

# Green Chemistry Approach to Fast and Highly Efficient One-Pot Synthesis of Bis-Isoxazolyl-1,2,5,6-Tetrahydro Pyridine-3-Carboxylates

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## ABSTRACT

The synthesis of the bis-isoxazolyl-1,2,5,6-tetrahydro pyridine-3-carboxylates is achieved in high yield without the production of toxic waste products by using room temperature ionic liquid (RTILs) triethyl ammonium acetate (TEAA). The RTIL TEAA played the dual role of efficient green solvent as well as recyclable catalyst.

**Keywords:** Bis-Isoxazolyl-1,2,5,6-Tetrahydro Pyridine-3-Carboxylates; Bis-Isoxazolyl-1,2,5,6-Tetrahydro Pyridine-3-Carboxylates; Green Synthesis

## 1. Introduction

Recently, there has been an increasing interest in the development of cleaner technologies to replace hazardous organic solvents with environmental benign solvents. Nowadays green chemistry emphasizes the optimization of synthetic methodologies to reduce pollution, cost and tedious work-ups. This new challenge has led to a growing interest in the field of organic synthesis. Among the several aspects of green chemistry, the reduction/replacement of volatile organic solvents from the reaction medium is of utmost importance. The use of a large excess of conventional volatile solvents required to conduct a chemical reaction creates ecological and economic concerns. The search for a nonvolatile and recyclable alternative solvent is thus holding a key role in this field of research. The use of fused organic salts, consisting of ions, is now emerging as a possible alternative. A proper choice of cations and anions is required to achieve ionic salts that are liquids at room temperature and are appropriately termed room temperature ionic liquids (RTILs). Common RTILs consists of *N,N*-dialkylimidazolium, alkylammonium, alkylphosphonium or *N*-alkylimidazolium as cations [1]. These innovative fluids are organic salts, whose cation, anion and the alkyl chain attached to organic cation can be varied to change their chemical and physical properties as per the needs of the chemical

process. A key feature of these liquids is their intrinsic ability to solvate a wide array of organic and inorganic substrates. They are blessed with qualities such as incredibly large liquidous range, negligible vapour pressure and recyclability [2]. In short, these ionic liquids have enlightened the way to environmentally benign procedures (3). The development of cleaner technologies is a major emphasis in green chemistry.

Several compounds consisting of reduced pyridine, like the 1,2,3,6-tetrahydropyridine **1** ring system is known to exhibit a variety of biological activities [4,5]. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) **2** was recently found to be neurotoxic, causing persistent parkinsonism in humans and other animal species [6-9]. Arecoline **3**, an alkaloid containing tetrahydropyridine ring system obtained from the betel nut (*Areca catechu*), the fruit of a palm tree, has been used previously as a leading centrally active muscarinic agent [10]. 3-Methoxy-5-methyl-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]-pyridinium **4** [11-13] and 3-methoxy-5-methyl-6,7-di-hydro-4*H*-thiopyrano[3,4-*d*]isoxazol-5-ium **5** [14] salts are muscarinic agonists and partial agonists bio iso-sterically derived from arecoline (**Figure 1**). Biological activity of substituted isoxazoles has made them a focus of medicinal chemistry over the years. Spirocyclic isoxazoles such as aerotionin, aerophobin-1, and zamamistatin are biologically active alkaloids [15]. Isoxazoles are potent analgesic, anti-inflammatory [16], antimicrobial [17], COX-2

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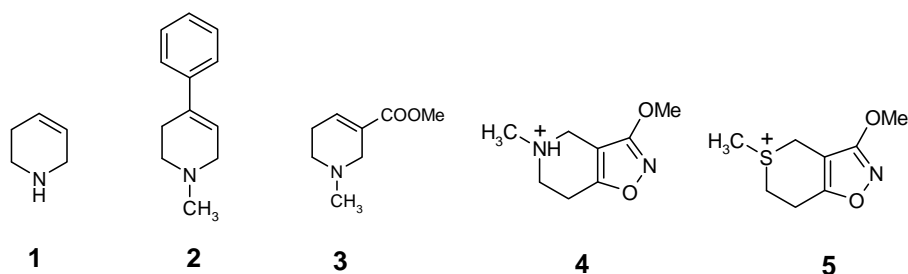


Figure 1. Biologically active tetrahydropyridines and arecoline analogs.

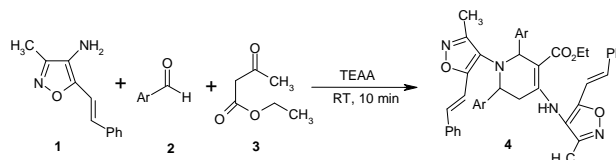
inhibitory [18], antitubercular [19], anticonvulsant [20], and anticancer agents [21]. In continuation of our studies on the synthesis of biologically important heterocyclic compounds [22-26], in the present work we have designed the synthesis of a novel tetrahydropyridine derivatives incorporated with isoxazole moiety utilizing an eco-friendly, reusable and inexpensive ionic liquid as solvent as well as a catalyst.

## 2. Results and Discussion

Literature search on the synthesis of tetrahydropyridines provide only few previous reports which utilizes the primary amine, aromatic aldehydes and  $\beta$ -diketones [27-34] for their synthesis. Therefore, we have further investigated this molecule of interest using greener approach and in search of better alternative over reported methods. Triethyl ammonium acetate (TEAA) ionic liquid (IL) has been found to be effective in aza/thia Michael reactions [35]. We report for the first time eco-friendly method for the synthesis of bis-isoxazolyl-1,2,5,6-tetrahydro pyridine-3-carboxylates by using cost effective TEAA ionic liquid (**Scheme 1**). To optimize the reaction condition, initial studies were conducted on the reaction of the isoxazole amine **1**, aromatic aldehyde **2** and  $\beta$ -ketone ester **3** as a model reaction in the presence of different catalysts and solvents. The reaction afforded bis-isoxazolyl-1,2,5,6-tetrahydro pyridine-3-carboxylates **4** in 30% - 75% yields at 60°C (**Table 1**).

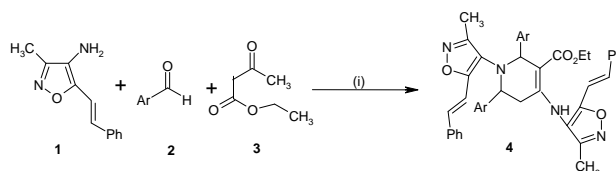
We further explored the reaction in the presence of TEAA ionic liquid. We started the five component reaction by examining the effect of TEAA ionic liquid on yield and time of the typical reaction of isoxazole amine **1**, aromatic aldehyde **2** and  $\beta$ -ketone ester **3** at room temperature. To our surprise, the use of TEAA ionic liquid decreased reaction time, temperature and resulted in improved yields. We also carried out the reaction in the presence of different ILs at room temperature. The results are summarized in **Table 2**. Among the ILs examined TEAA proved to be the most effective in terms of yields, reaction time, and more recyclability. Utilization of other ILs was found to be quite unsatisfactory.

Having established that, the best solvent and catalyst is TEAA for this transformation, the another advantage is,



Scheme 1. Synthesis of bis-isoxazolyl-1,2,5,6-tetrahydro pyridine-3-carboxylates by using TEAA IL.

Table 1. Effect of various catalysts and solvents on the synthesis of bis-isoxazolyl-1,2,5,6-tetrahydro pyridine-3-carboxylates.<sup>a</sup>



Entry	Catalyst (10 mol%)	Solvent	Time (min)	Yield <sup>b</sup> (%)
1	CAN	THF	30	75
2	Silica gel	EtOH	50	60
3	I <sub>2</sub>	CH <sub>3</sub> CN	46	50
4	InCl <sub>3</sub>	CH <sub>3</sub> CN	80	42
5	L-proline + TFA	CH <sub>3</sub> CN	74	45
6	<i>p</i> TSA	DMSO	55	48
7	ZnCl <sub>2</sub>	EtOH	45	30

<sup>a</sup>Reaction conditions: (i) isoxazole amine **1** (2 mmol), aldehyde **2** (2 mmol), EAA **3** (1 mmol) and catalyst 10 mol% in solvent (10 mL), 60°C. <sup>b</sup>Isolated yields.

Table 2. Optimization of reaction condition by using different ILs.<sup>a</sup>

Entry	IL	Time (min)	Yield <sup>b</sup> (%)
1	TEAA	10	98
2	[bmIm]BF <sub>4</sub>	20	45
3	[bmIm]OH	45	20
4	[bmIm]Br	35	15
5	[HMIIm]BF <sub>4</sub>	60	65

<sup>a</sup>Reaction conditions: isoxazole amine **1** (2 mmol), aldehyde **2** (2 mmol), EAA **3** (1 mmol) and IL (5 mL), RT. <sup>b</sup>Isolated yields.

it can be easily recovered after the completion of the reaction and can be reused in subsequent runs (five runs) without loss of efficiency and with negligible loss of IL (**Table 3**). The products were easily separated by simple extraction with ether and characterized by IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and mass spectroscopy and also by analytical data.

To investigate the scope of TEAA IL under the optimized reaction conditions, a number of bis-isoxazolyl-1,2,5,6-tetrahydro pyridine-3-carboxylate derivatives were synthesized and the results are summarized in **Table 4**. In all the cases, the products were obtained in excellent yields. The great advantages of the present procedure using TEAA in the synthesis of bis-isoxazolyl-1,2,5,6-tetrahydro pyridine-3-carboxylates are the mild conditions, high yields, short reaction times, simple experimental set-up and workup. Besides this, it is equally efficient and is compatible with different functional groups (electron releasing and electron attracting groups) and the approach proved to be of general applicability.

The plausible mechanism for the synthesis of bis-isoxazolyl-1,2,5,6-tetrahydro pyridine-3-carboxylates involves the formation of imine (**5**) and enamine (**6**) initially in the presence of IL. Then the enamine makes a nucleophilic attack on to imine, to form a Mannich type intermediate (**7**). This Mannich type intermediate (**7**) reacts with aldehyde to form (**8**) with the elimination of water molecule with the influence of IL. **8** undergoes spontaneous tautomerization and converts into (**9**). The tautomer (**9**) undergoes intramolecular Mannich type reaction to form intermediate (**10**), which tautomerises spontaneously to form bis-isoxazolyl-1,2,5,6-tetrahydro pyridine-3-carboxylate (**4**) (**Scheme 2**).

### 3. Conclusions

In conclusion, the present procedure that uses ammonium ionic liquid TEAA provides a fast and highly efficient methodology for the synthesis of bis-isoxazolyl-1,2,5,6-tetrahydro pyridine-3-carboxylates. The significant improvements noticed in this reaction are high yields, reduction in reaction time and avoids the usage of hazardous organic solvents. These reactions were clean, and

no by-products were detected under these conditions. To the best of our knowledge, this happens to be the first report for the construction of tetrahydropyridine ring by using isoxazole amine, aldehyde and EAA with TEAA ionic liquid, in which ionic liquid playing the dual role of solvent as well as catalyst. Moreover, this work clearly demonstrates that the potential of room temperature ionic liquid TEAA, to act as an efficient and recyclable catalyst, green solvent and shows much promise for future applications.

The authors are thankful to the Head, Department of Chemistry, Kakatiya University, Warangal for providing the facilities, the Director, Indian Institute of Chemical Technology, Hyderabad for recording  $^1\text{H}$  NMR, and Mass Spectral data. B. Kishore is thankful to UGC, New Delhi, for the award of a fellowship (JRF).

## 4. Experimental Part

All the melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Analytical TLC was performed on Merck precoated 60 F<sub>254</sub> silica gel plates. Visualization was done by exposure to iodine vapor. IR spectra (KBr pellet) were recorded on a Perkin Elmer BX series FT-IR spectrometer.  $^1\text{H}$  NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer.  $^{13}\text{C}$  NMR spectra were recorded on a Bruker 75 MHz spectrometer. Chemical shift values are given in ppm ( $\delta$ ) with tetramethyl silane as an internal standard. Mass spectral measurements were carried out by EI method on a Jeol JMC-300 spectrometer at 70 eV. Elemental analyses were performed on a Carlo Erba 106 and Perkin Elmer model 240 analyzers.

The IL TEAA was prepared according to the reported procedure [36-38].

### 4.1. Green Chemistry Approach of Fast and Highly Efficient One-Pot Synthesis of Bis-isoxazolyl-1,2,5,6-Tetrahydro Pyridine-3-Carboxylates; Typical Procedure

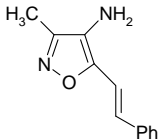
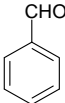
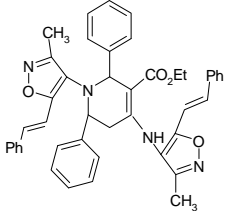
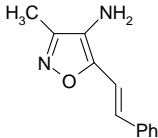
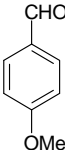
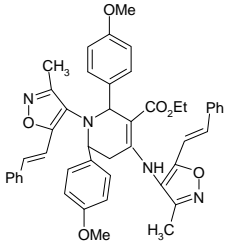
4-Amino-3-methyl-5-styrylisoxazole **1** (1 mmol), benzaldehyde **2a** (1 mmol), and ethyl aceto acetate **3** (0.5 mmol) were taken in IL TEAA (5 mL), and then reaction mixture was stirred at room temperature for 10 min. After the completion of the reaction (monitored by TLC), the reaction mixture was extracted with diethyl ether. The combined layers was separated and dried over anhyd.  $\text{Na}_2\text{SO}_4$ , and evaporated under reduced pressure to afford the crude product **4a**. The ionic liquid left over in the reaction was washed with ethyl acetate and dried at  $80^\circ\text{C}$  under vacuum and was reused for 5 consecutive runs. This procedure was followed for all the reactions listed in the **Table 4**.

**Table 3. Recycling of IL TEAA.**

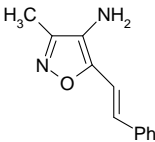
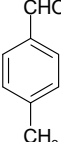
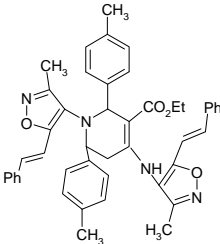
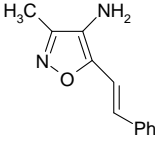
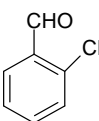
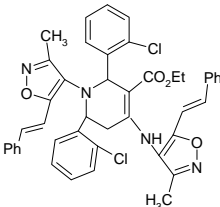
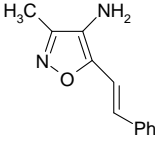
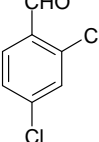
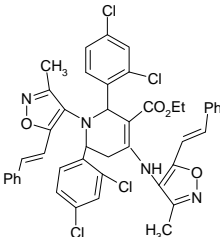
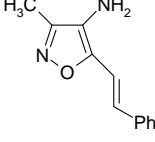
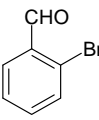
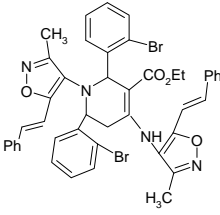
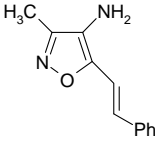
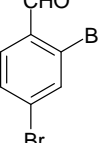
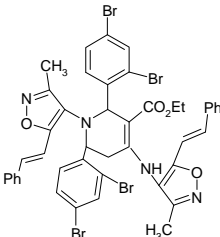
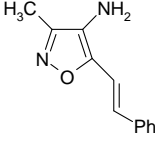
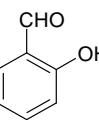
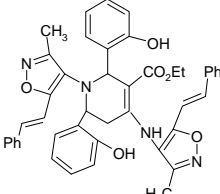
Run	IL recycled (in mL)	Yield <sup>a</sup> (%)
1	5	97
2	5	97
3	4.8	95
4	4.6	94
5	4.2	93

<sup>a</sup>Isolated yields.

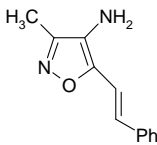
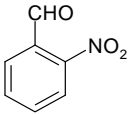
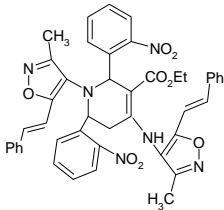
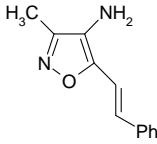
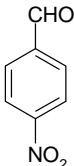
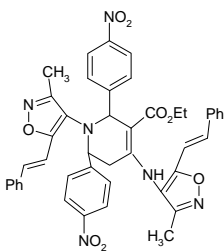
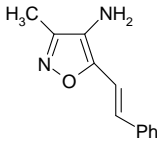
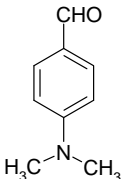
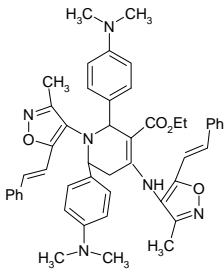
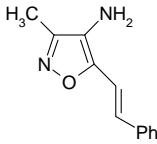
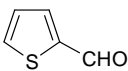
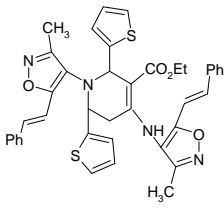
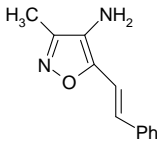
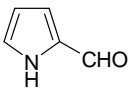
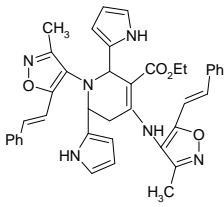
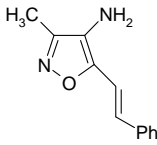
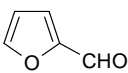
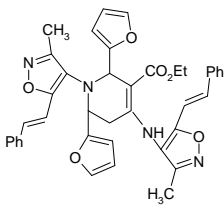
Table 4. Synthesis of bis-isoxazolyl-1,2,5,6-tetrahydro pyridine-3-carboxylates by using TEAA IL.<sup>a</sup>

Entry	Isoxazole amine <b>1</b>	Aldehyde <b>2</b>	Product <b>4</b>	Time (min)	Yield <sup>b</sup> <b>4</b> (%)
1				10	<b>4a</b> (96)
2				8	<b>4b</b> (98)

## Continued

3	 <b>1</b>	 <b>2c</b>	 <b>4c</b>	9	<b>4c (95)</b>
4	 <b>1</b>	 <b>2d</b>	 <b>4d</b>	10	<b>4d (96)</b>
5	 <b>1</b>	 <b>2e</b>	 <b>4e</b>	9	<b>4e (94)</b>
6	 <b>1</b>	 <b>2f</b>	 <b>4f</b>	10	<b>4f (94)</b>
7	 <b>1</b>	 <b>2g</b>	 <b>4g</b>	10	<b>4g (97)</b>
8	 <b>1</b>	 <b>2h</b>	 <b>4h</b>	9	<b>4h (96)</b>

## Continued

9	 <p><b>1</b></p>	 <p><b>2i</b></p>	 <p><b>4i</b></p>	10	<b>4i</b> (96)
10	 <p><b>1</b></p>	 <p><b>2j</b></p>	 <p><b>4j</b></p>	8	<b>4j</b> (95)
11	 <p><b>1</b></p>	 <p><b>2k</b></p>	 <p><b>4k</b></p>	10	<b>4k</b> (98)
12	 <p><b>1</b></p>	 <p><b>2l</b></p>	 <p><b>4l</b></p>	8	<b>4l</b> (98)
13	 <p><b>1</b></p>	 <p><b>2m</b></p>	 <p><b>4m</b></p>	8	<b>4m</b> (96)
14	 <p><b>1</b></p>	 <p><b>2n</b></p>	 <p><b>4n</b></p>	9	<b>4n</b> (96)

<sup>a</sup>Reaction conditions: isoxazole amine **1** (2 mmol), aldehyde **2** (2 mmol), EAA **3** (1 mmol) and TEAA IL (5 mL), RT stirring. <sup>b</sup>Isolated yields.

## 4.2. Spectral Data of Compounds (4a-n)

*Ethyl 4-(3-methyl-5-styrylisoxazol-4-ylamino)-1,2,5,6-tetrahydro-1-(3-methyl-5-styrylisoxazol-4-yl)-2,6-diphenylpyridine-3-carboxylate (4a)*

Brown solid; mp 221°C - 223°C. IR (KBr): 1665, 3428  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.32 (t, 3 H,  $J$  = 7.2 Hz,  $\text{OCH}_2\text{CH}_3$ ), 2.23 (s, 6 H, 2isoxazole- $\text{CH}_3$ ), 2.62 (dd, 1 H, CH,  $J$  = 15.2, 2.4 Hz), 2.76 (dd, 1 H, CH,  $J$  = 15.2, 5.7 Hz), 4.10 (q, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 5.23 (s, 1H, Ar-CH), 6.09 (t, 1 H, Ar-CH), 6.68 (d, 1 H, CH = CH,  $J$  = 12 Hz), 6.83 (d, 1 H, CH = CH,  $J$  = 12 Hz), 6.98 - 7.91 (m, 20 H, ArH), 8.93 (s, 1 H, NH,  $\text{D}_2\text{O}$  exchangeable).  $^{13}\text{C}$  NMR (75MHz,  $\text{DMSO}-d_6$ ):  $\delta$  = 10.31, 12.36, 32.42, 48.46, 54.16, 63.45, 101.42, 104.26, 123.42, 126.13, 127.32, 128.06, 128.68, 129.21, 134.61, 136.52, 139.11, 141.46, 151.34, 158.56. MS (ESI):  $m/z$  = 689.36  $[\text{M}+\text{H}]^+$ . Anal. Calcd for  $\text{C}_{44}\text{H}_{40}\text{N}_4\text{O}_4$ : C, 76.72; H, 5.85; N, 8.13. Found. C, 76.68; H, 5.81; N, 8.19.

*Ethyl 4-(3-methyl-5-styrylisoxazol-4-ylamino)-1,2,5,6-tetrahydro-2,6-bis(4-methoxyphenyl)-1-(3-methyl-5-styrylisoxazol-4-yl)pyridine-3-carboxylate (4b)*

Yellow solid; mp 215°C - 217°C. IR (KBr): 1661, 3442  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.26 (t, 3 H,  $J$  = 7.2 Hz,  $\text{OCH}_2\text{CH}_3$ ), 2.30 (s, 6 H, 2isoxazole- $\text{CH}_3$ ), 2.59 (dd, 1 H, CH,  $J$  = 15.2, 2.4 Hz), 2.74 (dd, 1 H, CH,  $J$  = 15.2, 5.7 Hz), 3.62 (s, 6 H, 2  $\text{OCH}_3$ ), 4.08 (q, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 5.24 (s, 1 H, Ar-CH), 6.04 (t, 1 H, Ar-CH), 6.68 (d, 1 H, CH = CH,  $J$  = 12 Hz), 6.72 (d, 1 H, CH = CH,  $J$  = 12 Hz), 7.00 - 7.96 (m, 18 H, ArH), 9.00 (s, 1 H, NH,  $\text{D}_2\text{O}$  exchangeable).  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  = 10.26, 12.41, 32.40, 48.42, 54.28, 63.37, 63.81, 101.36, 104.55, 123.32, 126.41, 128.21, 128.57, 129.17, 134.48, 136.44, 139.23, 141.38, 151.40, 158.32, 159.13. MS (ESI):  $m/z$  = 749.37  $[\text{M}+\text{H}]^+$ . Anal. Calcd for  $\text{C}_{46}\text{H}_{44}\text{N}_4\text{O}_6$ : C, 73.78; H, 5.92; N, 7.48. Found. C, 73.82; H, 5.87; N, 7.41.

*Ethyl 4-(3-methyl-5-styrylisoxazol-4-ylamino)-1,2,5,6-tetrahydro-1-(3-methyl-5-styrylisoxazol-4-yl)-2,6-dipicolylpyridine-3-carboxylate (4c)*

Brown solid; mp 211°C - 213°C. IR (KBr): 1661, 3442  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.09 (t, 3 H,  $J$  = 7.2 Hz,  $\text{OCH}_2\text{CH}_3$ ), 2.25 (s, 6H, 2isoxazole- $\text{CH}_3$ ), 2.46 (s, 6 H, 2 Ar- $\text{CH}_3$ ), 2.50 (dd, 1 H, CH,  $J$  = 15.2, 2.4 Hz), 2.71 (dd, 1 H, CH,  $J$  = 15.2, 5.7 Hz), 4.11 (q, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 5.24 (s, 1 H, Ar-CH), 6.00 (t, 1 H, Ar-CH), 6.61 (d, 1 H, CH = CH,  $J$  = 12 Hz), 6.74 (d, 1 H, CH = CH,  $J$  = 12 Hz), 7.11 - 7.83 (m, 18 H, ArH), 8.90 (s, 1 H, NH,  $\text{D}_2\text{O}$  exchangeable).  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  = 10.21, 12.33, 24.23, 32.26, 48.39, 54.22, 63.40, 101.56, 104.31, 123.40, 126.23, 128.18, 128.52, 129.19, 134.68, 136.50, 138.37, 139.05, 141.42, 151.39, 158.44. MS (ESI):  $m/z$  = 717.17  $[\text{M}+\text{H}]^+$ . Anal. Calcd for  $\text{C}_{46}\text{H}_{44}\text{N}_4\text{O}_4$ : C, 77.07; H, 6.19; N, 7.82. Found. C, 77.12;

H, 6.16; N, 7.80.

*Ethyl 4-(3-methyl-5-styrylisoxazol-4-ylamino)-2, 6-bis(2-chlorophenyl)-1,2,5,6-tetrahydro-1-(3-methyl-5-styrylisoxazol-4-yl)pyridine-3-carboxylate (4d)*

Pale yellow solid; mp 235°C - 237°C. IR (KBr): 1668, 3440  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.12 (t, 3 H,  $J$  = 7.2 Hz,  $\text{OCH}_2\text{CH}_3$ ), 2.22 (s, 6 H, 2isoxazole- $\text{CH}_3$ ), 2.53 (dd, 1 H, CH,  $J$  = 15.2, 2.4 Hz), 2.69 (dd, 1 H, CH,  $J$  = 15.2, 5.7 Hz), 4.07 (q, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 5.20 (s, 1 H, Ar-CH), 5.98 (t, 1 H, Ar-CH), 6.64 (d, 1H, CH = CH,  $J$  = 12 Hz), 6.70 (d, 1 H, CH = CH,  $J$  = 12 Hz), 7.01 - 7.91 (m, 18 H, ArH), 8.83 (s, 1 H, NH,  $\text{D}_2\text{O}$  exchangeable).  $^{13}\text{C}$  NMR (75MHz,  $\text{DMSO}-d_6$ ):  $\delta$  = 10.24, 12.33, 32.41, 48.46, 54.09, 63.31, 101.40, 104.19, 123.39, 126.24, 127.39, 128.61, 129.33, 134.21, 134.59, 136.47, 139.01, 141.39, 151.30, 158.62. MS (ESI):  $m/z$  = 757.29  $[\text{M}+\text{H}]^+$ . Anal. Calcd for  $\text{C}_{44}\text{H}_{38}\text{Cl}_2\text{N}_4\text{O}_4$ : C, 69.75; H, 5.05; N, 7.39. Found. C, 69.81; H, 5.07; N, 7.33.

*Ethyl 4-(3-methyl-5-styrylisoxazol-4-ylamino)-2,6-bis(2,4-dichlorophenyl)-1,2,5,6-tetrahydro-1-(3-methyl-5-styrylisoxazol-4-yl)pyridine-3-carboxylate (4e)*

Pale yellow solid; mp 228°C - 230°C. IR (KBr): 1665, 3438  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.10 (t, 3 H,  $J$  = 7.2 Hz,  $\text{OCH}_2\text{CH}_3$ ), 2.20 (s, 6H, 2isoxazole- $\text{CH}_3$ ), 2.49 (dd, 1 H, CH,  $J$  = 15.2, 2.4 Hz), 2.60 (dd, 1 H, CH,  $J$  = 15.2, 5.7 Hz), 4.12 (q, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 5.11 (s, 1 H, Ar-CH), 5.86 (t, 1 H, Ar-CH), 6.60 (d, 1 H, CH = CH,  $J$  = 12 Hz), 6.73 (d, 1H, CH = CH,  $J$  = 12 Hz), 6.98 - 7.87 (m, 16 H, ArH), 9.10 (s, 1H, NH,  $\text{D}_2\text{O}$  exchangeable).  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  = 11.09, 12.41, 32.38, 48.67, 54.03, 63.29, 101.38, 104.20, 123.57, 126.26, 128.55, 129.36, 134.38, 134.56, 134.78, 136.42, 139.35, 141.51, 151.29, 158.58. MS (ESI):  $m/z$  = 825.40  $[\text{M}+\text{H}]^+$ . Anal. Calcd for  $\text{C}_{44}\text{H}_{36}\text{Cl}_4\text{N}_4\text{O}_4$ : C, 63.93; H, 4.39; N, 6.78. Found. C, 63.97; H, 4.33; N, 6.74.

*Ethyl 4-(3-methyl-5-styrylisoxazol-4-ylamino)-2,6-bis(2-bromophenyl)-1,2,5,6-tetrahydro-1-(3-methyl-5-styrylisoxazol-4-yl)pyridine-3-carboxylate (4f)*

Pale brown solid; mp 224°C - 226°C. IR (KBr): 1670, 3441  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.09 (t, 3 H,  $J$  = 7.2 Hz,  $\text{OCH}_2\text{CH}_3$ ), 2.28 (s, 6 H, 2isoxazole- $\text{CH}_3$ ), 2.41 (dd, 1 H, CH,  $J$  = 15.2, 2.4 Hz), 2.63 (dd, 1 H, CH,  $J$  = 15.2, 5.7 Hz), 4.10 (q, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 5.25 (s, 1 H, Ar-CH), 5.78 (t, 1H, Ar-CH), 6.61 (d, 1 H, CH = CH,  $J$  = 12 Hz), 6.69 (d, 1 H, CH = CH,  $J$  = 12 Hz), 7.05 - 7.93 (m, 18 H, ArH), 9.08 (s, 1 H, NH,  $\text{D}_2\text{O}$  exchangeable).  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  = 10.16, 12.27, 32.53, 48.42, 54.17, 63.42, 101.33, 104.24, 123.48, 126.15, 127.46, 128.58, 129.45, 134.32, 134.68, 136.51, 139.12, 141.26, 151.44, 158.78. MS (ESI):  $m/z$  = 845.11  $[\text{M}+\text{H}]^+$ . Anal. Calcd for  $\text{C}_{44}\text{H}_{38}\text{Br}_2\text{N}_4\text{O}_4$ : C, 62.42; H, 4.52; N, 6.62. Found. C, 62.38; H, 4.51; N, 6.65.

*Ethyl 4-(3-methyl-5-styrylisoxazol-4-ylamino)-2,6-bis(2,4-dibromophenyl)-1,2,5,6-tetrahydro-1-(3-methyl-5-*

*styrylisoxazol-4-yl)pyridine-3-carboxylate (4g)*

Brown solid; mp 241°C - 243°C. IR (KBr): 1668, 3442  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.12 (t, 3 H,  $J$  = 7.2 Hz,  $\text{OCH}_2\text{CH}_3$ ), 2.24 (s, 6 H, 2isoxazole- $\text{CH}_3$ ), 2.48 (dd, 1 H, CH,  $J$  = 15.2, 2.4 Hz), 2.59 (dd, 1 H, CH,  $J$  = 15.2, 5.7 Hz), 4.20 (q, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 5.19 (s, 1 H, Ar-CH), 5.64 (t, 1 H, Ar-CH), 6.57 (d, 1 H, CH = CH,  $J$  = 12 Hz), 6.70 (d, 1 H, CH = CH,  $J$  = 12 Hz), 7.00 - 7.87 (m, 16 H, ArH), 8.87 (s, 1 H, NH,  $\text{D}_2\text{O}$  exchangeable).  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  = 10.14, 12.27, 24.38, 32.39, 48.25, 54.20, 63.43, 101.51, 104.44, 123.57, 126.34, 128.11, 128.39, 129.10, 134.56, 136.41, 138.28, 139.22, 141.35, 151.46, 158.61. MS (ESI):  $m/z$  = 1001.08  $[\text{M}+\text{H}]^+$ . Anal. Calcd for  $\text{C}_{44}\text{H}_{36}\text{Br}_4\text{N}_4\text{O}_4$ : C, 52.62; H, 3.61; N, 5.58. Found. C, 52.65; H, 3.68; N, 5.55.

*Ethyl 4-(3-methyl-5-styrylisoxazol-4-ylamino)-1,2,5,6-tetrahydro-2,6-bis(2-hydroxyphenyl)-1-(3-methyl-5-styrylisoxazol-4-yl)pyridine-3-carboxylate (4h)*

Brown solid; mp 203°C - 205°C. IR (KBr): 1657, 3445  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.09 (t, 3 H,  $J$  = 7.2 Hz,  $\text{OCH}_2\text{CH}_3$ ), 2.30 (s, 6 H, 2isoxazole- $\text{CH}_3$ ), 2.41 (dd, 1 H, CH,  $J$  = 15.2, 2.4 Hz), 2.60 (dd, 1 H, CH,  $J$  = 15.2, 5.7 Hz), 4.11 (q, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 5.18 (s, 1 H, Ar-CH), 5.52 (t, 1 H, Ar-CH), 6.62 (d, 1 H, CH = CH,  $J$  = 12 Hz), 6.71 (d, 1 H, CH = CH,  $J$  = 12 Hz), 7.04 - 7.93 (m, 18 H, ArH), 8.64 (s, 1 H, NH,  $\text{D}_2\text{O}$  exchangeable), 9.10 (s, 2 H, 2OH,  $\text{D}_2\text{O}$  exchangeable).  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  = 10.25, 12.31, 32.48, 48.36, 54.23, 63.56, 101.40, 104.38, 123.59, 126.11, 127.52, 128.47, 129.36, 134.41, 134.69, 136.72, 139.24, 141.31, 151.40, 158.55. MS (ESI):  $m/z$  = 721.37  $[\text{M}+\text{H}]^+$ . Anal. Calcd for  $\text{C}_{44}\text{H}_{40}\text{N}_4\text{O}_6$ : C, 73.32; H, 5.59; N, 7.77. Found. C, 73.37; H, 5.54; N, 7.71.

*Ethyl 4-(3-methyl-5-styrylisoxazol-4-ylamino)-1,2,5,6-tetrahydro-1-(3-methyl-5-styrylisoxazol-4-yl)-2,6-bis(2-nitrophenyl)pyridine-3-carboxylate (4i)*

Brown solid; mp 230°C - 232°C. IR (KBr): 1667, 3448  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.00 (t, 3 H,  $J$  = 7.2 Hz,  $\text{OCH}_2\text{CH}_3$ ), 2.30 (s, 6 H, 2isoxazole- $\text{CH}_3$ ), 2.40 (dd, 1 H, CH,  $J$  = 15.2, 2.4 Hz), 2.59 (dd, 1 H, CH,  $J$  = 15.2, 5.7 Hz), 4.21 (q, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 5.19 (s, 1 H, Ar-CH), 5.63 (t, 1 H, Ar-CH), 6.58 (d, 1 H, CH = CH,  $J$  = 12 Hz), 6.61 (d, 1 H, CH = CH,  $J$  = 12 Hz), 7.00 - 7.85 (m, 18 H, ArH), 8.85 (s, 1 H, NH,  $\text{D}_2\text{O}$  exchangeable).  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  = 10.27, 12.46, 32.53, 48.55, 54.23, 63.38, 101.57, 104.36, 123.55, 126.24, 127.41, 128.55, 129.31, 134.56, 136.67, 139.26, 141.54, 148.53, 151.20, 158.51. MS (ESI):  $m/z$  = 781.26  $[\text{M}+\text{H}]^+$ . Anal. Calcd for  $\text{C}_{44}\text{H}_{40}\text{N}_6\text{O}_8$ : C, 67.68; H, 5.16; N, 10.76. Found. C, 67.75; H, 5.19; N, 10.74.

*Ethyl 4-(3-methyl-5-styrylisoxazol-4-ylamino)-1,2,5,6-tetrahydro-1-(3-methyl-5-styrylisoxazol-4-yl)-2,6-bis(4-nitrophenyl)pyridine-3-carboxylate (4j)*

Pale brown solid; mp 237°C - 239°C. IR (KBr): 1655,

3438  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.05 (t, 3 H,  $J$  = 7.2 Hz,  $\text{OCH}_2\text{CH}_3$ ), 2.26 (s, 6 H, 2isoxazole- $\text{CH}_3$ ), 2.42 (dd, 1 H, CH,  $J$  = 15.2, 2.4 Hz), 2.51 (dd, 1 H, CH,  $J$  = 15.2, 5.7 Hz), 4.19 (q, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 5.25 (s, 1 H, Ar-CH), 5.59 (t, 1 H, Ar-CH), 6.60 (d, 1 H, CH = CH,  $J$  = 12 Hz), 6.73 (d, 1 H, CH = CH,  $J$  = 12 Hz), 6.97 - 7.85 (m, 18 H, ArH), 8.51 (s, 1 H, NH,  $\text{D}_2\text{O}$  exchangeable).  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  = 10.22, 12.41, 32.58, 48.63, 54.25, 63.32, 101.48, 104.40, 123.57, 126.26, 128.11, 128.71, 129.32, 134.54, 136.62, 139.26, 141.56, 148.52, 151.49, 158.60. MS (ESI):  $m/z$  = 781.05  $[\text{M}+\text{H}]^+$ . Anal. Calcd for  $\text{C}_{44}\text{H}_{40}\text{N}_6\text{O}_8$ : C, 67.68; H, 5.16; N, 10.76. Found. C, 67.70; H, 5.15; N, 10.77.

*Ethyl 4-(3-methyl-5-styrylisoxazol-4-ylamino)-2,6-bis(4-(dimethylamino)phenyl)-1,2,5,6-tetrahydro-1-(3-methyl-5-styrylisoxazol-4-yl)pyridine-3-carboxylate (4k)*

Orange solid; mp 219°C - 221°C. IR (KBr): 1660, 3441  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.10 (t, 3 H,  $J$  = 7.2 Hz,  $\text{OCH}_2\text{CH}_3$ ), 2.28 (s, 6 H, 2isoxazole- $\text{CH}_3$ ), 2.42 (dd, 1 H, CH,  $J$  = 15.2, 2.4 Hz), 2.53 (dd, 1 H, CH,  $J$  = 15.2, 5.7 Hz), 3.85 (s, 12 H, 2  $\text{N}(\text{CH}_3)_2$ ), 4.22 (q, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 5.27 (s, 1 H, Ar-CH), 6.00 (t, 1 H, Ar-CH), 6.63 (d, 1 H, CH = CH,  $J$  = 12 Hz), 6.71 (d, 1 H, CH = CH,  $J$  = 12 Hz), 7.02 - 7.97 (m, 18 H, ArH), 8.50 (s, 1 H, NH,  $\text{D}_2\text{O}$  exchangeable).  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  = 10.23, 12.43, 32.37, 40.55, 48.51, 54.23, 63.38, 101.40, 104.32, 123.41, 126.26, 128.18, 128.54, 129.36, 134.58, 136.62, 139.21, 141.52, 149.71, 151.43, 158.67. MS (ESI):  $m/z$  = 775.11  $[\text{M} + \text{H}]^+$ . Anal. Calcd for  $\text{C}_{48}\text{H}_{50}\text{N}_6\text{O}_4$ : C, 74.39; H, 6.50; N, 10.84. Found. C, 74.35; H, 6.51; N, 10.87.

*Ethyl 4-(3-methyl-5-styrylisoxazol-4-ylamino)-1,2,5,6-tetrahydro-1-(3-methyl-5-styrylisoxazol-4-yl)-2,6-di(thiophen-2-yl)pyridine-3-carboxylate (4l)*

Brown solid; mp 223°C - 225°C. IR (KBr): 1658, 3436  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.08 (t, 3 H,  $J$  = 7.2 Hz,  $\text{OCH}_2\text{CH}_3$ ), 2.20 (s, 6 H, 2isoxazole- $\text{CH}_3$ ), 2.45 (dd, 1 H, CH,  $J$  = 15.2, 2.4 Hz), 2.59 (dd, 1 H, CH,  $J$  = 15.2, 5.7 Hz), 4.08 (q, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 5.21 (s, 1 H, Ar-CH), 6.10 (t, 1 H, Ar-CH), 6.61 (d, 1 H, CH = CH,  $J$  = 12 Hz), 6.73 (d, 1 H, CH = CH,  $J$  = 12 Hz), 6.81 (dd, 2 H, 2thiophene-H), 7.23 (d, 2 H, 2thiophene-H), 7.31 (d, 2 H, 2thiophene-H), 7.52 - 7.97 (m, 10 H, ArH), 9.25 (s, 1 H, NH,  $\text{D}_2\text{O}$  exchangeable).  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  = 10.12, 12.22, 32.39, 48.40, 54.16, 63.55, 101.51, 104.23, 123.18, 123.50, 126.22, 126.86, 127.10, 129.31, 134.57, 136.43, 140.12, 141.61, 151.24, 158.50. MS (ESI):  $m/z$  = 701.33  $[\text{M}+\text{H}]^+$ . Anal. Calcd for  $\text{C}_{40}\text{H}_{36}\text{N}_4\text{O}_4\text{S}_2$ : C, 68.55; H, 5.18; N, 7.99. Found. C, 68.57; H, 5.13; N, 7.96.

*Ethyl 4-(3-methyl-5-styrylisoxazol-4-ylamino)-1,2,5,6-tetrahydro-1-(3-methyl-5-styrylisoxazol-4-yl)-2,6-di(1H-pyrrol-2-yl)pyridine-3-carboxylate (4m)*

Brown solid; mp 227°C - 229°C. IR (KBr): 1660, 3445



$\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.16 (t, 3 H,  $J$  = 7.2 Hz,  $\text{OCH}_2\text{CH}_3$ ), 2.30 (s, 6 H, 2isoxazole- $\text{CH}_3$ ), 2.48 (dd, 1 H, CH,  $J$  = 15.2, 2.4 Hz), 2.61 (dd, 1 H, CH,  $J$  = 15.2, 5.7 Hz), 4.11 (q, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 5.31 (s, 1 H, Ar-CH), 6.20 (t, 1 H, Ar-CH), 6.57 (d, 1 H, CH = CH,  $J$  = 12 Hz), 6.68 (d, 1 H, CH = CH,  $J$  = 12 Hz), 6.73 (dd, 2 H, 2pyrrole-H), 7.21 (d, 2 H, 2pyrrole-H), 7.30 (d, 2 H, 2pyrrole-H), 7.52 - 8.00 (m, 10H, ArH), 8.72 (s, 2 H, 2pyrrole-NH,  $\text{D}_2\text{O}$  exchangeable), 9.00 (s, 1 H, NH,  $\text{D}_2\text{O}$  exchangeable).  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  = 10.33, 12.30, 32.47, 48.50, 54.12, 63.42, 101.55, 104.32, 108.96, 109.11, 118.86, 123.57, 126.24, 129.32, 131.12, 134.58, 136.50, 141.40, 151.43, 158.66. MS (ESI):  $m/z$  = 667.10  $[\text{M}+\text{H}]^+$ . Anal. Calcd for  $\text{C}_{40}\text{H}_{38}\text{N}_6\text{O}_4$ : C, 72.05; H, 5.74; N, 12.60. Found. C, 72.11; H, 5.71; N, 12.58.

*Ethyl 4-(3-methyl-5-styrylisoxazol-4-ylamino)-2,6-di(furan-2-yl)-1,2,5,6-tetrahydro-1-(3-methyl-5-styrylisoxazol-4-yl)pyridine-3-carboxylate (4n)*

Pale yellow solid; mp  $209^\circ\text{C}$  -  $211^\circ\text{C}$ . IR (KBr): 1655,  $3432\text{ cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.05 (t, 3 H,  $J$  = 7.2 Hz,  $\text{OCH}_2\text{CH}_3$ ), 2.22 (s, 6 H, 2isoxazole- $\text{CH}_3$ ), 2.41 (dd, 1 H, CH,  $J$  = 15.2, 2.4 Hz), 2.59 (dd, 1 H, CH,  $J$  = 15.2, 5.7 Hz), 4.20 (q, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 5.26 (s, 1 H, Ar-CH), 6.18 (t, 1 H, Ar-CH), 6.60 (d, 1 H, CH = CH,  $J$  = 12 Hz), 6.74 (d, 1 H, CH = CH,  $J$  = 12 Hz), 6.69 (dd, 1 H, furan-H), 7.24 (d, 1 H, furan-H), 7.42 (d, 1 H, furan-H), 7.50 - 7.9 (m, 10 H, ArH), 8.92 (s, 1 H, NH,  $\text{D}_2\text{O}$  exchangeable).  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  = 10.26, 12.22, 32.34, 48.41, 54.10, 63.43, 101.41, 104.26, 106.77, 116.56, 123.39, 126.09, 129.22, 134.67, 136.55, 141.40, 142.10, 151.33, 152.62, 158.52. MS (ESI):  $m/z$  = 669.46  $[\text{M}+\text{H}]^+$ . Anal. Calcd for  $\text{C}_{40}\text{H}_{36}\text{N}_4\text{O}_6$ : C, 71.84; H, 5.43; N, 8.38. Found. C, 71.88; H, 5.41; N, 8.32.

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