An Efficient Approach to the Synthesis of Alkyl 7-Hydroxy-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-8-carboxylates via a One-Pot, Three-Component Reaction

Abdolali Alizadeh,* Marziyeh Hossein Abadi, Rashid Ghanbaripour

Department of Chemistry, Tarbiat Modares University, P.O. Box 14115-175, Tehran, Iran
Fax +98(21)88006544; E-mail: abdol_alizad@yahoo.com; E-mail: aalizadeh@modares.ac.ir

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Abstract: An efficient synthesis of alkyl 7-hydroxy-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-8-carboxylate derivatives by reaction between diamines, dialkyl acetylenedicarboxylates, and alkyl or aryl glyoxales is reported. Ease of handling, easy purification, and good yields are the main advantages of the presented method.

Key words: diamine, dialkyl acetylenedicarboxylate, glyoxale, alkyl 7-hydroxy-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-8-carboxylate, one-pot, three-component reaction

Nitrogen-containing heterocycles are a widespread structural motif, found as key elements of numerous drugs and designed medicinal agents in medicinal chemistry.[1] Additionally, they can act as biomimetic and active pharmacophores.[2] Among them, pyrroles are heterocycles of great importance because of their presence in numerous natural products like the porphyrin ring systems of chlorophyll, vitamin B12, heme, and various cytochrome enzymes.[1] Moreover, polysubstituted pyrroles have biological properties, such as antitumor,[3] antioxidant,[4] antifungal,[5] and ionotropic[6] activities, and they are poly (ADP-ribose) polymerase inhibitors [7] and AT1-selective angiotensin II receptor antagonists.[8]

Pyrrole-fused heterocyclic derivatives can be highlighted, and these compounds are widespread in natural products and bioactive agents, such as aptazapine and ketorolac.[2] Accordingly, the synthesis of new pyrroles and pyrrole-fused heterocyclic derivatives have been considered by chemists, and a range of methods have been reported for their synthesis.[9,10]

1,2,3,4-Tetrahydropyrrolo[1,2-*a*]pyrazine derivatives are one of the most important class of pyrrole-fused heterocycles due to their broad biological activities, including antihypersensitive,[11] antihypoxic,[12] psychotropic,[13] and antiarrhythmic properties.[14] Moreover, they are also reported as serotonin and noradrenaline reuptake inhibitors,[15] aldose reductase inhibitors,[16] and potassium channel ligands.[17] Besides these biological applications, this skeleton is widely present in natural products, such as hanishin, dibromophakellin, agelastatin A, longamide B, and cyclooroidin (Figure 1).[18] Although many methods have been reported for the synthesis of 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine, they suffer from some disadvantages such as multistep synthesis, tedious workup, and using expensive starting materials, so the development of novel strategies for the synthesis of their derivatives is still required.[19]

Accordingly, and as part of our program aimed at developing new routes for the synthesis of heterocyclic compounds,[20] we decided to synthesize alkyl 7-hydroxy-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-8-carboxylate by the reaction of dialkyl acetylenedicarboxylate **1**, glyoxals **2**, and aliphatic and aromatic 1,2-diamines in the presence of *p*-toluenesulfonic acid (PTSA).

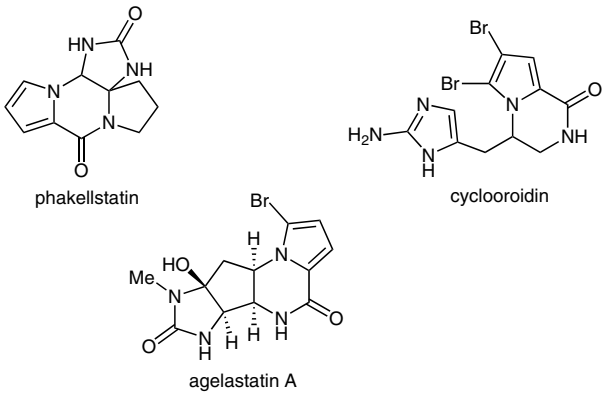

Figure 1 Some examples of natural products bearing the 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine moiety

To optimize the reaction conditions, we chose the reaction of dimethyl acetylenedicarboxylate (**1a**), ethylenediamine, and methylglyoxal (**2a**) as a model reaction. Various solvents, catalysts, and amounts of them have been studied in the model reaction. The best results were obtained by performing the reaction in ethanol in the presence of PTSA (10 mol%) at reflux for three hours.[21] The results are summarized in Table 1.

According to Table 1, increasing the amount of PTSA and/or using another catalysts failed to improve the yield (Table 1, entry 7–9) while decreasing the amount of PTSA led to reduced yield (Table 1, entry 6). Moreover, we have also performed the model reaction in the absence of PTSA, but these conditions suffered from disadvantages such as long reaction time and lower yield compared to using PTSA as catalyst (Table 1, entry 10).

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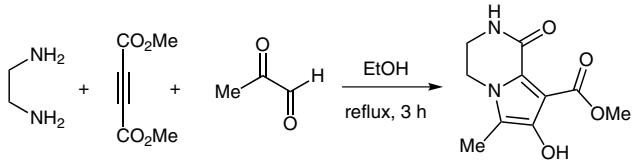
Table 1 Optimization of the Reaction Conditions



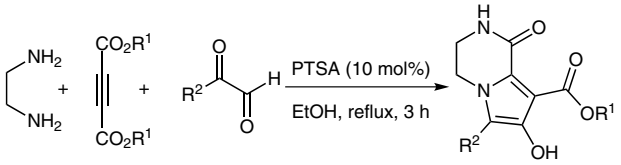
Entry	Solvent	Acids (mol%)	Yield (%)
1	EtOH	PTSA (10)	70[a]
2	THF	PTSA (10)	35[a]
4	MeCN	PTSA (10)	50[a]
5	$CHCl_3$	PTSA (10)	20[a]
6	EtOH	PTSA (5)	55[a]
7	EtOH	PTSA (15)	70[a]
8	EtOH	$FeCl_3$ (10)	40[a]
9	EtOH	AcOH (10)	48[a]
10	EtOH	–	60[b]

[a] Reflux, 3 h.
[b] Reflux, 72 h.

With the optimized reaction conditions in hand, we extended our study to different dialkyl acetylenedicarboxylates **1** and methyl- or arylglyoxals **2**. The results are summarized in Table 2.

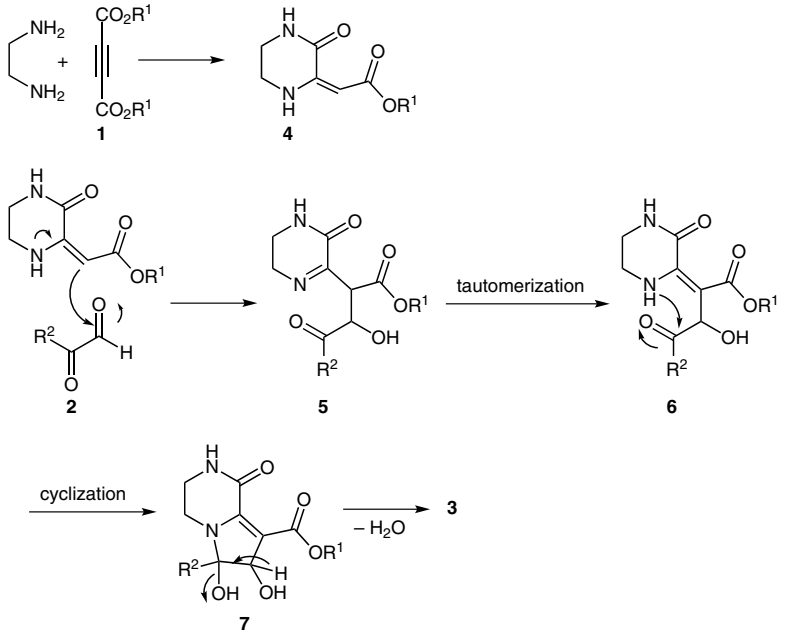
We also examined *o*-phenylenediamine instead of ethylenediamine but we did not observe any change in the reaction mixture probably related to low electron density at the nitrogen in *o*-phenylenediamine in comparison to ethylenediamine. In another attempt, when we used 1,3-diaminopropane and 1,4-diaminobutane instead of ethylenediamine, a complex mixture was obtained, which is related to the competition between polymerization and cyclization of diamines and dialkyl acetylenedicarboxylates. To expand the product derivatives, we decided to use 1,2-diaminopropane instead of ethylenediamine, but a complex mixture was obtained, because there are two possibilities for the reaction between 1,2-diaminopropane and dialkylacetylenedicarboxylates. These intermediates have also two possibilities to react with glyoxals. Therefore, four products can be obtained by the reaction of unsymmetrical diamines, dialkyl acetylenedicarboxylates, and glyoxals.

Table 2 Three-Component Synthesis of Alkyl 7-Hydroxy-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-8-carboxylate Derivatives **3a–f**



1 **2** **3**

Entry	Product **3**	R^1	R^2	Yield (%)
1	**3a**	Me	Me	70
2	**3b**	Et	Me	74
3	**3c**	Me	Ph	83
4	**3d**	Et	Ph	66
5	**3e**	Me	4-ClC_6H_4	76
6	**3f**	Et	4-ClC_6H_4	66



Scheme 1 Proposed mechanism for the formation of **3**

The molecular structures of all products **3a**–**f** were assigned by IR, mass, ^{1}H NMR, and ^{13}C NMR spectra, and their elemental analyses, as described for **3a**. The ^{1}H NMR spectrum of **3a** exhibited four singlet signals at δ = 2.20, 3.94, 7.28, and 8.39 ppm which are related to Me, OMe, NH, and OH groups. One multiplet and one triplet signal at δ = 3.65–3.68, and 3.95 ppm are related to CH_2 groups. The ^{1}H-decoupled ^{13}C NMR spectrum of **3a** showed ten distinct signals in agreement with the suggested structure. The most important peak is related to the pyrrole ring which appeared at δ = 103.4, 114.4, 118.2, and 145.9 ppm.

A plausible mechanism for the synthesis of product **3a**–**f** is proposed in Scheme 1.

Initial addition of ethylenediamine to dialkyl acetylenedicarboxylate leads to intermediate **4**, and subsequent attack of the resulting reactive intermediate **4** onto the glyoxal **2** results in the formation of intermediate **6**. Finally, cyclization and dehydration of this intermediate affords the desired product **3**.

To investigate the proposed mechanism, intermediate **4a** was synthesized separately, and it was added to methylglyoxal **2a** in solution in the presence PTSA, and the same product **3a** was obtained.

In summary, we have presented a powerful and efficient method to the synthesis of alkyl 7-hydroxy-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-8-carboxylate derivatives by the reaction of diamines, dialkyl acetylenedicarboxylates, and alkyl or aryl glyoxals. This is a simple method in comparison to the other methods. Good yields, easy purification, and use of simple and inexpensive starting materials are advantages of this method. Due to the importance of this class of compounds, the products can be considered for biological applications in the near future.

References and Notes

(1) (a) *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon Press: Oxford, **1996**. (b) Craig, P. N. In *Comprehensive Medicinal Chemistry*; Vol. 8; Drayton, C. J., Ed.; Pergamon: New York, NY, **1991**.

(2) (a) Hansch, C.; Sammes, P. G.; Taylor, J. B. *Comprehensive Medicinal Chemistry*; Vol. 2; Chapt. 7.; Pergamon: Oxford, **1990**. (b) Erlanson, D. A.; McDowell, R. S.; O'Brien, T. *J. Med. Chem.* **2004**, *4*, 3463. (c) Butler, M. S. *J. Nat. Prod.* **2004**, *67*, 2141.

(3) Denny, W. A.; Rewcastle, G. W.; Baguley, B. C. *J. Med. Chem.* **1990**, *33*, 814.

(4) Lehuede, J.; Fauconneau, B.; Barrier, L.; Ourakow, M.; Piriou, A.; Vierfond, J. M. *Eur. J. Med. Chem.* **1999**, *34*, 991.

(5) Del Poeta, M.; Schell, W. A.; Dykstra, C. C.; Jones, S.; Tidwell, R. R.; Czarny, A.; Bajic, M.; Kumar, A.; Boykin, D.; Perfect, J. R. *Antimicrob. Agents Chemother.* **1998**, *4*, 2495.

(6) (a) Jonas, R.; Klockow, M.; Lues, I.; Pruecher, H.; Schliep, H. J.; Wurziger, H. *Eur. J. Med. Chem.* **1993**, *28*, 129. (b) von der Saal, W.; Hoelck, J. P.; Kampe, W.; Mertens, A.; Mueller-Beckmann, B. *J. Med. Chem.* **1989**, *32*, 1481.

(7) Ferraris, D.; Ficco, R. P.; Dain, D.; Ginski, M.; Lautar, S.; Lee-Wisdom, K.; Liang, S.; Lin, Q.; Lu, M. X. C.; Morgan, L.; Thomas, B.; Williams, L. R.; Zhang, J.; Zhou, Y.; Kalish, V. J. *Bioorg. Med. Chem.* **2003**, *11*, 3695.

(8) Bovy, P. R.; Reitz, D. B.; Collins, J. T.; Chamberlain, T. S.; Olins, G. M.; Corpus, V. M.; McMahon, E. G.; Palomo, M. A.; Koepke, J. P.; Smits, G. J.; McGraw, D. E.; Gaw, J. F. *J. Med. Chem.* **1993**, *36*, 101.

(9) Trushkov, I. V.; Nevolina, T. A.; Shcherbinin, V. A.; Sorotskaya, L. N.; Butin, A. V. *Tetrahedron Lett.* **2013**, *54*, 3974.

(10) (a) Smith, N. D.; Huang, D.; Cosford, N. D. P. *Org. Lett.* **2002**, *4*, 3537. (b) Suryavanshi, P. A.; Sridharan, V.; Menéndez, J. C. *Tetrahedron* **2013**, *69*, 5401. (c) Chong, Q.; Xin, X.; Wang, C.; Wu, F.; Wan, B. *Tetrahedron* **2014**, *70*, 490. (d) Butin, A. V.; Nevolina, T. A.; Shcherbinin, V. A.; Uchuskin, M. G.; Serdyuk, O. V.; Trushkov, I. V. *Synthesis* **2010**, 2969. (e) El Kaim, L.; Grimaud, L.; Wagschal, S. *Chem. Commun.* **2011**, *47*, 1887. (f) Stroganova, T. A.; Butin, A. V.; Vasilin, V. K.; Nevolina, T. A.; Krapivin, G. D. *Synlett* **2007**, 1106. (g) Hashmi, A. S. K.; Pankajakshan, S.; Rudolph, M.; Enns, E.; Bander, T.; Rominger, F.; Frey, W. *Adv. Synth. Catal.* **2009**, *351*, 2855. (h) Petronijevic, F. R.; Wipf, P. *J. Am. Chem. Soc.* **2011**, *133*, 7704.

(11) Peresada, V. P.; Medvedev, O. S.; Likhosherstov, A. M.; Skoldinov, A. P. *Khim. Farm. Zh.* **1987**, *21*, 1054; *Chem. Abstr*. **1988**, *108*, 68298g.

(12) Seredenin, S. B.; Voronina, T. A.; Beshimov, A.; Peresada, V. P.; Likhosherstov, A. M. RU 2099055, **1997**; *Chem. Abstr*. **1998**, *128*, 290245j

(13) Seredenin, S. B.; Voronina, T. A.; Likhosherstov, A. M.; Peresada, Y. P.; Molodavkin, G. M.; Halikas, J. A. US 5378846, **1995**; *Chem. Abstr*. **1995**, *123*, 83350w

(14) Likhosherstov, A. M.; Filippova, O. V.; Peresada, V. P.; Kryzhanovskii, S. A.; Vititnova, M. B.; Kaverina, N. V.; Reznikov, K. M. *Pharm. Chem. J.* **2003**, *37*, 6.

(15) Merla, B.; Christoph, T.; Oberboersch, S.; Schiene, K.; Bahrenberg, G.; Frank, R.; Kuehnert, S.; Schroeder, W. WO 2008046581, **2008**; *Chem. Abstr*. **2009**, *148*, 495982g

(16) Negoro, T.; Murata, M.; Ueda, S.; Fujitani, B.; Ono, Y.; Kuromiya, A.; Komiya, M.; Suzuki, K.; Matsumoto, J. I. *J. Med. Chem.* **1998**, *41*, 4118.

(17) Merla, B.; Christoph, T.; Oberboersch, S.; Schiene, K.; Bahrenberg, G.; Frank, R.; Kuehnert, S.; Schroeder, W. WO 2008046582, **2008**; *Chem. Abstr*. **2008**, *148*, 472076a

(18) (a) Tilvi, S.; Moriou, C.; Martin, M. T.; Gallard, J. F.; Sorres, J.; Patel, K.; Petek, S.; Debitus, C.; Ermolenko, L.; Al-Mourabit, A. *J. Nat. Prod.* **2010**, *73*, 720. (b) Al-Mourabit, A.; Zancanella, M. A.; Tilvic, S.; Romo, D. *Nat. Prod. Rep.* **2011**, *28*, 1229. (c) Papeo, G.; Gómez-Zurita Frau, M. A.; Borghi, D.; Varasi, M. *Tetrahedron Lett.* **2005**, *46*, 8635.

(19) (a) Hewlett, N. M.; Tepe, J. J. *Org. Lett.* **2011**, *13*, 4550. (b) Cheng, G.; Wang, X.; Bao, H.; Cheng, C.; Liu, N.; Hu, Y. *Org. Lett.* **2012**, *14*, 1062. (c) Bhowmik, S.; Kumar, A. K. S.; Batra, S. *Tetrahedron Lett.* **2013**, *54*, 2251. (d) Bandini, M.; Bottoni, A.; Eichholzer, A.; Miscione, G. P.; Stenta, M. *Chem. Eur. J.* **2010**, *16*, 12462. (e) Voskressensky, L. G.; Titov, A. A.; BorisovaT, N.; Listratova, A. V.; Borisov, R. S.; Kulikova, L. N.; Varlamov, A. V. *Tetrahedron* **2010**, *66*, 5140. (f) Trost, B. M.; Osipov, M.; Dong, G. *J. Am. Chem. Soc.* **2010**, *132*, 15800. (g) Mukherjee, S.; Sivappa, R.; Yousufuddin, M.; Lovely, C. J. *Org. Lett.* **2010**, *12*, 4940. (h) Imaoka, T.; Akimoto, T.; Iwamoto, O.; Nagasawa, K. *Chem. Asian J.* **2010**, *5*, 1810. (i) Trost, B. M.; Osipov, M.; Dong, G. *Org. Lett.* **2010**, *12*, 1276.

(20) (a) Alizadeh, A.; Ghanbaripour, R.; Zhu, L. G. *Synlett* **2013**, *24*, 2124. (b) Alizadeh, A.; Ghanbaripour, R.; Zhu, L. G. *Synth. Commun.* **2013**, *43*, 2575. (c) Alizadeh, A.; Ghanbaripour, R. *Helv. Chim. Acta* **2013**, *96*, 473. (d) Alizadeh, A.; Sedighian, H.; Bayat, F. *Synlett* **2014**, *24*, 389. (e) Alizadeh, A.; Ghanbaripour, R.; Zhu, L. G. *Tetrahedron* **2014**, *70*, 2048. (f) Alizadeh, A.; Zohreh, N. *ACS Comb. Sci.* **2013**, *15*, 278.

(21) To a solution of ethylenediamine (1 mmol) in EtOH (2 mL), dimethyl acetylenedicarboxylate (1 mmol) was added dropwise at r.t. After 30 min, methylglyoxal (1 mmol) and PTSA (0.1 mmol) were added to the reaction mixture, and the solution was stirred for 2.5 h at reflux conditions. Upon completion (3 h), monitored by TLC, the solvent was cooled at an ice bath, and the precipitate was filtered to afford the pure products **3a**–**f**.

Methyl 7-Hydroxy-6-methyl-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-8-carboxylate (3a)

Pale orange powder; 0.156 g, 70% yield; mp 187–189 °C. IR (KBr): 3211 (NH), 3099 (OH), 1715 (CO_2Me), 1675 (NCO), 1219 and 1146 (CO) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.20 (s, 3 H, CH_3), 3.65–3.68 (m, 2 H, CH_2NH), 3.94 (s, 3 H, OMe), 3.95 (t, $^3J_{HH}$ = 5.6 Hz, 2 H, CH_2N), 7.28 (s, 1 H, NH), 8.39 (s, 1 H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.9 (CH_3), 39.3 (CH_2NH), 41.6 (CH_2N), 52.1 (OMe), 103.4 (C^6), 114.4 (C^8), 118.2 (C^{8a}), 145.9 (COH), 159.3 (CO_2CH_3), 167.5 (NCO). MS: *m/z* = 225 [M^+ + 1], 224 [M^+], 192, 164, 136, 123, 107, 95, 79, 66, 53. Anal. Calcd (%) for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.40. Found: C, 53.51; H, 5.46; N, 12.38.

Ethyl 7-Hydroxy-6-methyl-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-8-carboxylate (3b)

Pale brown powder; 0.178 g, 74%; mp 178–179 °C. IR (KBr): 3393 (NH), 3193 (OH), 1710 (CO_2Et), 1668 (NCO), 1335, 1225 and 1150 (CO) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (t, $^3J_{HH}$ = 7.0 Hz, 3 H, CH_2CH_3), 2.12 (s, 3 H, CH_3), 3.56–3.59 (m, 2 H, CH_2NH), 3.87 (t, $^3J_{HH}$ = 5.7 Hz, 2 H, CH_2N), 4.32 (q, $^3J_{HH}$ = 7.0 Hz, 2 H, CH_2CH_3), 7.01 (s, 1 H, NH), 8.28 (s, 1 H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.9 (CH_3), 14.2 (CH_3), 39.3 (CH_2NH), 41.6 (CH_2N), 60.9 (OCH_2), 103.9 (C^6), 114.3 (C^8), 118.3 (C^{8a}), 145.8 (COH), 159.2 (CO_2Et), 166.9 (NCO). MS: *m/z* = 239 [M^+ + 1], 238 [M^+], 192, 164, 136, 123, 107, 95, 80, 67, 53. Anal. Calcd (%) for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.36; H, 5.87; N, 11.82.

Methyl 7-Hydroxy-1-oxo-6-1,2,3,4-tetrahydrophenylpyrrolo[1,2-*a*]pyrazine-8-carboxylate (3c)

Pale yellow powder; 0.238 g, 83% yield; mp 90–92 °C. IR (KBr): 3350 (NH), 3235 (OH), 1706 (CO_2Me), 1664 (NCO), 1580 and 1481 (Ar), 1348, 1225 and 1141 (CO) cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ = 3.69–3.65 (m, 2 H, CH_2NH), 3.98 (s, 3 H, OMe), 4.11 (t, $^3J_{HH}$ = 5.9 Hz, 2 H, CH_2N), 6.59 (s, 1 H, NH), 7.35–7.39 (m, 1 H, CH_{para} of Ph), 7.44–7.50 (m, 4 H, 2 × CH_{ortho} and 2 × CH_{meta} of Ph), 8.80 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39. 7 (CH_2NH), 43.1 (CH_2N), 52.2 (OMe), 103.7 (C^6), 118.7 (C^8), 119.6 (C^{8a}), 128.0 (CH_{para} of Ph), 128.3 (C_{ipso}), 128.7 (2 × CH_{ortho} of Ph), 129.4 (2 × CH_{meta} of Ph), 146.6 (COH), 158.9 (CO_2Me), 167.6 (NCO). MS: *m/z* = 287 [M^+ + 1], 287 [M^+], 279, 262, 254, 219, 205, 167, 149, 132, 121, 113, 104, 93, 83, 71, 57. Anal. Calcd (%) for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93, N, 9.79. Found: C, 62.97; H, 5.01; N, 9.86.

Ethyl 7-Hydroxy-1-oxo-6-1,2,3,4-tetrahydrophenylpyrrolo[1,2-*a*]pyrazine-8-carboxylate (3d)

Pale yellow powder; 0.198 g 66% yield; mp 213–214 °C. IR (KBr): 3184 (NH), 3064 (OH), 1708 (CO_2Et), 1665 (NCO), 1580 and 1481 (Ar), 1300, 1239 and 1197 (CO) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.45 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_2CH_3), 3.10–3.64 (m, 2 H, CH_2NH), 4.11 (t, $^3J_{HH}$ = 5.6 Hz, 2 H, CH_2N), 4.45 (q, $^3J_{HH}$ = 7.2 Hz, 2 H, CH_2CH_3), 7.12 (s, 1 H, NH), 7.36–7.40 (m, 1 H, CH_{para} of Ph), 7.46–7.51 (m, 4 H, 2 × CH_{ortho} and 2 × CH_{meta} of Ph), 8.75 (s, 1 H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (CH_3), 39.6 (CH_2NH), 43.1 (CH_2N), 61.1 (OCH_2), 104.1 (C^6), 118.6 (C^8), 119.8 (C^{8a}), 127.9 (CH_{para} of Ph), 128.4 (C_{ipso}), 128.7 (2 × CH_{ortho} of Ph), 129.4 (2 × CH_{meta} of Ph), 146.4 (COH), 159.2 (CO_2Et), 166.9 (NCO). MS: *m/z* = 301 [M^+ + 1], 300 [M^+], 254, 225, 211, 198, 183, 169, 155, 141, 128, 115, 104, 95, 77, 67, 53. Anal. Calcd (%) for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37, N, 9.33. Found: C, 64.01; H, 5.49; N, 9.30.

Methyl 7-Hydroxy-1-oxo-6-(4-chlorophenyl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-8-carboxylate (3e)

Pale beige powder; 0.245 g, 86% yield; mp 203–204 °C. IR (KBr): 3325 (NH), 3200 (OH), 1710 (CO_2Me), 1660 (NCO), 1574 and 1481 (Ar), 1299, 1233 and 1138 (C–O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.63–3.68 (m, 2 H, CH_2NH), 3.99 (s, 3 H, OMe), 4.10 (t, $^3J_{HH}$ = 5.8 Hz, 2 H, CH_2N), 6.84 (s, 1 H, NH), 7.41 (d, $^3J_{HH}$ = 8.8 Hz, 2 H, 2 × CH of Ar), 7.46 (d, $^3J_{HH}$ = 8.4 Hz, 2 H, 2 × CH of Ar), 8.85 (s, 1 H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.6 (CH_2NH), 43.1 (CH_2N), 52.3 (OMe), 103.7 (C^6), 117.5 (C^8), 120.0 (C^{8a}), 126.7 (C_{ipso}), 129.0 (2 × CH of Ar), 130.7 (2 × CH of Ar), 133.9 ($C_{ipso}Cl$), 146.8 (COH), 158.9 (CO_2Me), 167.5 (NCO). MS: *m/z* = 322 [M^+ + 2], 321 [M^+ + 1], 320 [M^+], 288, 262, 253, 232, 189, 175, 162, 151, 137, 123, 111, 95, 80, 67, 53. Anal. Calcd (%) for $C_{15}H_{13}ClN_2O_4$: C, 66.02; H, 5.30; N, 13.39. Found: C, 65.98; H, 5.45; N, 13.43.

Ethyl 7-Hydroxy-1-oxo-6-(4-chlorophenyl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-8-carboxylate (3f)

Yellow powder; 0.223 g, 66% yield; mp 243–244 °C. IR (KBr): 3181 (NH), 3073 (OH), 1713 (CO_2Et), 1677 (NCO), 1566 and 1476 (Ar), 1302, 1224 and 1150 (CO) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.45 (t, $^3J_{HH}$ = 7.0 Hz, 3 H, CH_2CH_3), 3.63–3.68 (m, 2 H, CH_2NH), 4.10 (t, $^3J_{HH}$ = 5.8 Hz, 2 H, CH_2N), 4.46 (q, $^3J_{HH}$ = 7.0 Hz, 2 H, CH_2CH_3), 6.51 (s, 1 H, NH), 7.41 (d, $^3J_{HH}$ = 8.8 Hz, 2 H, 2 × CH of Ar), 7.46 (d, $^3J_{HH}$ = 8.8 Hz, 2 H, 2 × CH of Ar), 8.84 (s, 1 H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (CH_3), 39.7 (CH_2NH), 43.1 (CH_2N), 61.3 (OCH_2), 104.2 (C^6), 117.4 (C^8), 120.1 (C^{8a}), 126.8 (C_{ipso}), 129.0 (2 × CH of Ar), 130.5 (2 × CH of Ar), 133.9 ($C_{ipso}Cl$), 146.7 (COH), 158.7 (CO_2Et), 166.9 (NCO). MS: *m/z* = 336 [M^+ + 2], 335 [M^+ + 1], 334 [M^+], 288, 259, 245, 232, 203, 189, 175, 162, 138, 123, 111, 95, 80, 67, 53. Anal. Calcd (%) for $C_{16}H_{15}ClN_2O_4$: C, 57.41; H, 4.52; N, 8.37. Found: C, 57.32; H, 4.47; N, 8.31.

