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Interesting results of catalytic hydrogenation of 3-(2-nitrophenyl)-isoxazoles and 3-(nitro-substituted-phenyl)-2-isoxazolines §

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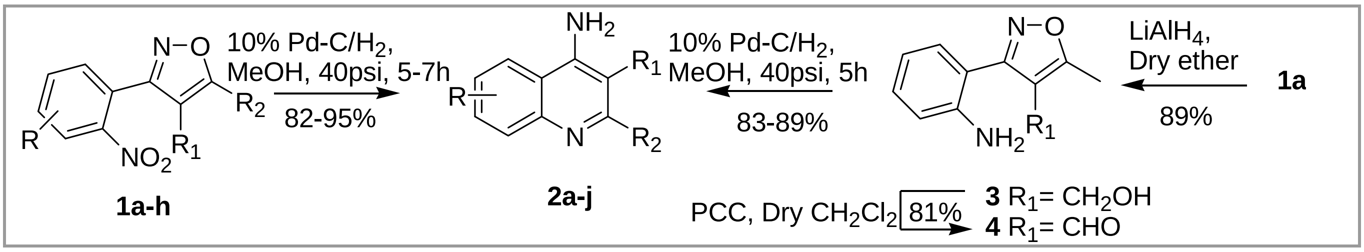
Abstract: The Pd-C-assisted hydrogenolysis of substituted 3-(2-nitrophenyl)-isoxazoles, irrespective of substitution on the isoxazole ring, invariably leads to reduction of nitro to amino group with concomitant regiospecific ring closure to yield substituted 4-quinolinamines. In contrast similar hydrogenation of 3-(nitro substituted phenyl)-2-isoxazolines results in reduction of the nitro group only with conservation of isoxazoline ring to yield 3-(amino substituted phenyl)-2-isoxazolines.

Key words: Isoxazole, 2-isoxazoline, 4-aminoquinoline, hydrogenation, Pd-C, ring transformation, regiospecific.

Hydrogenation of 3-(2-nitrophenyl)-substituted isoxazole derivatives can be utilized for the synthesis of substituted 2- and 3-formyl-4-aminoquinoline[1] derivatives. There are two reports[2,3] wherein 3-(2-nitrophenyl)-5-phenyl-isoxazole and 3-(2-nitrophenyl)-5-methyl-4-isoxazolecarboxylate were hydrogenated in the presence of Raney Ni in acetic acid for 20 h or ethanol at room temperature to furnish 4-quinolinamine derivatives. However, in our hands the reaction in acetic acid did not work well and the hydrogenation at room temperature took a long times and several side products were formed. Since the previous reports described only one example each, no comments were made on the scope and limitation of the synthetic strategy. In principle, if the regiospecificity of the ring closure reaction between the amino group present on the phenyl and the carbonyl group generated by the cleavage of the isoxazole ring is maintained even in the presence of different groups on the isoxazole nucleus this would become an alternate and convenient route to substituted 4-aminoquinolines which happens to be the substructural unit of several pharmacologically active compounds with antimalarial,[4] antiulcer,[5] immuno-stimulant,[6] anti-HIV,[7] AChE inhibitory[8] and noniceptin antagonist[9] activity. In addition, this procedure may serve as a method to obtain fluorinated 4-aminoquinoline derivatives which otherwise require complex strategies.[10] In order to evaluate the scope of this procedure to generate substituted 4-quinolinamines, we investigated several different substitutions on the isoxazole nucleus employing Pd-C. Compared to Raney-Ni mediated reaction it was observed that the reaction is fast and smooth in the presence of Pd-C. Additionally the ring closure reaction between the amino and the carbonyl groups generated by lysis of the isoxazole ring is highly regiospecific even in the presence of another formyl group. As an extension of this study we also explored the hydrogenolysis of 3-(2-nitrophenyl)-isoxazoline system. Surprisingly the isoxazoline ring, which is otherwise known to readily undergo catalytic hydrogenolysis, is highly stable to ring cleavage when a nitrophenyl substitution is present on it. Our results on the catalytic hydrogenations of substituted 3-(2-nitrophenyl)-2-isoxazoles and 3-(nitro substituted phenyl)-2-isoxazolines are presented in this communication.

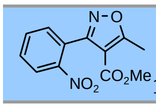
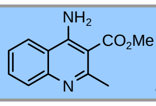
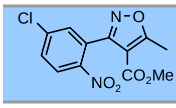
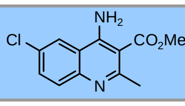
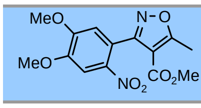
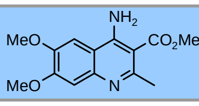
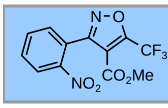
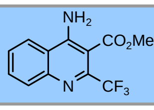
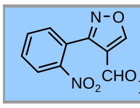
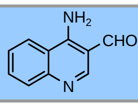
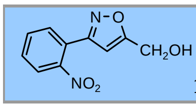
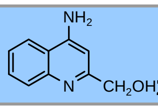
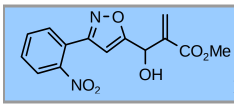
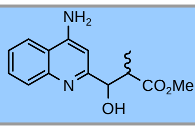
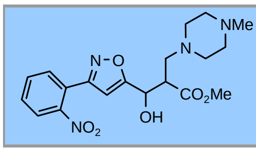
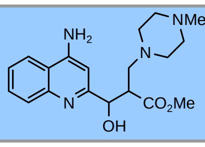
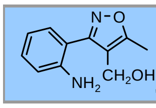
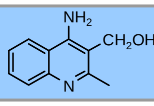
3-(2-Nitrophenyl)-5-methyl-isoxazole-4-carboxylate **(1a)** was prepared through an earlier reported[11] procedure and subjected to Pd-C-mediated catalytic hydrogenation to afford the 2-methyl-3-methoxycarbonyl-4-quinolinamine **(2a)** in 5-7 h and excellent yields (Scheme 1). To assess the general applicability of the procedure several other substituted 2-nitro-phenyl substrates **(2b-d)** were evaluated with similar outcome (Table 1). Subsequently it was decided to hydrogenate the 3-(2-nitro-phenyl)-4-isoxazolecarbaldehyde **(1e)**. In principle, if the ring opening of the isoxazole and the subsequent cyclization is highly regiospecific then it would lead to 4-amino-3-formyl-quinoline. On the other hand after the reduction of the nitro group to amino group there is a possibility that it forms a Schiff base with the formyl group on the isoxazole ring resulting in 3-acetyl-4-quinolinamine. Hence, the compound **1e** was synthesized through the literature method[12] and hydrogenated. This reaction resulted in the formation of 4-amino-3-formyl quinoline in excellent yield suggesting that the intramolecular cyclization between the amino group on the phenyl ring and the carbonyl group generated from the cleavage of the isoxazole ring is regiospecific. We have been interested in the transformations of Baylis-Hillman derivatives afforded from substituted isoxazolecarbaldehydes to other heterocycles.[13] Consequently, two of the Baylis-Hillman derivatives (**1g** and **1h**) (entry 7 and 8) obtained from 3-(2-nitrophenyl)-5-isoxazolecarbaldehyde were also hydrogenated to afford the corresponding 4-quinolinamine derivatives **2g** and **2h**.

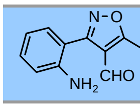
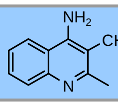
Mechanistically, the initial step is the reduction of the nitro group followed by the ring fission (Scheme 2) and subsequent cyclization. The evidence for it was obtained



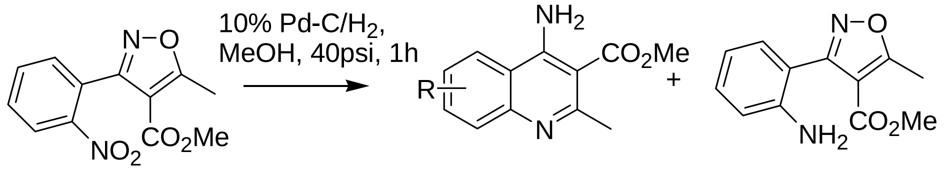
Scheme 1.

Table 1 Physical parameters of substituted 4-quinolinamines

S. No	Starting substrate	Product	Yield (%)	Physical appearance	Mp °C	Mass (ES+ or FAB+) *m/z*
1	 **1a**	 **2a**	89	Brown solid	162-165 (158-160)[1]	217.33
2	 **1b**	 **2b**	82	Yellow solid	188-190	251
3	 **1c**	 **2c**	85	Dark brown solid	145-147	277.27
4	 **1d**	 **2d**	88	Yellow solid	135-137	271
5	 **1e**	 **2e**	90	Yellow solid	250-252 (258)[1]	173.16
6	 **1f**	 **2f**	89	Brown solid	152-154	175
7	 **1g**	 **2g**	93	Brown solid	100-102	261
8	 **1h**	 **2h**	86	Brown solid	78-80	359.1
9	 **3**	 **2i**	83	Off white solid	156-158	189.13

10	 **4**	 **2j**	89	Yellow solid	227-229 (262)[1]	187

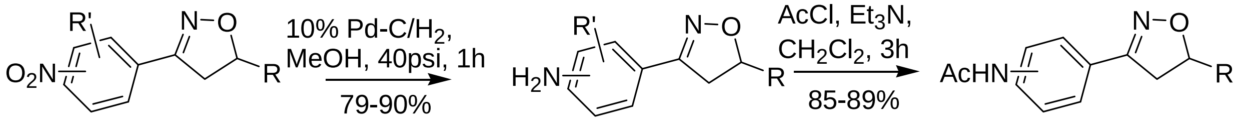
by arresting the hydrogenation reaction in 1 h, which gave 3-(2-amino-phenyl)-isoxazole **(5a)** along with the expected 4-quinolinamine derivative (Scheme 2). Though during the hydrogenation of 3-(2- nitro-phenyl)-4-isoxazolecarbaldehyde **(1e)** we could isolate only the 4-amino-3-formyl quinoline, it was envisaged that if the nitro group is reduced by circumventing the hydrogenolysis the internal cyclization through the Schiff base formation between the amino group on the phenyl ring and the formyl group on the isoxazole ring is possibile. Indeed a literature report indicated the formation of isoxazolo-(4,3-c)-quinoline from the 3-(2-azido-phenyl)-isoxazoles by the reaction with triphenylphosphine leading to imino-phosphorane which cyclizes through aza-Wittig.[14] Hence, compound **1a** was reduced with $LiAlH_4$ to furnish the product **4**. However, all attempts to perform the intramolecular cyclization with this substrate failed to yield the desired result. Nevertheless, similar to 3-(2-nitrophenyl) substituted isoxazoles, the catalytic hydrogenation of compound **4** yielded the corresponding 3-formyl-4-aminoquinoline derivative **2j** in high yield. Thus, irrespective of the functional groups present on the isoxazole ring, the Pd-C-promoted catalytic hydrogenation invariably leads to substituted 4-quinolinamines.



1a **2a** **5a**

Scheme 2.

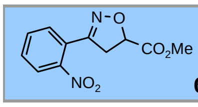
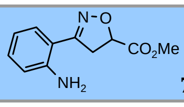
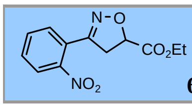
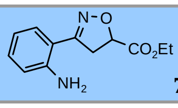
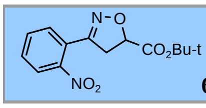
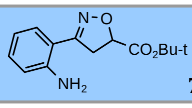
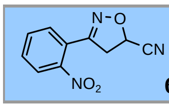
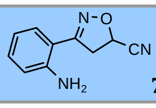
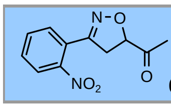
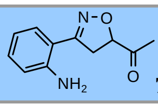
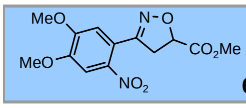
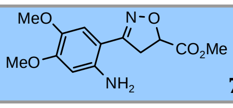
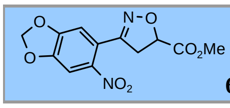
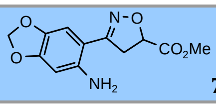
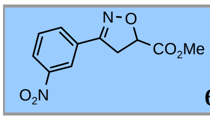
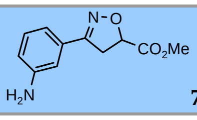
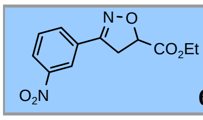
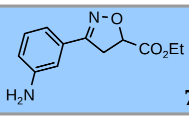
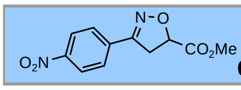
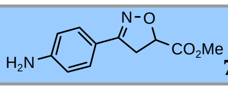
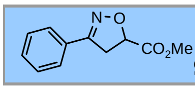
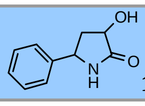
These results prompted us to explore similar hydrogenolysis in 3-(2-nitrophenyl)-2-isoxazolines. It is generally accepted that 2-isoxazolines undergo ring cleavage to yield diketo or beta-keto hydroxy system under hydrogenation conditions in the presence of Pd-C or Raney-Ni with few exceptions.[15] Because of this reason the selective reduction of the nitro group on the phenyl ring attached to the isoxazoline nucleus has been achieved either by $SnCl_2$ or H_2S in conc. ammonia.[16,17] However none of the earlier workers have ever reported the results with 3-(nitro substituted phenyl)-2-isoxazolines. Thus 3-(2-nitro phenyl)-2-isoxazolines **6a-g** were hydrogenated in the presence of Pd-C to yield the products 7a-g (Scheme 3, Table 2). The structure of products 7a-g was proven by the X-ray crystallography of a representative product 7d.[18] Further support for the presence of amino group was obtained by carrying out the acetylation of a representative compound **7a** to furnish the acetyl derivative **8a**. Thus, our results indicate that the reduction of nitro group in these substrates is highly chemoselective. In order to evaluate whether this observation was restricted to Pd-C-promoted reactions, hydrogenations of compounds **6a-c** were also carried out in the presence of Raney-Ni. Surprisingly, here too similar products **(7a-c)** were afforded in 2 h in good yields. The reduction of the nitro group was complete in 1-2 h and continuing the reaction even for more than 24 h in the presence of Pd-C or Raney-Ni did not led to any change as the isolated products were the anilines only. In our quest to further evaluate the behavior of 3-(nitro substituted phenyl) derivatives of 2-isoxazolines, 3-(3-nitrophenyl)-2-isoxazolines and 3-(4-nitrophenyl)-2-isoxazolines were synthesized and subjected to Pd-C and Raney-Ni-promoted hydrogenations. Similar to 2-nitrophenyl derivatives, these compounds too did not undergo ring cleavage as evident from their spectroscopic and analytical data. The presence of the amino group on the phenyl ring was further established by the preparation of the corresponding acetates **(8i** and **8j)**. To prove that this unusual observation is restricted to the nitro phenyl derivatives of 2-isoxazolines, the 3-phenyl-5-methoxycarbonyl-2-isoxazoline **(9)** was hydrogenated in the presence of Pd-C and Raney-Ni separately. As reported, under these conditions hydrogenolysis did occur to yield the corresponding 3-hydroxy-5-phenyl-2-pyrrolidinone **(10)** (Scheme 4).



6a-j **7a-j** **8a,i,j**

Scheme 3.

Table 2 Physical parameters of 3-(aminosubstituted phenyl)-2-isoxazolines **7a-j** via scheme 3.

S. No	Starting substrate	Product	Yield	Physical appearance	Mp °C	Mass[a] (FAB+) m/z
1	 **6a**	 **7a**	88	Brown solid	58-60	220 (M$^+$), 221 (M$^+$+1)
2	 **6b**	 **7b**	86	Brown solid	88-90	234 (M$^+$), 235 (M$^+$+1)
3	 **6c**	 **7c**	89	Brown solid	102-104	262 (M$^+$), 263 (M$^+$+1)
4	 **6d**	 **7d**	79	Off white solid	82-84	187 (M$^+$), 188 (M$^+$+1)
5	 **6e**	 **7e**	83	Brown oil	-	204 (M$^+$), 205 (M$^+$+1)
6	 **6f**	 **7f**	81	Yellow solid	128-130	280 (M$^+$), 281 (M$^+$+1)
7	 **6g**	 **7g**	84	Off white solid	132-134	264 (M$^+$), 265 (M$^+$+1)
8	 **6h**	 **7h**	85	Brown solid	78-80	220 (M$^+$), 221 (M$^+$+1)
9	 **6i**	 **7i**	79	Brown solid	80-82	234 (M$^+$), 235 (M$^+$+1)
10	 **6j**	 **7j**	81	Pale yellow solid	110-112	220 (M$^+$), 221 (M$^+$+1)
11	 **9**	 **10**	69	White solid	146-148 (150)	178

[a]It was observed that all anilines show peaks for (M+) and (M++1) in FAB Mass spectra.

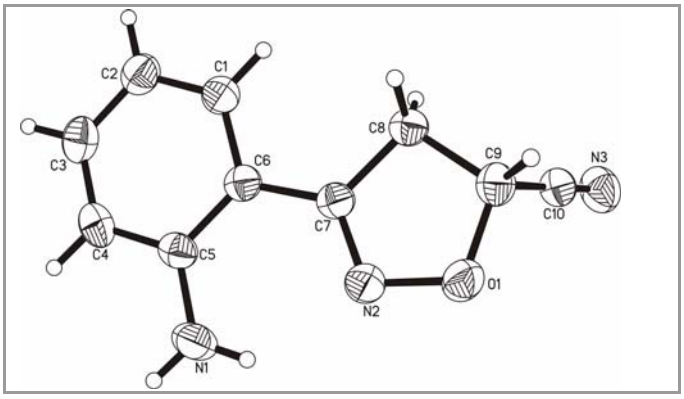
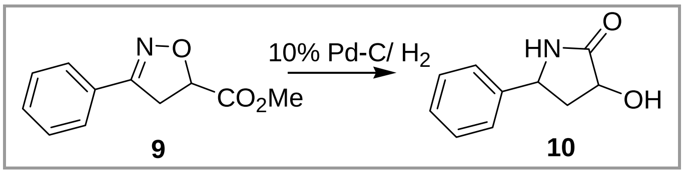


Figure 1. *ORTEP* diagram showing the crystal structure of **7d** with atomic numbering scheme for non-H atoms only at 30% probability level.



Scheme 4.

In summary we have demonstrated the general applicability of the Pd-C-mediated hydrogenolysis of substituted 3-(2-nitrophenyl)-isoxazoles which invariably results in the formation of substituted 4-quinolinamines through reduction of the nitro group to amino group followed by isoxazole ring cleavage and concomitant regiospecific ring closure. This can be treated as an easy and alternate method to achieve the synthesis of this important class of heterocycle with desired substitutions. On the other hand it has been shown that the 2-isoxazoline ring is retained during the catalytic hydrogenation if the 3-position is substituted with nitro-phenyl group. Work is underway to explore the usefulness of this methodology to obtain compounds of medicinal interest.

Melting points are uncorrected and were determined in capillary tubes on a hot stage apparatus containing silicon oil. IR spectra were recorded using a Perkin Elmer RX I FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on either a 300 or a 200 MHz FT spectrometer, using TMS as an internal standard (chemical shifts in δ values, *J* in Hz). The FABMS were recorded on JEOL/ SX-102 spectrometers and ESMS were recorded through direct flow injections in Merck M-8000 LCMS system. Elemental analyses were performed on a Carlo Erba 1108 microanalyzer or Elementar's Vario EL *III* microanalyzer. Compound **1g** and **1h** were prepared as published earlier.[19]

Hydrogenation of substituted isoxazoles in the presence of Pd-C. Representative Procedure

To the methanolic solution of compound **1a** (0.4 g, 1.85 mmol), 100 mg of 10% Pd-C was added under nitrogen atmosphere. The atmosphere of the vessel was replaced by hydrogen gas. The reaction was carried out on the Parr assembly at 40 psi at rt for 5-7 h. Thereafter, the catalyst was filtered over celite and the filtrate was evaporated to yield a residue. This residue upon column chromatography over silica gel using chloroform: methanol (1-3%) as eluent yielded 0.26 g of compound **2a** as brown solid.

4-Amino-2-methyl-quinoline-3-carboxylic acid methyl ester (2a)

ν_{max} (KBr) 1734 (CO_2CH_3), 3363 (brs, NH_2) cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ= 2.81 (s, 3H, CH_3), 3.95 (s, 3H, CO_2CH_3), 7.01 (brs, 2H, NH_2, exchangeable with D_2O), 7.42 (t, 1H, *J*= 7.5 Hz, ArH), 7.68 (t, 1H, *J*= 7.5 Hz, ArH), 7.75 (d, 1H, *J*= 8.1 Hz, ArH), 7.87 (d, 1H, *J*= 8.1 Hz, ArH)

^{13}C NMR ($CDCl_3$, 50.32 MHz) δ= 28.3, 51.9, 102.6, 117.4, 121.1, 125.3, 129.4, 131.6, 147.9, 154.2, 159.9, 170.3

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.69; H, 5.52; N, 12.90.

4-Amino-6-chloro-2-methyl-quinoline-3-carboxylic acid methyl ester (2b)

ν_{max} (KBr) 1738 (CO_2CH_3), 3382 (brs, NH_2) cm^{-1}

^{1}H NMR ($CDCl_3$+DMSOd_6, 300 MHz) δ= 2.85 (s, 3H, CH_3), 3.99 (s, 3H, CO_2CH_3), 7.62-7.69 (m, 1H, ArH), 7.87-7.99 (m, 1H, ArH), 8.54-8.58 (m, 1H, ArH)

Anal. Calcd. for $C_{12}H_{11}ClN_2O_2$: C, 57.49; H, 4.42; N, 11.17. Found: C, 57.38; H, 4.46; N, 11.20.

4-Amino-6,7-dimethoxy-2-methyl-quinoline-3-carboxylic acid methyl ester (2c)

ν_{max} (KBr) 1733 (CO_2CH_3), 3385 (brs, NH_2) cm^{-1}

^{1}H NMR ($CDCl_3$+DMSOd_6, 300 MHz) δ= 2.57 (s, 3H, CH_3), 3.88 (s, 9H, 2 x OCH_3 and CO_2CH_3), 7.62, 7.69 (2s br merged, 2H, ArH)

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.80; H, 5.78; N, 10.30.

4-Amino-2-trifluoromethyl-quinoline-3-carboxylic acid methyl ester (2d)

ν_{max} (KBr) 1733 (CO_2CH_3), 3434 (brs, NH_2) cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 3.96 (s, 3H, CO_2CH_3), 6.63 (brs, 2H, NH_2), 7.60, 7.64 (m, 1H, ArH), 7.75-7.85 (m, 2H, ArH), 8.08 (d, 1H, *J*= 8.4 Hz, ArH)

^{13}C NMR ($CDCl_3$, 50.32 MHz) δ= 52.8, 101.7, 118.4, 119.1, 120.9, 124.6, 127.9, 131.1, 132.2, 146.7, 153.1, 168.3

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 61.04; H, 6.05; N, 10.04.

4-Amino-quinoline-3-carbaldehyde (2e)

ν_{max} (KBr) 1710 (CHO), 3428 (brs, NH_2) cm^{-1}

^{1}H NMR (CDCl$_3$+DMSOd$_6$, 200 MHz) δ= 7.45-7.52 (m, 1H, ArH), 7.70-7.78 (m, 1H, ArH), 7.90 (d, 1H, *J*= 8.6 Hz, ArH), 8.27 (d, 1H, *J*= 8.4 Hz, ArH), 8.67 (s, 1H, ArH), 9.97 (s, 1H, CHO)

^{13}C NMR (DMSOd$_6$, 50.32 MHz) δ= 109.3, 118.2, 124.1, 125.6, 129.5, 132.6, 149.1, 153.9, 155.1, 155.9, 193.4

Anal. Calcd. for $C_{10}H_8N_2O$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.68; H, 4.62; N, 16.30.

(4-Amino-quinolin-2-yl)-methanol (2f)

ν_{max} (KBr) 3331 (brs, NH$_2$) cm^{-1}

^{1}H NMR (CDCl$_3$+DMSOd$_6$, 300 MHz) δ= 4.51 (s, 2H, CH$_2$), 6.74, 6.79 (2s merged, 3H, ArH and NH$_2$), 7.33-7.35 (m, 1H, ArH), 7.56-7.58 (m, 1H, ArH), 7.68 (d, 1H, *J*= 7.8 Hz, ArH), 8.10 (d, 1H, *J*= 7.8 Hz, ArH)

^{13}C NMR (DMSOd$_6$, 50.32 MHz) δ= 64.9, 99.5, 118.1, 122.7, 123.4, 128.3, 129.4, 147.9, 152.6, 162.4

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.84; H, 5.72; N, 16.20

3-(4-Amino-quinolin-2-yl)-3-hydroxy-2-methyl-propionic acid methyl ester (2g)

ν_{max} (KBr) 1724 (CO$_2$CH$_3$), 3366 (brs, NH$_2$) cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) δ= 1.15 (d, 3H, *J*= 7.2 Hz, CH$_3$), 2.78-2.88 (m, 1H, CH), 3.67 (s, 3H, CO$_2$CH$_3$), 4.90 (d, 1H, *J*= 5.4 Hz), 6.58 (s, 1H, ArH), 7.41-7.46 (m, 1H, ArH), 7.62-7.67 (m, 1H, ArH), 7.75 (d, 1H, *J*= 8.1 Hz, ArH), 7.93 (d, 1H, *J*= 8.1 Hz, ArH)

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.56; H, 6.12; N, 10.60.

3-(4-Amino-quinolin-2-yl)-3-hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-propionic acid methyl ester (2h)

ν_{max} (KBr) 1731 (CO$_2$CH$_3$), 3396 (brs, NH$_2$) cm^{-1}

^{1}H NMR (DMSOd$_6$, 300 MHz) δ= 2.26 (s, 3H, NCH$_3$), 2.30-2.45 (m, 8H, 4 x CH$_2$N), 2.60-2.70 (m, 1H, NCH$_2$), 3.05-3.15 (m, 1H, C*H*CH$_2$), 3.63 (s, 3H, CO$_2$CH$_3$), 4.96 (d, 1H, *J*= 1.8 Hz, CHOH), 6.75 (s, 2H, NH$_2$), 7.47-7.51 (m, 1H, ArH), 7.68-7.75 (m, 2H, ArH), 7.83-7.89 (m, 1H, ArH), 8.22-8.26 (m, 1H, ArH)

Anal. Calcd. for $C_{19}H_{26}N_4O_3$: C, 63.67; H, 7.31; N, 15.63. Found: C, 63.56; H, 7.12; N, 150.60.

4-Amino-2-methyl-quinolin-3-yl)-methanol (2i)

ν_{max} (KBr) 3433 (brs, NH$_2$) cm^{-1}

^{1}H NMR (CDCl$_3$+ DMSOd$_6$, 300 MHz) δ= 2.55 (s, 3H, CH$_3$), 4.63 (s, 2H, CH$_2$), 6.59 (brs, 2H, NH$_2$), 7.33 (t, 1H, *J*= 7.8 Hz, ArH), 7.55 (t, 1H, *J*= 7.8 Hz, ArH), 7.66 (d, 1H, *J*= 8.1 Hz, ArH), 8.16 (d, 1H, *J*= 8.1 Hz, ArH).

^{13}C NMR (DMSOd$_6$, 50.32 MHz) δ= 22.9, 56.4, 111.7, 117.9, 122.3, 123.3, 127.5, 128.9, 146.4, 149.8, 157.2.

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.04; H, 6.35; N, 14.60.

4-Amino-2-methyl-quinoline-3-carbaldehyde (2j)

ν_{max} (KBr) 1707 (CHO), 3312 (brs, NH$_2$) cm^{-1}

^{1}H NMR (CDCl$_3$+DMSOd$_6$, 300 MHz) δ= 2.71 (s, 3H, CH$_3$), 6.04 (brs, 2H, NH$_2$), 7.50 (t, 1H, *J*= 7.5 Hz, ArH), 7.75 (t, 1H, *J*= 7.5 Hz, ArH), 7.88 (d, 1H, *J*= 8.1 Hz, ArH), 7.98 (d, 1H, *J*= 8.1 Hz, ArH), 9.05 (s, 1H, CHO), 9.89 (brs, 1H, NH$_2$)

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.04; H, 5.35; N, 15.12.

Synthesis of compound 4

LiAlH$_4$ reduction of ***1a***: To a stirred solution of compound **1a** (1.5 g, 5.72 mmol) in dry ether (40 mL) was added LiAlH$_4$ (0.33 g, 8.6 mmol) in portions at 0^{o}C. The ice bath was removed and the reaction was allowed to proceed at rt for 1h. Upon completion the reaction mixture was carefully decomposed with ice-cold 10% NaOH solution. The precipitate was filtered and the filtrate was washed thoroughly with water. The organic layer was dried and evaporated to yield a residue. This residue upon column chromatography over silica gel (60-120) using hexane:EtOAc (40:60, v/v) gave 0.95 g (82%) of pure **3** as brown oil.

PCC oxidation of ***3***: To the stirred solution of compound **3** (0.5 g, 2.45 mmol) in dry CH$_2$Cl$_2$ was added PCC (1.05 g, 4.9 mmol) and the reaction was allowed to proceed at rt for 16 h. Thereafter the reaction mixture was filtered through a silica gel column using hexane: EtOAc (50:50, v/v) as eluent to afford 0.4 g (81%) of compound **4** as orange solid.

[3-(2-Amino-phenyl)-5-methyl-isoxazol-4-yl]-methanol (3)

ν_{max} (Neat) 3443 (brs, NH$_2$ and OH) cm^{-1}

^{1}H NMR (CDCl$_3$, 200 MHz) δ= 2.52 (s, 3H, CH$_3$), 3.58 (s, 2H, C*H$_2$*OH), 7.54-7.60 (m, 3H, ArH), 8.12-8.17 (m, 1H, ArH).

Mass (ES+) *m/z* 205.40 (M$^+$+1)

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.58; H, 6.05; N, 13.60.

3-(2-Amino-phenyl)-5-methyl-isoxazole-4-carbaldehyde (4)

mp 134-136°C

ν_{max} (KBr) 1684 (CHO), 3432 (brs, NH$_2$) cm^{-1}

^{1}H NMR (CDCl$_3$, 200 MHz) δ= 2.80 (s, 3H, CH$_3$), 7.54-7.58 (m, 1H, ArH), 7.70-7.76 (m, 2H, ArH), 8.25-8.29 (m, 1H, ArH), 9.79 (s, 1H, CHO)

^{13}C NMR (CDCl$_3$, 50.32 MHz) δ= 12.4, 116.5, 123.8, 125.4, 131.7, 132.7, 134.0, 148.8, 159.9, 177.0, 183.1

Mass (FAB+) *m/z* 203 (M$^+$+1)

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.04; H, 5.15; N, 14.06.

3-(2-Amino-phenyl)-5-methyl-isoxazole-4-carboxylic acid methyl ester (5a)

Yellow solid, mp 192-194°C

ν_{max} (KBr) 1733 (CO$_2$CH$_3$), 3391 (brs, NH$_2$) cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) δ= 2.91 (s, 3H, CH$_3$), 3.98 (s, 3H, CO$_2$CH$_3$), 7.00 (brs, 2H, NH$_2$), 7.59 (t, 1H, *J*= 7.5 Hz, ArH), 7.83 (t, 1H, *J*= 7.5 Hz, ArH), 7.99 (d, 1H, *J*= 8.1 Hz, ArH), 8.82 (d, 1H, *J*= 8.4 Hz, ArH)

Mass (ES+) *m/z* 233.4 (M$^+$+1), 255.0 (M$^+$+Na)

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.20; H, 5.34, N, 12.15.

Synthesis of 3-(nitro substituted phenyl)-2-isoxazolines

These isoxazolines were prepared as described in the literature.[20]

3-(2-Nitro-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester (6a)

87% as yellow oil

ν_{max} (Neat) 1743 (CO$_2$CH$_3$) cm^{-1}

^{1}H NMR (CDCl$_3$, 200 MHz) δ= 3.54-3.62 (m, 2H, CH$_2$), 3.87 (s, 3H, CO$_2$CH$_3$), 5.23-5.32 (m, 1H, CH), 7.58-7.72 (m, 3H, ArH), 8.10-8.14 (m, 1H, ArH)

Mass (FAB+) *m/z* 251 (M$^+$+1)

Anal. Calcd. for $C_{11}H_{10}N_2O_5$: C, 52.80; H, 4.03; N, 11.20. Found: C, 52.87; H, 4.08, N, 11.25.

3-(2-Nitro-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (6b)

83% as brown oil

ν_{max} (Neat) 1743 (CO$_2$Et) cm^{-1}

^{1}H NMR (CDCl$_3$, 200 MHz) δ= 1.36 (t, 3H, *J*= 7.1 Hz, C*H*$_3$ CH$_2$), 3.45-3.70 (m, 2H, C*H*$_2$CH), 4.31 (q, 2H, *J*= 7.1 Hz, C*H*$_2$CH$_3$), 5.21-5.30 (m, 1H, C*H*CH$_2$), 7.27-7.76 (m, 3H, ArH), 8.10-8.13 (m, 1H, ArH)

Mass (FAB+) *m/z* 265 (M$^+$+1)

Anal. Calcd. for $C_{12}H_{12}N_2O_5$: C, 54.55; H, 4.58; N, 10.60. Found: C, 54.61; H, 4.50; N, 10.65.

3-(2-Nitro-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester (6c)

80% as yellow solid, mp 76-78°C

νmax (KBr) 1738 (CO$_2$^{t}Bu) cm^{-1}

^{1}H NMR (CDCl$_3$, 200 MHz) δ= 1.54 (s, 9H, 3 x CH$_3$), 3.47-3.58 (m, 2H, CH$_2$CH), 5.09-5.18 (m, 1H, CHCH$_2$), 7.58-7.74 (m, 3H, ArH), 8.08-8.12 (m, 1H, ArH)

Mass (FAB+) *m/z* 293 (M$^+$+1)

Anal. Calcd. for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.58. Found: C, 57.62; H, 5.58; N, 9.62.

3-(2-Nitro-phenyl)-4,5-dihydro-isoxazole-5-carbonitrile (6d)

77% as off white solid, mp 122-124°C

ν_{max} (KBr) 2248 (CN) cm^{-1}

^{1}H NMR (CDCl$_3$, 200 MHz) δ= 3.52-3.88 (m, 2H, C*H*$_2$CH), 5.43-5.51 (m, 1H, C*H*CH$_2$), 7.60-7.78 (m, 3H, ArH), 8.17-8.22 (m, 1H, ArH)

Mass (FAB+) *m/z* 218 (M$^+$+1)

Anal. Calcd. for $C_{10}H_7N_3O_3$: C, 55.30; H, 3.25; N, 19.35. Found: C, 55.43; H, 3.21; N, 19.38.

1-[3-(2-Nitro-phenyl)-4,5-dihydro-isoxazol-5-yl]-ethanone (6e)

79% as brown oil

ν_{max} (Neat) 1722 (COCH$_3$) cm^{-1}

^{1}H NMR (CDCl$_3$, 200 MHz) δ= 2.42 (s, 3H, CH$_3$), 3.48-3.53 (m, 2H, C*H*$_2$CH), 5.06-5.15 (m, 1H, C*H*CH$_2$), 7.52-7.72 (m, 3H, ArH), 8.08-8.13 (m, 1H, ArH)

Mass (FAB+) *m/z* 235 (M$^+$+1)

Anal. Calcd. for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.49; H, 4.33; N, 11.92.

3-(4,5-Dimethoxy-2-nitro-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester (6f)

75% as pale yellow solid, mp 130-132°C

ν_{max} (KBr) 1732 (CO$_2$CH$_3$) cm^{-1}

^{1}H NMR (CDCl$_3$, 200 MHz) δ= 3.50-3.61 (m, 2H, C*H*$_2$CH); 3.82 (s, 3H, CO$_2$CH$_3$), 3.99 (s, 6H, 2XOCH$_3$), 5.24-5.29 (m, 1H, C*H*CH$_2$), 6.96 (s, 1H, ArH), 7.72 (s, 1H, ArH)

Mass (FAB+) *m/z* 311 (M$^+$+1)

Anal. Calcd. for $C_{13}H_{14}N_2O_6$: C, 53.06; H, 4.80; N, 9.52. Found: C, 53.16; H, 4.75; N, 9.46.

3-(6-Nitro-benzo[1,3]dioxol-5-yl)-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester (6g)

76% as pale yellow solid, mp 121-123°C.

ν_{max} (KBr) 1754 (CO$_2$CH$_3$) cm^{-1}

^{1}H NMR (CDCl$_3$, 200 MHz) δ= 3.47-3.57 (m, 2H, C*H*$_2$CH), 3.86 (s, 3H, CO$_2$CH$_3$), 5.22-5.30 (m, 1H, C*H*CH$_2$), 6.19 (s, 2H, CH$_2$), 6.93 (s, 1H, ArH), 7.63 (s, 1H, ArH)

Mass (FAB+) *m/z* 295 (M$^+$+1)

Anal. Calcd. for $C_{12}H_{10}N_2O_7$: C, 48.99; H, 3.43; N, 9.52. Found: C, 48.92; H, 3.35; 9.46.

3-(3-Nitro-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester (6h)

81% as white solid, mp 92-94°C.

ν_{max} (KBr) 1755 (CO$_2$CH$_3$) cm^{-1}

^{1}H NMR (CDCl$_3$, 200 MHz) δ= 3.68-3.76 (m, 2H, C*H*$_2$CH), 3.85 (s, 3H, CO$_2$CH$_3$), 5.24-5.33 (m, 1H, C*H*CH$_2$), 7.62 (t, 1H, *J*= 8.0 Hz, ArH), 8.10 (d, 1H, *J*= 7.8 Hz, ArH), 8.27-8.32 (m, 1H, ArH), 8.45 (s, 1H, ArH).

Mass (FAB+) *m/z* 251 (M$^+$+1)

Anal. Calcd. for $C_{11}H_{10}N_2O_5$: C, 52.80; H, 4.03; N, 11.20. Found: C, 52.92; H, 4.13, N, 11.27.

3-(3-Nitro-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (6i)

83% as white solid, mp 65-67°C

ν_{max} (KBr) 1748 (CO$_2$Et) cm^{-1}; ^{1}H NMR (CDCl$_3$, 200 MHz) δ= 1.34 (t, 3H, *J*= 7.2 Hz, C*H*$_3$CH$_2$), 3.66-3.72 (m, 2H, C*H*$_2$CH), 4.30 (q, 2H, *J*= 7.2 Hz, C*H*$_2$CH$_3$), 5.20-5.30 (m, 1H, C*H*CH$_2$), 7.58-7.66 (m, 1H, ArH), 8.08-8.13 (m, 1H, ArH), 8.26-8.32 (m, 1H, ArH), 8.44-8.46 (m, 1H, ArH)

Mass (FAB+) *m/z* 265 (M^++1)

Anal. Calcd. for $C_{12}H_{12}N_2O_5$: C, 54.55; H, 4.58; N, 10.60. Found: C, 54.64; H, 4.63; N, 10.66.

3-(4-Nitro-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester (6j)

86% as off white solid, mp 159-161°C.

ν_{max} (KBr) 1755 (CO_2CH_3) cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 3.66-3.72 (m, 2H, C*H*$_2$CH), 3.84 (s, 3H, CO_2CH_3), 5.24-5.33 (m, 1H, C*H*CH_2), 7.86 (d, 2H, *J*= 8.5 Hz, ArH), 8.28 (d, 2H, *J*= 8.5 Hz, ArH); mass (FAB+) *m/z* 251 (M^++1)

Anal. Calcd. for $C_{11}H_{10}N_2O_5$: C, 52.80; H, 4.03; N, 11.20. Found: C, 52.96, H, 4.12, N, 11.26.

Hydrogenation of substituted isoxazolines - Representative Procedure

Pd-C-mediated. To the methanolic solution of compound **6a** (0.75 g, 3.0 mmol), 125 mg of 10% Pd-C was added under nitrogen atmosphere. The atmosphere of the vessel was replaced by hydrogen gas. The reaction was carried out on the Parr assembly at 40 psi at rt for 1h. Thereafter, the catalyst was filtered over celite and the filtrate was evaporated to yield a residue. This residue upon column chromatography over silica gel using hexane:EtOAc (90:10, v/v) as eluent yielded 0.58 g (88%) of compound **7a** as brown solid.

Raney-Ni-mediated. A mixture of compound **6a** (0.67 g, 2.68 mmol) and Raney-Ni (0.1 g wet) in methanol (10 mL) was subjected to hydrogenation at 40 psi in the Parr assembly for 3 h. The catalyst was removed by filtration over celite and the filtrate was concentrated. The residue thus obtained was subjected to column chromatography over silica gel using hexane:EtOAc (90:10, v/v) as eluent to afford 0.50 g (85%) of pure **7a** as brown solid.

3-(2-Amino-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester (7a)

ν_{max} (KBr) 1741 (CO_2CH_3), 3467 (brs, NH_2) cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 3.72-3.83 (m, 5H, 2H, C*H*$_2$CH and 3H, CO_2CH_3), 5.06-5.15 (m, 1H, C*H*CH_2), 6.71-6.75 (m, 2H, ArH), 7.14-7.27 (m, 2H, ArH)

^{13}C NMR ($CDCl_3$, 50.32 MHz) δ= 40.8, 53.2, 76.6, 110.9, 116.3, 116.8, 130.0, 131.5, 147.3, 157.8, 171.3

HRMS Calcd. for $C_{11}H_{12}N_2O_3$: 220.0848. Found: 220.0837.

3-(2-Amino-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (7b)

ν_{max} (KBr) 1738 (CO_2Et), 3447 (brs, NH_2) cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 1.33 (t, 3H, *J*= 7.2 Hz, C*H*$_3$$CH_2$), 3.71-3.76 (m, 2H, C*H*$_2$CH), 4.27 (q, 2H, *J*= 7.2 Hz, C*H*$_2$$CH_{3,}$), 5.05, 5.10 (dd, 1H, J_1= 8.4 Hz, J_2= 1.0 Hz, C*H*CH_2), 5.63 (brs, 2H, NH_2), 6.66-6.75 (m, 2H, ArH), 7.14-7.23 (m, 2H, ArH)

^{13}C NMR ($CDCl_3$, 50.32 MHz) δ= 14.5, 40.8, 62.4, 76.8, 111.0, 116.3, 116.8, 130.0, 131.5, 147.3, 157.7, 170.8

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.65; H, 6.16; N, 12.03.

3-(2-Amino-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester (7c)

ν_{max} (KBr) 1732 ($CO_2{}^tBu$), 3449 (brs, NH_2) cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 1.51 (s, 9H, 3 x CH_3), 3.67 (d, 2H, *J*= 9.2 Hz, C*H*$_2$CH), 4.96 (t, 1H, *J*= 9.2 Hz C*H*CH_2), 5.62 (brs, 2H, NH_2), 6.66-6.75 (m, 2H, ArH), 7.14-7.23 (m, 2H, ArH)

^{13}C NMR ($CDCl_3$, 50.32 MHz) δ= 28.4, 40.7, 77.4, 111.2, 116.3, 116.8, 130.0, 131.4, 147.3, 157.6, 169.7

Anal. Calcd. for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 63.89; H, 6.73; N, 10.60.

3-(2-Amino-phenyl)-4,5-dihydro-isoxazole-5-carbonitrile (7d)

ν_{max} (KBr) 2249, 2213 (CN), 3466 (brs, NH_2) cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 3.81-3.86 (m, 2H, C*H*$_2$CH), 5.28 (t, 1H, *J*= 8.6 Hz, C*H*CH_2), 5.60 (brs, 2H, NH_2), 6.69-6.78 (m, 2H, ArH), 7.09-7.24 (m, 2H, ArH)

^{13}C NMR ($CDCl_3$, 50.32 MHz) δ= 42.9, 65.5, 109.8, 116.6, 117.2, 117.7, 129.5, 130.1, 132.3, 147.5, 160.0

Anal. Calcd. for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.26; H, 4.89; N, 22.49.

1-[3-(2-Amino-phenyl)-4,5-dihydro-isoxazol-5-yl]-ethanone (7e)

ν_{max} (Neat) 1721 ($COCH_3$), 3470 (brs, NH_2) cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 2.36 (s, 3H, $COCH_3$), 3.58-3.70 (m, 2H, C*H*$_2$CH), 4.90, 4.95 (dd, 1H, J_1= 6.6 Hz, J_2= 4.80 Hz, C*H*CH_2), 6.68-6.75 (m, 2H, ArH), 7.15-7.24 (m, 2H, ArH)

^{13}C NMR ($CDCl_3$, 50.32 MHz) δ= 26.7, 39.3, 83.1, 111.1, 116.3, 117.0, 130.2, 131.6, 147.2, 158.4, 208.2

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.76; H, 6.12; N, 13.86.

3-(2-Amino-4,5-dimethoxy-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester (7f)

ν_{max} (KBr) 1744 (CO_2CH_3), 3457 (brs, NH_2) cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 3.70-3.74 (m, 2H, C*H*$_2$CH), 3.81 (s, 6H, 2 x OCH_3), 3.87(s, 3H, CO_2CH_3), 5.09 (t, 1H, *J*= 9.2 Hz, C*H*CH_2), 6.26 (s, 1H, ArH), 6.61 (s, 1H, ArH)

^{13}C NMR ($CDCl_3$, 50.32 MHz) δ= 41.2, 53.2, 56.1, 57.5, 76.4, 99.9, 102.5, 113.6, 141.1, 143.4, 152.7, 157.3, 171.5

Anal. Calcd. for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 59.20; H, 6.21; N, 10.72.

3-(6-Amino-benzo[1,3]dioxol-5-yl)-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester (7g)

ν_{max} (KBr) 1740 (CO_2CH_3), 3450 (brs, NH_2) cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 3.67 (d, 2H, *J*= 8.8 Hz, C*H*$_2$CH), 3.82 (s, 3H, CO_2CH_3), 5.07 (t, 1H, *J*= 8.8 Hz, C*H*CH$_2$), 5.89 (s, 2H, OCH_2O), 6.27 (s, 1H, ArH);), 6.58 (s, 1H, ArH)

^{13}C NMR ($CDCl_3$, 50.32 MHz) δ= 41.3, 53.2, 76.4, 97.3, 101.6, 102.8, 108.0, 139.7, 144.6, 150.6, 157.4, 171.4

Anal. Calcd. for $C_{12}H_{12}N_2O_5$: C, 54.55; H, 4.58; N, 10.60. Found: C, 54.89; H, 4.66; N, 10.66.

3-(3-Amino-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester(7h)

ν_{max} (KBr) 1742 (CO_2CH_3), 3449 (brs, NH_2) cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 3.58-3.72 (m, 2H, C*H*$_2$CH), 3.82 (3H, CO_2CH_3), 5.13, 5.18 (dd, 1H, J_1= 8.2 Hz, J_2= 1.6 Hz, C*H*CH$_2$), 6.72-6.77 (m, 1H, ArH), 6.96-7.23 (m, 3H, ArH).

^{13}C NMR ($CDCl_3$, 50.32 MHz) δ=39.5, 53.2, 78.2, 113.2, 117.6, 117.7, 129.7, 130.1, 147.3, 156.8, 171.2.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.80; H, 5.46; N, 12.85.

3-(3-Amino-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (7i)

ν_{max} (KBr) 1716 (CO_2Et); 3451 (brs, NH_2) cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 1.33 (t, 3H, *J*= 7.2 Hz, CH_3), 3.57-3.62 (m, 2H, C*H*$_2$CH), 4.27 (q, 2H, *J*= 7.1 Hz, C*H*$_2$CH$_3$), 5.11, 5.16 (dd, 1H, J_1= 8.6 Hz, J_2= 1.4 Hz, C*H*CH$_2$), 6.72-6.77 (m, 1H, ArH), 6.96-7.23 (m, 3H, ArH).

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.42; H, 5.88; N, 12.06.

3-(4-Amino-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester (7j)

ν_{max} (KBr) 1742 (CO_2CH_3), 3458 (brs, NH_2) cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ= 3.55-3.59 (m, 2H, C*H*$_2$CH), 3.78 (s, 3H, CO_2CH_3), 5.10 (t, 1H, *J*= 9.2 Hz, C*H*CH$_2$), 6.63 (d, 2H, *J*= 8.6 Hz, ArH), 7.43 (d, 2H, *J*= 8.6 Hz, ArH).

^{13}C NMR ($CDCl_3$, 50.32 MHz) δ=39.7, 53.1, 77.9, 115.0, 118.5, 128.9, 149.3, 156.4, 171.5.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.12; H, 5.72; N, 12.58.

Acetylation of 3-(aminophenyl)-2-isoxazolines- Representative procedure

To the stirred solution of compound **7a** (0.30 g, 1.36mmol) in dry dichloromethane (3 mL) was added triethylamine (0.28 mL, 2.04 mmol) followed by drop-wise addition of a solution of acetyl chloride (0.19 mL, 2.72mmol) in dry dichloromethane (3 mL) at 0 °C. After the addition was complete, the reaction was continued at room temperature for 2 h. The reaction mixture was extracted with dichloromethane (2 x 15 mL) and water (20 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated to obtain an oily residue. The residue was purified through column chromatography over silica gel with hexane:ethyl acetate (80:20, v/v) as eluent to obtain 0.35 g (86%) of **8a** as pale yellow solid.

3-(2-Acetylamino-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester (8a)

mp 150-152°C

ν_{max} (KBr) 1755 (CO_2CH_3), 3458 (NH) cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 2.23 (s, 3H, $COCH_3$), 3.75-3.81 (m, 2H, C*H*$_2$CH), 3.85 (s, 3H, CO_2CH_3), 5.14, 5.19 (dd, 1H, J_1= 7.8 Hz, J_2= 2.4 Hz, C*H*CH$_2$), 7.08-7.16 (m, 1H, ArH), 7.28-7.32 (m, 1H, ArH), 7.41-7.49 (m, 1H, ArH), 8.69-8.73 (m, 1H, ArH), 10.49 (brs, 1H, NH)

^{13}C NMR ($CDCl_3$, 50.32 MHz) δ= 25.9, 40.6, 53.4, 77.0, 115.3, 120.9, 123.3, 129.7, 132.0, 138.7, 157.8, 169.7, 170.6

Mass (FAB+) *m*/*z* 263 (M$^+$+1)

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.29; H, 5.41; N, 10.72.

3-(3-Acetylamino-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (8i)

86% as colourless oil

ν_{max} (Neat) 1740 (CO_2Et); 3306 (NH) cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ= 1.33 (t, 3H, *J*= 7.1 Hz, C*H*$_3$CH$_2$), 2.19 (s, 3H, $COCH_3$), 3.59-3.66 (m, 2H, C*H*$_2$CH), 4.25 (q, 2H, *J*= 7.1 Hz, C*H*$_2$CH$_3$), 5.16 (t, 1H, *J*= 9.2 Hz, C*H*CH$_2$), 7.31-7.44 (m, 2H, ArH), 7.64-7.68 (m, 1H, ArH), 7.79 (s, 1H, ArH)

Mass (FAB+) *m*/*z* 277 (M$^+$+1)

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.55; H, 6.58; N, 10.68.

3-(4-Acetylamino-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester. (8j)

89% as white solid, mp 127-129°C.

ν_{max} (KBr) 1759 (CO_2CH_3); 3528 (NH) cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 2.20 (s, 3H, $COCH_3$), 3.63 (d, 2H, *J*= 9.0 Hz, C*H*$_2$CH), 3.82 (s, 3H, CO_2CH_3), 5.18 (t, 1H, *J*= 9.1 Hz, C*H*CH$_2$), 7.54-7.59 (m, 4H, ArH)

Mass (FAB+) *m*/*z* 263 (M$^+$+1)

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.23; H, 5.25; N, 10.44.

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(18) orthorhombic, $P2_12_12_1$, a = 5.770 (1), b = 9.925 (2), c = 16.153 (3) Å, V = 915.4 (3) Å^3, Z = 4, D_c = 1.358g cm^{-3}, μ (Mo-K$_\alpha$) = 0.09 mm^{-1}, F(000) = 392.0, colourless block, crystal dimensions 0.225 x 0.175 x 0.150 mm, 1370 reflections measured (R$_{int}$ = 0.019), 1230 unique, R = 0.0456 [$(\Delta/\sigma)_{max}$ = 000)], wR$_2$ = 0.1087 for 1270 on F values of reflections with I>2σ(I), S = 1.028 for all data and 128 parameters. Unit cell determination and intensity data collection (2θ = 50°) were performed on a Bruker P4 diffractometer at 293 (2) K. Structure solutions was performed by direct methods and refinements by full-matrix least-squares methods on F^2. Programs: XSCANS [Siemens Analytical X-ray Instrument Inc.: Madison, WI, USA, 1996) was used for data collection and data processing], SHELXTL-NT [(Bruker Axs Inc.: Madison, Wisconsin, USA 1997) was used for structure determination, refinements and molecular graphics]. Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB21EZ, UK (CCDC deposition no. of compound **7d: *********) .

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