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A novel mesoionic ring system: unusual cyclization of thio- and amino-acid derivatives of 6-azauracil

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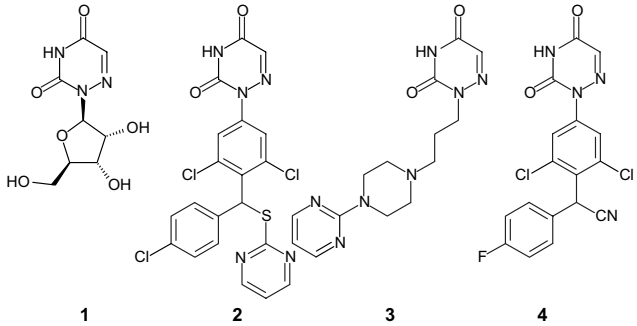
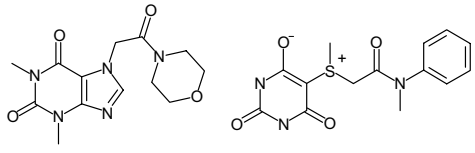
Abstract—Novel mesoionic heterocyclic structures **8** have been obtained via the internal cyclization of thio- and amino-acid derivatives of 6-azauracil **7b–d**. These compounds undergo ring-opening reactions with amines to yield the respective 6-azauracil amides (**9**) in good yields under microwave irradiation.

6-Azauracil ring system is well represented in both chemical and biological literature. Compounds (Fig. 1) containing this template were described to possess anticancer (**1**),[1] anti-depressant/hypnotic (**1**),[2] antiallergic/antiasthmatic (**2**),[3] anxiolitic/antidepressant (**3**),[4] and anticoccidial properties (**4**).[5] Similar compounds containing acetamide appendages **5** (teomorfolin)[6] and **6**[7] (Fig. 2) display hypolipidemic and non-opioid analgesic activities, respectively.



1 **2** **3** **4**

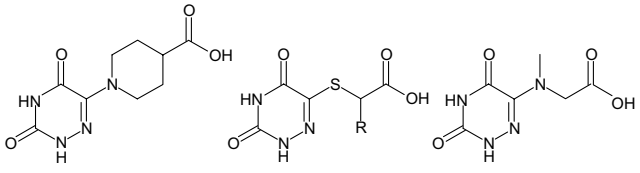
Figure 1.



5 **6**

Figure 2.

In our ongoing effort to identify templates for the synthesis of compound libraries biased against specific biological targets,[8] we investigated the synthetic potential of carboxylic acids **7a–d** (Fig. 3) available from 5-bromoazauracil.[9]



7a **7b**, R = H **7c**, R = Et **7d**

Figure 3.

Keywords: Mesoionic structures; X-ray analysis; 6-Azauracil; Microwave; Amidation reaction.
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Reaction of the CDI-activated carboxylic acid **7a** with a diverse set of amines proceeded as expected to yield the respective amide derivatives at room temperature.[10] Under the same reaction conditions, acids **7b–d** afforded very low yields of the respective amides. Furthermore, the reactions were very sluggish even at elevated temperatures up to 120 °C in DMSO. Notably, treatment of **7b–d** with CDI in DMA at room temperature resulted in almost instant precipitation of a product. LC/MS analysis of the isolated solids revealed [M−18] molecular ions, suggesting that in all three cases the reactions proceeded via formal dehydration of the parent carboxylic acids **7b–d**. ^{1}H NMR analysis of precipitates indicated that the anticipated aliphatic protons from the amino acid portion of the molecules were not present (Table 1). Instead, a weaker field singlet (integrating for 1H instead of the expected 2H) was observed at 6.30 ppm for **7b** or 6.45 ppm for **7d**. The only aliphatic protons for the precipitated product from **7c** were corresponding to the shifts of ethyl group.

Based on both spectral and literature evidences, we proposed two possible structures for the intermediates (Fig. 4). Structure **A** is the result of the CDI-mediated intramolecular cyclization of **7** via a lactonization step involving the C4 oxygen atom.[11] Alternatively, nucleophilic attack of the carbonyl group with nucleophilic N6 of the triazine ring system could lead to the formation of a mesoionic bicyclic system **B**. It is expected that both ring systems would have imidazolium counterion due to the strong acidic nature of protons on the triazole ring. This would explain the 2H and 1H proton singlets at 7.3 and 8.5 ppm, respectively, in the ^{1}H NMR spectrum of each precipitate.

Structural characterization of the product derived from **7d** upon treatment with CDI was conducted via X-ray crystallography.[12] Suitable crystalline material was obtained by recrystallization from water/ethanol. Data unequivocally revealed the zwitterionic character of the molecule in accordance with the proposed structure **B**. Imidazolium cation and crystalline water molecules were observed in the spectrum as well (Fig. 5). Although mesoionic heterocycles are well known in the literature, both imidazo[2,1-*f*][1,2,4]triazin-4-one (X = NR), as well as the analogous thiazo heterocycle (X = S) are novel heterocyclic ring systems.[13]

Based on these data, we reasoned that the encountered 'low reactivity' of carboxylic acids **7b–d** toward amines under the experimental conditions is due to the formation of the respective pseudo-aromatic intermediates **8b–d** (Scheme 1). These species were stable toward heating at 100–120 °C in DMSO with the diverse set of

Table 1. ^{1}H NMR chemical shifts of aliphatic protons

Compd	Before CDI (ppm)	After CDI (ppm)
7b	CH_2: 3.75 singlet	6.30 singlet 1H
7c	CH: 3.98 triplet	None
7d	CH_2: 4.25 singlet	6.45 singlet 1H

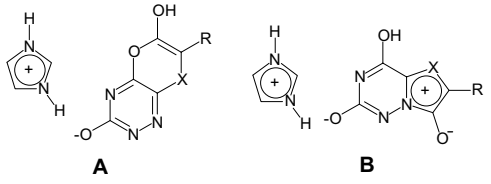


Figure 4. Proposed structures for products of CDI treatment with **7b–d**.

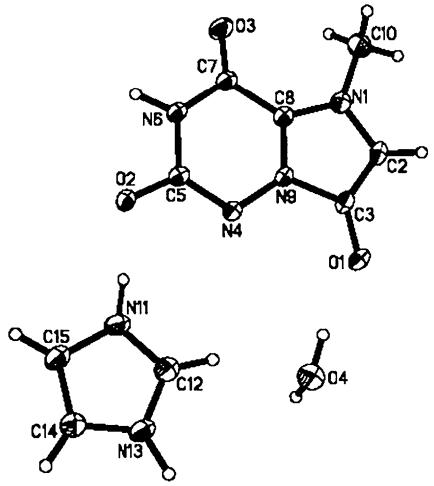
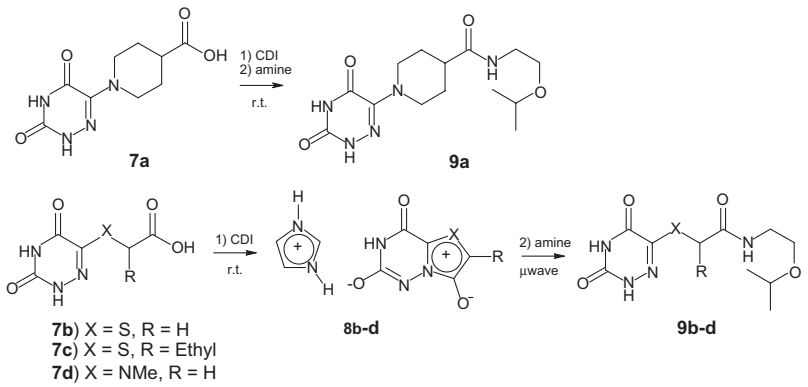


Figure 5. ORTEP plot for X-ray crystal structure of **8d**.



Scheme 1.

amines. However, the microwave irradiation in the same solvent in the presence of amines yielded the desired amides in good to excellent yield (41–82%). For example, both aliphatic primary and secondary amines (e.g., 1 equiv of 2-aminoethyl isopropyl ether) reacted with salts **8** to afford the expected amides **9** (Scheme 1).[14]

All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, LC/MS, and elemental analysis.[15]

In summary, we have discovered a convenient route to novel bicyclic mesoionic heterocycles derived from 6-azauracil. These compounds were successfully converted to the respective open-chain products in good yields under microwave irradiation. Further efforts are in progress to study both the scope and the limitations of this ring-opening reaction.

Acknowledgments

The authors would like thank Dr. Scott R. Wilson from University of Illinois for solving the X-ray structure.

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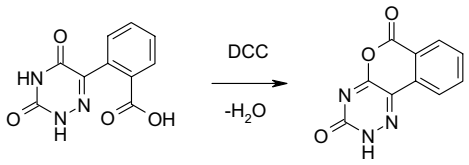
10. Isonipecotic acid adduct (**7a**, 6.0 g, 25 mmol) was dissolved in 40 mL DMA and CDI (5.0 g, 1.2 equiv) was added with rapid stirring. After 6 h, an aliquot of solution (0.50 mL) was transferred by pipet to tubes containing amine (0.25 mmol) and the mixture was shaken for 16 h. Water (2 mL) was added to ppt product. Centrifugation/decantation was performed and repeated twice with fresh water. The yield using 2-aminoethyl isopropyl ether (**9a**) was 78%.
11. Similar transformations have been reported, see for example: Hejsek, M.; Slouka, J.; Bekarek, V.; Lycka, A. *Collect. Czech. Chem. Commun.* **1992**, *57*, 123–133.



12. Crystallographic data (excluding structure factors) for the structures in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 265693. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or email: deposit@ccdc.cam.ac.uk].
13. For selected examples of mesoionic aromatics, see: Molina, P.; Arques, A.; Cartagena, I.; Valcarcel, M. V. *Synthesis* **1984**, 881–884; Avalos, M.; Babiano, R.; Cintas, P.; Clemente, F. R.; Gordillo, R.; Jimeńez, J. L.; Palacios, J. C. *J. Org. Chem.* **2003**, *68*, 6338–6348; Avalos, M.; Babiano, R.; Cintas, P.; Clemente, F. R.; Gordillo, R.; Jimeńez, J. L.; Palacios, J. C. *J. Org. Chem.* **2001**, *66*, 5139–5145; Edstrom, E. D.; Wei, Y.; Gordon, M. *J. Org. Chem.* **1994**, *59*, 2473–2481.
14. General experimental procedure: **7b–d** (1 mmol) were treated with 1.2 equiv CDI in DMA (20 mL) at room temperature for 2–4 h. The resulting solids were filtered, washed with DMA, ether, dried in vacuo to yield quantitative yields of mesoionic intermediates **8b–d**. These compounds were then added to DMSO (1 mL) to yield 0.36 M suspensions in microwave vials followed by the addition of 0.36 mmol of amine. Mixtures were subjected to microwave heating at 150 °C for 600 s. After cooling, analytically pure products were obtained by diluting the reaction mixtures with 2.0 mL of water, collecting the resulting precipitate, washing it with cold EtOH and ether. Yields were 58%, 82%, and 41% for **9b**, **c**, and **d**, respectively.
15. Compound **7a**: mp: 284 °C (dec); ^{1}H NMR (DMSO-d_6) δ 1.58 (m, 2H), 1.82 (m, 2H), 2.40 (m, 1H), 2.72 (m, 2H), 3.78 (m, 2H), 11.39 (s, 1H), 11.72 (s, 1H), 12.16 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 27.2, 40.1, 46.5, 145.1, 149.2, 154.5, 175.8; LCMS m/z = 239 (M−l); Anal. Calcd for $C_9H_{12}N_4O_4$: C, 45.00; H, 5.04; N, 23.32. Found: C, 44.71; H, 5.37; N, 23.57.
Compound **7b**: mp: 234 °C (dec); ^{1}H NMR (DMSO-d_6) δ 3.75 (s, 2H), 12.07 (s, 1H), 12.27 (s, 1H), 12.70 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 31.4, 143.8, 149.0, 155.6, 169.5; LCMS m/z = 202 (M−l); Anal. Calcd for $C_5H_5N_3O_4S$: C, 29.56; H, 2.48; N, 20.68; S, 15.78. Found: C, 27.29; H, 3.01; N, 19.12; S, 14.49.
Compound **7c**: mp: 202–204 °C; ^{1}H NMR (DMSO-d_6) δ 0.98 (t, J = 7.6 Hz, 3H), 1.82 (m, 1H), 1.88 (m, 1H), 3.98 (t, J = 6.8 Hz, 1H), 12.13 (s, 1H), 12.32 (s, 1H), 12.87 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 11.4, 24.6, 47.1, 143.3, 148.8, 155.4, 172.0; LCMS m/z = 230 (M−l); Anal. Calcd for $C_7H_9N_3O_4S$: C, 36.36; H, 3.92; N, 18.17; S, 13.87. Found: C, 34.73; H, 3.92; N, 17.25; S, 12.38.
Compound **7d**: mp: 256 °C (dec); ^{1}H NMR (DMSO-d_6) δ 2.89 (s, 3H), 4.25 (s, 2H), 11.32 (s, 1H), 11.72 (s, 1H), 12.50 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 38.8, 52.6, 144.1, 149.1, 154.7, 171.7; LCMS m/z = 199 (M−l); Anal. Calcd for

$C_6H_8N_4O_4$: C, 36.01; H, 4.03; N, 27.99. Found: C, 36.05; H, 3.90; N, 28.23.

Compound **8b**: mp: 210 °C (dec); ^{1}H NMR (D_2O) δ 6.30 (s, 1H), 7.45 (s, 2H), 8.71 (s, 1H); LCMS *m*/*z* = 184 (M−l).Compound **8c**: mp: 210 °C (dec); ^{1}H NMR (D_2O) δ 1.25 (t, *J* = 7.6 Hz, 3H), 2.77 (q, *J* = 7.6 Hz, 2H), 7.46 (s, 2H), 8.65 (s, 1H); LCMS *m*/*z* = 212 (M−l).

Compound **8d**: mp: 258 °C (dec); ^{1}H NMR (D_2O) δ 3.99 (s, 3H), 6.45 (s, 1H), 7.47 (s, 2H), 8.68 (s, 1H); LCMS *m*/*z* = 181 (M−l).

Compound **9a**: mp: 256–257 °C; ^{1}H NMR(DMSO-d_6) δ 1.06 (d, *J* = 6.0 Hz, 6H), 1.5–1.7 (m, 4H), 2.30 (m, 1H), 2.62 (t, *J* = 11.2 Hz, 2H), 3.15 (q, *J* = 6.0 Hz, 2H), 3.33 (t, *J* = 6.0 Hz, 2H), 3.51 (m, *J* = 6.0 Hz, 1H), 3.89 (d, *J* = 12.8 Hz, 2H), 7.78 (t, *J* = 5.6 Hz, 1H), 11.39 (s, 1H), 11.72 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.9, 27.7, 38.7, 41.6, 46.7, 65.9, 70.6, 145.0, 149.1, 154.4, 174.0; LCMS *m*/*z* = 326 (M+l); Anal. Calcd for $C_{14}H_{23}N_5O_4$: C, 51.68; H, 7.13; N, 21.52. Found: C, 51.43; H, 6.96; N, 21.74.

Compound **9b**: mp: 182–183 °C; ^{1}H NMR (DMSO-d_6) δ 1.06 (d, *J* = 6.0 Hz, 6H), 3.17 (q, *J* = 6.0 Hz, 2H), 3.34 (t, *J* = 6.0 Hz, 2H), 3.52 (m, *J* = 6.0 Hz, 1H), 3.65 (s, 2H), 8.07 (t, *J* = 5.6 Hz, 1H), 12.18 (br s, 1H), 12.30 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.9, 32.5, 39.3, 65.7, 70.6, 143.7, 148.7, 155.3, 166.4; LCMS *m*/*z* = 289 (M+l); Anal. Calcd for $C_{10}H_{16}N_4O_4S$: C, 41.66; H, 5.59; N, 19.43; S, 11.12. Found: C, 40.62; H, 5.48; N, 19.07; S, 11.68.

Compound **9c**: mp: 179–181 °C; ^{1}H NMR (DMSO-d_6) δ 0.89 (t, *J* = 7.6 Hz, 3H), 1.05 (d, *J* = 6.0 Hz, 6H), 1.80 (m, 2H), 3.15 (m, 1H), 3.23 (m, 1H), 3.35 (t, *J* = 6.0 Hz, 2H), 3.51 (m, *J* = 6.0 Hz, 1H), 4.00 (t, *J* = 6.8 Hz, 1H), 8.19 (t, *J* = 5.6 Hz, 1H), 12.12 (s, 1H), 12.30 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 11.2, 21.8, 25.5, 39.2, 47.9, 65.6, 70.6, 143.5, 148.7, 155.3, 169.4; LCMS *m*/*z* = 317 (M+l); Anal. Calcd for $C_{12}H_{20}N_4O_4S$: C, 45.56; H, 6.37; N, 17.71; S, 10.13. Found: C, 44.13; H, 6.31; N, 17.22; S, 10.26.

Compound **9d**: mp: 192–193 °C; ^{1}H NMR (DMSO-d_6) δ 1.06 (d, *J* = 6.0 Hz, 6H), 2.77 (s, 3H), 3.16 (q, *J* = 6.0 Hz, 2H), 3.34 (t, *J* = 6.0 Hz, 2H), 3.52 (m, *J* = 6.0 Hz, 1H), 4.11 (s, 2H), 7.84 (t, *J* = 5.6 Hz, 1H), 11.28 (s, 1H), 11.67 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.9, 38.4, 38.8, 53.8, 65.8, 70.6, 144.6, 149.0, 154.5, 168.9; LCMS *m*/*z* = 286 (M+l); Anal. Calcd for $C_{11}H_{19}N_5O_4$: C, 46.31; H, 6.71; N, 24.55. Found: C, 46.13; H, 6.39; N, 24.72.