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A route to functionalized pyrimidines from carbohydrates via amine-driven dehydrative ring transformations

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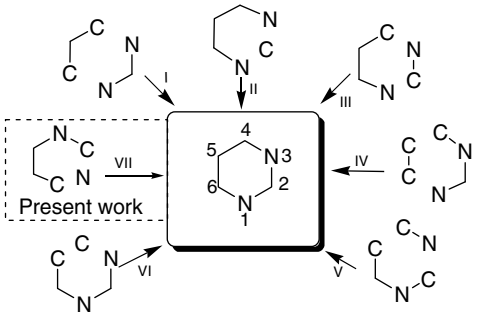
Abstract

A novel and expeditious synthetic protocol for functionalized pyrimidines using unprotected aldoses as biorenewable resources is reported. The synthesis involves aza-Michael addition of aromatic amines to aldose-derived 1,3-oxazin-2-ones(thiones) followed by dehydrative ring transformation to afford 4-polyhydroxyalkylpyrimidin-2-ones(thiones) in excellent yields. This is a one-pot Montmorillonite K-10 clay-catalyzed amine-driven process proceeding under solvent-free microwave irradiation conditions.

Keywords: Carbohydrates; Pyrimidines; Mineral-catalyzed; Microwaves; Solvent-free; 1,3-Oxazin-2-ones(thiones)

Pyrimidines are an important class of compounds and have widespread applications from pharmaceuticals to materials.[1] A number of synthetic pharmacophores with antibacterial, antimicrobial, antifungal and antimycotic activities[2–4] are based on the pyrimidyl motif. Also, pyrimidines are present in numerous natural products and, significantly, in the pyrimidine and purine bases ribo- and deoxyribonucleosides.[5] The electron-deficient nature of pyrimidines can impart highly electron-accepting ability to conjugated polymers.[6] In addition, conjugate molecules which have a pyrimidine core as the key unit have received much attention recently, and they are prospective candidates for light-emitting devices.[7] Owing to their strong deactivation towards electrophilic substitution and greater reactivity in nucleophilic additions and substitutions,[5a,f,8] pyrimidines may become increasingly important as interesting structural coordinating substituted ligands for pyridyl units in supramolecular metallo-grid-like architectures[9] and in novel inorganic/organic hybrid type molecular wires.[10]

These unique properties have triggered renewed interest to develop new synthetic methods which enable rapid access to pyrimidines. In most of the cases, construction of the pyrimidine ring is based on the bis-nucleophile plus bis-electrophile methods[11] or cross coupling reactions[12] and is restricted to methods involving Pinner synthesis via 3,4- and 1,6- (I);[11] 1,2- and 2,3- (II);[13] 1,2- and 3,4- (III);[14] 4,5- and 1,6- (IV);[15] 2,3- and 4,5- (V) bond forming reactions.[16] Recently, a four component coupling strategy was reported for pyrimidine synthesis by 3,4- and 4,5- (VI) bond forming reactions[17] (Scheme 1). However, in



Scheme 1.

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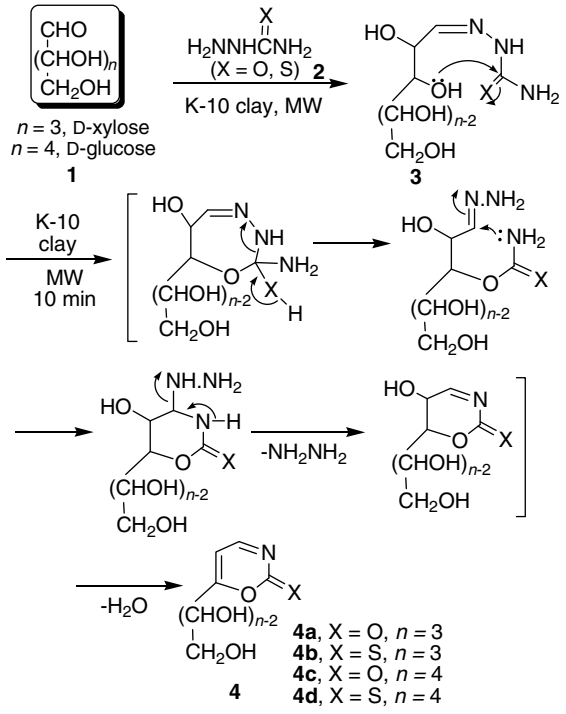
most of the established methods, condensation occurs between two-nitrogen-containing building blocks, viz. amidines, guanidines, ureas, isoureas, thioureas and isothioureas, and 1,3-dielectrophilic three-carbon units under alkaline conditions. The literature records only a few examples of pyrimidine synthesis using one-nitrogen-containing building blocks.[14,18]

In this Letter, we disclose a novel approach, viz. 1,2- and 1,6-bond forming reactions (VII, Scheme 1) for pyrimidine synthesis using D-glucose-/D-xylose-derived 1,3-oxazin-2-ones(thiones) **4** and aromatic amines **5** as structural variants of the building blocks. The present synthesis of functionalized pyrimidines results from our quest for novel solvent-free heterocyclization strategies,[19] especially using carbohydrates as raw materials.[20] Furthermore, the present synthetic protocol is in accord with 'renewable resources', a new and rapidly developing concept in environmental and chemical sciences that concerns the wide use of biorenewable materials for industry.[21]

1,3-Oxazin-2-ones(thiones) **4**, the starting materials for the envisaged synthetic protocol, were synthesized in 79–85% yields by a solvent-free microwave (MW) irradiation of D-glucose/D-xylose **1**, semi(thiosemi)carbazide **2** and M ontmorillonite K-10 clay via acid-catalyzed domino cycloisomerization, dehydrazination and dehydration of semi(thiosemi)carbazones **3** (Scheme 2).[22] The mechanism shown in Scheme 2 is supported by the formation of hydrazine during the reaction detected using the *p*-dimethylaminobenzaldehyde method.[23] It was noted that other mineral catalysts, viz. silica gel and neutral or basic



Scheme 2. Formation of 1,3-oxazin-2-ones(thiones) **4** from D-glucose/D-xylose **1**.

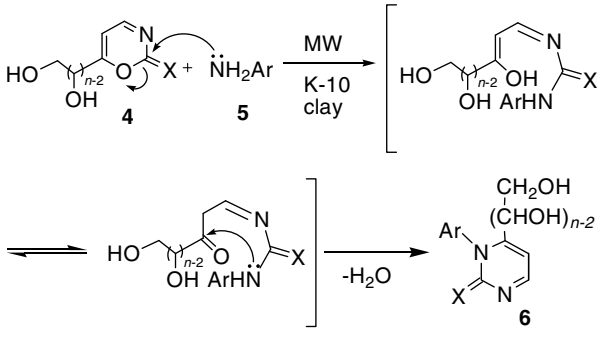
Table 1
Solvent-free synthesis of compounds **4** and **6** catalyzed by Montmorillonite K-10 clay

Product	Time[a] (min)	Yield[b,c] (%)
4a	10	82
4b	10	81
4c	10	79
4d	10	85
6a	12	88
6b	9	91
6c	9	85
6d	10	83
6e	11	92
6f	11	89
6g	8	87
6h	12	94
6i	9	93
6j	12	83
6k	10	92
6l	10	91

[a] Microwave irradiation time at 90 °C.
[b] Yield of isolated and purified products.
[c] All compounds gave C, H and N analyses within ±0.35% and satisfactory spectral (IR, ^{1}H NMR, ^{13}C NMR and EIMS) data.

alumina, were far less effective resulting in either no reaction (in the case of basic alumina) or very low yields (15–28%) of **4** (in the cases of silica gel and neutral alumina).

The target polyhydroxyalkyl pyrimidines **6** were obtained in 83–94% yields[24] (Table 1) by solvent-free microwave (MW) irradiation of an intimate mixture of 1,3-oxazin-2-ones(thiones) **4** and aromatic amines **5** in the presence of K-10 clay via amine-driven dehydrative ring transformations (Scheme 3). The use of other mineral catalysts, viz. silica gel, neutral or basic alumina, resulted in relatively low yields of **6** (21–32%). Formation of compounds **6** may be rationalized by the nucleophilic attack of the nitrogen of aromatic amines **5** on C-2 of the oxazine ring driving the dehydrative ring transformation to afford **6** (Scheme 3).



6	X	n	Ar	6	X	n	Ar
a	O	3	Ph	**g**	O	4	Ph
b	O	3	4-ClC$_6$H$_4$	**h**	O	4	4-ClC$_6$H$_4$
c	O	3	4-MeOC$_6$H$_4$	**i**	O	4	4-MeOC$_6$H$_4$
d	S	3	Ph	**j**	S	4	Ph
e	S	3	4-ClC$_6$H$_4$	**k**	S	4	4-ClC$_6$H$_4$
f	S	3	4-MeOC$_6$H$_4$	**l**	S	4	4-MeOC$_6$H$_4$

Scheme 3. A plausible mechanism for the formation of pyrimidines **6**.

In summary, we have documented an original and practical route for the synthesis of novel polyhydroxyalkylpyrimidines of remarkable pharmacological potential from unprotected aldoses as biorenewable resources. The synthesis is effected under Montmorillonite K-10 clay catalysis and solvent-free microwave irradiation conditions.

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References and notes

1. Brown, D. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1996; Vol 3, Chapter 2.13.
2. Ahluwalia, V. K.; Kaila, N.; Bala, S. *Indian J. Chem.* **1987**, *26B*, 700.
3. El-Hashash, M. A.; Mahmoud, M. R.; Madboli, S. A. *Indian J. Chem.* **1993**, *32B*, 449.
4. Keutzberger, A.; Gillessen, J. *Arch. Pharm.* **1985**, *318*, 370.
5. (a) Brown, D. J. In *The Pyrimidines*; Weissberger, A., Ed.; The Chemistry of Heterocyclic Compounds; Wiley Interscience: New York, 1970; Vol. 16; (b) Lister, J. H. In *Fused Pyrimidines, Part II, The Purines*; Weissberger, A., Taylor, E. C., Eds.; The Chemistry of Heterocyclic Compounds; Wiley Interscience: New York, 1971; Vol. 24; (c) Hoffmann, M. G. In *Houben-Weyl, Methoden der Organischen Chemie*; Schaumann, E., Ed.; G. Thieme: Stuttgart, 1996; Vol. E9; (d) Hurst, D. T. In *An Introduction to the Chemistry and Biochemistry of Pyrimidines, Purines and Pteridines*; Wiley: Chichester, 1980; (e) Bojarski, J. T.; Mokrosz, J. L.; Bartón, H. J.; Paluchowska, M. H. *Adv. Heterocycl. Chem.* **1985**, *38*, 229; (f) Brown, D. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 3; Chapter 2.13.
6. (a) Gompper, R.; Mair, H.-J.; Polborn, K. *Synthesis* **1997**, 696; (b) Kanbara, T.; Kushida, T.; Saito, N.; Kuwajima, I.; Kubota, K.; Yamamoto, T. *Chem. Lett.* **1992**, 583.
7. Wong, K.-T.; Hung, T.-S.; Lin, Y.; Wu, C.-C.; Lee, G.-H.; Peng, S.-M.; Chou, C. H.; Su, Y. O. *Org. Lett.* **2002**, *4*, 513.
8. (a) Eicher, T.; Hauptmann, S. *Chemie der Heterocyclen*; Georg Thieme: Stuttgart, New York, 1994; p 398; (b) Gilchrist, T. L. In *Heterocyclenchemie*; Neunhoeffer, H., Ed.; Wiley-VCH: New York, 1995; p 270.
9. (a) Lehn, J.-M. *Supramolecular Chemistry-Concepts and Perspectives*; VCH: Weinheim, 1995; Chapter 9; (b) Hanan, G. S.; Volkmer, D.; Schubert, U. S.; Lehn, J.-M.; Baum, G.; Fenske, D. *Angew. Chem., Int. Ed.* **1997**, *36*, 1842; (c) Semenov, A.; Spatz, J. P.; Möller, M.; Lehn, J.-M.; Sell, B.; Schubert, D.; Weidl, C. H.; Schubert, U. S. *Angew. Chem., Int. Ed.* **1999**, *38*, 2547.
10. (a) Harriman, A.; Ziessel, R. *Coord. Chem. Rev.* **1998**, *171*, 331; (b) Harriman, A.; Ziessel, R. *Chem. Commun.* **1996**, 1707.
11. (a) Taylor, E. C.; Knoff, R. J.; Meyer, R. F.; Holmes, A.; Hoefle, M. L. *J. Am. Chem. Soc.* **1960**, *82*, 5711; (b) Inoue, S.; Saggiomo, A. J.; Nodiff, E. A. *J. Org. Chem.* **1961**, *26*, 4504; (c) Bredereck, H.; Effenberger, F.; Botsch, H.; Rehn, H. *Chem. Ber.* **1965**, *98*, 1081; (d) Chauhan, S. M. S.; Junjappa, H. *Synthesis* **1974**, 880; (e) Kreutzberger, A.; Tesch, U.-H. *Chem. Ber.* **1976**, *109*, 3255; (f) Potts, K. T.; Cipullo, M. J.; Ralli, P.; Theodoridis, G. *J. Org. Chem.* **1983**, *48*, 4841; (g) Kvita, V. *Synthesis* **1986**, 786; (h) Schenone, P.; Sansebastiano, L.; Mosti, L. *J. Heterocycl. Chem.* **1990**, *27*, 295; (i) Papet, A.-L.; Marsura, A. *Synthesis* **1993**, 478; (j) Yamanaka, H.; Takekawa, T.; Morita, K.; Ishihara, T.; Gupton, J. T. *Tetrahedron Lett.* **1996**, *37*, 1829; (k) Wang, T.; Cloudsdale, I. S. *Synth. Commun.* **1997**, *27*, 2521; (l) Ghosh, U.; Katzenellenbogen, J. A. *J. Heterocycl. Chem.* **2002**, *39*, 1101.
12. (a) Schmaker, J. M.; Delia, T. J. *J. Org. Chem.* **2001**, *66*, 7125; (b) Turck, A.; Pré, N.; Lepretre-Gaquere, A.; Queguiner, G. *Heterocycles* **1998**, *49*, 205.
13. Eilingfeld, H.; Patsch, M.; Scheuermann, H. *Chem. Ber.* **1968**, *101*, 2426.
14. (a) Sing, Y. L.; Lee, L. F. *J. Heterocycl. Chem.* **1989**, *26*, 7; (b) Alberola, A.; Andrês, C.; Ortega, A. G.; Pedrosa, R.; Vicente, M. *Synth. Commun.* **1987**, *17*, 1309.
15. (a) Guzmân, A.; Romero, M.; Talamâs, F. X.; Villena, R.; Greenhouse, R.; Muchowski, J. M. *J. Org. Chem.* **1996**, *61*, 2470; (b) Guzmân, A.; Romero, M.; Talamâs, F. X.; Muchowski, J. M. *Tetrahedron Lett.* **1992**, *24*, 3449.
16. (a) Pourzal, A.-A. *Synthesis* **1983**, 717; (b) Martínez, A. G.; Fernandez, A. H.; Alvarez, R. M.; Losada, M. C. S.; Vilchez, D. M.; Subramanian, L. R.; Hanack, M. *Synthesis* **1990**, 881; (c) Martînez, A. G.; Fernândez, A. H.; Fraile, A. G.; Subramanian, L. R.; Hanack, M. *J. Org. Chem.* **1992**, *57*, 1627; (d) Martínez, A. G.; Fernândez, A. H.; Âlvarez, R. M.; Vilchez, M. D. M.; Gutiêrrez, M. L. L.; Subramanian, L. R. *Tetrahedron* **1999**, *55*, 4825; (e) Ghosez, L.; Jnoff, E.; Bayard, P.; Sainte, F.; Beaudegnies, R. *Tetrahedron* **1999**, *55*, 3387.
17. Sakai, N.; Aoki, Y.; Sasada, T.; Konakahara, T. *Org. Lett.* **2005**, *7*, 4705.
18. (a) Kakiya, H.; Yagi, K.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* **2002**, *124*, 9032; (b) Karpov, A. S.; Müller, T. J. J. *Synthesis* **2003**, 2815; (c) Zhao, F.-L.; Liu, J.-T. *J. Fluorine Chem.* **2004**, *125*, 1491.
19. (a) Yadav, L. D. S.; Rai, A.; Rai, V. K.; Awasthi, C. *Tetrahedron Lett.* **2008**, *49*, 687; (b) Yadav, L. D. S.; Awasthi, C.; Rai, V. K.; Rai, A. *Tetrahedron Lett.* **2007**, *48*, 8033; (c) Yadav, L. D. S.; Rai, V. K. *Tetrahedron* **2007**, *63*, 6924; (d) Yadav, L. D. S.; Rai, V. K. *Tetrahedron Lett.* **2006**, *47*, 395; (e) Yadav, L. D. S.; Yadav, S.; Rai, V. K. *Green Chem.* **2006**, *8*, 455; (f) Yadav, L. D. S.; Yadav, S.; Rai, V. K. *Tetrahedron* **2005**, *61*, 10013.
20. (a) Yadav, L. D. S.; Rai, A.; Rai, V. K.; Awasthi, C. *Synlett* **2007**, 1905; (b) Yadav, L. D. S.; Awasthi, C.; Rai, V. K.; Rai, A. *Tetrahedron Lett.* **2007**, *48*, 4899.
21. *Renewable Bioresources: Scope and Modification for Non-Food Applications*; Stevens, C. V., Verhé, R. G., Eds.; John Wiley and Sons: Chichester, England, 2004.
22. *General procedure for the synthesis of 1,3-oxazin-2-ones(thiones)* **4**: Thoroughly mixed D-xylose/D-glucose (1 mmol) **1**, semicarbazide hydrochloride/thiosemicarbazide (1 mmol) **2**, sodium acetate (1 mmol) and Montmorillonite K-10 clay (0.10 g) were taken in a 20 mL vial and subjected to microwave irradiation in a CEM Discover Focused Microwave Synthesis System for 10 min at 90 °C. After the completion of the reaction as indicated by TLC, water (10 mL) was added to precipitate the crude product, which was recrystallized from ethanol to afford analytically pure sample of **4**. Physical data of representative compounds: Compound **4a**: White solid, yield 82%, mp 145–148 °C. IR (KBr) ν_{max} 3392, 3386, 3011, 1692 cm^{-1}. ^1H NMR (400 MHz; DMSO-d_6) δ: 4.11 (dd, 1H, $J_{2'H_a,2'H_b} = 10.1$ Hz, $J_{1'H,2'H_a} = 5.4$ Hz, 2′H_a), 4.30 (dd, 1H, $J_{1'H,2'H_a} = 5.4$ Hz, $J_{1'H,2'H_b} = 2.9$ Hz, 1′H), 4.63 (dd, 1H, $J_{2'H_a,2'H_b} = 10.1$ Hz, $J_{1'H,2'H_b} = 2.9$ Hz, 2′H_b), 4.93–5.21 (br s, 2H, 2 × OH, exchangeable with D_2O), 7.48 (d, 1H, $J_{5H,6H} = 8.1$ Hz, 5-H), 7.89 (d, 1H, $J_{5H,6H} = 8.1$ Hz, 4-H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 64.5, 65.3, 73.7, 86.2, 105.9, 174.5. MS (FAB) m/z 158 (MH^+). Anal. Calcd for $C_6H_7NO_4$: C, 45.86; H, 4.49; N, 8.91. Found: C, 46.17; H, 4.58; N, 8.79. Compound **4c**: White solid, yield 79%, mp153–155 °C. IR (KBr): 3399–3382, 3008, 1689 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ: 3.88 (ddd, 1H, $J_{2'H,3'H_a} = 5.4$ Hz, $J_{1'H,2H} = 4.6$ Hz, $J_{2'H,3'H_b} = 2.7$ Hz, 2′H), 4.03 (dd, 1H, $J_{3'H_a,3'H_b} = 10.5$ Hz, $J_{2'H,3'H_a} = 5.4$ Hz, 3′H_a), 4.37 (d, 1H, $J_{1'H,2'H} = 4.6$ Hz, 1′H), 4.59 (dd, 1H, $J_{3'H_a,3'H_b} = 10.5$ Hz, $J_{2'H,3'H_b} = 2.7$ Hz, 3′H_b), 5.01–5.37 (br s, 3H, 3 × OH, exchangeable with D_2O), 7.51 (d, 1H, $J_{4H,5H} = 8.1$ Hz, 5-H), 7.85 (d, 1H, $J_{4H,5H} = 8.1$ Hz, 4-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 64.3, 65.9, 71.7, 73.5, 86.5, 106.3, 174.8. MS (FAB) $m/z = 188$ [MH^+].

Anal. Calcd for $C_7H_9NO_5$: C, 44.92; H, 4.85; N, 7.48. Found: C, 44.69; H, 4.73; N, 7.73.

23. Audrieth, L. F.; Ogg, B. A. *The Chemistry of Hydrazines*; John Wiley and Sons: New York, 1951.
24. *General procedure for the synthesis of 4-polyhydroxyalkylpyrimidin-2-ones(thiones)* **6**: An intimate solvent-free mixture of 1,3-oxazin-2-one(thione) **4** (2.4 mmol) and aromatic amine **5** (2.4 mmol) in the presence of Montmorillonite K-10 clay (0.25 g) was taken in a 20 mL vial and subjected to MW irradiation in a CEM Discover Focused Microwave Synthesis System at 90 °C for 8–12 min. After the completion of the reaction as indicated by TLC, water (10 mL) was added to precipitate the crude product, which was recrystallized from ethanol to give an analytically pure sample of **6** as a white solid. Physical data of representative compounds: Compound **6a**: White solid, yield 88%, mp 168–170 °C. IR (KBr): 3398, 3013, 1696, 1607, 1579, 1454 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ: 3.73 (dd, 1H, $J_{2'H_a,2'H_b} = 10.4$ Hz, $J_{1'H,2'H_a} = 5.5$ Hz, $2'H_a$), 4.09 (dd, 1H, $J_{2'H_a,2'H_b} = 10.4$ Hz, $J_{1'H,2'H_b} = 2.9$ Hz, $2'H_b$), 4.30 (dd, 1H, $J_{1'H,2'H_a} = 5.5$ Hz, $J_{1'H,2'H_b} = 2.9$ Hz, 1′H), 5.01–5.16 (br s, 2H, $2 \times$ OH, exchangeable with D_2O), 7.13–7.55 (m, $5H_{arom}$), 7.91 (d, 1H, $J_{5H,6H} = 7.5$ Hz, 5-H), 8.04 (d, 1H, $J_{5H,6H} = 7.5$ Hz, 6-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 63.9, 71.6, 125.9, 127.4, 128.1, 129.3, 131.9, 134.7, 136.4, 173.1. MS (FAB) $m/z = 233$ [MH^+]. Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.83; H, 5.43; N, 11.98. Compound **6g**: White solid, yield 87%, mp 131–133 °C. IR (KBr): 3395, 3017, 1693, 1598, 1585, 1455 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ: 3.51 (ddd, 1H, $J_{2'H,3'H_a} = 5.6$ Hz, $J_{1'H,2'H} = 4.2$ Hz, $J_{2'H,3'H_b} = 2.8$ Hz, 2′H), 3.71 (dd, 1H, $J_{3'H_a,3'H_b} = 10.3$ Hz, $J_{2'H,3'H_a} = 5.6$ Hz, $3'H_a$), 4.01 (dd, 1H, $J_{3'H_a,3'H_b} = 10.3$ Hz, $J_{2'H,3'H_b} = 2.8$ Hz, $3'H_b$), 4.22 (d, 1H, $J_{1'H,2'H} = 4.2$ Hz, 1′H), 5.03–5.21 (br s, 3H, $3 \times$ OH, exchangeable with D_2O), 7.09–7.59 (m, $5H_{arom}$), 7.95 (d, 1H, $J_{5H,6H} = 7.6$ Hz, 5-H), 8.06 (d, 1H, $J_{5H,6H} = 7.6$ Hz, 6-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 63.3, 71.8, 81.7, 126.4, 128.2, 129.5, 130.3, 132.5, 134.9, 136.8, 173.3. MS (FAB) $m/z = 263$ [MH^+]. Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.89; H, 5.21; N, 10.47.