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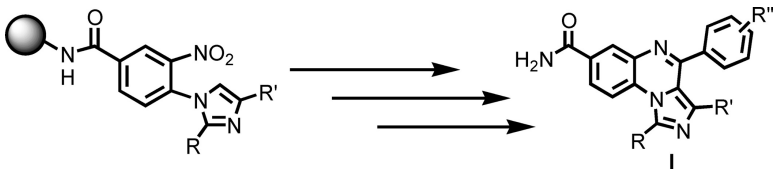

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A Modified Strategy for Pictet−Spengler Reaction Leading to the Synthesis of Imidazoquinoxalines on Solid Phase

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An alternative strategy for Pictet−Spengler reaction involving an N-1 linked aromatic amine of imidazole and aldehydes is described. This is in contrast to a typical Pictet−Spengler reaction, which involves an aliphatic amine attached to the carbon of an activated aromatic nucleus and an aldehyde. Our strategy commences with the nucleophilic replacement of fluorine in resin-bound *o*-fluoro-nitrobenzoic acid with mono- or disubstituted imidazole, followed by reduction of the nitro group to give an N1 linked aromatic amine of the resin-bound imidazole. This was subsequently treated with an aldehyde in toluene at 80 °C and then oxidized in the presence of DDQ to give resin-bound imidazoquinoxalines. Finally, acidolytic cleavage furnished the desired compounds in high yields and purities.

Introduction

The formation of C−C bonds is an important process in synthetic organic chemistry. Among the variety of methods reported for its formation, the Pictet−Spengler reaction[1] is one reaction that has been extensively utilized for synthetic purposes for the last ∼100 years. It involves the acid-catalyzed condensation of an aldehyde with an aliphatic amine attached to a sufficiently reactive aromatic nucleus to form imine, which is often activated by Bronsted acids. Final, endo cyclization between a carbon nucleophile of a sufficiently reactive aromatic moiety and the activated iminium ion results in a new C−C bond, forming a *N*-heterocyclic ring (Figure 1). However, despite being an attractive strategy, its use has been limited only to Trp or tryptamine (**A**)/His or histamines (**B**), and dopamine/tyramine (**C**) as amine substrates (Figure 1), thereby invariably resulting in the formation of heterocycles based on either tetrahydro-β-carboline (THBC)/tetrahydroimidazopyridines (THIP) or tetrahydroisoquinolines (THIQ).[2]

To date, although a variety of methods have been reported[3] for carrying out the Pictet−Spengler reaction, the strategy in all cases has remained unchanged, as described in Figure 1. Even on solid phase, which provides new routes for heterocycles, the use of the Pictet−Spengler reaction has been restricted to the generation of only THBC, THIP, and THIQ ring systems.[4] In general, three different solid-phase versions of Pictet−Spengler reaction have been pursued: (i) one in which the amine and the C nucleophile are attached to the solid-support, (ii) one in which the aldehyde is attached to the solid support, and finally, (iii) one in which all the three components are attached to the solid support.

Results and Discussion

As opposed to the general precedent in the field of Pictet−Spengler reaction (Figure 1), our research has been focused on the use of aromatic amines instead of aliphatic amines along with the change in the position of the amine functionality in the reactive aromatic nucleus (Figure 2). In the first instance, we proposed to derivatize the N1 of a suitably substituted imidazole derivative (an activated aromatic nucleus) with an aromatic amine to get **D** (Figure 2). An analogy between the imidazole derivative **D** and histamine (**B**) can be drawn from the fact that whereas in the former, an aromatic amine functionality is present at a distance of two carbons from N1, in the latter, an aliphatic amine is present at a distance of two carbons from the C-4 (**B**; Figure 1). Furthermore, in both the substrates, the C-5 that is involved in C−C bond formation is adjacent to the N1 on one side and C-4 on the other side, which is considered to be a prerequisite for Pictet−Spengler reaction. It is also worth mentioning that the Schiff's base of aromatic amines will be more electrophilic in nature than Schiff's base of aliphatic amines, which in turn will facilitate C−C bond formation for aromatic amines.[5] Finally, it is pertinent that such a strategy, which is different from the traditional route, will lead to the synthesis of a six-membered heterosystem with two nitrogens called imidazoquinoxaline instead of THIP (a six-membered heterosystem with one nitrogen), usually

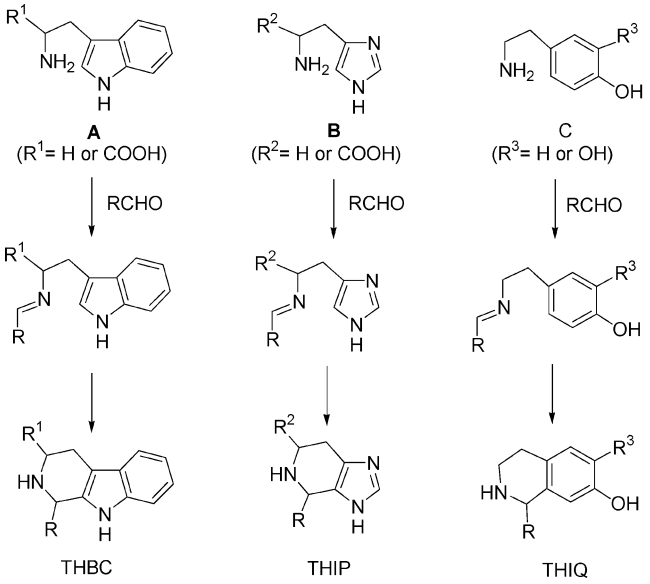

Figure 1. A typical Pictet−Spengler reaction leading to the formations of THBC, THIP, and THIQ.

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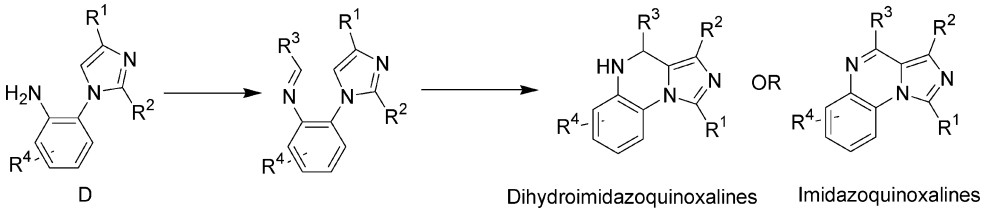
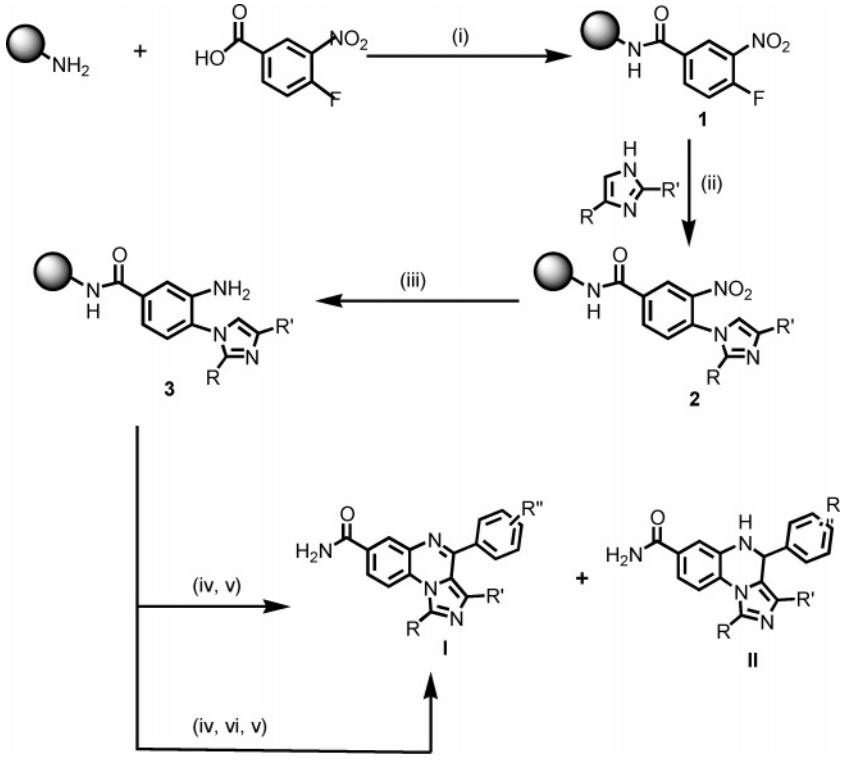


Figure 2. A modified strategy for Pictet−Spengler reaction involving an aromatic amine linked to the N1 of the imidazole.

Scheme 1



Reaction conditions: (i) DIC (3 equiv), HOBt (3 equiv), DMF, o/n; (ii) K_2CO_3 in DMF, 60 °C, 16 h; (iii) 1 M $SnCl_2 \cdot 2H_2O$, DMF, 5 h; (iv) aldehyde (20 equiv), toluene, 48 h, 80 °C; (v) 50% TFA/DCM, 2 h; (vi) DDQ (2 equiv), THF/DCM, 6 h.

obtained from imidazole-based substrates, such as histamine or His (**B**; Figure 1).

In view of these observations, we examined the utility of derivative **D** as an amine substrate for Pictet−Spengler reaction. Herein, we describe a solid-phase strategy for the application of the Pictet−Spengler reaction involving an aromatic amine linked to the N1 of the imidazole ring and an aldehyde, leading to the formation of imidazoquinoxalines. To the best of our knowledge, this is the first report dealing with an alternate strategy for Pictet−Spengler reaction since its discovery, which in turn leads to the synthesis of a heterosystem other than THBC, THIP, and THIQ. The studies are a continuation of our interest in new solid-phase strategies[6] for the synthesis of *N*-heterocycles of biological interest with high chemical diversity.

The solid-phase strategy for the synthesis of imidazoquinoxalines via the Pictet−Spengler reaction from resin-bound imidazole is outlined in Scheme 1. To generate resin-bound imidazoles, we identified *o*-fluoronitrobenzoic acid as one of the most appropriate building blocks. The three functional groups can be selectively manipulated by using a COOH group as the anchoring group for loading onto the resin; a fluoro group for nucleophilic substitution by the NH of the imidazoles; and finally, a NO_2 group as a precursor for aromatic amines. Thus, our synthesis commenced with the loading of *o*-fluoronitrobenzoic acid onto the Rink amide resin (Novabiochem; loading capacity 0.63 mmol/gm). The completion of the reaction was confirmed by a negative Kaiser test. Next, the fluoro group in resin **1** was replaced by treating it with 4-methyl-2-phenylimidazole in the presence of K_2CO_3 using DMF as solvent at 60 °C to give resin **2**. This was followed by reduction of the resin-bound NO_2 group by treating it with 1 M $SnCl_2 \cdot 2H_2O$ in DMF for 5 h to afford resin **3**. Finally, the Pictet−Spengler reaction was carried out by treating resin **3** with *p*-ethoxybenzaldehyde in EtOH for 24 h at 80 °C. The final product was cleaved from the resin by treating the resin **4** with 50% TFA−DCM. The solvent was evaporated and then freeze-dried after dissolving in ^{t}BuOH−water (4:1). As evident by both HPLC and TLC, the product was found to be a mixture of two components with traces of unreacted amine as the third component. The two spots were separated by column chromatography and characterized by ESMS and NMR. One of the components with a lower R_f on TLC and with a mass of 424.48 Da was found to be 4-(4-ethoxyphenyl)-3-methyl-1-phenyl-4,5-dihydroimidazo[1,5-*a*]quinoxaline-7-carboxylic acid amide (based on **II**; Scheme 1), and the second component with a higher R_f and a mass of 422.49 Da was

Table 1. ESMS, Yields and Purities of Imidazoquinoxalines (**I**)

entry no.	R^1	R^2	R^3	ESMS (M + H)	% yield (crude/isolated[a])	t_R[b] (min)	HPLC purity[c] at 220 nm (%)
I(1)	C_6H_5	CH_3	4-CH_3	393.47	92/72	13.43	95
I(2)	CH_3	H	4-CH_3	317.49	80/50	10.62	80
I(3)	C_6H_5	CH_3	H	379.87	94/73	12.33	95
I(4)	C_6H_5	CH_3	4-OCH_2CH_3	423.67	94/74	13.74	88
I(5)	C_6H_5	CH_3	4-NO_2	424.67	90/70	12.50	87
I(6)	CH_3	H	H	303.42	82/52	8.19	75
I(7)	CH_3	H	4-NO_2	348.53	87/45	10.63	65
I(8)	CH_3	H	4-OCH_2CH_3	349.63	86/57	11.81	67
I(9)	CH_2CH_3	CH_3	4-CH_3	345.67	90/73	11.20	88
I(10)	CH_2CH_3	CH_3	H	331.47	90/72	9.66	80
I(11)	CH_2CH_3	CH_3	4-NO_2	376.60	88/65	8.41	90
I(12)	CH_2CH_3	CH_3	4-OCH_2CH_3	375.73	94/70	13.42	73
I(13)	C_6H_5	CH_3	2-OH	395.59	91/73	10.52	92
I(14)	CH_3	H	2-OH	319.43	85/52	10.44	80
I(15)	CH_2CH_3	CH_3	2-OH	347.50	89/71	8.54	94
I(16)	C_6H_5	CH_3	4-Cl	413.94	90/74	13.94	96
I(17)	CH_3	H	4-Cl	337.89	88/54	11.36	68
I(18)	CH_2CH_3	CH_3	4-Cl	365.97	89/72	12.15	96

[a] Compounds obtained after purification from the silica gel chromatography. [b] Retention time on HPLC(C18 reversed-phase column; 150 × 4.8 mm; 5 μm) with a linear gradient of 0−100% CH_3CN in water over 25 min, flow rate of 1.0 mL/min, and UV detection at 220/254 nm. [c] Purity of crude products obtained after cleavage from the resin.

identified as 4-(4-ethoxyphenyl)-3-methyl-1-phenylimidazo-[1,5-*a*]quinoxaline-7-carboxylic acid amide (based on **I**; Scheme 1), an oxidized product of the first component. Of these two, dihydroimidazoquinoxaline (**II**) had moderate stability, because even after purification, it had a tendency to undergo slow oxidation to imidazoquinoxaline (**I**). Such an oxidation for dihydroimidazoquinoxaline to imine was reported earlier by TenBrink et al.[7] We, therefore, envisioned that by using oxidizing agents in the final step, our synthetic strategy for Pictet−Spengler reaction can be successfully used for the synthesis of imidazoquinoxalines (**I**) in quantitative yields. Interestingly, imidazoquinoxalines are common structural motifs that are found in a variety of biologically important and medicinally useful agents. These molecules range from being antagonists to full agonists on the γ-aminobutyric acid A chloride ion channel complex, without displaying typical benzodiazepin side effects.[8] They also exhibited adenosine A1- and A2a-receptor activity, inhibition of cAMP and cGMP phosphodiestrase, and IgE-mediated passive cutaneous anaphylaxis. Some compounds also exhibited glycine/NMDA receptor antagonists and AMPA receptor antagonists.[9]

In addition, a careful survey of the literature revealed that its synthesis on solid phase has not been reported to date. In solution phase, several groups[7,10] have reported its synthesis; however, none of the methods involved Pictet−Spengler reaction. We, therefore, proceeded with our modified Pictet−Spengler strategy for the selective synthesis of imidazoquinoxalines on solid phase. For this, the resin **3** after Pictet−Spengler reaction was oxidized and treated with DDQ for 5 h at room temperature, followed by acidolytic cleavage to yield imidazoquinoxalines (**I**) as the only product. However, the presence of unreacted amine component in the reaction product prompted us to optimize the conditions for the Pictet−Spengler reaction. Thus, a variety of reaction conditions, such as AcOH/EtOH, PTSA/EtOH, pyridine, and toluene, were applied. Of these, reaction in toluene with a 20-fold excess of aldehydes for 48 h provided the best results in terms of yield and purity. The same strategy was applied to 2-substituted imidazoles, and they, too, provided the desired compounds based on imidazoquinoxalines (**I**), albeit in lower isolated yields than disubstituted imidazoles. This may be attributed to the better reactivity of 2, 4-disubstituted imidazoles in comparison to 2-substituted imidazoles.

Thus, it is clearly evident that our aromatic amine-derived substrate **D** can be an additional substrate in the line of previously known aliphatic amine-derived substrates **A**, **B**, and **C** (Figure 1) that has been used to date for Pictet−Spengler reaction. To demonstrate the generality and utility of our strategy via substrate **D**, we extended our methodology to other aldehydes bearing several type of substituents, for example, 4-nitrobenzaldehyde, 4-ethoxybenzaldehyde, 4-chlorobenzaldehyde, salicylaldehyde, benzaldehyde, and 4-methylaldehyde. The electron-withdrawing and electron-donating substituents on aldehydes had no significant affect on the yield and purity of the final compounds. The crude products obtained after the acidolytic cleavage from the resin were purified on silica gel chromatography using MeOH−$CHCl_3$ as an eluant to furnish imidazoquinoxalines (**I**). The compounds were isolated in good to excellent yields (Table 1), ranging from 50 to 74%. The monosubstituted imidazoles furnished compounds in lower yield in comparison to disubstituted imidazoles. All compounds were characterized using HPLC, ESMS, and ^{1}H NMR.

Conclusions

In summary, we have developed a modified solid-phase strategy for the Pictet−Spengler reaction involving an aromatic amine linked to N1 of imidazole and an aldehyde. This method can be used for the generation of large libraries of imidazoquinoxaline-based compounds using an automated synthesizer. Our strategy also opens up possibilities for the design and synthesis of a variety of aryl/aliphatic amine substrates derived from an activated aromatic nucleus that can be used for the generation of heterosystem using the Pictet−Spengler reaction. Studies are in progress with N-1- and C-4-substituted aryl/aliphatic amines in the imidazoles and N-substituted aryl/aliphatic amines in the indoles as possible amine substrates for the Pictet−Spengler reaction.

Experimental Section

General. Rink amide AM resin (1% divinylbenzene, 100−200 mesh, 0.63 mmol/g substitution), and amino acids were purchased from Novabiochem, Switzerland. *N*-Hydroxybenzotriazole (HOBt) was purchased from Janseen Chemica, Belgium. Aldehydes, *o*-flouronitrobenzoic acid, and imidazoles were purchased from Lancaster and Sigma-Aldrich Chemical Company. Anhydrous solvents were used for reactions. All other reagents were obtained from commercial sources and were used without further purification. The reactions were carried out in polypropylene syringes of 5-mL capacity, which were shaken on an orbital shaker IKA-VIBRAX-VXR. The ^{1}H and ^{13}C NMR spectra were obtained on a 300-MHz spectrometer, and chemical shifts were reported in parts per million (δ) relative to TMS. Because of solubility properties, the solvent used was DMSO-d_6. RP-HPLC analysis of crude products was carried out on an Agilent liquid chromatograph using a 5 μm, 4.8 × 150 mm C-18 reversed-phase column with a linear gradient of 0−100% ACN in water (v/v) over 25 min. The flow rate was 1.0 mL/min, and UV detection was observed at 220/254 nm. Mass spectra were recorded using electron spray ionization (ESI).

General Experimental Procedure for Imidazoquinoxalines. The Fmoc groups of Rink amide AM resin (0.063 mmol; 100 mg) were removed by treating with 25% piperidine in DMF (1 mL) twice for 5 and 25 min. The resin was filtered and washed with DMF (9 × 2 mL). The resin so obtained was coupled with *o*-fluoronitrobenzoic acid (10-fold) by using HOBt (3 equiv), DIC (3 equiv) and DMF (1 mL) as solvent for 16 h at room temperature. The resin was filtered; washed successively with DMF (3 × 2 mL), MeOH (3 × 2 mL), DCM (3 × 2 mL), and ether (3 × 2 mL); and, finally, dried in vacuo. Completion of the reaction was confirmed by a negative Kaiser test. The resin **1** so obtained was next treated with imidazole (10-fold) and K_2CO_3 (10-fold) in DMF at 60 °C for 16 h. The resin was filtered; washed successively with dioxane/water (4:1; 5 × 2 mL), DMF (3 × 2 mL), MeOH (3 × 2 mL), DCM (3 × 2 mL), and ether (3 × 2 mL); and, finally, dried in vacuo. The nitro group of resin **2** was reduced to amine with 1 M $SnCl_2 \cdot 2H_2O$ in DMF (1 mL) for 5 h at room temperature. Thereupon the resin was washed successively with DMF (3 × 2 mL), MeOH (3 × 2 mL), DCM (3 × 2 mL), and ether (3 × 2 mL) and, finally, dried in vacuo to give **3**. It was then treated with aldehydes (20 equiv) in toluene at 80 °C for 48 h. The resin was filtered and washed successively with DMF (3 × 2 mL), MeOH (3 × 2 mL), DCM (3 × 2 mL), and ether (3 × 2 mL) and, finally, dried in vacuo. The resulting resin was treated with DDQ (2 equiv) in THF/DCM (1:1; 1 mL) for 5 h at room temperature and then washed successively with DMF (3 × 2 mL), MeOH (3 × 2 mL), DCM (3 × 2 mL), and ether (3 × 2 mL) and, finally, dried in vacuo. The final compounds were cleaved from the resin using 50% TFA/DCM for 2 h at room temperature. The excess TFA mixture was evaporated, and the residue was freeze-dried after dissolving in ^{t}BuOH/water (4:1). The crude products were purified by column chromatography on silica gel using MeOH−$CHCl_3$ as an eluant to give the desired imidazoquinoxalines.

3-Methyl-1-phenyl-4-*p*-tolylimidazo[1,5-*a*]quinoxaline-7-carboxylic Acid Amide I (1). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ = 8.39 (d, 1H, J = 1.2 Hz, ArH), 8.09 (brs, 1H, NH), 7.72−7.57 [m (o), 8H, ArH], 7.48 (brs, 1H, NH), 7.41 (d, 2H, J = 7.8 Hz, ArH), 7.33 (d, 1H, J = 9.0 Hz, ArH), 2.45 (s, 3H, CH_3), 2.09 (s, 3H, CH_3).

1-Methyl-4-*p*-tolylimidazo[1,5-*a*]quinoxaline-7-carboxylic Acid Amide I (2). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ = 8.49 (s, 1H, ArH), 8.39 (d, 1H, J = 8.4 Hz, ArH), 8.26 (brs, 1H, NH), 8.09 (d, 1H, J = 8.4 Hz, ArH), 7.94 (d, 2H, J = 7.8 Hz, ArH), 7.84 (s, 1H, ArH), 7.54 (brs, 1H, NH), 7.41 (d, 2H, J = 8.1 Hz, ArH), 3.08 (s, 3H, CH_3), 2.42 (s, 3H, CH_3).

3-Methyl-1,4-diphenylimidazo[1,5-*a*]quinoxaline-7-carboxylic Acid Amide I (3). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ = 8.41 (d, 1H, J = 1.5 Hz, ArH), 8.09 (brs, 1H, NH), 7.74−7.59 [m (o), 11H, ArH], 7.49 (brs, 1H, NH), 7.33 (d, 1H, J = 8.7 Hz, ArH), 2.05 (s, 3H, CH_3).

4-(4-Ethoxyphenyl)-3-methyl-1-phenylimidazo[1,5-*a*]-quinoxaline-7-carboxylic Acid Amide I (4). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ = 8.39 (s, 1H, ArH), 8.08 (brs, 1H, NH, 7.71−7.61 (m, 8H, ArH), 7.48 (brs, 1H, NH), 7.32 (d, 1H, J = 8.7 Hz), 7.11 (d, 2H, J = 8.7 Hz, ArH), 4.13 (q, 2H, J = 6.9 Hz CH_2), 2.13 (s, 3H, CH_3), 1.39 (t, 3H, J = 6.9 Hz, CH_3).

3-Methyl-4-(4-nitrophenyl)-1-phenylimidazo[1,5-a]quinoxaline-7-carboxylic Acid Amide I (5). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ = 8.43 (d, 2H, J = 8.7 Hz, ArH), 8.37 (s, 1H, ArH), 8.17 (brs, 1H, NH), 7.96 (d, 2H, J = 8.4 Hz, ArH), 7.72−7.64 [m (o), 6H, ArH], 7.47 (brs, 1H, NH), 7.33 (d, 1H, J = 9.0 Hz, ArH), 2.05 (s, 3H, CH_3).

1-Methyl-4-phenylimidazo[1,5-*a*]quinoxaline-7-carboxylic Acid Amide I (6). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ = 8.51 (s, 1H, ArH), 8.38 (d, 1H, J = 9.0 Hz, ArH), 8.25 (brs, 1H, NH), 8.10 (d, 1H, J = 8.7 Hz, ArH), 8.03 [brm (o), 2H, ArH], 7.84 (s, 1H, ArH), 7.61 [brm (o), 3H, ArH], 7.55 (brs, 1H, NH), 3.08 (s, 3H, CH_3).

1-Methyl-4-(4-nitrophenyl)-imidazo[1,5-*a*]quinoxaline-7-carboxylic Acid Amide (7). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ = 8.41 [d (o), 3H, J = 7.5 Hz, ArH], 8.19 (d, 1H, J = 8.1 Hz, ArH), 8.11 (brs, 1H, NH), 7.99 (d, 1H, J = 8.1 Hz, ArH), 7.91 (d, 2H, J = 8.4 Hz, ArH), 7.64 (s, 1H, ArH), 7.52 (brs, 1H, NH), 3.07 (s, 3H, CH_3).

4-(4-Ethoxyphenyl)-1-methylimidazo[1,5-*a*]quinoxaline-7-carboxylic Acid Amide I (8). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ = 8.47 (s, 1H, ArH), 8.36 (d, 1H, J = 8.7 Hz, ArH), 8.23 (brs, 1H, NH), 8.06 (d, 1H, J = 8.7 Hz, ArH), 8.00 (d, 2H, J = 8.4 Hz, ArH), 7.87 (s, 1H, ArH), 7.51 (brs, 1H, NH), 7.12 (d, 2H, J = 8.4 Hz, ArH), 4.13 (q, 2H, J = 6.8 Hz, CH_2), 3.07 (s, 3H, CH_3), 1.37 (t, 3H, J = 6.8 Hz, CH_3).

1-Ethyl-3-methyl-4-*p*-tolylimidazo[1,5-*a*]quinoxaline-7-carboxylic Acid Amide I (9). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ = 8.38 (s, 1H, ArH), 8.25 (d, 1H, J = 8.7 Hz, ArH), 8.18 (brs, 1H, NH), 8.04 (d, 2H, J = 7.5 Hz, ArH), 7.49 (d (o), 3H, J = 7.5 Hz, ArH, NH), 7.35 (d, 2H, J = 7.8 Hz, ArH), 3.40−3.34 (overlapped with water, 2H, CH_2), 2.41 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 1.43 (t, 3H, J = 7.2 Hz, CH_3).

1-Ethyl-3-methyl-4-phenylimidazo[1,5-*a*]quinoxaline-7-carboxylic Acid Amide I (10). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ = 8.40 (d, 1H, J = 1.8 Hz, ArH), 8.27 (d, 1H, J = 8.7 Hz, ArH), 8.18 (brs, 1H, NH), 8.06 (dd, 1H, J = 8.7, 1.8 Hz, ArH), 7.62−7.55 [m(o), 5H, ArH], 7.51 (brs, 1H, NH), 3.39 (overlapped with water, 2H, CH_2), 1.96 (s, 3H, CH_3), 1.44 (t, 3H, J = 7.2 Hz, CH_3).

1-Ethyl-3-methyl-4-(4-nitrophenyl)-imidazo[1,5-*a*]quinoxaline-7-carboxylic Acid Amide I (11). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ = (DMSO-d_6) δ 8.41 [brd (o), 3H, J = 7.5 Hz, ArH], 8.28 (d, 1H, J = 8.4 Hz, ArH), 8.21 (brs, 1H, NH), 8.09 (d, 1H, J = 8.7 Hz, ArH), 7.92 (d, 2H, J = 8.1 Hz, ArH), 7.54 (brs, 1H, NH), 3.43 (overlapped with water, 2H, CH_2), 1.99 (s, 3H, CH_3), 1.44 (t, 3H, J = 7.0 Hz, CH_3).

4-(4-Ethoxyphenyl)-1-ethyl-3-methylimidazo[1,5-*a*]quinoxaline-7-carboxylic Acid Amide I(12). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ = 8.37 (s, 1H, ArH), 8.23 (d, 1H, J = 8.7 Hz, ArH), 8.17 (brs, 1H, NH), 8.02 (d, 1H, J = 8.7 Hz, ArH), 7.53 (d, 2H, J = 8.7 Hz, ArH), 7.49 (brs, 1H, NH), 7.06 (d, 2H, J = 8.7 Hz, ArH), 4.10 (q, 2H, J = 6.9 Hz, CH_2), 3.40−3.35 [(overlapped with water), 2H, CH_2], 2.03 (s, 3H, CH_3), 1.42 (t, 3H, J = 7.3 Hz, CH_3), 1.36 (t, 3H, J = 7.0 Hz, CH_3).

4-(2-Hydroxyphenyl)-3-methyl-1-phenylimidazo[1,5-*a*]-quinoxaline-7-carboxylic Acid Amide I(13). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ = (DMSO-d_6) δ 9.78 (s, 1H, OH), 8.38 (s, 1H, ArH), 8.08 (brs, 1H, NH), 7.74−7.69 [m (o), 3H, ArH], 7.64−7.62 [m (o), 3H, ArH], 7.48 (brs, 1H, NH), 7.42−7.28 [m (o), 3H, ArH], 7.04−6.97 [m (o), 2H, ArH], 2.03 (s, 3H, CH_3).

4-(2-Hydroxyphenyl)-1-methylimidazo[1,5-*a*]quinoxaline-7-carboxylic Acid Amide I (14). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ = 11.99 (s, 1H, OH), 8.47 (s, 1H, ArH), 8.39 (d, 1H, J = 9.0 Hz, ArH), 8.24 (brs, 1H, NH), 8.10 (d, 1H, J = 8.7 Hz, ArH), 7.89 [d (o), 2H, J = 5.7 Hz, ArH], 7.56 (s, 1H, NH), 7.43 (t, 1H, J = 6.9 Hz, ArH), 7.05−6.98 [m (o), 2H, ArH], 3.08 (s, 3H, CH_3).

1-Ethyl-4-(2-hydroxyphenyl)-3-methylimidazo[1,5-*a*]-quinoxaline-7-carboxylic Acid Amide I (15). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ = 9.76 (s, 1H, OH), 8.35 (s, 1H, ArH), 8.23 (d, 1H, J = 8.7 Hz, ArH), 8.18 (brs, 1H, NH), 8.04 (d, 1H, 8.7 Hz, ArH), 7.49 (brs, 1H, NH), 7.35 (t, 1H, J = 7.6 Hz, ArH), 7.25 (d, 1H, J = 7.2 Hz, ArH), 6.99−6.92 [m (o), 2H, ArH], 3.35 (overlapped with water, 2H, CH_2), 1.91 (s, 3H, CH_3), 1.41 (t, 3H, J = 7.1 Hz, CH_3).

4-(4-Chlorophenyl)-3-methyl-1-phenylimidazo[1,5-*a*]-quinoxaline-7-carboxylic Acid Amide I (16). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ = 8.41 (s, 1H, ArH), 8.09 (brs, 1H, NH), 7.75−7.63 [m (o), 10H, ArH], 7.50 (brs, 1H, NH), 7.34 (d, 1H, J = 8.7 Hz, ArH), 2.10 (s, 3H, CH_3).

4-(4-Chlorophenyl)-1-methylimidazo[1,5-*a*]quinoxaline-7-carboxylic Acid Amide I (17). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ = 8.52 (s, 1H, ArH), 8.39 (d, 1H, J = 8.4 Hz, ArH), 8.24 (brs, 1H, NH), 8.12 [d (o), 1H, J = 9.0 Hz], 8.06 (d, 2H, J = 7.8 Hz, ArH), 7.88 (s, 1H, ArH), 7.66 (d, 2H, J = 7.8 Hz, ArH), 7.55 (brs, 1H, NH), 3.09 (s, 1H, CH_3).

4-(4-Chlorophenyl)-1-ethyl-3-methylimidazo[1,5-*a*]quinoxaline-7-carboxylic Acid Amide I (18). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ = 8.37 (s, 1H, ArH), 8.23 (d, 1H, J = 9.0 Hz, ArH), 8.19 (brs, 1H, NH), 8.03 (d, 1H, J = 8.7 Hz, ArH), 7.61 [s (o), 4H], 7.52 (brs, 1H, NH), 3.34 (q, 2H, J = 7.5 Hz, CH_2), 1.97 (s, 3H, CH_3), 1.41 (t, 3H, J = 7.2 Hz, CH_3).

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Note Added after ASAP Posting. Due to a production error, the version posted on February 3, 2003, contained "iodized" in the Abstract. The corrected version, containing "oxidized", was posted on February 7, 2005.

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