An easy access to 3a,4-dihydro-3*H*-chromeno[4,3-*c*]isoxazoles and functionalized isoxazolines[1]

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Dedicated to Dr. A. V. Rama Rao on his 70th birthday

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Abstract

2-Allyloxybenzaldoximes on treatment with ceric ammonium nitrate (CAN) at room temperature afforded 3a,4-dihydro-3*H*-chromeno[4,3-*c*]isoxazoles while benzaldoximes on interaction with Baylis-Hillman adduct in the presence of CAN produced functionalized isoxazolines.

Keywords: 3a,4-Dihydro-3*H*-chromeno[4,3-*c*]isoxazole, functionalized isoxazoline, 2-allyloxybenzaldoximes, Baylis-Hillman adduct, ceric ammonium nitrate (CAN)

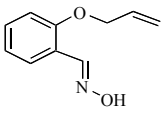
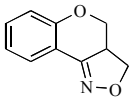
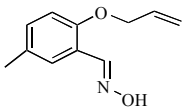
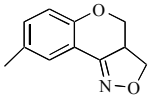
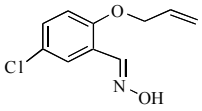
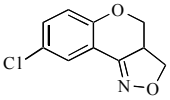
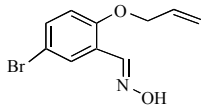
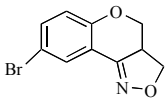
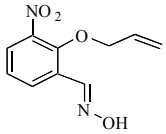
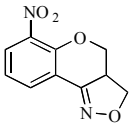
Introduction

Isoxazolines are important pharmacophores in several pharmacologically important molecules.[2] They are also useful intermediates for the synthesis of a wide variety of bioactive natural products.[2] During our recent work on the synthesis of natural and unnatural biopotent compounds we were interested in the construction of 3a,4-dihydro-3*H*-chromeno[4,3-*c*]isoxazoles. Chromano system is present in various naturally occurring bioactive compounds[3] and thus it is expected that chromano-isoxazolines may possess interesting bioactivity. The use of CAN in the synthesis of isoxazolines via 1,3-dipolar cycloadditions of the *in situ* formed nitrile oxide is known.[4] The process has been applied here for the synthesis of chromano-isoxazolines. Some functionalized isoxazolines have also been prepared from Baylis-Hillman adducts such as 3-hydroxy-2-methylene-alkanoates and 3-hydroxy-2-methylene-alkanenitrile.[5]

Results and Discussion

We have observed that the 2-allyloxybenzaldoximes (**1**) on treatment with ceric ammonium nitrate (CAN) can easily be converted into 3a,4-dihydro-3*H*-chromeno[4,3-*c*]isoxazoles in single (Scheme 1) step Several 3a,4-dihydro-3*H*-chromeno[4,3-*c*]isoxazoles (Table 1) were prepared in good yields following the method at room temperature.

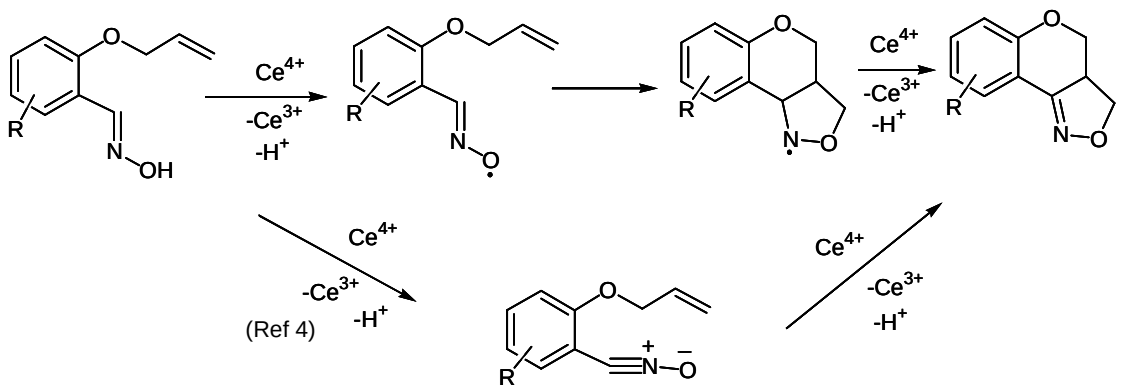
Table 1. Preparation of 3a,4-dihydro-3*H*-chromeno[4,3-*c*]isoxazoles[=] using CAN[=]

Substrate	Product	Time (h)	Isolated yield (%)[‡]
	 **2a**	0.5	86
	 **2b**	0.5	85
	 **2c**	1	75
	 **2d**	1.5	72
	 **2e**	3	69

[=] The structures of the products were established from their spectral (^{1}H NMR and MS) data.

[‡] Deoximation product (~5%) was obtained in each case.

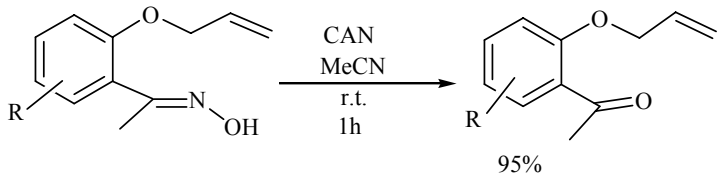
A larger number of analogues can also easily be prepared with the similar procedure. The aromatic ring may contain both electron-donating and electron-withdrawing groups. The reaction was completed with a short period of time (0.5-3h). Deoximation product was also obtained in very minor quantity (~5%) in each case along with **2**. Previously the above cyclization was carried out with NaOCl using a base catalyst.[6] However, the yields of the products were reported by different workers to be highly variable (42-93%).



Scheme 1

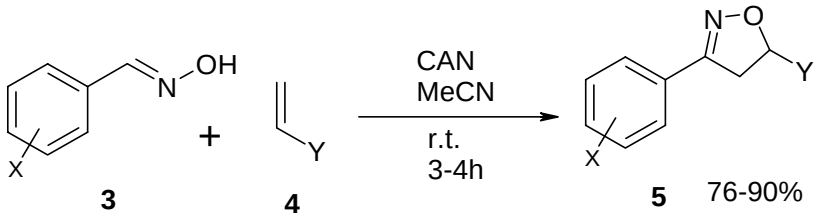
The mechanisms of the formation of **2** have been proposed in Scheme 1. An alternative mechanism has also been shown involving a 1,3-dipolar intramolecular cycloaddition of nitrile oxide formed *in situ* with the double bond of the allyl group.

The present method was not applicable for a ketoxime and in this case deoximation compound was found to be the sole product under the present experimental conditions (Scheme 2).



Scheme 2

Some functionalized isoxazolines have also been prepared by using Baylis-Hillman adducts, 3-hydroxy-2-methylene-alkanoates and 3-hydroxy-2-methylene-alkanenitriles[5]. To ascertain regiochemistry[4] under our present experimental conditions at first some aldoximes were treated with activated alkenes in the presence of CAN (Scheme 3) and the products were characterized.

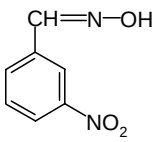
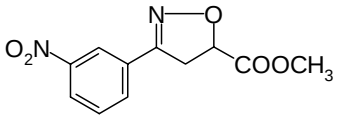
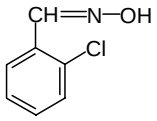
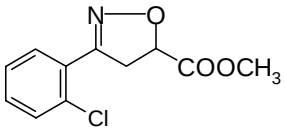
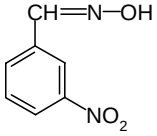
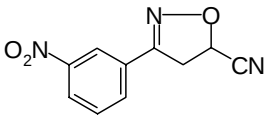
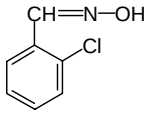
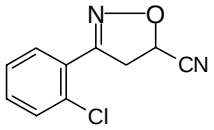
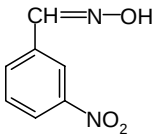
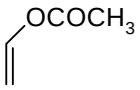
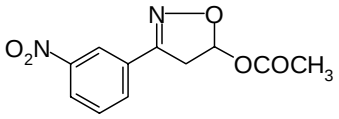
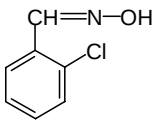
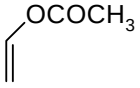
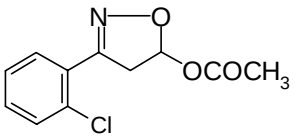


Scheme 3

Several aldoximes on treatment with different activated alkenes such as methyl acrylate and acrylonitrile in the presence of CAN formed the isoxazolines (Table 2). The reaction proceeded at room temperature and the yields were very high. The aldoximes containing electron-donating or electron-withdrawing groups reacted similarly. Vinyl acetate also reacted with aldoximes to

form isoxazolines. Deoximation product from aldoxime was formed as minor product (~5%) in each case.

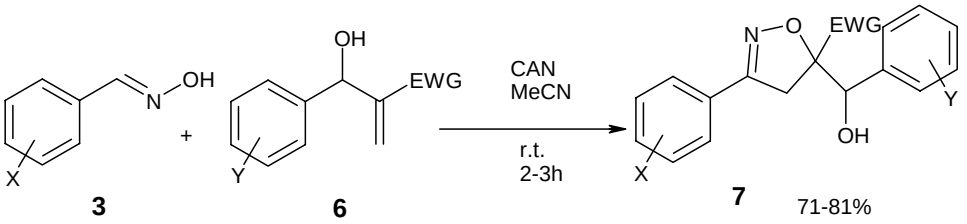
Table 2. Preparation of simple isoxazolines using CAN[†]

Aldoxime	Alkene	Product	Time (h)	Isolated yield (%)[‡]
		 **5a**	2	90
		 **5b**	2.5	89
		 **5c**	2	86
		 **5d**	2	82
		 **5e**	3	76
		 **5f**	2.5	78

[†]The structures of the products were established from their spectral (^{1}H NMR and MS) data.
[‡]deoximation product (~5%) was obtained in each case.

The reaction led to a 1,3-dipolar intermolecular cycloaddition involving nitrile oxide dipole formed *in situ* and the double bond of the alkene. In the ^{1}H NMR spectra of the products an aliphatic proton was observed at the downfield (around δ 5.2, dd) but no -OCH_2- group was observed. The products were thus characterized as 3-phenyl-5-carboxylate isoxazolines (**5**) and the other regioisomers were not at all formed.

The above observation has now been applied to the preparation of functionalized isoxazolines from Baylis-Hillman adducts (**6**) by reacting with aldoximes in the presence of CAN (Scheme 4).

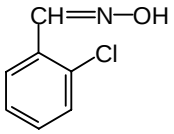
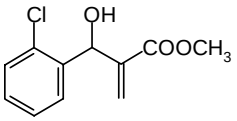
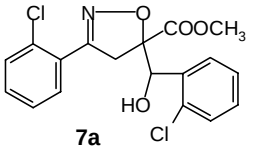
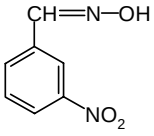
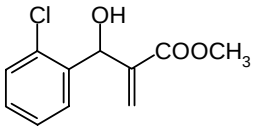
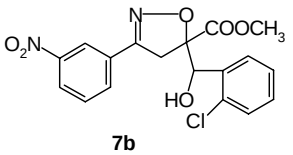
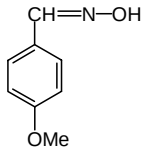
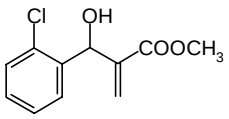
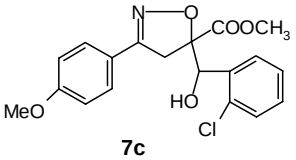
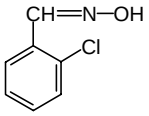
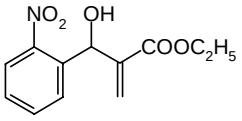
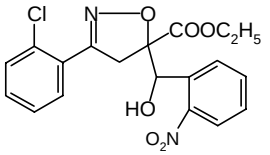
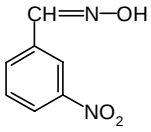
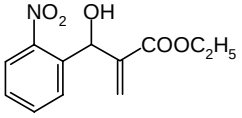
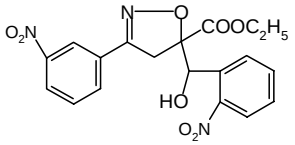
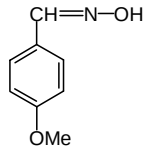
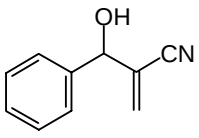
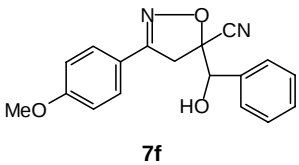
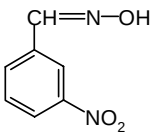
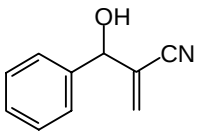
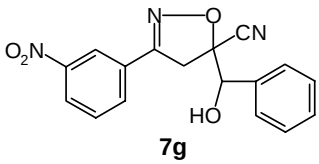


Scheme 4

We have utilized the Baylis-Hillman adducts for the preparation of a series of functionalized isoxazolines (Table 3). The aldoximes containing both electron-donating and electron-withdrawing groups were used. The electron-with drawing group present in the Baylis-Hillman adducts were esters as well as nitriles. The experimental procedure for the preparation of isoxazolines using CAN is simple. The structures of all the isoxazolines were established from their spectral (^{1}H NMR and MS) data. It is interesting to mention that we got here only one set of diastereomer of the compound **7** (as evident from TLC experiments (solvent systems: hexane-EtOAc, 7:3, 4:1 and 6:4) and ^{1}H NMR data of the crude cycloadducts).

In conclusion, we have demonstrated the interaction of aldoximes with intramolecular and intermolecular olefinic bonds in the presence of CAN to prepare isoxazolines derivatives. Different 3a,4-dihydro-3H-*c*hromeno[4,3-*c*]isoxazoles and functionalized isoxazolines have easily been prepared. The Baylis-Hillman adducts have efficiently been converted into isoxazolines. The mild experimental conditions, availability of the non-expensive reagents, operational simplicity, rapid conversions and high yields of the products are the attractive features of the present protocol. The prepared isoxazolines are expected to show some interesting biological properties under proper evaluation.

Table 3. Preparation of functionalized isoxazolines using CAN[†]

Aldoxime	Baylis–Hillman adducts	Product	Time (h)	Isolated yield (%)[‡]
		 **7a**	2.5	80
		 **7b**	2	78
		 **7c**	2	79
		 **7d**	2.5	81
		 **7e**	2	80
		 **7f**	3	75
		 **7g**	3	71

[†] The structures of the products were established from their spectral (^{1}H NMR and MS) data.
[‡]deoximation product (~5%) was obtained in each case.

Experimental Section

General Procedures. Spectra were recorded with the following instruments: ^{1}H NMR: Varian Gemini 200 MHz and MS: VG Micromass 7070H (70eV). Column chromatography was performed on silica gel (BDH 100-200 mesh) and TLC with silica gel GF_{254}. The spots were detected in an iodine chamber and under UV light.

Preparation of *O*-allyloxybenzaldoximes. 2-allyloxybenzaldoximes could easily be prepared[7] from an *ortho*-hydroxybenzaldehyde by treatment with allyl bromide (K_2CO_3, DMF, r.t., overnight) followed by oximation with $NH_2OH.HCl$ (MeOH/pyridine, reflux, 1h).

Compounds 1a, c and d are known.[6] The spectral and analytical data of 1b and e are given below:

1b. viscous; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.62 (1H, brs), 8.24 (1H, s), 7.50 (1H, d, *J*=2.0 Hz), 7.08 (1H, dd, *J*=8.0, 2.0 Hz), 6.74 (1H, d, *J*=8.0 Hz), 6.02 (1H, m), 5.38 (1H, d, *J*=10.0 Hz), 5.26 (1H, d, *J*=8.0 Hz), 4.55 (2H, d, *J*=4.0 Hz), 2.27 (3H, s); MS (EI): m/z 191 (M+.) (Found: C, 68.62; H, 6.71; N, 7.34, $C_{11}H_{13}NO_2$ requires: C, 68.75; H, 6.77; N, 7.29 %)

1e. m.p. 64-65 ^{o}C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.42 (1H, brs), 8.53 (1H, S), 8.12 (1H, dd, *J*=8.0, 2.0 Hz), 7.82 (1H, dd, *J*=8.0, 2.0 Hz), 7.06 (1H, t, *J*=8.0 Hz), 6.04 (1H, m), 5.42 (1H, d, *J*=10.0 Hz), 5.23 (1H, 1H, d, *J*=8.0 Hz), 4.52 (2H, d, *J*=4.0 Hz); MS (EI): m/z 190 (M+.) Found: C, 63.24; H, 5.32; N, 14.63. $C_{10}H_{10}N_2O_2$ requires: C, 63.16; H, 5.26; N, 14.74%)

All the benzaldoximes reported in Tables 2 and 3 are known compounds.[8]

General procedure for the preparation of 3a,4-dihydro-3*H*-chromeno[4,3-*c*]isoxazoles

Oxime (1, 1 mmol) was taken in MeCN (5 ml) and CAN (2.2 mmol) was added. The mixture was stirred at room temperature. The reaction was monitored by TLC. After completion water (10 ml) was added and the mixture was extracted with EtOAc (3x10 ml), washed with water (3x10 ml) and dried (Na_2SO_4). The concentrated extract was subjected to column chromatography over silica gel using hexane-EtOAc (4:1) as eluent to yield 3a,4-dihydro-3*H*-chromeno[4,3-*c*]isoxazole (2) and the corresponding deoximation product.

General procedure for the preparation of simple and functionalized isoxazolines

An aldoxime (**3**, 1 mmol) and an alkene (**4**) or Baylis-Hillman adduct (**6**) (1.2 mmol) were taken in MeCN (10 ml). CAN (2.2 mmol) was added and the mixture was stirred at room temperature. After completion (TLC) water (15 ml) was added and the product was extracted with EtOAc (3x10 ml). The extract washed with water (3x10 ml), dried (Na_2SO_4) and concentrated. The residue was subjected to column chromatography over silica gel using hexane-EtOAc (4:1) as eluent to obtain pure isoxazoline (**5** or **7**) along with minor deoximation product. Compounds **2a**, **c** and **d** are known [4b,6] and their melting points matched well with those reported earlier. The spectral and analytical data of unknown isoxazolines are given below.

2b. m.p. 142^{o}C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.52 (1H, d, *J*=2.0 Hz), 7.08 (1H, dd, *J*=8.0, 2.0 Hz), 6.78 (1H, d, *J*=8.0 Hz), 4.71-4.58 (2H, m), 4.04 (1H, m), 3.92-3.80 (2H, m), 2.29 (3H, s);

MS (EI): m/z 189 ($M^{+\cdot}$) (Found: C, 69.92; H, 5.71; N, 7.52. $C_{11}H_{11}NO_2$ requires: C, 69.84; H, 5.82; N, 7.41%)

2e. m.p. 136-138°C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.06 (1H, dd, *J*=8.0, 2.0 Hz), 7.88 (1H, dd, *J*=8.0, 2.0 Hz), 7.08 (1H, t, *J*=8.0 Hz), 4.92 (1H, dd, *J*=11.0, 5.0 Hz), 4.72 (1H, m), 4.18 (1H, m), 4.02-3.86 (2H, m); MS (EI): m/z 220 ($M^{+\cdot}$) (Found: C, 54.48; H, 3.58; N, 12.79. $C_{10}H_8N_2O_4$ requires: C, 54.55; H, 3.64; N, 12.73%)

5a. m.p. 99-100°C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.44 (1H, d, *J*=2.0 Hz), 8.28 (1H, dd, *J*=8.0, 2.0 Hz), 8.10 (1H, dd, *J*=8.0, 2.0 Hz), 7.68 (1H, t, *J*=8.0 Hz), 5.28 (1H, dd, *J*=8.0, 2.0 Hz), 3.82 (3H, s), 3.78-3.62 (2H, m); MS (EI): m/z 250 ($M^{+\cdot}$) (Found: C, 52.87; H, 3.92; N, 11.24. $C_{11}H_{10}N_2O_5$ requires: C, 52.80; H, 4.00; N, 11.20%)

5b. semisolid; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.72 (1H, dd, *J*=8.0, 2.0 Hz), 7.42-7.23 (3H, m), 5.16 (1H, dd, *J*=8.0, 4.0 Hz), 3.86-3.74 (2H, m), 3.82 (3H, s); MS (EI): m/z 239, 241 ($M^{+\cdot}$) (Found: C, 55.26; H, 4.23; N, 5.81. $C_{11}H_{10}ClNO_3$ requires: C, 55.12; H, 4.18; N, 5.85%)

5c. m.p. 106-107°C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.46 (1H, d *J*=2.0 Hz), 8.35 (1H, dd, *J*=8.0, 2.0 Hz), 8.09 (1H, dd, *J*=8.0, 2.0 Hz), 7.69 (1H, t, *J*=8.0 Hz), 5.48 (1H, dd, *J*=8.0, 6.0 Hz), 3.84-3.75 (2H, m); MS (EI): m/z 217 ($M^{+\cdot}$) (Found: C, 55.24; H, 3.18; N, 19.32. $C_{10}H_7N_3O_3$ requires: C, 53.30; H, 3.23; N, 19.36%).

5d. semisolid; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.74 (1H, dd, *J*=8.0, 2.0 Hz), 7.50-7.28 (3H, m), 5.38 (1H, dd, *J*=8.0, 4.0 Hz), 3.98 (1H, dd, *J*=10.0, 8.0 Hz), 3.80 (1H, dd, *J*=10.0, 4.0 Hz); MS (EI): m/z 206, 208 ($M^{+\cdot}$) (Found: C, 58.18; H, 3.45; N, 13.48. $C_{10}H_7ClN_2O$. requires: C, 58.11; H, 3.39; N, 13.55%).

5e. m.p. 104-105°C: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.42 (1H, d, *J*=2.0 Hz), 8.30 (1H, dd, *J*=8.0, 2.0 Hz), 8.14 (1H, dd, *J*=8.0, 2.0 Hz), 7.67 (1H, t, *J*=8.0 Hz), 6.83 (1H, d, *J*=4.0 Hz), 3.68 (1H, dd, *J*=10.0, 4.0 Hz), 3.40 (1H, d, *J*=10.0 Hz), 2.06, (3H, s); MS (EI): m/z 250 ($M^{+\cdot}$) (Found: C, 52.74; H, 4.02; N, 11.14. $C_{11}H_{10}N_2O_5$ requires: C, 52.80; H, 4.00; N, 11.20%).

5f. semisolid ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.79 (1H, dd, *J*==8.0, 2.0 Hz), 7.48-7.23 (3H, m), 6.80 (1H, d, *J*=6.0 Hz), 3.82 (1H, dd, *J*= 10.0, 6.0 Hz), 3.42 (1H, d, *J*=10.0 Hz), 2.16 (3H, s); MS (EI): m/z 239, 241 ($M^{+\cdot}$) (Found: C, 55.04; H, 4.26; N, 5.80. $C_{11}H_{10}ClNO_3$ requires: C, 55.12; H, 4.18; N, 5.85%).

7a. m.p. 132-133°C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.70 (2H, d, *J*=8.0 Hz), 7.42-7.14 (6H, m), 5.72 (1H, d, *J*=6.0 Hz), 3.85 (3H, s), 3.80-3.65 (2H, m), 3.12 (1H, d, *J*=6.0 Hz); MS (EI): m/z 379, 381, 383 ($M^{+\cdot}$) (Found: C, 56.89; H, 3.91; N, 3.62. $C_{18}H_{15}Cl_2NO_4$ requires: C, 56.84, H, 3.95; N, 3.68%).

7b. m.p. 222-224°C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.35 (1H, d, *J*=2.0 Hz), 8.24 (1H, dd, *J*=8.0, 2.0 Hz), 8.01 (1H, dd, *J*=8.0, 2.0 Hz), 7.67 (1H, dd, *J*=8.0, 2.0 Hz), 7.56 (1H, t, *J*=8.0 Hz), 7.39-7.34 (2H, m), 7.28 (1H, m), 5.84 (1H, d, *J*=6.0 Hz), 3.85 (3H, s), 3.72-3.63 (2H, m), 2.92 (1H, d, *J*=6.0 Hz); MS (EI): m/z 390, 392 ($M^{+\cdot}$) (Found: C, 55.24; H, 3.92; N, 7.21. $C_{18}H_{15}ClN_2O_6$ requires: C, 55.31, H, 3.84; N, 7.17%).

7c. m.p. 179-180°C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.65-7.28 (6H, m), 6.94 (2H, d, *J*=8.0 Hz), 5.08 (1H, brs), 3.84 (3H, s), 3.81 (3H, s), 3.59 (2H, brs), 3.30 (1H, brs); MS (EI) : m/z 375, 377 ($M^{+\cdot}$) (Found: C, 60.78; H, 4.82; N, 3.68. $C_{19}H_{18}ClNO_5$ requires: C, 60.72, H, 4.79; N, 3.73%).
7d. m.p. 98-100°C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.94(2H, t, *J*=8.0 Hz), 7.62 (1H, t, *J*=8.0 Hz), 7.58-7.42 (2H, m), 7.39-7.22 (3H, m), 6.02 (1H, brs), 4.22 (2H, q, *J*=7.0 Hz), 3.82-3.73 (2H, m), 3.36 (1H, brs), 1.28 (3H, d, *J*=7.0 Hz); MS (EI) : m/z 404, 406 ($M^{+\cdot}$) (Found: C, 56.42; H, 4.24; N, 6.81. $C_{19}H_{17}ClN_2O_6$ requires: C, 56.37, H, 4.20; N, 6.92%).
7e. m.p. 168-169°C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.22-7.52 -(8H, m), 6.08 (1H, brs), 4.20 (2H, q, *J*=7.0 Hz), 3.83-3.68 (2H, m), 3.42 (1H, brs), 1.21 (3H, t, *J*=7.0 Hz); MS (EI): m/z 415 ($M^{+\cdot}$) (Found: C, 54.86; H, 4.02; N, 10.23. $C_{19}H_{17}N_3O_8$ requires: C, 54.94, H, 4.10; N, 10.12%).
7f. viscous; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.62-7.33 (7H, m), 6.92 (2H, d, *J*=8.0 Hz), 4.94 (1H, brs), 3.82 (3H, s), 3.62 (2H, brs), 3.37 (1H, brs); MS (EI): m/z 308 ($M^{+\cdot}$) (Found: C, 70.24; H, 5.14; N, 9.12. $C_{18}H_{16}N_2O_3$ requires: C, 70.13, H, 5.20; N, 9.09%)
7g. viscous; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.68-7.30 (7H, m), 6.96-6.78 (2H, m), 4.94 (1H, brs), 3.58 (2H, brs), 3.36 (1H, brs); MS (EI): m/z 323 ($M^{+\cdot}$) (Found: C, 63.24; H, 4.13; N, 13.07. $C_{17}H_{13}N_3O_4$ requires: C, 63.16, H, 4.03; N, 13.00%)

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