Intramolecular 1,3-Dipolar Nitrile Oxide Cycloaddition Using Baylis–Hillman Derivatives: Stereoselective Synthesis of Tricyclic Chromenoisoxazolines

Manickam Bakthadoss,* Jayakumar Srinivasan, Raman Selvakumar

Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai 600 025, India
Fax +91(44)22352494; E-mail: bhakthadoss@yahoo.com

Received 20 October 2011; revised 15 December 2011

Abstract: A novel protocol for the construction of tricyclic chromenoisoxazoline frameworks via an intramolecular 1,3-dipolar nitrile oxide cycloaddition (INOC) reaction using Baylis–Hillman derivatives is described for the first time. The INOC reaction leads to a novel class of angularly substituted fused tricyclic chromenoisoxazolines, with the creation of two rings and two adjacent stereocenters, one of them being an all-carbon quaternary center, in a unique fashion. The tricyclic chromenoisoxazolines are obtained in a highly stereoselective fashion with good yields.

Key words: 1,3-dipolar nitrile oxide cycloaddition, chromenoisoxazolines, stereoselective synthesis, tricyclic framework

1,3-Dipolar cycloaddition reactions afford complex heterocycles with multiple stereocenters, which are useful in the construction of many natural products and pharmaceuticals.[1] The synthesis of complex heterocyclic compounds is a very challenging and attractive area in the field of organic chemistry.[2] The 1,3-dipolar cycloaddition of nitrile oxides to alkenes and alkynes affords isoxazolines and isoxazoles.[3] It is pertinent to note that isoxazolines exhibit important biological activities, such as antibacterial,[4a] antiplatelet,[4b] antiviral,[4c] anticonvulsant,[4d] immunostimulatory[4e] and antihypertensive,[4f] besides being valuable synthons in the synthesis of α,β-unsaturated ketones, β-hydroxy ketones and γ-amino alcohols.[5] There are numerous examples of these N,O-heterocycles being used as a key building block in the total synthesis of natural and unnatural compounds such as biotin,[6a] sarkomycin,[6b] specionin,[6c] phyllanthocin,[6d] testosterone,[6e] epothilones,[6f] macrospelides,[6g] L-carbafuranomycin[6h] and gabosine.[6i]

There has been a flurry of activity in the synthesis of benzopyran derivatives due to their proven biological activity and medicinal utility. For example, benzopyran derivatives posses antiplatelet,[7a] antipsychotic and antidepressant activities.[7b] Some benzopyran derivatives also have anti-HIV activity.[7c–f]

The Baylis–Hillman (BH) reaction is one of the important carbon–carbon bond-forming reactions and has seen enormous growth in the recent past. The utility of the Baylis–Hillman adducts can be found in the synthesis of a variety of natural products and medicinally relevant compounds.[8,9]

The isoxazoline and benzopyran moieties are interesting targets (Figure 1) in the development of new drug leads in medicinal chemistry and in the synthesis of a wide variety of natural products, which attracted us to develop a new protocol for the synthesis of substituted tricyclic

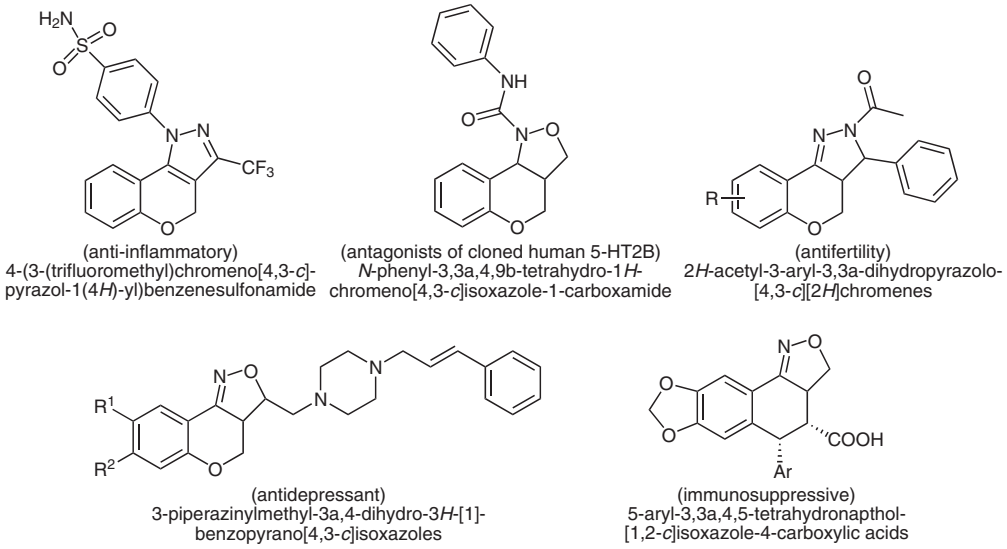


Figure 1 Some benzopyran- and isoxazole-containing bioactive compounds

SYNTHESIS 2012, 44, 755–766
Advanced online publication: 13.02.2012
DOI: 10.1055/s-0031-1289707; Art ID: Z98911SS

chromenoisoxazoline derivatives using Baylis–Hillman chemistry. It is well documented that tricyclic compounds containing isoxazole and benzopyran units are known for their various bioactive properties such as antidepressant,[10] immunosuppressive,[11] antifertility[12] and anti-inflammatory activities.[13] They also act as selective antagonists of cloned human 5-HT_{2B}[14] (Figure 1). Thus, we speculated that newly synthesized libraries of tricyclic chromenoisoxazolines may also have similar activity.

In continuation of our interest in Baylis–Hillman chemistry,[15] herein we report the first synthesis of angularly substituted fused tricyclic chromenoisoxazoline frameworks through in situ formation of nitrile oxide followed by an intramolecular 1,3-dipolar nitrile oxide cycloaddition (INOC) reaction sequence. The retrosynthetic approach to the fused tricyclic chromenoisoxazoline derivative **5** involves a nitrile oxide precursor **B** as the key intermediate, which would be derived from aldoxime derivative **4** via benzohydroximinoyl chloride intermediate **A**. The aldoxime derivative **4** can be synthesized from the *O*-cinnamyl salicylaldehyde derivative **3** and hydroxylamine hydrochloride ($NH_2OH{\cdot}HCl$). Finally, the *O*-cinnamyl salicylaldehyde derivative **3** can be generated from the bromo derivative **2** of the Baylis–Hillman adduct according to the retrosynthetic strategy shown in Scheme 1.

To synthesize the fused tricyclic chromenoisoxazoline compound **5a**, we first prepared *O*-cinnamyl salicylaldehyde derivative **3a** and treated it with hydroxylamine hydrochloride in the presence of 50% aqueous sodium hydroxide, which furnished the necessary aldoxime derivative **4a** in excellent yield (96%). Aldoxime derivative **4a** was treated with *N*-chlorosuccinimide in the presence of triethylamine at 0–10 °C for five hours, which successfully afforded the desired compound **5a** in 70% yield. Encouraged by this result, we prepared a variety of aldoxime derivatives **4b–m** and treated them with *N*-chlorosuccinimide in the presence of triethylamine at 0–10 °C for five hours, which successfully led to the desired fused tricyclic chromenoisoxazolines **5b–m** in 72–82% yield (Table 1, entries 2–13). It is worth mentioning that this is the first report for the formation of a fused tricyclic skeleton with an electron-withdrawing functional group at the angular position via an INOC reaction as a key step. Interestingly, the Baylis–Hillman derivatives were utilized as a substrate for the INOC reaction for the first time.

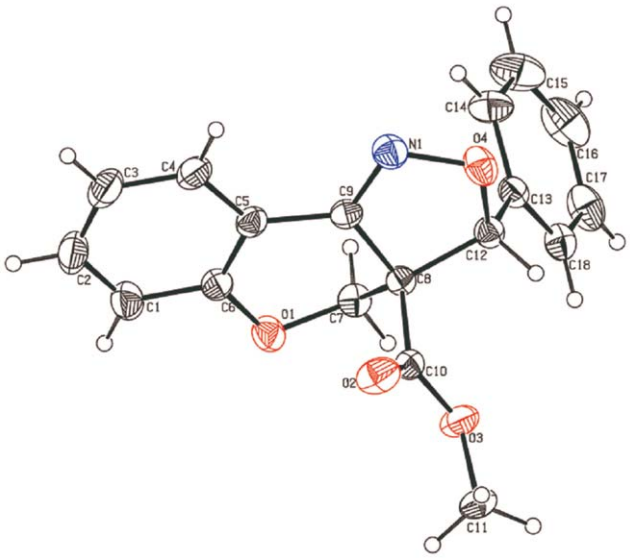
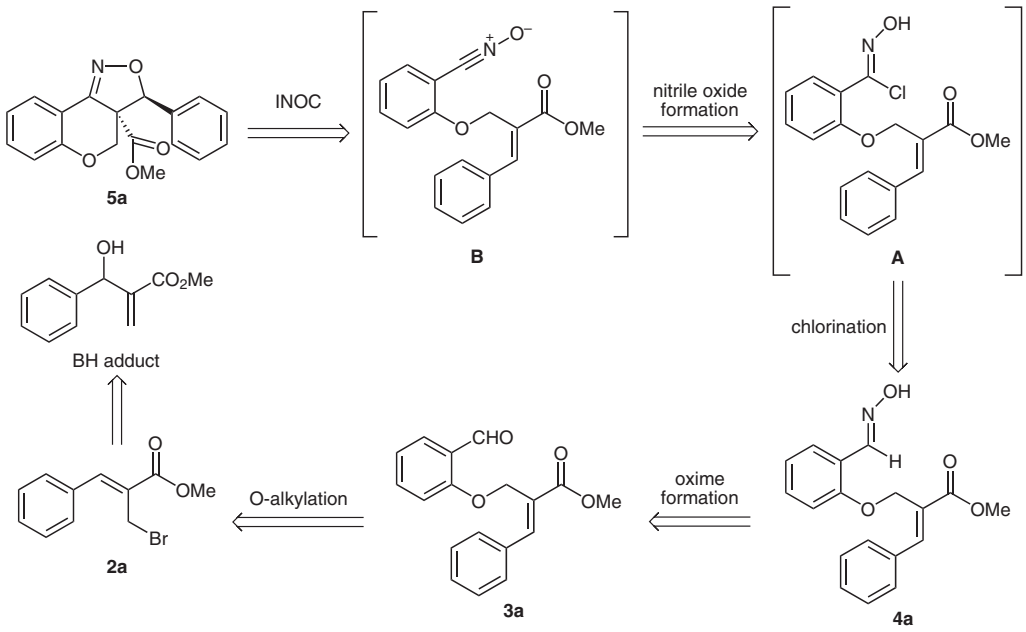


Figure 2 X-ray crystal structure of **5a**

To check the generality of the reaction and its applicability to the Baylis–Hillman derivatives **6a–g** synthesized from acrylonitrile, we prepared a variety of aldoxime derivatives **8a–l** from **7a–l** in very good yields. Treatment of the aldoxime derivatives **8a–l** with *N*-chlorosuccinimide



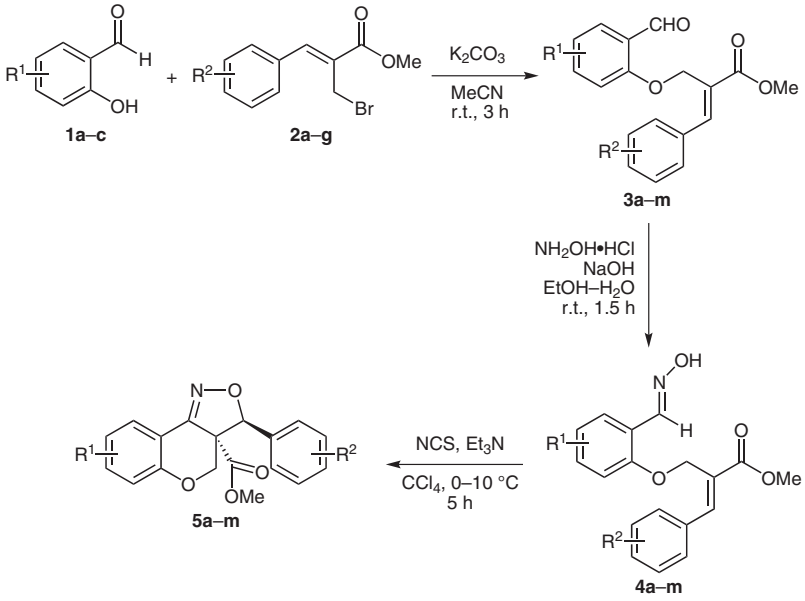
Scheme 1 Retrosynthetic approach to the tricyclic chromenoisoxazolines

in the presence of triethylamine at 0–10 °C for five hours smoothly led to the desired tricyclic chromenoisoxazolines **9a–l** with the nitrile functionality at the angular position in 62–70% yield (Table 2, entries 1–12).

The stereochemistry of compound **5a** was confirmed by ^{1}H NMR data and X-ray crystal analysis[16] (Figure 2). The crystal structure of compound **5a** shows that the relative stereochemistry of the aryl group and the adjacent ester moiety is in the *anti* orientation, which is presumably due to the initial *E* geometry of the double bond present in compound **3a**. We have also confirmed the relative stereochemistry of compound **9d** by X-ray crystallographic analysis[16] (Figure 3). The crystal structure of compound **9d** shows that the nitrile moiety and the aryl group are in the *syn* orientation, which is presumably due to the initial *cis* geometry of the aryl and nitrile groups in the double bond of compound **7d**.

In conclusion, we have developed an efficient and general route for the synthesis of fused tricyclic chromenoisoxazoline frameworks via an intramolecular 1,3-dipolar ni-

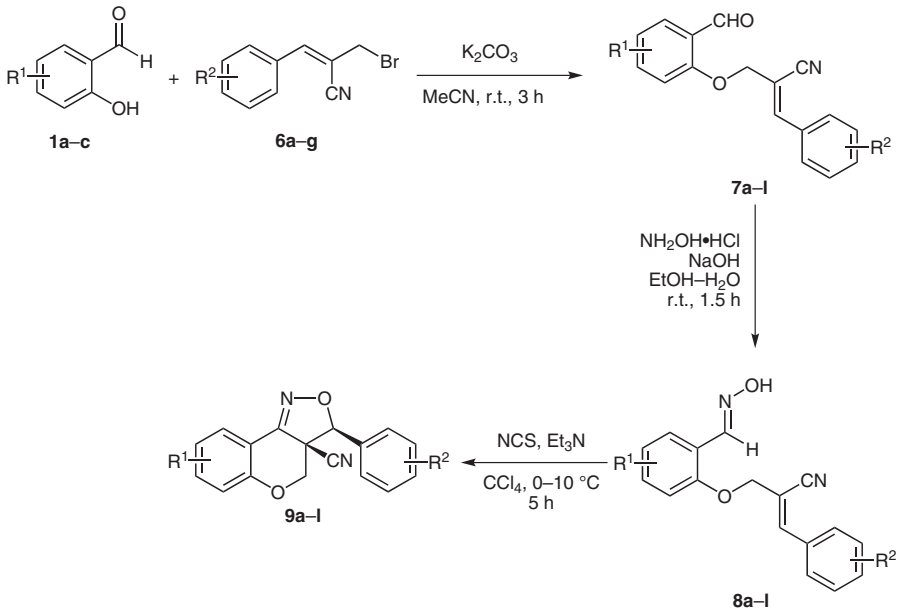
Table 1 Synthesis of Tricyclic Chromenoisoxazolines Using Baylis–Hillman Derivatives **2a–g**



Entry	R^1	R^2	Aldoxime[a,b]	Yield[c] (%)	Isoxazoline[b,d]	Yield[e] (%)
1	H	H	**4a**	96	**5a**[f]	70
2	H	2-Me	**4b**	97	**5b**	72
3	H	4-Me	**4c**	95	**5c**	73
4	H	4-Et	**4d**	91	**5d**	74
5	H	4-*i*-Pr	**4e**	89	**5e**	82
6	H	2-OMe	**4f**	96	**5f**	80
7	H	4-Cl	**4g**	94	**5g**	81
8	5-Br	H	**4h**	87	**5h**	79
9	5-Br	4-Me	**4i**	88	**5i**	75
10	5-Br	4-Et	**4j**	85	**5j**	76
11	3-OEt	H	**4k**	93	**5k**	79
12	3-OEt	4-Me	**4l**	94	**5l**	78
13	3-OEt	4-Et	**4m**	92	**5m**	74

[a] All reactions were carried out using the *O*-cinnamyl derivative **3a–m** (4 mmol) and $NH_2OH{\cdot}HCl$ (6 mmol).
[b] All products gave satisfactory IR, ^{1}H NMR, ^{13}C NMR and mass spectra.
[c] Pure products **4a–m** were obtained by recrystallization (EtOAc).
[d] All reactions were carried out using aldoxime **4a–m** (2 mmol) with NCS (4 mmol) in the presence of Et_3N (4 mmol).
[e] Yield of the pure product **5a–m** obtained after column chromatography (silica gel 60–120 mesh; EtOAc–hexanes, 5:95).
[f] Structure was further confirmed by single-crystal X-ray analysis.[16]

Table 2 Synthesis of Tricyclic Chromenoisoxazolines Using Baylis–Hillman Derivatives **6a–g**



Entry	R^1	R^2	Aldoxime[a,b]	Yield[c] (%)	Isoxazoline[b,d]	Yield[e] (%)
1	H	H	**8a**	87	**9a**	62
2	H	2-Me	**8b**	97	**9b**	67
3	H	4-Me	**8c**	96	**9c**	65
4	H	4-Et	**8d**	95	**9d**[f]	66
5	H	4-*i*-Pr	**8e**	93	**9e**	63
6	H	2-OMe	**8f**	96	**9f**	68
7	H	4-Cl	**8g**	98	**9g**	62
8	5-Br	H	**8h**	86	**9h**	63
9	5-Br	4-Me	**8i**	94	**9i**	67
10	5-Br	4-Et	**8j**	88	**9j**	68
11	3-OEt	H	**8k**	88	**9k**	70
12	3-OEt	4-*i*-Pr	**8l**	92	**9l**	69

[a] All reactions were carried out using the *O*-cinnamyl derivative **7a–l** (4 mmol) and $NH_2OH{\cdot}HCl$ (6 mmol).
[b] All products gave satisfactory IR, ^1H NMR, ^{13}C NMR and mass spectra.
[c] Pure products **8a–l** were obtained by recrystallization (EtOAc).
[d] All reactions were carried out using aldoxime **8a–l** (2 mmol) with NCS (4 mmol) in the presence of Et_3N (4 mmol).
[e] Yield of the pure product **9a–l** obtained after column chromatography (silica gel 60–120 mesh; EtOAc–hexanes, 7:93).
[f] Structure was further confirmed by single-crystal X-ray analysis.[16]

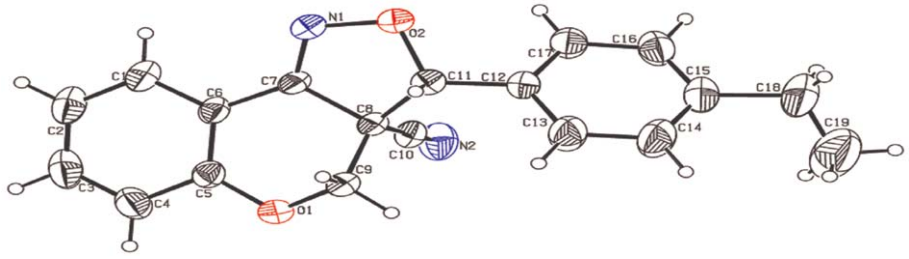


Figure 3 X-ray crystal structure of **9d**

trile oxide cycloaddition strategy using Baylis–Hillman derivatives for the first time. The new [3+2]-cycloaddition reaction leads to a novel class of angularly substituted fused tricyclic chromenoisoxazolines, with the creation of two rings and two contiguous stereocenters, one of them being an all-carbon quaternary center, in a unique fashion. The fused tricyclic chromenoisoxazolines were obtained in a highly stereoselective fashion with good yields.

Commercial reagents were used as received without further purification. Solvents were distilled prior to use. Column chromatography was performed on silica gel. Melting points were measured on a Superfit (India) capillary apparatus and are uncorrected. IR spectra were run neat on a Bruker Tensor 27 spectrophotometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz or 100 MHz) spectra were recorded in $CDCl_3$ as solvent and TMS as internal standard on a Bruker instrument. Mass spectra were recorded on a Thermo Finnigan spectrometer. All products were isolated as colorless solids

Methyl (*E*)-2-({2-[(*E*)-(Hydroxyimino)methyl]phenoxy}methyl)-3-phenylacrylate (4a); Typical Procedure

To a stirred soln of *O*-allylic salicylaldehyde derivative **3a** (1.20 g, 4 mmol) in EtOH–H_2O (1:1, 10 mL) was added NH_2OH·HCl (0.42 g, 6 mmol) in the presence of 50% aq NaOH (0.48 mL) at r.t. Then, the reaction mixture was stirred at r.t. for 1.5 h. After completion of the reaction as evidenced by TLC, the reaction mixture was concentrated under reduced pressure. The resulting crude mass was diluted with H_2O (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine (2 × 10 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the crude product was purified by recrystallization (EtOAc) to obtain pure aldoxime **4a** as a colorless solid; yield: 1.19 g (96%); mp 122–124 °C.

IR (neat): 3251, 1718, 1634, 1592, 1239 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.75 (br s, 1 H), 3.87 (s, 3 H), 4.88 (s, 2 H), 6.95–7.46 (m, 8 H), 7.78 (d, *J* = 7.5 Hz, 1 H), 8.08 (s, 1 H), 8.52 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.45, 63.64, 113.04, 121.35, 121.47, 126.52, 126.92, 128.81, 129.62, 129.72, 131.28, 134.36, 146.01, 146.31, 156.65, 167.61.

Methyl (*E*)-2-({2-[(*E*)-(Hydroxyimino)methyl]phenoxy}methyl)-3-*o*-tolylacrylate (4b)

Yield: 1.26 g (97%); mp 78–79 °C.

IR (neat): 3241, 1720, 1634, 1594, 1238 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.79 (br s, 1 H), 2.32 (s, 3 H), 3.88 (s, 3 H), 4.79 (s, 2 H), 6.85 (d, *J* = 8.4 Hz, 1 H), 6.97 (t, *J* = 7.5 Hz, 1 H), 7.14–7.33 (m, 5 H), 7.75 (d, *J* = 7.2 Hz, 1 H), 8.13 (s, 1 H), 8.49 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.98, 52.42, 63.93, 113.22, 121.41, 126.10, 126.45, 127.77, 128.92, 129.50, 130.24, 131.18, 133.68, 137.19, 144.84, 146.32, 156.68, 167.44.

Methyl (*E*)-2-({2-[(*E*)-(Hydroxyimino)methyl]phenoxy}methyl)-3-*p*-tolylacrylate (4c)

Yield: 1.24 g (95%); mp 140 °C.

IR (neat): 3262, 1717, 1629, 1587, 1242 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.73 (br s, 1 H), 2.36 (s, 3 H), 3.86 (s, 3 H), 4.88 (s, 2 H), 6.96–7.03 (m, 2 H), 7.19 (d, *J* = 7.8 Hz, 2 H), 7.36 (d, *J* = 7.5 Hz, 3 H), 7.88 (d, *J* = 7.8 Hz, 1 H), 8.05 (s, 1 H), 8.51 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.40, 52.33, 63.65, 112.95, 121.30, 121.35, 125.93, 126.35, 129.54, 129.74, 131.24, 131.53, 140.16, 146.08, 146.54, 156.65, 167.68.

Methyl (*E*)-3-(4-Ethylphenyl)-2-({2-[(*E*)-(hydroxyimino)methyl]phenoxy}methyl)acrylate (4d)

Yield: 1.23 g (91%); mp 122–124 °C.

IR (neat): 3264, 1716, 1629, 1579, 1240 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.5 Hz, 3 H), 1.84 (br s, 1 H), 2.65 (q, *J* = 7.5 Hz, 2 H), 3.86 (s, 3 H), 4.89 (s, 2 H), 6.99 (t, *J* = 8.7 Hz, 2 H), 7.21 (d, *J* = 8.1 Hz, 2 H), 7.33–7.40 (m, 3 H), 7.78 (d, *J* = 7.8 Hz, 1 H), 8.06 (s, 1 H), 8.52 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.25, 28.74, 52.36, 63.69, 113.00, 121.34, 121.38, 125.93, 126.45, 128.36, 129.87, 131.25, 131.77, 146.15, 146.36, 146.42, 156.69, 167.76.

Methyl (*E*)-2-({2-[(*E*)-(Hydroxyimino)methyl]phenoxy}methyl)-3-(4-isopropylphenyl)acrylate (4e)

Yield: 1.26 g (89%); mp 123 °C.

IR (neat): 3190, 1709, 1630, 1586, 1237 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (d, *J* = 6.9 Hz, 6 H), 2.90 (septet, *J* = 6.9 Hz, 1 H), 3.85 (s, 3 H), 4.89 (s, 2 H), 6.99 (t, *J* = 7.8 Hz, 2 H), 7.24 (d, *J* = 8.1 Hz, 2 H), 7.38 (t, *J* = 8.1 Hz, 3 H), 7.78 (d, *J* = 7.8 Hz, 1 H), 8.06 (s, 1 H), 8.30 (br s, 1 H), 8.52 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.76, 34.04, 52.38, 63.67, 112.97, 121.38, 125.89, 126.47, 126.97, 129.94, 131.25, 131.89, 146.16, 146.28, 151.02, 156.69, 167.80.

Methyl (*E*)-2-({2-[(*E*)-(Hydroxyimino)methyl]phenoxy}methyl)-3-(2-methoxyphenyl)acrylate (4f)

Yield: 1.31 g (96%); mp 120–121 °C.

IR (neat): 3254, 1697, 1627, 1592, 1232 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.77 (br s, 1 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 4.84 (s, 2 H), 6.88–7.00 (m, 4 H), 7.29–7.41 (m, 3 H), 7.76 (d, *J* = 7.5 Hz, 1 H), 8.24 (s, 1 H), 8.51 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.30, 55.53, 64.17, 110.55, 113.03, 120.70, 121.29, 123.52, 126.34, 126.71, 130.22, 131.21, 131.31, 141.85, 146.43, 156.76, 157.84, 167.55.

Methyl (*E*)-3-(4-Chlorophenyl)-2-({2-[(*E*)-(hydroxyimino)methyl]phenoxy}methyl)acrylate (4g)

Yield: 1.30 g (94%); mp 142 °C.

IR (neat): 3284, 1717, 1635, 1592, 1237 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.69 (br s, 1 H), 3.86 (s, 3 H), 4.84 (s, 2 H), 6.95–7.04 (m, 2 H), 7.33–7.41 (m, 5 H), 7.77 (dd, J_1 = 1.7 Hz, J_2 = 7.7 Hz, 1 H), 8.01 (s, 1 H), 8.48 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.53, 63.42, 112.95, 121.29, 121.61, 126.59, 127.37, 129.09, 130.90, 131.32, 132.74, 135.91, 144.64, 146.23, 156.44, 167.33.

Methyl (*E*)-2-({4-Bromo-2-[(*E*)-(hydroxyimino)methyl]phenoxy}methyl)-3-phenylacrylate (4h)

Yield: 1.36 g (87%); mp 148 °C.

IR (neat): 3381, 1700, 1621, 1589, 1234 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.94 (br s, 1 H), 3.86 (s, 3 H), 4.85 (s, 2 H), 6.83 (d, *J* = 9.0 Hz, 1 H), 7.37–7.43 (m, 6 H), 7.89 (d, *J* = 2.4 Hz, 1 H), 8.08 (s, 1 H), 8.41 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.49, 63.95, 114.00, 114.78, 123.30, 126.54, 128.84, 129.05, 129.53, 129.82, 133.66, 134.22, 145.18, 146.22, 155.56, 167.46.

Methyl (*E*)-2-({4-Bromo-2-[(*E*)-(hydroxyimino)methyl]phenoxy}methyl)-3-*p*-tolylacrylate (4i)
Yield: 1.42 g (88%); mp 163–165 °C.

IR (neat): 3436, 1706, 1632, 1594, 1236 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 3 H), 3.86 (s, 3 H), 4.86 (s, 2 H), 6.85 (d, *J* = 8.7 Hz, 1 H), 7.19 (d, *J* = 7.8 Hz, 2 H), 7.32 (d, *J* = 8.1 Hz, 2 H), 7.42 (dd, J_1 = 2.4 Hz, J_2 = 8.7 Hz, 1 H), 7.70 (br s, 1 H), 7.90 (d, *J* = 2.4 Hz, 1 H), 8.05 (s, 1 H), 8.40 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.40, 52.40, 64.03, 113.95, 114.77, 123.33, 125.58, 129.03, 129.58, 129.67, 131.41, 133.63, 140.31, 145.19, 146.35, 155.60, 167.62.

Methyl (*E*)-2-({4-Bromo-2-[(*E*)-(hydroxyimino)methyl]phenoxy}methyl)-3-(4-ethylphenyl)acrylate (4j)
Yield: 1.45 g (85%); mp 164–165 °C.

IR (neat): 3434, 1716, 1600, 1590, 1242 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.5 Hz, 3 H), 2.66 (q, *J* = 7.5 Hz, 2 H), 3.86 (s, 3 H), 4.87 (s, 2 H), 6.85 (d, *J* = 8.7 Hz, 1 H), 7.22 (d, *J* = 8.1 Hz, 2 H), 7.35 (d, *J* = 7.8 Hz, 3 H), 7.43 (dd, J_1 = 2.4 Hz, J_2 = 9.0 Hz, 1 H), 7.92 (d, *J* = 2.4 Hz, 1 H), 8.05 (s, 1 H), 8.40 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.25, 28.74, 52.40, 63.99, 113.92, 114.73, 123.26, 125.53, 128.40, 129.00, 129.79, 131.62, 133.65, 145.24, 146.37, 146.57, 155.60, 167.61.

Methyl (*E*)-2-({2-Ethoxy-6-[(*E*)-(hydroxyimino)methyl]phenoxy}methyl)-3-phenylacrylate (4k)
Yield: 1.32 g (93%); mp 102–104 °C.

IR (neat): 3426, 1722, 1627, 1560, 1234 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 6.9 Hz, 3 H), 3.85 (s, 3 H), 4.02 (q, *J* = 6.9 Hz, 2 H), 4.99 (s, 2 H), 6.89 (d, *J* = 7.5 Hz, 1 H), 7.02 (t, *J* = 7.8 Hz, 1 H), 7.33–7.63 (m, 6 H), 8.02 (s, 1 H), 8.15 (br s, 1 H), 8.57 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.81, 52.30, 64.11, 67.40, 114.27, 117.58, 124.26, 126.43, 127.87, 128.56, 129.40, 129.99, 134.48, 145.55, 147.11, 152.21, 167.98.

Methyl (*E*)-2-({2-Ethoxy-6-[(*E*)-(hydroxyimino)methyl]phenoxy}methyl)-3-*p*-tolylacrylate (4l)
Yield: 1.39 g (94%); mp 124 °C.

IR (neat): 3244, 1711, 1630, 1511, 1234 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, *J* = 6.9 Hz, 3 H), 2.38 (s, 3 H), 3.83 (s, 3 H), 4.04 (q, *J* = 6.9 Hz, 2 H), 5.01 (s, 2 H), 6.89 (d, *J* = 8.1 Hz, 1 H), 7.02 (t, *J* = 8.1 Hz, 1 H), 7.22 (d, *J* = 7.8 Hz, 2 H), 7.34 (d, *J* = 7.8 Hz, 1 H), 7.55 (d, *J* = 7.8 Hz, 2 H), 7.99 (s, 1 H), 8.58 (s, 1 H), 8.80 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.83, 21.47, 52.28, 64.15, 67.60, 114.31, 117.59, 124.27, 126.45, 126.87, 129.35, 130.20, 131.65, 139.82, 145.75, 146.99, 147.17, 152.24, 168.19.

Methyl (*E*)-2-({2-Ethoxy-6-[(*E*)-(hydroxyimino)methyl]phenoxy}methyl)-3-(4-ethylphenyl)acrylate (4m)
Yield: 1.41 g (92%); mp 112–114 °C.

IR (neat): 3289, 1710, 1631, 1506, 1266 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.5 Hz, 3 H), 1.35 (t, *J* = 6.9 Hz, 3 H), 2.68 (q, *J* = 7.5 Hz, 2 H), 3.83 (s, 3 H), 4.04 (q, *J* = 6.9 Hz, 2 H), 5.01 (s, 2 H), 6.89 (d, *J* = 7.5 Hz, 1 H), 7.02 (t, *J* = 8.1 Hz, 1 H), 7.25 (d, *J* = 7.8 Hz, 2 H), 7.35 (d, *J* = 7.8 Hz, 1 H), 7.56 (d, *J* = 8.1 Hz, 2 H), 7.99 (s, 1 H), 8.38 (br s, 1 H), 8.57 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.83, 15.41, 28.80, 52.23, 64.12, 67.54, 114.26, 117.59, 124.24, 126.47, 126.94, 128.14, 130.25, 131.91, 145.74, 146.06, 147.11, 152.24, 168.17.

Methyl 3-Phenyl-3*H*-chromeno[4,3-*c*]isoxazole-3a(4*H*)-carboxylate (5a); Typical Procedure
To a soln of aldoxime **4a** (0.63 g, 2 mmol) in CCl_4 (10 mL) at 0–10 °C was added NCS (0.54 g, 4 mmol) over 3 h. After this period, Et_3N (0.57 mL, 4 mmol) was added and the reaction mixture was stirred well at r.t. for 2 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, and the resulting crude mass was diluted with H_2O (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine (2 × 10 mL) and dried (Na_2SO_4). The organic layer was concentrated and the residue was purified by column chromatography (silica gel 60–120 mesh; EtOAc–hexanes, 5:95) to provide the desired pure product **5a** as a colorless solid; yield: 0.43 g (70%); mp 130–132 °C.

IR (neat): 1737, 1608, 1570, 1256 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.23 (d, *J* = 11.1 Hz, 1 H), 3.79 (s, 3 H), 4.51 (d, *J* = 10.8 Hz, 1 H), 5.91 (s, 1 H), 6.88 (d, *J* = 8.4 Hz, 1 H), 7.05 (t, *J* = 7.5 Hz, 1 H), 7.26–7.37 (m, 6 H), 7.95 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.60, 62.46, 69.78, 87.30, 113.63, 117.42, 122.17, 125.13, 125.91, 128.92, 129.01, 132.39, 132.24, 149.24, 154.57, 170.94.

MS: *m*/*z* = 310 [M^+ + 1].

Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.82; H, 4.84; N, 4.62.

Methyl 3-*o*-Tolyl-3*H*-chromeno[4,3-*c*]isoxazole-3a(4*H*)-carboxylate (5b)
Yield: 0.46 g (72%); mp 152–153 °C.

IR (neat): 1736, 1608, 1572, 1286 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 3.31 (d, *J* = 10.8 Hz, 1 H), 3.80 (s, 3 H), 4.51 (d, *J* = 10.8 Hz, 1 H), 6.12 (s, 1 H), 6.88 (d, *J* = 8.4 Hz, 1 H), 7.05 (t, *J* = 7.2 Hz, 1 H), 7.15–7.35 (m, 5 H), 7.96 (dd, J_1 = 1.5 Hz, J_2 = 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.04, 53.58, 62.62, 69.31, 85.17, 113.66, 117.41, 122.13, 125.91, 125.96, 126.75, 128.72, 130.86, 132.32, 133.39, 133.61, 149.01, 154.62, 170.94.

MS: *m*/*z* = 324 [M^+ + 1].

Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.51; H, 5.22; N, 4.40.

Methyl 3-*p*-Tolyl-3*H*-chromeno[4,3-*c*]isoxazole-3a(4*H*)-carboxylate (5c)
Yield: 0.47 g (73%); mp 98–100 °C.

IR (neat): 1742, 1610, 1571, 1259 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 3 H), 3.25 (d, *J* = 10.8 Hz, 1 H), 3.79 (s, 3 H), 4.49 (d, *J* = 11.1 Hz, 1 H), 5.88 (s, 1 H), 6.88 (d, *J* = 8.4 Hz, 1 H), 7.05 (t, *J* = 6.9 Hz, 1 H), 7.12–7.34 (m, 5 H), 7.95 (dd, J_1 = 1.5 Hz, J_2 = 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.14, 53.55, 62.38, 69.78, 87.37, 113.70, 117.40, 122.12, 125.08, 125.89, 129.64, 132.26, 132.32, 138.79, 149.20, 154.58, 171.00.

MS: *m*/*z* = 324 [M^+ + 1].

Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.63; H, 5.21; N, 4.42.

Methyl 3-(4-Ethylphenyl)-3*H*-chromeno[4,3-*c*]isoxazole-3a(4*H*)-carboxylate (5d)
Yield: 0.50 g (74%); mp 128–130 °C.

IR (neat): 1740, 1611, 1573, 1250 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.5 Hz, 3 H), 2.63 (q, *J* = 7.5 Hz, 2 H), 3.25 (d, *J* = 11.1 Hz, 1 H), 3.79 (s, 3 H), 4.50 (d, *J* = 11.1 Hz, 1 H), 5.88 (s, 1 H), 6.88 (d, *J* = 8.4 Hz, 1 H), 7.05 (t, *J* = 7.5 Hz, 1 H), 7.15–7.34 (m, 5 H), 7.95 (dd, J_1 = 1.4 Hz, J_2 = 8.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.43, 28.52, 53.56, 62.41, 69.79, 87.39, 113.71, 117.40, 122.12, 125.15, 125.89, 128.46, 132.32, 132.48, 145.13, 149.20, 154.58, 171.02.

MS: *m*/*z* = 338 [M$^+$ + 1].

Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.14; H, 5.77; N, 4.23.

Methyl 3-(4-Isopropylphenyl)-3*H*-chromeno[4,3-*c*]isoxazole-3a(4*H*)-carboxylate (5e)
Yield: 0.58 g (82%); mp 132–133 °C.

IR (neat): 1735, 1610, 1571, 1255 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (d, *J* = 6.9 Hz, 6 H), 2.88 (septet, *J* = 6.9 Hz, 1 H), 3.25 (d, *J* = 11.1 Hz, 1 H), 3.79 (s, 3 H), 4.51 (d, *J* = 11.1 Hz, 1 H), 5.88 (s, 1 H), 6.88 (d, *J* = 8.4 Hz, 1 H), 7.05 (t, *J* = 7.5 Hz, 1 H), 7.16–7.35 (m, 5 H), 7.95 (dd, J_1 = 1.5 Hz, J_2 = 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.83, 23.91, 33.83, 53.56, 62.42, 69.81, 87.39, 113.72, 117.40, 122.12, 125.14, 125.90, 127.03, 132.31, 132.59, 149.19, 149.76, 154.58, 171.03.

MS: *m*/*z* = 352 [M$^+$ + 1].

Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.83; H, 6.09; N, 4.09.

Methyl 3-(2-Methoxyphenyl)-3*H*-chromeno[4,3-*c*]isoxazole-3a(4*H*)-carboxylate (5f)
Yield: 0.54 g (80%); mp 114–115 °C.

IR (neat): 1737, 1610, 1490, 1249 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.37 (d, *J* = 11.1 Hz, 1 H), 3.80 (s, 3 H), 3.89 (s, 3 H), 4.76 (d, *J* = 11.1 Hz, 1 H), 6.21 (s, 1 H), 6.86–7.33 (m, 7 H), 7.92 (dd, J_1 = 1.5 Hz, J_2 = 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.39, 55.38, 62.10, 68.93, 83.73, 110.13, 113.37, 117.42, 121.10, 121.90, 123.53, 125.85, 126.90, 129.82, 132.29, 149.51, 154.89, 155.45, 170.25.

MS: *m*/*z* = 340 [M$^+$ + 1].

Anal. Calcd for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.05; N, 4.13. Found: C, 67.23; H, 4.96; N, 4.22.

Methyl 3-(4-Chlorophenyl)-3*H*-chromeno[4,3-*c*]isoxazole-3a(4*H*)-carboxylate (5g)
Yield: 0.56 g (81%); mp 140–142 °C.

IR (neat): 1737, 1610, 1572, 1298 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.23 (d, *J* = 11.1 Hz, 1 H), 3.79 (s, 3 H), 4.50 (d, *J* = 11.1 Hz, 1 H), 5.88 (s, 1 H), 6.89 (d, *J* = 8.1 Hz, 1 H), 7.06 (t, *J* = 7.2 Hz, 1 H), 7.20–7.37 (m, 5 H), 7.94 (dd, J_1 = 1.7 Hz, J_2 = 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.70, 62.48, 69.70, 86.56, 113.44, 117.46, 122.29, 125.91, 126.62, 129.27, 132.57, 133.77, 134.86, 149.35, 154.54, 170.73.

MS: *m*/*z* = 345 [M$^+$ + 1].

Anal. Calcd for $C_{18}H_{14}ClNO_4$: C, 62.89; H, 4.10; N, 4.07. Found: C, 62.78; H, 3.98; N, 4.17.

Methyl 8-Bromo-3-phenyl-3*H*-chromeno[4,3-*c*]isoxazole-3a(4*H*)-carboxylate (5h)
Yield: 0.61 g (79%); mp 156–158 °C.

IR (neat): 1701, 1609, 1530, 1264 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.19 (d, *J* = 11.1 Hz, 1 H), 3.81 (s, 3 H), 4.50 (d, *J* = 11.1 Hz, 1 H), 5.93 (s, 1 H), 6.78 (d, *J* = 9.0 Hz, 1 H), 7.23–7.42 (m, 6 H), 8.08 (d, *J* = 2.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.71, 61.97, 69.90, 87.57, 114.55, 115.42, 119.27, 125.04, 128.26, 129.05, 129.08, 134.92, 135.09, 148.27, 153.47, 170.64.

MS: *m*/*z* = 390 [M$^+$ + 2].

Anal. Calcd for $C_{18}H_{14}BrNO_4$: C, 55.69; H, 3.63; N, 3.61. Found: C, 55.74; H, 3.51; N, 3.72.

Methyl 8-Bromo-3-*p*-tolyl-3*H*-chromeno[4,3-*c*]isoxazole-3a(4*H*)-carboxylate (5i)
Yield: 0.60 g (75%); mp 136–138 °C.

IR (neat): 1711, 1606, 1512, 1260 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 3 H), 3.21 (d, *J* = 11.1 Hz, 1 H), 3.80 (s, 3 H), 4.48 (d, *J* = 11.1 Hz, 1 H), 5.90 (s, 1 H), 6.77 (d, *J* = 8.7 Hz, 1 H), 7.14 (q, *J* = 8.1 Hz, 4 H), 7.39 (dd, J_1 = 2.4 Hz, J_2 = 9.0 Hz, 1 H), 8.07 (d, *J* = 2.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.15, 53.66, 61.90, 69.91, 87.67, 114.52, 115.51, 119.25, 125.00, 128.25, 129.73, 131.95, 135.03, 138.97, 148.24, 153.49, 170.72.

MS: *m*/*z* = 404 [M$^+$ + 2].

Anal. Calcd for $C_{19}H_{16}BrNO_4$: C, 56.73; H, 4.01; N, 3.48. Found: C, 56.83; H, 4.10; N, 3.54.

Methyl 8-Bromo-3-(4-ethylphenyl)-3*H*-chromeno[4,3-*c*]isoxazole-3a(4*H*)-carboxylate (5j)
Yield: 0.63 g (76%); mp 141 °C.

IR (neat): 1720, 1605, 1462, 1247 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.5 Hz, 3 H), 2.63 (q, *J* = 7.5 Hz, 2 H), 3.21 (d, *J* = 11.1 Hz, 1 H), 3.80 (s, 3 H), 4.49 (d, *J* = 11.1 Hz, 1 H), 5.90 (s, 1 H), 6.77 (d, *J* = 8.7 Hz, 1 H), 7.17 (q, *J* = 8.4 Hz, 4 H), 7.39 (dd, J_1 = 2.6 Hz, J_2 = 8.9 Hz, 1 H), 8.07 (d, *J* = 2.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.41, 28.52, 53.66, 61.91, 69.91, 87.67, 114.51, 115.50, 119.25, 125.06, 128.24, 128.53, 132.15, 135.02, 145.30, 148.23, 153.47, 170.72.

MS: *m*/*z* = 418 [M$^+$ + 2].

Anal. Calcd for $C_{20}H_{18}BrNO_4$: C, 57.71; H, 4.36; N, 3.36. Found: C, 57.78; H, 4.29; N, 3.47.

Methyl 6-Ethoxy-3-phenyl-3*H*-chromeno[4,3-*c*]isoxazole-3a(4*H*)-carboxylate (5k)
Yield: 0.56 g (79%); mp 155–157 °C.

IR (neat): 1768, 1603, 1484, 1254 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (t, *J* = 6.9 Hz, 3 H), 3.23 (d, *J* = 11.1 Hz, 1 H), 3.79 (s, 3 H), 4.03 (q, *J* = 6.9 Hz, 2 H), 4.62 (d, *J* = 11.1 Hz, 1 H), 5.94 (s, 1 H), 6.90 (d, *J* = 8.1 Hz, 1 H), 6.98 (t, *J* = 7.8 Hz, 1 H), 7.25–7.38 (m, 5 H), 7.56 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.66, 53.60, 62.40, 64.50, 70.26, 87.45, 114.53, 115.03, 117.24, 121.97, 125.05, 128.89, 128.98, 135.22, 144.59, 147.99, 149.32, 170.73.

MS: *m*/*z* = 354 [M$^+$ + 1].

Anal. Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.91; H, 5.36; N, 4.06.

Methyl 6-Ethoxy-3-*p*-tolyl-3*H*-chromeno[4,3-*c*]isoxazole-3a(4*H*)-carboxylate (5l)
Yield: 0.57 g (78%); mp 160–161 °C.

IR (neat): 1764, 1602, 1489, 1256 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.40 (t, *J* = 6.9 Hz, 3 H), 2.32 (s, 3 H), 3.25 (d, *J* = 11.1 Hz, 1 H), 3.78 (s, 3 H), 4.03 (q, *J* = 6.9 Hz, 2 H), 4.61 (d, *J* = 11.1 Hz, 1 H), 5.90 (s, 1 H), 6.89 (dd, J_1 = 1.2 Hz, J_2 = 8.1 Hz, 1 H), 6.97 (t, *J* = 7.8 Hz, 1 H), 7.14 (s, 4 H), 7.55 (dd, J_1 = 1.5 Hz, J_2 = 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.64, 21.38, 53.49, 62.31, 64.46, 70.18, 87.44, 114.56, 115.03, 117.16, 121.93, 125.26, 129.59, 132.27, 138.69, 144.61, 148.00, 149.27, 170.80.

MS: *m*/*z* = 368 [M^+ + 1].

Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.72; H, 5.68; N, 3.90.

Methyl 6-Ethoxy-3-(4-ethylphenyl)-3*H*-chromeno[4,3-*c*]isoxazole-3a(4*H*)-carboxylate (5m)
Yield: 0.56 g (74%); mp 154–156 °C.

IR (neat): 1768, 1606, 1486, 1258 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 7.5 Hz, 3 H), 1.40 (t, *J* = 6.9 Hz, 3 H), 2.61 (q, *J* = 7.5 Hz, 2 H), 3.25 (d, *J* = 11.1 Hz, 1 H), 3.78 (s, 3 H), 4.03 (q, *J* = 6.9 Hz, 2 H), 4.61 (d, *J* = 11.1 Hz, 1 H), 5.91 (s, 1 H), 6.89 (d, *J* = 7.5 Hz, 1 H), 6.98 (t, *J* = 8.1 Hz, 1 H), 7.14–7.19 (m, 4 H), 7.55 (dd, J_1 = 1.2 Hz, J_2 = 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.63, 15.46, 28.47, 53.48, 62.33, 64.43, 70.19, 87.44, 114.55, 114.98, 117.13, 121.94, 125.25, 128.16, 132.51, 144.58, 145.03, 148.00, 149.24, 170.73.

MS: *m*/*z* = 382 [M^+ + 1].

Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.26; H, 5.99; N, 3.76.

(*E*)-2-({2-[(*E*)-(Hydroxyimino)methyl]phenoxy}methyl)-3-phenylacrylonitrile (8a); Typical Procedure
To a stirred soln of *O*-allylic salicylaldehyde derivative **7a** (1.06 g, 4 mmol) in EtOH–H_2O (1:1, 10 mL) was added NH_2OH·HCl (0.42 g, 6 mmol) in the presence of 50% aq NaOH (0.48 mL) at r.t. Then, the reaction mixture was stirred at r.t. for 1.5 h. After completion of the reaction as evidenced by TLC, the reaction mixture was concentrated under reduced pressure. The resulting crude mass was diluted with H_2O (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine (2 × 10 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the crude product was purified by recrystallization (EtOAc) to obtain pure aldoxime **8a** as a colorless solid; yield: 0.97 g (87%); mp 136–138 °C.

IR (neat): 3415, 2217, 1625, 1589, 1237 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.82 (br s, 1 H), 4.82 (s, 2 H), 6.94 (d, *J* = 8.4 Hz, 1 H), 7.04 (t, *J* = 7.5 Hz, 1 H), 7.26–7.81 (m, 8 H), 8.58 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 69.71, 106.32, 112.88, 117.25, 121.50, 122.21, 127.23, 129.00, 129.22, 131.08, 131.30, 132.65, 146.06, 146.12, 155.66.

(*E*)-2-({2-[(*E*)-(Hydroxyimino)methyl]phenoxy}methyl)-3-*o*-tolylacrylonitrile (8b)
Yield: 1.13 g (97%); mp 135–136 °C.

IR (neat): 3248, 2210, 1590, 1490, 1246 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.30 (s, 3 H), 4.85 (s, 2 H), 6.96 (d, *J* = 8.1 Hz, 1 H), 7.05 (t, *J* = 7.5 Hz, 1 H), 7.21–7.41 (m, 4 H), 7.53 (s, 1 H), 7.77 (d, *J* = 7.8 Hz, 1 H), 7.88 (d, *J* = 6.9 Hz, 1 H), 8.03 (br s, 1 H), 8.58 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.71, 69.24, 108.32, 112.32, 116.98, 121.54, 122.25, 126.46, 127.40, 127.91, 130.56, 130.61, 131.27, 132.00, 137.33, 144.82, 146.08, 155.55.

(*E*)-2-({2-[(*E*)-(Hydroxyimino)methyl]phenoxy}methyl)-3-*p*-tolylacrylonitrile (8c)
Yield: 1.12 g (96%); mp 134 °C.

IR (neat): 3228, 2210, 1600, 1581, 1239 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.76 (br s, 1 H), 2.39 (s, 3 H), 4.79 (s, 2 H), 6.93 (d, *J* = 8.1 Hz, 1 H), 7.03 (t, *J* = 7.8 Hz, 1 H), 7.24 (d, *J* = 8.1 Hz, 2 H), 7.36 (t, *J* = 8.1 Hz, 1 H), 7.73 (q, *J* = 7.8 Hz, 3 H), 8.39 (s, 1 H), 8.57 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.57, 69.90, 104.95, 112.96, 117.53, 121.53, 122.15, 127.19, 129.27, 129.70, 129.98, 131.28, 141.74, 146.13, 146.18, 155.75.

(*E*)-3-(4-Ethylphenyl)-2-({2-[(*E*)-(hydroxyimino)methyl]phenoxy}methyl)acrylonitrile (8d)
Yield: 1.16 g (95%); mp 104–106 °C.

IR (neat): 3282, 2215, 1601, 1585, 1243 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.5 Hz, 3 H), 2.69 (q, *J* = 7.5 Hz, 2 H), 4.79 (s, 2 H), 6.94 (d, *J* = 8.4 Hz, 1 H), 7.03 (t, *J* = 7.5 Hz, 1 H), 7.26 (t, *J* = 6.9 Hz, 3 H), 7.36 (t, *J* = 7.5 Hz, 1 H), 7.75 (t, *J* = 6.9 Hz, 3 H), 8.36 (br s, 1 H), 8.58 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.22, 28.87, 69.92, 105.02, 112.95, 117.51, 121.58, 122.15, 127.10, 128.52, 129.37, 129.61, 130.19, 131.24, 146.15, 147.98, 155.74.

(*E*)-2-({2-[(*E*)-(Hydroxyimino)methyl]phenoxy}methyl)-3-(4-isopropylphenyl)acrylonitrile (8e)
Yield: 1.19 g (93%); mp 139 °C.

IR (neat): 3256, 2220, 1626, 1591, 1241 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.24 (d, *J* = 6.9 Hz, 6 H), 2.92 (septet, *J* = 6.9 Hz, 1 H), 4.78 (s, 2 H), 6.92 (d, *J* = 8.4 Hz, 1 H), 7.01 (t, *J* = 7.5 Hz, 1 H), 7.23–7.37 (m, 4 H), 7.74 (d, *J* = 7.8 Hz, 3 H), 8.57 (s, 1 H), 9.11 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.72, 34.17, 69.86, 104.98, 112.96, 117.59, 121.49, 122.15, 127.12, 127.23, 129.44, 130.33, 131.31, 146.13, 146.22, 152.55, 155.73.

(*E*)-2-({2-[(*E*)-(Hydroxyimino)methyl]phenoxy}methyl)-3-(2-methoxyphenyl)acrylonitrile (8f)
Yield: 1.18 g (96%); mp 148–149 °C.

IR (neat): 3214, 2273, 1629, 1594, 1231 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.87 (s, 3 H), 4.18 (s, 2 H), 6.91–7.79 (m, 9 H), 8.09 (d, *J* = 7.5 Hz, 1 H), 8.60 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.62, 69.89, 106.08, 110.85, 112.87, 117.50, 120.85, 121.57, 121.87, 122.02, 126.92, 128.48, 131.20, 132.46, 141.36, 146.22, 155.81, 157.70.

(*E*)-3-(4-Chlorophenyl)-2-({2-[(*E*)-(hydroxyimino)methyl]phenoxy}methyl)acrylonitrile (8g)
Yield: 1.23 g (98%); mp 146–147 °C.

IR (neat): 3327, 2215, 1627, 1598, 1234 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.81 (s, 2 H), 6.93 (d, *J* = 8.4 Hz, 1 H), 7.05 (t, *J* = 7.5 Hz, 1 H), 7.25 (d, *J* = 7.5 Hz, 1 H), 7.35–7.44 (m, 3 H), 7.76 (t, *J* = 8.4 Hz, 4 H), 8.57 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 69.56, 107.05, 112.87, 116.91, 121.58, 122.31, 127.20, 129.30, 130.41, 131.08, 131.27, 137.08, 144.36, 146.10, 155.57.

(*E*)-2-({4-Bromo-2-[(*E*)-(hydroxyimino)methyl]phenoxy}methyl)-3-phenylacrylonitrile (8h)
Yield: 1.23 g (86%); mp 166–167 °C.

IR (neat): 3360, 2231, 1620, 1592, 1242 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.65 (br s, 1 H), 4.79 (s, 2 H), 6.82 (d, *J* = 8.7 Hz, 1 H), 7.44–7.47 (m, 4 H), 7.79 (d, *J* = 3.3 Hz, 3 H), 7.92 (d, *J* = 2.4 Hz, 1 H), 8.49 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 70.12, 105.92, 114.57, 114.82, 117.12, 123.56, 129.05, 129.24, 129.60, 131.26, 132.46, 133.67, 144.85, 146.40, 154.61.

(*E*)-2-({4-Bromo-2-[(*E*)-(hydroxyimino)methyl]phenoxy}methyl)-3-*p*-tolylacrylonitrile (8i)
Yield: 1.39 g (94%); mp 156–157 °C.

IR (neat): 3380, 2229, 1617, 1592, 1242 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 3 H), 4.77 (s, 2 H), 6.82 (d, *J* = 9.0 Hz, 1 H), 7.24 (t, *J* = 7.8 Hz, 4 H), 7.44 (dd, J_1 = 2.3 Hz, J_2 = 8.9 Hz, 1 H), 7.71 (d, *J* = 8.1 Hz, 2 H), 7.90 (d, *J* = 2.1 Hz, 1 H), 8.49 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.60, 70.29, 94.36, 104.48, 114.60, 114.74, 123.53, 129.30, 129.44, 129.56, 129.76, 133.66, 142.00, 144.90, 146.56, 154.67.

(*E*)-2-({4-Bromo-2-[(*E*)-(hydroxyimino)methyl]phenoxy}methyl)-3-(4-ethylphenyl)acrylonitrile (8j)
Yield: 1.35 g (88%); mp 132 °C.

IR (neat): 3345, 2211, 1623, 1591, 1244 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.5 Hz, 3 H), 2.68 (q, *J* = 7.5 Hz, 2 H), 4.76 (s, 2 H), 6.80 (d, *J* = 8.7 Hz, 1 H), 7.25 (t, *J* = 7.8 Hz, 3 H), 7.43 (dd, J_1 = 2.3 Hz, J_2 = 8.9 Hz, 1 H), 7.73 (d, *J* = 8.1 Hz, 2 H), 7.87 (d, *J* = 2.4 Hz, 1 H), 8.48 (br s, 1 H), 8.52 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.23, 28.89, 70.25, 104.47, 114.65, 114.72, 117.46, 123.48, 128.57, 129.43, 129.65, 130.00, 133.69, 144.91, 146.65, 148.21, 154.68.

(*E*)-2-({2-Ethoxy-6-[(*E*)-(hydroxyimino)methyl]phenoxy}methyl)-3-phenylacrylonitrile (8k)
Yield: 1.13 g (88%); mp 142–144 °C.

IR (neat): 3246, 2043, 1631, 1579, 1265 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (t, *J* = 6.9 Hz, 3 H), 4.09 (q, *J* = 6.9 Hz, 2 H), 4.78 (s, 2 H), 6.94 (d, *J* = 8.1 Hz, 1 H), 7.06 (t, *J* = 8.1 Hz, 1 H), 7.25 (s, 1 H), 7.33 (d, *J* = 7.2 Hz, 1 H), 7.42 (t, *J* = 3.6 Hz, 3 H), 7.78 (dd, J_1 = 2.6 Hz, J_2 = 6.7 Hz, 2 H), 8.57 (s, 1 H), 8.77 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.93, 64.51, 74.13, 107.27, 114.78, 117.78, 118.19, 124.99, 126.31, 128.93, 129.18, 130.86, 132.92, 145.56, 146.19, 146.49, 151.88.

(*E*)-2-({2-Ethoxy-6-[(*E*)-(hydroxyimino)methyl]phenoxy}methyl)-3-(4-isopropylphenyl)acrylonitrile (8l)
Yield: 1.33 g (92%); mp 159 °C.

IR (neat): 3387, 2216, 1578, 1464, 1268 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 6.9 Hz, 6 H), 1.48 (t, *J* = 6.9 Hz, 3 H), 2.93 (septet, *J* = 6.9 Hz, 1 H), 4.09 (q, *J* = 6.9 Hz, 2 H), 4.78 (s, 2 H), 6.93 (d, *J* = 8.1 Hz, 1 H), 7.05 (t, *J* = 7.8 Hz, 1 H), 7.29–7.34 (m, 4 H), 7.73 (d, *J* = 8.1 Hz, 2 H), 8.57 (s, 1 H), 8.78 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.93, 23.70, 34.14, 64.52, 74.31, 105.96, 114.79, 118.07, 118.18, 124.91, 126.36, 127.04, 129.37, 130.56, 145.60, 146.22, 146.68, 151.90, 152.26.

3-Phenyl-3*H*-chromeno[4,3-*c*]isoxazole-3a(4*H*)-carbonitrile (9a); Typical Procedure
To a soln of aldoxime **8a** (0.56 g, 2 mmol) in CCl_4 (10 mL) at 0–10 °C was added NCS (0.54 g, 4 mmol) over 3 h. After this period, Et_3N (0.57 mL, 4 mmol) was added and the reaction mixture was stirred well at r.t. for 2 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, and the resulting crude mass was diluted with H_2O (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine (2 × 10 mL) and dried (Na_2SO_4). The organic layer was concentrated and the residue was purified by column chromatography (silica gel 60–120 mesh; EtOAc–hexanes, 7:93) to provide the desired pure product **9a** as a colorless solid; yield: 0.34 g (62%); mp 136–138 °C.

IR (neat): 2232, 1614, 1490, 1250 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.41 (d, *J* = 10.8 Hz, 1 H), 4.82 (d, *J* = 10.5 Hz, 1 H), 5.46 (s, 1 H), 7.06 (d, *J* = 8.4 Hz, 1 H), 7.12 (t, *J* = 7.5 Hz, 1 H), 7.42–7.52 (m, 6 H), 7.88 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.16, 70.61, 87.75, 111.15, 114.01, 117.99, 123.12, 126.07, 126.72, 129.11, 130.11, 131.88, 133.89, 150.13, 154.72.

MS: *m*/*z* = 277 [M$^+$ + 1].

Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.81; H, 4.31; N, 10.18.

3-*o*-Tolyl-3*H*-chromeno[4,3-*c*]isoxazole-3a(4*H*)-carbonitrile (9b)
Yield: 0.39 g (67%); mp 144–146 °C.

IR (neat): 2234, 1613, 1513, 1290 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.30 (s, 3 H), 4.44 (d, *J* = 10.8 Hz, 1 H), 4.87 (d, *J* = 10.5 Hz, 1 H), 5.77 (s, 1 H), 7.05 (d, *J* = 8.4 Hz, 1 H), 7.12 (t, *J* = 7.8 Hz, 1 H), 7.23–7.82 (m, 5 H), 7.88 (dd, J_1 = 1.4 Hz, J_2 = 8.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.42, 54.33, 70.78, 85.06, 111.22, 114.11, 117.89, 123.10, 126.04, 126.78, 127.46, 129.82, 129.96, 130.82, 133.76, 135.11, 149.65, 154.52.

MS: *m*/*z* = 291 [M$^+$ + 1].

Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.56; H, 4.79; N, 9.70.

3-*p*-Tolyl-3*H*-chromeno[4,3-*c*]isoxazole-3a(4*H*)-carbonitrile (9c)
Yield: 0.38 g (65%); mp 155–157 °C.

IR (neat): 2243, 1609, 1511, 1290 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.41 (s, 3 H), 4.39 (d, *J* = 10.8 Hz, 1 H), 4.80 (d, *J* = 10.8 Hz, 1 H), 5.43 (s, 1 H), 7.06 (d, *J* = 8.4 Hz, 1 H), 7.12 (td, J_1 = 1.1 Hz, J_2 = 7.6 Hz, 1 H), 7.28–7.47 (m, 5 H), 7.88 (dd, J_1 = 1.5 Hz, J_2 = 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.34, 54.06, 70.67, 87.89, 111.23, 114.06, 117.96, 123.08, 126.07, 126.68, 128.69, 129.77, 133.80, 140.18, 150.11, 154.69.

MS: *m*/*z* = 291 [M$^+$ + 1].

Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.52; H, 4.78; N, 9.72.

3-(4-Ethylphenyl)-3*H*-chromeno[4,3-*c*]isoxazole-3a(4*H*)-carbonitrile (9d)
Yield: 0.40 g (66%); mp 148 °C.

IR (neat): 2251, 1620, 1578, 1237 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.5 Hz, 3 H), 2.70 (q, *J* = 7.5 Hz, 2 H), 4.39 (d, *J* = 10.8 Hz, 1 H), 4.80 (d, *J* = 10.8 Hz, 1 H), 5.43 (s, 1 H), 7.05 (d, *J* = 8.4 Hz, 1 H), 7.12 (t, *J* = 7.5 Hz, 1 H), 7.32 (d, *J* = 8.1 Hz, 2 H), 7.42 (d, *J* = 8.1 Hz, 2 H), 7.47 (d, *J* = 1.2 Hz, 1 H), 7.87 (dd, J_1 = 1.2 Hz, J_2 = 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.30, 28.68, 54.02, 70.64, 87.90, 111.23, 114.11, 117.97, 123.08, 126.05, 126.82, 128.57, 128.87, 133.81, 146.41, 150.14, 154.71.

MS: *m*/*z* = 305 [M^+ + 1].

Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 75.02; H, 5.21; N, 9.21.

3-(4-Isopropylphenyl)-3*H*-chromeno[4,3-*c*]isoxazole-3a(4*H*)-carbonitrile (9e)
Yield: 0.40 g (63%); mp 152–154 °C.

IR (neat): 2247, 1604, 1568, 1254 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (d, *J* = 6.9 Hz, 6 H), 2.96 (septet, *J* = 6.9 Hz, 1 H), 4.40 (d, *J* = 10.8 Hz, 1 H), 4.81 (d, *J* = 10.8 Hz, 1 H), 5.43 (s, 1 H), 7.06 (dd, J_1 = 0.6 Hz, J_2 = 8.4 Hz, 1 H), 7.12 (td, J_1 = 0.9 Hz, J_2 = 7.7 Hz, 1 H), 7.33–7.47 (m, 5 H), 7.88 (dd, J_1 = 1.5 Hz, J_2 = 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.80, 23.88, 34.00, 53.97, 70.66, 87.97, 111.26, 114.08, 117.99, 123.10, 126.08, 126.91, 127.18, 128.89, 133.81, 150.17, 151.05, 154.72.

MS: *m*/*z* = 319 [M^+ + 1].

Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.56; H, 5.78; N, 8.89.

3-(2-Methoxyphenyl)-3*H*-chromeno[4,3-*c*]isoxazole-3a(4*H*)-carbonitrile (9f)
Yield: 0.42 g (68%); mp 163–165 °C.

IR (neat): 2236, 1608, 1573, 1259 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.90 (s, 3 H), 4.43 (d, *J* = 11.1 Hz, 1 H), 5.01 (d, *J* = 11.1 Hz, 1 H), 5.77 (s, 1 H), 6.95–7.46 (m, 6 H), 7.77 (d, *J* = 7.2 Hz, 1 H), 7.86 (dd, J_1 = 1.5 Hz, J_2 = 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.64, 55.40, 71.64, 83.55, 110.18, 111.31, 114.26, 117.84, 121.13, 121.39, 122.84, 126.01, 127.04, 130.55, 133.61, 150.07, 154.85, 156.03.

MS: *m*/*z* = 307 [M^+ + 1].

Anal. Calcd for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.64; H, 4.52; N, 9.22.

3-(4-Chlorophenyl)-3*H*-chromeno[4,3-*c*]isoxazole-3a(4*H*)-carbonitrile (9g)
Yield: 0.39 g (62%); mp 160–162 °C.

IR (neat): 2241, 1602, 1497, 1252 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.39 (d, *J* = 11.1 Hz, 1 H), 4.83 (d, *J* = 10.8 Hz, 1 H), 5.48 (s, 1 H), 6.97 (d, *J* = 9.0 Hz, 1 H), 7.49–7.55 (m, 6 H), 8.01 (d, *J* = 7.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.71, 70.68, 88.06, 112.81, 113.60, 115.53, 119.85, 126.69, 128.34, 129.27, 130.24, 131.53, 136.62, 149.08, 153.60.

MS: *m*/*z* = 312 [M^+ + 1].

Anal. Calcd for $C_{17}H_{11}ClN_2O_2$: C, 65.71; H, 3.57; N, 9.02. Found: C, 65.62; H, 3.47; N, 9.09.

8-Bromo-3-phenyl-3*H*-chromeno[4,3-*c*]isoxazole-3a(4*H*)-carbonitrile (9h)
Yield: 0.45 g (63%); mp 165–167 °C.

IR (neat): 2244, 1605, 1456, 1254 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.40 (d, *J* = 10.8 Hz, 1 H), 4.81 (d, *J* = 10.8 Hz, 1 H), 5.44 (s, 1 H), 7.07 (d, *J* = 8.4 Hz, 1 H), 7.13 (t, *J* = 7.5 Hz, 1 H), 7.44–7.50 (m, 5 H), 7.87 (dd, J_1 = 1.4 Hz, J_2 = 8.0 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 54.17, 70.54, 87.09, 110.98, 113.77, 118.01, 123.22, 126.14, 128.14, 129.44, 130.34, 134.02, 136.21, 150.13, 154.68.

MS: *m*/*z* = 357 [M^+ + 2].

Anal. Calcd for $C_{17}H_{11}BrN_2O_2$: C, 57.49; H, 3.12; N, 7.89. Found: C, 57.56; H, 3.19; N, 7.93.

8-Bromo-3-*p*-tolyl-3*H*-chromeno[4,3-*c*]isoxazole-3a(4*H*)-carbonitrile (9i)
Yield: 0.49 g (67%); mp 170–172 °C.

IR (neat): 2235, 1605, 1462, 1253 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 3 H), 4.36 (d, *J* = 10.8 Hz, 1 H), 4.80 (d, *J* = 10.8 Hz, 1 H), 5.44 (s, 1 H), 6.95 (d, *J* = 9.0 Hz, 1 H), 7.29 (d, *J* = 7.8 Hz, 2 H), 7.38 (d, *J* = 8.1 Hz, 2 H), 7.52 (dd, J_1 = 2.7 Hz, J_2 = 8.7 Hz, 1 H), 7.99 (d, *J* = 2.4 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.37, 53.63, 70.75, 88.20, 112.91, 113.70, 115.53, 119.83, 126.67, 128.36, 129.35, 129.83, 136.57, 140.36, 149.08, 153.59.

MS: *m*/*z* = 371 [M^+ + 2].

Anal. Calcd for $C_{18}H_{13}BrN_2O_2$: C, 58.56; H, 3.55; N, 7.59. Found: C, 58.62; H, 3.48; N, 7.62.

8-Bromo-3-(4-ethylphenyl)-3*H*-chromeno[4,3-*c*]isoxazole-3a(4*H*)-carbonitrile (9j)
Yield: 0.52 g (68%); mp 163 °C.

IR (neat): 2241, 1598, 1467, 1282 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.5 Hz, 3 H), 2.70 (q, *J* = 7.5 Hz, 2 H), 4.37 (d, *J* = 11.1 Hz, 1 H), 4.80 (d, *J* = 10.8 Hz, 1 H), 5.44 (s, 1 H), 6.96 (d, *J* = 9.0 Hz, 1 H), 7.32 (d, *J* = 8.1 Hz, 2 H), 7.41 (d, *J* = 8.1 Hz, 2 H), 7.52 (dd, J_1 = 2.4 Hz, J_2 = 9.0 Hz, 1 H), 7.99 (d, *J* = 2.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.29, 28.69, 53.59, 70.74, 88.26, 112.92, 113.69, 115.54, 119.83, 126.81, 128.37, 128.52, 128.64, 136.56, 146.61, 149.10, 153.59.

MS: *m*/*z* = 385 [M^+ + 2].

Anal. Calcd for $C_{19}H_{15}BrN_2O_2$: C, 59.55; H, 3.95; N, 7.31. Found: C, 59.62; H, 3.89; N, 7.40.

6-Ethoxy-3-phenyl-3*H*-chromeno[4,3-*c*]isoxazole-3a(4*H*)-carbonitrile (9k)
Yield: 0.45 g (70%); mp 168–170 °C.

IR (neat): 2248, 1607, 1468, 1268 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (t, *J* = 6.9 Hz, 3 H), 4.13 (q, *J* = 6.9 Hz, 2 H), 4.42 (d, *J* = 10.8 Hz, 1 H), 4.93 (d, *J* = 10.5 Hz, 1 H), 5.48 (s, 1 H), 6.99–7.50 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.68, 53.98, 64.82, 70.92, 87.92, 111.86, 113.83, 116.39, 117.26, 122.88, 126.73, 129.10, 130.11, 131.84, 144.82, 148.24, 150.21.

MS: *m*/*z* = 321 [M^+ + 1].

Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.32; H, 4.94; N, 8.85.

6-Ethoxy-3-(4-isopropylphenyl)-3*H*-chromeno[4,3-*c*]isoxazole-3a(4*H*)-carbonitrile (9l)
Yield: 0.49 g (69%); mp 165–166 °C.

IR (neat): 2248, 1609, 1464, 1266 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (d, *J* = 6.9 Hz, 6 H), 1.48 (t, *J* = 6.9 Hz, 3 H), 2.96 (septet, *J* = 6.9 Hz, 1 H), 4.12 (q, *J* = 6.9 Hz, 2 H), 4.40 (d, *J* = 10.8 Hz, 1 H), 4.91 (d, *J* = 10.8 Hz, 1 H), 5.44 (s, 1 H), 6.99–7.47 (m, 7 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.68, 23.79, 23.85, 33.98, 53.75, 64.81, 70.94, 88.07, 111.95, 113.98, 116.34, 117.24, 122.84, 126.93, 127.17, 128.88, 144.82, 148.22, 150.24, 151.00.

MS: *m*/*z* = 363 [M^+ + 1].

Anal. Calcd for $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73. Found: C, 72.80; H, 6.02; N, 7.84.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

Acknowledgment

We thank CSIR, UGC and DST-PURSE (New Delhi) for financial support. We also thank DST-FIST for the NMR facility. J.S. thanks UGC for his fellowship, and R.S. thanks CSIR for his JRF.

References

(1) (a) Padwa, A.; Pearson, W. H. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products,* In *The Chemistry of Heterocyclic Compounds*, Vol. 59; John Wiley & Sons: New York, **2002**. (b) Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (c) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765.

(2) (a) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Buriol, L.; Machado, P. *Chem. Rev.* **2009**, *109*, 4140. (b) Krchňák, V.; Holladay, M. W. *Chem. Rev.* **2002**, *102*, 61. (c) Meißner, A.; Groth, U. *Synlett* **2010**, 1051. (d) Sarodnick, G.; Linker, T.; Heydenreich, M.; Koch, A.; Starke, I.; Fürstenberg, S.; Kleinpeter, E. *J. Org. Chem.* **2009**, *74*, 1282. (e) Marrero, J. G.; Harwood, L. M. *Tetrahedron Lett.* **2009**, *50*, 3574. (f) Campbell, M. J.; Johnson, J. S. *Synthesis* **2010**, 2841. (g) Gao, Z. X.; Wang, M.; Wang, S.; Yao, Z. J. *Org. Lett.* **2009**, *11*, 3678. (h) Huang, K. S. L.; Lee, E. H.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **2000**, *65*, 499. (i) Nair, V.; Suja, T. D. *Tetrahedron* **2007**, *63*, 12247. (j) Hentschel, F.; Lindel, T. *Synthesis* **2010**, 181.

(3) (a) Caramella, P.; Grunager, P. *Nitrile Oxides and Imines,* In *1,3-Dipolar Cycloaddition Chemistry*, Vol. 1; Padwa, A., Ed.; John Wiley & Sons: New York, **1984**, 291. (b) Kudya, I.; Jozwik, J.; Romanski, J.; Raczko, J.; Jurczak, J. *Tetrahedron: Asymmetry* **2005**, *16*, 2257. (c) Padwa, A. *Angew. Chem.* **1976**, *88*, 131. (d) Singh, V.; Singh, V.; Batra, S. *Eur. J. Org. Chem.* **2008**, 5446. (e) Das, B.; Holla, H.; Mahender, G.; Banerjee, J.; Reddy, M. R. *Tetrahedron Lett.* **2004**, *45*, 7347.

(4) (a) Kang, Y. K.; Shin, K. J.; Yoo, K. H.; Seo, K. J.; Lee, C.; Park, S. Y.; Kim, D. J.; Park, S. W. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 95. (b) Xue, C.; Roderick, J.; Mousa, S.; Olson, R. E.; De Grado, W. F. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3499. (c) Diana, G. D.; McKinlay, M. A.; Brisson, C. J.; Zalay, E. S.; Mirallas, J. V.; Salvador, U. J. *J. Med. Chem.* **1985**, *28*, 748. (d) Lepage, F.; Tombert, F.; Cuvier, G.; Marivain, A.; Gillardin, J. M. *Eur. J. Med. Chem.* **1992**, *27*, 581. (e) Ryng, S.; Macho, Z.; Wieczorek, Z.; Zimecki, M.; Mokrosz, M. *Eur. J. Med. Chem.* **1998**, *33*, 831. (f) Dallanoce, C.; Meroni, G.; De Amici, M.; Hoffman, C.; Klotz, K.-N.; De Micheli, C. *Bioorg. Med. Chem.* **2006**, *14*, 4393.

(5) Huisgen, R. *1,3-Dipolar Cycloaddition: Introduction, Survey, Mechanism,* In *1,3-Dipolar Cycloaddition Chemistry*, Vol. 1; Padwa, A., Ed.; John Wiley & Sons: New York, **1984**.

(6) (a) Confalone, P. N.; Pizzolato, G.; Confalone, D. L.; Uskovic, M. R. *J. Am. Chem. Soc.* **1980**, *102*, 1954. (b) Kozikowski, A. P.; Stein, P. D. *J. Am. Chem. Soc.* **1982**, *104*, 4023. (c) Curran, D. P.; Jacobs, P. B.; Elliott, R. L.; Kim, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 5280. (d) Martin, S. F.; Dappen, M. S.; Dupre, B.; Murphy, C. J.; Colapret, J. A. *J. Org. Chem.* **1989**, *54*, 2209. (e) Ihara, M.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1990**, *55*, 4497. (f) Bode, J. W.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 3611. (g) Paek, S.-M.; Seo, S.-Y.; Kim, S.-H.; Jung, J.-W.; Lee, Y.-S.; Jung, J.-K.; Suh, Y.-G. *Org. Lett.* **2005**, *7*, 3159. (h) Lee, J. Y.; Schiffer, G.; Jager, V. *Org. Lett.* **2005**, *7*, 2317. (i) Shing, T. K. M.; So, K. M.; Kwok, W. S. *Org. Lett.* **2009**, *11*, 5070.

(7) (a) Lin, G. N.; Lu, C. M.; Lin, H. C.; Fang, S. C.; Shieh, B. J.; Hsu, M. F.; Wang, J. P.; Ko, F. N.; Teng, C. M. *J. Nat. Prod.* **1996**, *59*, 834. (b) Winn, M.; Arendsen, D.; Dodge, P.; Dren, A.; Dunnigan, D.; Hallas, R.; Hwang, K.; Kyncl, J.; Lee, Y. H.; Plotnikoff, N.; Zaugg, H. Y.; Dalzell, H.; Razdan, R. K. *J. Med. Chem.* **1976**, *19*, 461. (c) Kashiwuada, Y.; Yamazaki, K.; Ikeshiro, Y.; Yamagishi, T.; Fujioka, T.; Mihashi, K.; Mizuki, K.; Cosentino, L. M.; Fowke, K.; Natschke, S. L. M.; Lee, K. H. *Tetrahedron* **2001**, *57*, 1559. (d) Kurdyumov, A. V.; Hsung, R. P.; Ihlen, K.; Wang, J. *Org. Lett.* **2003**, *5*, 3935. (e) Kang, Y.; Mei, Y.; Du, Y.; Jin, Z. *Org. Lett.* **2003**, *5*, 4481. (f) Hu, H.; Harrison, T. J.; Wilson, P. D. *J. Org. Chem.* **2004**, *69*, 3782.

(8) (a) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447. (b) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (c) Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2009**, *109*, 1. (d) Basavaiah, D.; Rao, K. V.; Reddy, R. J. *Chem. Soc. Rev.* **2007**, *36*, 1581. (e) Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511. (f) Basavaiah, D.; Rao, P. D.; Hyma, S. R. *Tetrahedron* **1996**, *52*, 8001. (g) Ciganek, E. *Org. React.* **1997**, *51*, 201.

(9) (a) Basavaiah, D.; Rao, J. S.; Reddy, R. J. *J. Org. Chem.* **2004**, *69*, 7379. (b) Basavaiah, D.; Krishnamacharyula, M.; Hyma, R. S.; Sarma, P. K. S.; Kumaragurubaran, N. *J. Org. Chem.* **1999**, *64*, 1197. (c) Basavaiah, D.; Reddy, R. M.; Kumaragurubaran, N.; Sharada, D. S. *Tetrahedron* **2002**, *58*, 3693. (d) Basavaiah, D.; Sarma, P. K. S. *J. Chem. Soc., Chem. Commun.* **1992**, 955. (e) Weichert, A.; Hoffmann, H. M. R. *J. Org. Chem.* **1991**, *56*, 4098. (f) Zulykama, Y.; Perumal, P. T. *Tetrahedron Lett.* **2009**, *50*, 3892.

(10) Andrés, J. I.; Alcázar, J.; Alonso, J. M.; Alvarez, R. M.; Bakker, M. H.; Biesmans, I.; Cid, J. M.; De Lucas, A. I.; Fernández, J.; Font, L. M.; Hens, K. A.; Iturrino, L.; Lenaerts, I.; Martínez, S.; Megens, A. A.; Pastor, J.; Vermote, P. C. M.; Steckler, T. *J. Med. Chem.* **2005**, *48*, 2054.

(11) Gordaliza, M.; Faircloth, G. T.; Castro, M. A.; Miguel del Corral, J. M.; López-Vázquez, M. L.; Feliciano, A. S. *J. Med. Chem.* **1996**, *39*, 2865.

(12) Sangwan, N. K.; Rastogi, S. N. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1981**, *20*, 135.

(13) Prasanna, S.; Manivannan, E.; Chaturvedi, C. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2097.

(14) Kwon, Y. J.; Saubern, S.; Macdonald, J. M.; Huang, X. P.; Setola, V.; Roth, B. L. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5488.

(15) (a) Bakthadoss, M.; Sivakumar, G.; Kannan, D. *Org. Lett.* **2009**, *11*, 4466. (b) Bakthadoss, M.; Sivakumar, N. *Synlett* **2011**, 1296. (c) Bakthadoss, M.; Sivakumar, N.; Devaraj, A. *Synthesis* **2011**, 611. (d) Basavaiah, D.; Bakthadoss, M.; Pandiaraju, S. *Chem. Commun.* **1998**, 1639. (e) Bakthadoss, M.; Sivakumar, N. *Synlett* **2009**, 1014. (f) Bakthadoss, M.;

Sivakumar, N.; Sivakumar, G.; Murugan, G. *Tetrahedron Lett.* **2008**, *49*, 820. (g) Bakthadoss, M.; Sivakumar, N.; Devaraj, A.; Sharada, D. S. *Synthesis* **2011**, 2136. (h) Bakthadoss, M.; Murugan, G. *Eur. J. Org. Chem.* **2010**, 5825. (i) Basavaiah, D.; Bakthadoss, M.; Jayapal Reddy, G. *Synthesis* **2001**, 919.

(16) The structures of compounds **5a** and **9d** were confirmed by single-crystal X-ray data. These data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 791956 (**5a**) and 791957 (**9d**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk] or via www.ccdc.cam.ac.uk/data_request/cif.

