (100), 153 (29), 125 (33), 89 (26), 63 (39).

HRMS (ESI-Orbitrap): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_9ClNO_3$: 238.0271; found: 238.0277.

1-Phenyl-1,4-dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-one (1d)

White solid; yield: 79% (110 mg); mp 200–201 °C.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.51–7.46 (m, 1 H), 7.42–7.33 (m, 3 H), 7.25–7.15 (m, 3 H), 7.09–7.03 (m, 1 H), 6.98–6.94 (m, 1 H), 5.04 (s, 2 H), 4.66 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.0, 152.5, 149.0, 146.7, 131.0, 129.5 (2 C), 125.4, 124.7, 124.4 (2 C), 123.4, 117.0, 115.5, 109.9, 82.8, 63.5.

EI-MS: *m*/*z* (%) = 279 (M^+, 32), 248 (100), 220 (19), 204 (36), 167 (21), 77 (57).

HRMS (ESI-Orbitrap): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{14}NO_3$: 280.0974; found: 280.0989.

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7-Methyl-1-phenyl-1,4-dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-one (1e)

White solid; yield: 34% (50.4 mg); mp 198–199 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.38–7.32 (m, 3 H), 7.23–7.19 (m, 1 H), 7.18–7.14 (m, 2 H), 6.98–6.93 (m, 1 H), 6.84–6.80 (m, 1 H), 5.04 (s, 2 H), 4.66 (s, 2 H), 2.38 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.0, 150.8, 149.5, 147.0, 132.0, 129.5 (2 C), 125.8, 125.3, 124.4 (2 C), 123.0, 122.4, 115.3, 109.9, 82.9, 63.4, 15.3.

EI-MS: *m*/*z* (%) = 293 (M^+, 42), 263 (58), 262 (100), 218 (32), 180 (23), 77 (63).

HRMS (ESI-Orbitrap): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}NO_3$: 294.1125; found: 294.1133.

9-Chloro-1-phenyl-1,4-dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-one (1f)

Yellow solid; yield: 38% (59.4 mg); mp 195–197 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.56–7.52 (m, 1 H), 7.45–7.37 (m, 3 H), 7.30–7.24 (m, 1 H), 7.23–7.19 (m, 2 H), 6.87–6.86 (m, 1 H), 5.03 (s, 2 H), 4.67 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.4, 151.0, 147.7, 146.0, 130.5, 129.5 (2 C), 127.2, 125.6, 124.4 (2 C), 123.7, 118.9, 116.8, 110.5, 82.6, 63.3.

EI-MS: *m*/*z* (%) = 313 (M^+, 39), 283 (59), 282 (100), 238 (17), 77 (78).

HRMS (ESI-Orbitrap): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{13}ClNO_3$: 314.0578; found: 314.0578.

1-(4-Fluorophenyl)-1,4-dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-one (1h)

Yellowish solid; yield: 82% (121.5 mg); mp 185–186 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.53–7.46 (m, 1 H), 7.43–7.38 (m, 1 H), 7.27–7.16 (m, 4 H), 7.12–7.07 (m, 1 H), 6.96 (dd, *J* = 8.1, 1.5 Hz, 1 H), 5.00 (s, 2 H), 4.65 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.2 (J_{C-F} = 142.7 Hz), 158.5, 152.5, 149.0, 143.2 (J_{C-F} = 2.9 Hz), 143.1, 131.1, 126.6 (2 C, J_{C-F} = 5.1 Hz), 126.5, 124.5, 123.6, 117.1, 116.7 (2 C, J_{C-F} = 22.7 Hz), 116.2, 115.4, 110.1, 83.0, 63.4.

EI-MS: *m*/*z* (%) = 297 (M^+, 41), 267 (64), 266 (100), 246 (27), 222 (44), 185 (29), 75 (21).

HRMS (ESI-Orbitrap): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{13}FNO_3$: 298.0874; found: 298.0873.

1-(4-Chlorophenyl)-1,4-dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-one (1i)

Yellowish solid; yield: 40% (62 mg); mp 216–218 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.53–7.47 (m, 1 H), 7.43–7.37 (m, 3 H), 7.24–7.18 (m, 2 H), 7.14–7.08 (m, 1 H), 6.96 (dd, *J* = 8.1, 1.5 Hz, 1 H), 5.03 (s, 2 H), 4.65 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.8, 152.4, 148.5, 145.4, 130.9, 129.5, 129.2 (2 C), 126.0 (2 C), 124.3, 123.5, 116.9, 115.2, 110.4, 82.6, 63.3.

EI-MS: *m*/*z* (%) = 313 (M^+, 39%), 283 (36), 248 (100), 207 (38), 204 (56), 111 (31), 75 (32).

HRMS (ESI-Orbitrap): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{13}ClNO_3$: 314.0584; found: 314.0603.

1-Benzyl-1,4-dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-one (1j)

White solid; yield: 49% (71.8 mg); mp 136–137 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.63–7.56 (m, 2 H), 7.51–7.40 (m, 5 H), 7.38–7.27 (m, 2 H), 4.59 (s, 2 H), 4.57 (s, 2 H), 4.55 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.9, 153.1, 152.4, 137.2, 131.5, 128.8 (2 C), 127.5, 127.1 (2 C), 124.2, 122.9, 117.3, 115.8, 108.5, 78.7, 63.1, 55.6.

EI-MS: *m*/*z* (%) = 293 (M^+, 13), 202 (15), 91 (100), 65 (12).

HRMS (ESI-Orbitrap): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}NO_3$: 294.1125; found: 294.1126.

1-Phenethyl-1,4-dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-one (1k)

Yellowish solid; yield: 56% (86 mg); mp 119–120 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.56–7.45 (m, 1 H), 7.46 (dd, *J* = 8, 1.4 Hz, 1 H), 7.36 (dd, *J* = 8.3, 1.0 Hz, 1 H), 7.28–7.20 (m, 6 H), 4.74 (s, 2 H), 4.50 (s, 2 H), 3.54 (t, *J* = 7.3 Hz, 2 H), 3.06 (t, *J* = 7.3 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.9, 153.1, 152.3, 138.7, 131.2, 128.9 (2 C), 128.2 (2 C), 126.3, 123.9, 123.5, 117.0, 115.8, 108.5, 78.3, 63.0, 54.0, 34.7.

HRMS (ESI-Orbitrap): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{17}NNaO_3$: 330.1101; found: 330.1098.

1-*n*-Butyl-1,4-dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-one (1l)

White solid; yield: 39% (51.1 mg); mp 68–70 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.70–7.65 (m, 1 H), 7.63–7.56 (m, 1 H), 7.43–7.36 (m, 2 H), 4.64 (s, 2 H), 4.50 (s, 2 H), 3.34–3.26 (m, 2 H), 1.79–1.69 (m, 2 H), 1.37–1.25 (m, 2 H), 0.90 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.0, 153.4, 152.4, 131.3, 124.2, 123.5, 117.2, 115.9, 108.0, 78.4, 63.1, 52.5, 30.8, 19.6, 13.7.

EI-MS: *m*/*z* (%) = 259 (M^+, 37), 242 (20), 186 (100), 174 (16), 115 (39), 77 (13).

HRMS (ESI-Orbitrap): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{18}NO_3$: 260.1287; found: 260.1299.

2,4-Dimethyl-1,4-dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-one (1m)

White solid; mixture of 1,3-*cis*- and 1,3-*trans*-isomers (~2.2:1); yield: 90% (104 mg); mp 248–250 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ (major) = 8.17 (br s, 1 H, NH), 8.01 (dd, *J* = 7.8, 1.2 Hz, 1 H, H-8), 7.61–7.55 (m, 1 H, H-9), 7.37–7.29 (m, 2 H, H-7 and H-10), 5.03 (q, *J* = 7.4 Hz, 1 H, H-2), 4.71 (q, *J* = 7.4 Hz, 1 H, H-4), 1.45 (d, *J* = 7.4 Hz, 3 H, Me-2), 1.41 (d, *J* = 7.4 Hz, 3 H, Me-4); δ (minor) = 8.09 (br s, 1 H, NH), 7.99 (dd, *J* = 7.8, 1.2 Hz, 1 H, H-8), 7.61–7.55 (m, 1 H, H-9), 7.37–7.29 (m, 2 H, H-7 and H-10), 4.84 (q, *J* = 7.4 Hz, 1 H, H-2), 4.82 (q, *J* = 7.4 Hz, 1 H, H-4), 1.47 (d, *J* = 7.4 Hz, 3 H, Me-2), 1.45 (d, *J* = 7.4 Hz, 6 H, Me-4).

^{13}C NMR (100 MHz, DMSO-d_6): δ (major) = 159.6, 152.9, 147.5, 132.0, 123.8, 123.7, 117.2, 114.4, 96.5, 72.9, 67.8, 20.6, 20.5; δ (minor) = 159.1, 152.4, 149.1, 132.4, 123.8, 123.0, 117.0, 114.1, 97.6, 78.8, 70.6, 20.3, 19.8.

EI-MS: *m*/*z* (%) = 231 (M^+, 30), 216 (100), 198 (54), 186 (387), 130 (23), 91 (18), 77 (12).

HRMS (ESI-Orbitrap): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}NO_3$: 232.0974; found: 232.0984.

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1-(Prop-2-yn-1-yl)-1,4-dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-one (5)

A solution of **1a** (1.015 g, 5 mmol) in DMF (15 mL) was treated with KOH (0.396 g, 6.6 mmol). After stirring for 15 min, propargyl bromide (0.5 mL, 6.6 mmol) was added and the mixture was further stirred at r.t. for 5 h. Then, H_2O (20 mL) was added and the product was extracted with EtOAc (4 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to afford **5** as a white solid; yield: 792 mg (66%); mp 124–125 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.78–7.73 (m, 1 H), 7.64–7.58 (m, 1 H), 7.44–7.38 (m, 2 H), 4.72 (s, 2 H), 4.53 (s, 2 H), 4.16 (d, *J* = 2.5 Hz, 2 H), 3.33 (t, *J* = 2.5 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.6, 152.2, 151.8, 131.3, 124.0, 123.0, 116.9, 115.6, 109.5, 79.5, 79.0, 75.5, 62.7, 42.0.

EI-MS: *m*/*z* (%) = 241 (M^+, 80), 212 (42), 202 (100), 128 (53), 102 (39), 77 (24).

HRMS (ESI-Orbitrap): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{12}NO_3$: 242.0817; found: 242.0830.

Aryl Azides; General Procedure

The corresponding aniline (5 mmol) was added to a stirred solution of 6 N HCl, maintained at 0 °C in an ice bath. The solution was first treated with $NaNO_2$ (0.414 g, 6 mmol) and, 10 min later, with NaN_3 (0.390 g, 6 mmol). The reaction mixture was stirred in the ice bath for 30 min, when H_2O (20 mL) was added and the organic product was extracted with EtOAc. The product was used directly in the next step.

Alkyl Azides; General Procedure

A stirred solution of the corresponding halide (5 mmol) in DMSO (10 mL) was treated with NaN_3 (390 mg, 6 mmol) and the reaction mixture was stirred overnight at r.t. Then, H_2O (20 mL) was added and the organic product was extracted with EtOAc. The product was used directly in the next step.

1,4-Disubstituted 1,2,3-Triazoles 6a–e; General Procedure

A stirred solution of alkyne **5** (0.241 g, 1 mmol) in MeOH (5 mL) was successively treated with sodium ascorbate (10 mg, 5 mol%), urea (3 mg, 5 mol%) and $CuSO_4{\cdot}5H_2O$ (12 mg, 5 mol%). The reaction mixture was stirred for 15 min at r.t. when the azide (1.2 mmol of alkyl azide; 2 mmol of aryl azide) was added. After the reaction was judged complete by TLC, H_2O (20 mL) was added and the product was extracted with EtOAc (4 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography.

1-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-1,4-dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-one (3a)

White solid; yield: 96% (358 mg); mp 155–157 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.35 (s, 1 H), 8.13 (dd, *J* = 8, 1.3 Hz, 1 H), 7.65–7.59 (m, 1 H), 7.46–7.27 (m, 7 H), 5.63 (s, 2 H), 4.61 (s, 2 H), 4.53 (s, 2 H), 4.51 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.0, 152.8, 152.5, 143.6, 136.0, 131.5, 128.7 (2 C), 128.0, 127.7 (2 C), 124.3, 124.2, 123.8, 117.1, 115.9, 109.3, 78.2, 63.0, 52.9, 47.1.

HRMS (ESI-Orbitrap): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{19}N_4O_3$: 375.1452; found: 375.1457.

1-((1-Phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-1,4-dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-one (3b)

White solid; yield: 68% (245 mg); mp 159–161 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.00 (s, 1 H), 8.22–8.17 (m, 1 H), 7.96–7.91 (m, 2 H), 7.66–7.57 (m, 3 H), 7.53–7.47 (m, 1 H), 7.47–7.40 (m, 2 H), 4.66 (s, 2 H), 4.57 (s, 2 H), 4.55 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.0, 152.7, 152.5, 144.4, 136.6, 131.4, 129.8 (2 C), 128.6, 124.3, 123.7, 122.3, 120.0 (2 C), 117.0, 115.9, 109.5, 78.0, 63.0, 46.9.

HRMS (ESI-Orbitrap): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{17}N_4O_3$: 361.1295; found: 361.1300.

1-((1-(*p*-Tolyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1,4-dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-one (3c)

White solid; yield: 69% (257 mg); mp 221–222 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.88 (s, 1 H), 8.21–8.15 (m, 1 H), 7.83–7.78 (m, 2 H), 7.67–7.61 (m, 1 H), 7.48–7.38 (m, 4 H), 4.69 (s, 2 H), 4.60 (s, 2 H), 4.56 (s, 2 H), 2.40 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.7, 152.6, 152.4, 144.0, 138.0, 134.2, 131.2, 129.9 (2 C), 124.0, 123.6, 122.0, 119.8 (2 C), 116.9, 115.8, 109.2, 78.0, 62.9, 46.8, 20.3.

HRMS (ESI-Orbitrap): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{19}N_4O_3$: 375.1452; found: 375.1457.

1-((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1,4-dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-one (3d)

White solid; yield: 65% (254 mg); mp 237 °C (dec).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.98 (s, 1 H), 8.19–8.14 (m, 1 H), 8.01–7.95 (m, 2 H), 7.71–7.61 (m, 3 H), 7.48–7.42 (m, 2 H), 4.67 (s, 2 H), 4.60 (s, 2 H), 4.55 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.7, 152.5, 152.4, 144.4, 132.8, 131.2, 129.6 (2 C), 124.0, 123.5, 122.2, 121.6 (2 C), 116.9, 115.7, 109.2, 78.0, 62.8, 46.8.

HRMS (ESI-Orbitrap): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{16}ClN_4O_3$: 395.0905; found: 395.0909.

1-((1-((7-Methoxycoumarin-4-yl)methyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1,4-dihydro-2*H*,5*H*-chromeno[4,3-*d*][1,3]oxazin-5-one (6e)

Golden solid; yield: 84% (395 mg); mp 194–196 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.39 (s, 1 H), 8.08 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.78 (d, *J* = 8.7 Hz, 1 H), 7.65–7.58 (m, 1 H), 7.44–7.36 (m, 2 H), 7.03–6.97 (m, 2 H), 5.95 (d, *J* = 1.1 Hz, 2 H), 5.76 (s, 1 H), 4.66 (s, 2 H), 4.62 (s, 2 H), 4.51 (s, 2 H), 3.89 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.6, 159.5, 158.7, 154.9, 152.4, 152.3, 149.9, 143.7, 131.2, 125.6, 124.9, 123.9, 123.6, 116.9, 115.7, 112.1, 110.4, 110.3, 109.1, 101.0, 78.3, 62.7, 55.8, 49.1, 47.1.

HRMS (ESI-Orbitrap): *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{21}N_4O_6$: 473.1456; found: 473.1464.

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Supporting Information

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