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A novel class of compounds: synthesis of 5,5′-carbonyl-bis(5,6-dihydro-4*H*-furo- and thieno-[2,3-*c*]pyrrol-4-ones)

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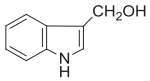
ABSTRACT

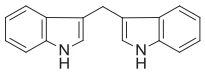
We hereby report the first synthesis of novel class of compounds, 5,5′-carbonyl-bis(5,6-dihydro-4*H*-thieno- and furo-[2,3-*c*]pyrrol-4-one starting from methyl 2-(2-methoxy-2-oxoethyl) thiophene- and furan-3-carboxylate, respectively. The ester functionalities connected to methylene group were regiospecifically converted to the desired monoacyl azides. Curtius rearrangement of acyl azides followed by hydrolysis of the formed isocyanates gave the symmetrical urea derivatives. Cyclization of the ester groups provided the target compounds.

1. Introduction

Indole-3-carbinol (**1**), a key bioactive food component in cruciferous vegetables, has multiple anticarcinogenic and antitumorigenic properties.[1,2] 3,3′-Diindolylmethane (DIM) **2** is a major metabolite derived from the digestion of indole-3-carbinol (**1**) and found also in vegetables, such as broccoli.[2]

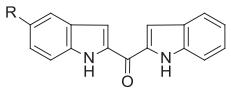


1



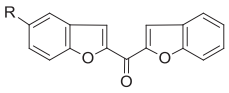
2

Recent studies have shown that diindolylmethane and some derivatives possess potential radical scavenging activities associated with cancer cells.[3] Furthermore, DIM controls growth of various tumour cells, such as breast cancer, prostate cancer, lung cancer etc.[4] Additionally, diindolylmethane modulates metabolism of oestrogen and testosterone.[5] Recently, it has been shown that the substituted bis(1*H*-2-indolyl)methanone derivative **3** inhibits autophosphorylation of platelet-derived growth factor (PDGF) receptor tyrosine kinase in intact cells.[6]



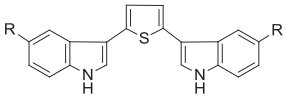
R = -OH
-CH_2OCH_3
-$CH_2N(CH_3)_2$

3



4

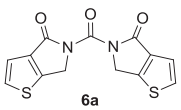
R = -H
-CH_3



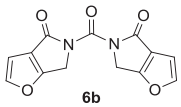
5

R = -H
-Me
-OMe
-Cl
-Br

Furthermore, a series of bis(benzo)[*b*]furan-2-ylmethanones **4** were synthesized and tested for inhibition of PDGF receptor autophosphorylation. Most of the derivatives showed strong activity.[7] More recently, Diana et al.[8] synthesized bis-indolylthiophenes of type **5** and tested in various human cancer cells. It was shown that those compounds show antiproliferative activity.[8]



6a



6b

We herein report the synthesis of a novel class of compounds, namely 5,5′-carbonyl-bis(5,6-dihydro-4*H*-thieno- and furo-[2,3-*c*]pyrrol-4-one) **6a** and **6b** with similar structure of those compounds reported above.

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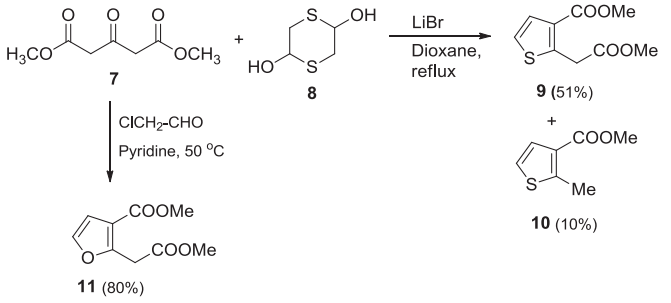
Our plan for the construction of the desired heterocyclic ring systems involved an intermolecular reaction of the isocyanate (**16**), which can be generated by Curtius rearrangement of the corresponding acyl azide with the corresponding amine followed by two intramolecular cyclization reaction.[9]

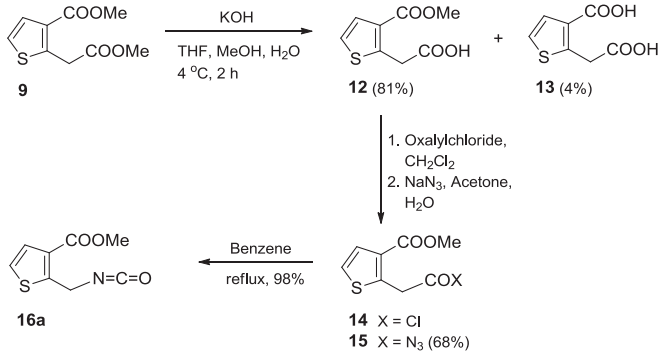
2. Results and discussion

The synthesis of the key compounds began with readily available dimethyl acetone-1,3-dicarboxylate (**7**) as reported in the literature. Reaction of dimethyl acetone-1,3-dicarboxylate with 2,5-dihydroxy-1,4-dithiane, which is a dimer mercapto-acetaldehyde, in the presence of lithium bromide in dioxane gave the diester **9** in 51% yield (Scheme 1).[10] Additionally, the methyl derivative **10**[11] was also formed as the side product in a yield of 10%.



Scheme 1. The synthesis of thiophene and furan diesters **9** and **11**.

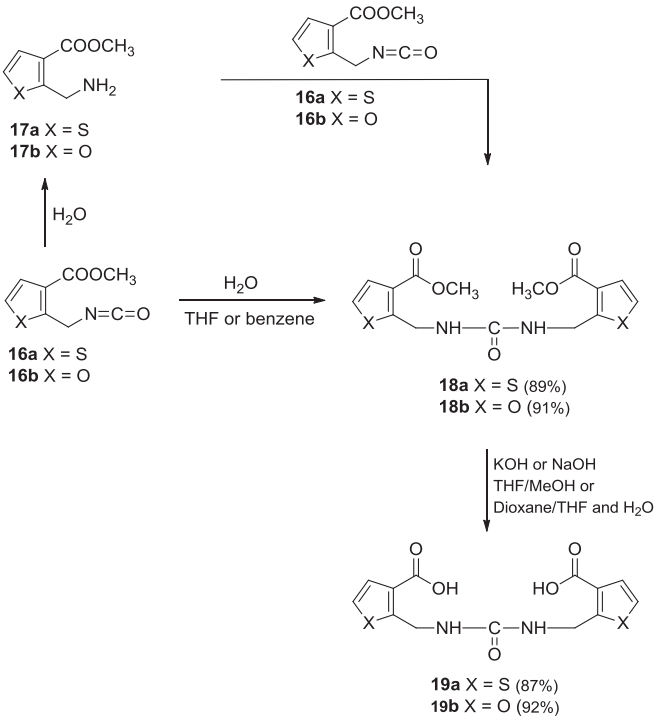
Treatment of dimethyl acetonedicarboxylate **7** with chloroacetaldehyde in the presence of pyridine yielded the diester **11** in 80% yield.[12] Recently, we reported that the reactivity of the ester carbonyl groups in **11** is different.[13] The ester functionality connected to the CH_2 group is more reactive than the other. Therefore, for regiospecific formation of the monoacid **12**, the diester **9** was treated with KOH at 4 °C (Scheme 2). The desired monoacid was formed in 81% yield. The fully hydrolyzed diacid **13** was also formed as the byproduct in 4% yield.



Scheme 2. The synthesis of isocyanate **16a**.

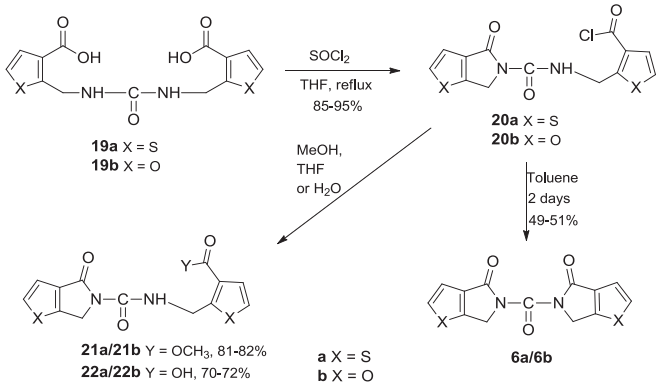
The monoacid **12** was treated with oxalyl chloride in methylene chloride at room temperature followed by reaction of the formed acyl chloride **14** with NaN_3 to give monoazide derivative **15** in 68% yield. Finally, **15** was heated to reflux in benzene for 1 h to give the corresponding isocyanate **16a** in high yield (Scheme 2). The isocyanate **16b** was synthesized as described before.[13]

The reaction of isocyanates **16a**/**16b** with water in THF or benzene yielded the urea derivatives **18a**/**18b** in 89 and 91% yields. We assume that the isocyanates first undergo hydrolysis with water and form the corresponding amines **17a**/**17b**, which add to the unreacted isocyanates to form the urea derivatives **18a**/**18b**. To prove the mechanism of the formation of urea derivative **18b**, the isocyanate **16b** was hydrolyzed with water in the presence of HCl. The formed amine **17b** was treated with isocyanate **16b** to give the urea **18b** in excellent yield. We assume that the rate of the addition of amine to isocyanate is faster than the rate of hydrolysis of isocyanate with water.[14] For ring-closure process, the urea derivatives **18a**/**18b** were submitted first to hydrolysis reaction. Treatment of **18a** and **18b** with KOH (THF/MeOH) or NaOH (Dioxane/THF) afforded the diacids **19a** and **19b** as outlined in Scheme 3.



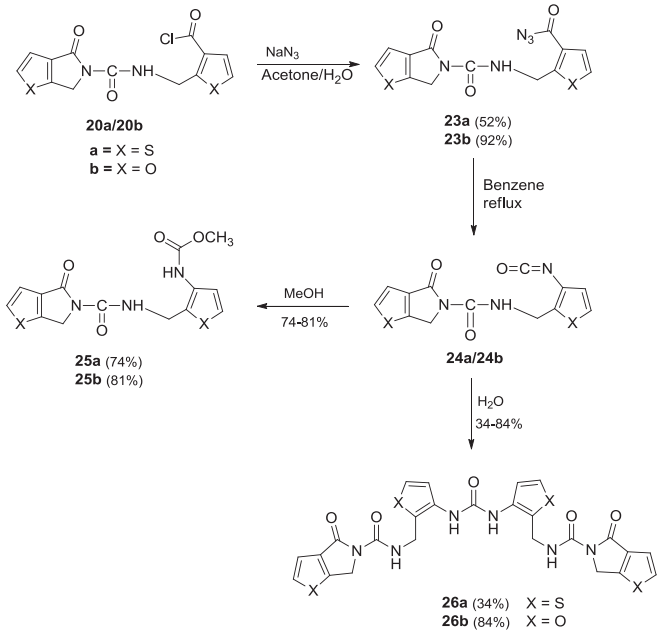
Scheme 3. The synthesis of urea derivatives **18a** and **18b**.

To conduct the ring-closing process, diacids **19a**/**19b** were reacted with thionyl chloride in tetrahydrofuran at reflux. NMR analysis indicated that only one acyl chloride functionality underwent cyclization process, whereas the other group was retained (Scheme 4). To prove the structures of **20a**/**20b**, MeOH and water was added to the reaction mixture and the formed esters **21a**/**21b** and the acids **22a**/**22b** were characterized by NMR spectral analysis. The formation of those products supported the structures of **20a** and **20b**. However, when the acid chlorides **20a**/**20b** were heated to reflux in toluene for two days, the desired cyclization products **6a** and **6b** were formed in 49 and 51% yields, respectively. The symmetrical structures of **6a** and **6b** were confirmed by ^1H NMR and ^{13}C NMR spectra showing seven distinct resonance signals as well as with HRMS.



Scheme 4. Synthesis of cyclized urea derivatives **6a**/**6b**.

The novel structures **6a** and **6b** with possible biological activities have stimulated efforts to synthesize novel systems having polyring systems with three urea units. Key reaction, hydrolysis of isocyanates **16a**/**16b**, previously used to construct the title compounds **6a** and **6b**, was applied to synthesize **26a** and **26b**. Treatment of acyl chlorides **20a**/**20b** with NaN_3 in acetone furnished acyl azides **23a**/**23b**, which were heated to reflux in benzene to affect the transformation of acyl azide functionalities to the corresponding isocyanates **24a** and **24b** (Scheme 5). Treatment of isocyanates in benzene with MeOH afforded the urethanes **25a** and **25b** in 74 and 81% yields, respectively. Hydrolysis of isocyanates **24a** and **24b** with water provided the symmetrical compounds **26a** and **26b** in high yields. High resolution mass spectrum as well as the elemental analysis clearly indicated the molecular composition of **26b** as $C_{25}H_{20}O_9N_6$. Furthermore, the presence of 13 distinct carbon resonances also supported the presence of symmetrical structures in **26a** and **26b**.



Scheme 5. Synthesis of carbonyl-bisfuro- and thieno[2,3-*c*]pyrrol-4-ones **26a**/**26b**.

3. Conclusion

In conclusion, we have described an effective approach to utilize the synthetic potential of thiophene and furan diesters **9** and **11** for the preparation for novel heterocyles,[15] such as carbonyl-bisthieno- and furo[2,3-*c*]pyrrol-4-ones **6a** and **6b**.

4. Experimental section

4.1. General

Melting points were determined on a Thomas-Hoover capillary melting point apparatus. IR spectra were recorded on a Perkin–Elmer 980 spectrometer. NMR spectra were recorded on a Bruker instrument at 400 MHz for ^1H and 100.6 MHz for ^{13}C NMR. Apparent splitting is given in all cases. Column chromatography was performed on silica gel (60-mesh, Merck) TLC was carried out on Merck 0.2 mm silica gel 60 F_{254} analytical aluminium plates. All substances reported in this paper are in their racemic form.

*4.1.1. Methyl 2-(2-methoxy-2-oxoethyl)-3-thienoate (**9**).* A solution of dimethyl acetone-1,3-dicarboxylate (**7**) (51.4 g, 0.296 mol) in 1,4-dioxane (75 mL) and then LiBr (28.2 g, 0.325 mol) were added to a stirred suspension of 2,5-dihydroxy-1,4-dithiane (30.0 g, 0.197 mol) in 1,4-dioxane (300 mL). The mixture was stirred at reflux for 20 h. The mixture was filtered into a separating funnel and extracted with ethyl acetate (500 mL) and water (70 mL). The water layer was re-extracted with ethyl acetate (2×250 mL) and the combined organic layers were washed with aq HCl (500 mL, 1 M), aq $NaHCO_3$ (5%), aq NaOH (500 mL, %10) and then with brine (500 mL). The solution was dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by column chromatography (350 g) eluting with hexane/ethyl acetate (7:2) and then (5:2) to give monoester **10** as the first fraction. The desired diester **9** was isolated as the second fraction.

*4.1.2. Methyl 2-methyl-3-thienoate (**10**)[11].* Colourless oil (4.6 g, 10%), ν_{max} (ATR) 3099, 2952, 1740, 1707, 1633, 1537, 1435, 1262, 1193, 1175, 1014 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.31 (d, J=5.4 Hz, 1H), 6.91 (d, J=5.4 Hz, 1H), 3.77 (s, 3H), 2.67 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 164.0, 149.4, 129.2, 128.0, 121.0, 51.3, 15.3.

*4.1.3. Methyl 2-(2-methoxy-2-oxoethyl)-3-thienoate (**9**)[10].* Colourless oil (32.3 g, 51%), ν_{max} (ATR) 3099, 2950, 1708, 1680, 1536, 1435, 1260, 1195, 1096 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.46 (d, J=5.4 Hz, 1H), 7.17 (d, J=5.4 Hz, 1H), 4.24 (s, 2H), 3.86 (s, 3H), 3.76 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 170.4, 163.6, 143.9, 129.5, 129.0, 123.3, 52.2, 51.5, 34.3.

*4.1.4. [3-(Methoxycarbonyl)-2-thienyl]acetic acid (**12**).* A solution of KOH (50 mL, 100 mmol, 2 M) in methanol was added to a stirred solution of diester **9** (13.0 g, 60.7 mmol) in THF (150 mL) and water (10 mL) at 4 °C, and then the mixture was stirred for 2 h without removing the ice-bath. After the completion of the reaction, water (300 mL) was added. The mixture was extracted with ethyl acetate (250 mL). The water layer was acidified to pH=2 with HCl and extracted with ethyl acetate (3×250 mL). The combined organic layers were washed with water (250 mL), dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by column chromatography (silica gel, 180 g) eluting with hexane/ethyl acetate (2:1), (1:1) and finally with ethyl acetate to give monoacid **12** as the first fraction. White solid (9.80 g, 81%), mp 106–107 °C; [Found: C, 48.24; H, 3.91. $C_8H_8O_4S$ requires C, 47.99; H, 4.03%]; R_f (5% MeOH/EtOAc) 0.71; ν_{max} (ATR): 3107, 3094, 2948, 1702, 1539, 1430, 1397, 1280, 1218, 1192, 1014 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.47 (d, J=5.4 Hz, 1H), 7.19 (d, J=5.4 Hz, 1H), 4.25 (s, 2H), 3.89 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 173.8, 164.3, 143.2, 129.6, 129.1, 123.6, 51.9, 34.7.

*4.1.5. 2-(Carboxymethyl)-3-thienoic acid (**13**).* The diacid **13** was isolated as the second fraction. White solid (0.45 g, 4%), mp 207–209 °C; [Found: C, 45.31; H, 3.28. $C_7H_6O_4S$ requires C, 45.16; H, 3.25%]; R_f (10% MeOH/EtOAc) 0.27; ν_{max} (ATR) 3106, 3095, 2879, 2628, 2534, 1697, 1662, 1537, 1447, 1284, 1216, 1149 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 12.61 (br s, 2H), 7.41 (d, J=5.4 Hz, 1H), 7.34 (d, J=5.4 Hz, 1H), 4.14 (s, 2H); δ_C (100.6 MHz, DMSO-d_6) 171.1, 164.2, 144.3, 130.2, 128.8, 123.8, 34.0.

*4.1.6. 1-{[3-(Methoxycarbonyl)-2-thienyl]acetyl}triaza-1,2-dien-2-ium (**15**).* Oxalyl chloride (3.1 mL, 36.4 mmol) and then DMF (3 drops) were added to a stirred solution of the acid **12** (5.6 g, 28 mmol) in dichloromethane (150 mL) at room temperature. The reaction mixture was stirred for 1 h and the solvent was evaporated. The residue was dissolved in acetone (150 mL) and cooled to 0 °C. To this solution, a solution of NaN_3 (2.73 g, 42 mmol) in water (6 mL) was added and stirred for 1 h. Water (250 mL) was added to reaction mixture and extracted with ethyl acetate (3×250 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated to give acyl azide **15** as a colourless oil (4.21 g, 68%,

purity >95%); ν_{max} (ATR) 2952, 2138, 1706, 1538, 1437, 1328, 1264, 1180, 1150, 1061, 1012 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.38 (d, J=5.4 Hz, 1H), 7.11 (d, J=5.4 Hz, 1H), 4.15 (s, 2H), 3.78 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 176.7, 163.5, 142.5, 129.9, 129.1, 123.7, 51.7, 36.6.

*4.1.7. Methyl 2-(isocyanatomethyl)-3-thienoate (**16a**).* The acyl azide **15** (6.0 g, 27.0 mmol) was dissolved in dry benzene (150 mL) and heated at reflux for 75 min. The solvent was evaporated to give isocyanate **16a** as a colourless oil (5.20, 98%, purity >95%); ν_{max} (ATR): 2952, 2247, 1706, 1537, 1437, 1326, 1265, 1196, 1159, 1088, 1014 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.36 (d, J=5.3 Hz, 1H), 7.11 (d, J=5.3 Hz, 1H), 4.95 (s, 2H), 3.80 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 163.3, 149.2, 128.3, 127.9, 124.5, 123.3, 51.8, 41.8.

*4.1.8. Methyl 2-({[({[3-(methoxycarbonyl)-2-thienyl]methyl}amino) carbonyl]amino}methyl)-3-thienoate (**18a**).* H_2O (5 mL) was added dropwise to a stirred solution of the isocyanate **16a** (5.1 g, 25.9 mmol) in THF (150 mL) and stirred at 50 °C for 1 h. During the reaction, a white solid precipitated. The mixture was allowed to cool to room temperature, filtered on a filter paper, washed with hexane/ethyl acetate (1:1) and allowed to dry to give dimer urea derivative **18a** as a white solid (4.20 g, 89%), mp 211–212 °C; [Found: C, 49.22; H, 4.33; N, 7.38. $C_{15}H_{16}N_2O_5S_2$ requires C, 48.90; H, 4.38; N, 7.60%]; R_f (50% EtOAc/hexane) 0.52; ν_{max} (ATR) 3312, 3026, 2946, 1711, 1623, 1583, 1528, 1425, 1343, 1262, 1193, 1155, 1084, 1003 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 7.40 (d, J=5.3 Hz, 2H), 7.34 (d, J=5.3 Hz, 2H), 6.92 (t, J=6.1 Hz, 2H), 4.67 (d, J=6.1 Hz, 4H), 3.80 (s, 6H); δ_C (100.6 MHz, DMSO-d_6) 163.1, 157.4, 155.9, 128.6, 126.2, 123.4, 51.6, 38.6.

*4.1.9. Methyl 2-({[({[3-(methoxycarbonyl)-2-furyl]methyl}amino)carbonyl]amino}-methyl)-3-furoate (**18b**).* H_2O (3 mL) was added dropwise to a stirred solution of the isocyanate **16b** (5.1 g, 28.2 mmol) in dry benzene (100 mL), stirred at 50 °C for 2 h and then at room temperature for 18 h. The solvent was evaporated and the crude product was purified by crystallization with hexane/ethyl acetate (5:1) to give the urea **18b** as a white solid (4.3 g, 91%), mp 141–143 °C; [Found: 53.32; H, 4.83; N, 8.10. $C_{15}H_{16}N_2O_7$ requires C, 53.57; H, 4.80; N, 8.33%]; R_f (50% EtOAc/hexane) 0.40; ν_{max} (KBr) 3336, 2958, 1714, 1631, 1442, 1315, 1268, 1202, 1095 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.29 (d, J=1.8 Hz, 2H), 6.65 (d, J=1.8 Hz, 2H), 5.59 (br s, 2H,), 4.67 (d, J=6.2 Hz, 4H), 3.83 (s, 6H); δ_C (100.6 MHz, $CDCl_3$) 164.4, 158.8, 157.4, 141.4, 114.4, 110.6, 51.7, 36.9.

*4.1.10. 2-{[({[(3-Carboxy-2-thienyl)methyl]amino}carbonyl)amino]-methyl}-3-thienoic acid (**19a**).* A solution of KOH (43.5 mL, 87 mmol, 2 M) in methanol was added to a stirred solution of urea **18a** (4.0 g, 10.9 mmol) in THF (300 mL), MeOH (80 mL) and H_2O (0.8 mL). The mixture was heated at reflux for 1 h and monitored by TLC. After the completion of the reaction, a solid precipitated. The precipitate was filtered, washed with ethyl acetate and dissolved in water (60 mL). The solution was acidified with aq HCl (5 M) to pH=2 and during the acidification product precipitated. The solid filtered, washed with ethyl acetate/dichloromethane (1:1) and allowed to dry to give diacid **19a** as a white solid (3.23 g, 87%), mp 242–243 °C; [Found: C, 45.62; H, 3.32; N, 7.95. $C_{13}H_{12}N_2O_5S_2$ requires C, 45.87; H, 3.55; N, 8.23%]; R_f (10% MeOH/EtOAc) 0.32; ν_{max} (ATR) 3327, 3113, 2850, 2608, 2549, 1669, 1628, 1580, 1452, 1345, 1293, 1249, 1194, 1086 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 12.72 (br s, 2H), 7.35 (d, J=5.3 Hz, 2H), 7.30 (d, J=5.3 Hz, 2H), 6.87 (t, J=6.1 Hz, 2H,), 4.66 (d, J=6.1 Hz, 4H); δ_C (100.6 MHz, DMSO-d_6) 164.2, 157.5, 154.9, 129.1, 127.8, 123.0, 38.4.

*4.1.11. 2-{[({[(3-Carboxy-2-furyl)methyl]amino}carbonyl)amino]-methyl}-3-furoic acid (**19b**).* A solution of NaOH (45 mL, 45 mmol, 1 M) was added to a stirred solution of urea **18b** (3.0 g, 8.9 mmol) in THF (200 mL) and dioxane (80 mL) and the resulting mixture was stirred at 50 °C for 3 h. Further aq NaOH (20 mL, 20 mmol, 1 M) was added and stirred for 2 h. The reaction was monitored on TLC. After the completion of the reaction, the solution was acidified with 1 M of HCl to pH=2 and then extracted with AcOEt (3×250 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$ and the solvent was evaporated to give the diacid **19b** as a white solid (2.54 g, 92%), mp 255–257 °C; [Found: C, 50.42; H, 3.96; N 9.11. $C_{11}H_{15}N_2O_7$ requires C, 50.65; H, 3.92; N, 9.09%]; R_f (10% MeOH/EtOAc) 0.25; ν_{max} (ATR) 3348, 3139, 2879, 1692, 1628, 1518, 1448, 1318, 1259, 1220, 1125, cm^{-1}; δ_H (400 MHz, DMSO-d_6) 12.75 (br s, 2H), 7.63 (d, J=1.9 Hz, 2H), 6.64 (d, J=1.9 Hz, 2H), 6.49 (t, J=5.6 Hz, 2H), 4.5 (d, J=5.6 Hz, 4H); δ_C (100.6 MHz, DMSO-d_6) 164.3, 158.6, 157.3, 141.9, 114.4, 110.8, 35.7.

*4.1.12. 2-({[(4-Oxo-4,6-dihydro-5H-thieno[2,3-c]pyrrol-5-yl)carbonyl]amino}methyl)-3-thienoyl chloride (**20a**).* $SOCl_2$ (1.0 mL, 13.67 mmol) was added to a suspension of the diacid **19a** (1.0 g, 2.90 mmol) in dry THF (40 mL) and the mixture heated at reflux for 3 h. The solvent and excess $SOCl_2$ were evaporated to give product **20a** as a white solid (0.85 g, 85%), purity 90% determined by NMR. ν_{max} (ATR) 3230, 3149, 3125, 1705, 1672, 1540, 1515, 1465, 1316, 1265, 1140, 1091, 1037 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.06 (t, J=6.0 Hz, 1H), 7.54 (d, J=5.4 Hz, 1H), 7.36 (d, J=5.1 Hz, 1H), 7.21 (d, J=5.1 Hz, 1H), 7.11 (d, J=5.4 Hz, 1H), 4.89 (d, J=6.0 Hz, 2H), 4.85 (s, 2H); δ_C (100.6 MHz, $CDCl_3$) 165.2, 161.6, 155.5, 152.9, 152.5, 138.6, 132.0, 131.4, 131.3, 123.2, 120.6, 47.5, 38.7.

*4.1.13. 2-({[(4-Oxo-4,6-dihydro-5H-furo[2,3-c]pyrrol-5-yl)carbonyl] amino}methyl)-3-furoyl chloride (**20b**).* $SOCl_2$ (1.9 mL, 25.97 mmol) was added to a suspension of the diacid **19b** (2.0 g, 6.49 mmol) in dry THF (80 mL) and heated at reflux for 3 h. The solvent and excess $SOCl_2$ were evaporated to give product **20b** as a white solid (1.9 g, 95%), purity 95% determined by NMR. ν_{max} (ATR): 3337, 3157, 3133, 1699, 1592, 1540, 1511, 1461, 1443, 1319, 1255, 1154, 1076 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.84 (br t, J=5.1 Hz, 1H), 7.57 (d, J=2.0 Hz, 1H), 7.37 (d, J=2.0 Hz, 1H), 6.81 (d, J=2.0 Hz, 1H), 6.66 (d, J=2.0 Hz, 1H), 4.86 (d, J=6.0 Hz, 2H), 4.76 (s, 2H); δ_C (100.6 MHz, $CDCl_3$) 168.5, 165.3, 162.1, 159.9, 153.5, 149.7, 142.4, 120.8, 119.7, 112.9, 106.3, 45.2, 36.8.

*4.1.14. Methyl 2-({[(4-oxo-4,6-dihydro-5H-thieno[2,3-c]pyrrol-5-yl) carbonyl]amino}-methyl)-3-thienoate (**21a**).* Dry MeOH (2 mL) was added to a stirred solution of the acyl chloride **20a** (250 mg, 0.73 mmol) in dry THF (25 mL) and stirred at 60 °C for 2 h. The solvent and excess MeOH were evaporated. The crude product was purified by column chromatography eluting with ethyl acetate/dichloromethane/hexane (1:1:1) to give ester **21a** as a white solid (200 mg, 81%), mp 186–187 °C; [Found: C, 50.13; H, 3.42; N, 7.96. $C_{14}H_{12}N_2O_4S_2$ requires C, 49.99; H, 3.60; N, 8.33%]; R_f (50% EtOAc/hexane) 0.69; ν_{max} (ATR) 3280, 3100, 3079, 2951, 1698, 1674, 1525, 1473, 1455, 1440, 1391, 1353, 1275, 1151, 1101 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.09 (br t, J=6.0 Hz, 1H), 7.36 (d, J=5.3 Hz, 1H), 7.34 (d, J=5.0 Hz, 1H), 7.19 (d, J=5.0 Hz, 1H), 7.05 (d, J=5.3 Hz, 1H), 4.92 (d, J=6.3 Hz, 2H), 4.84 (s, 2H), 3.85 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 165.1, 163.6, 162.8, 152.3, 150.1, 138.8, 131.0, 129.4, 128.7, 122.9, 120.5, 51.8, 47.4, 37.7.

*4.1.15. Methyl 2-({[(4-oxo-4,6-dihydro-5H-furo[2,3-c]pyrrol-5-yl)-carbonyl]amino}-methyl)-3-furoate (**21b**).* The same procedure was used as described above using acyl chloride **20b** (500 mg, 1.62 mmol) to give ester **21b** as a white solid (400 mg, 82%), mp 126–127 °C; [Found: C, 55.61; H, 3.95; N 9.32. $C_{14}H_{12}N_2O_6$ requires C, 55.27; H, 3.98; N, 9.21%]; R_f (50% EtOAc/hexane) 0.56; ν_{max} (ATR) 3288, 3148, 3126, 1715, 1678, 1539, 1514, 1500, 1462, 1306, 1282, 1275, 1163, 1137, 1090, 1036 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.83 (br t, J=5.4 Hz, 1H), 7.56 (d, J=2.0 Hz, 1H), 7.33 (d, J=1.9 Hz, 1H), 6.69 (d,

J=1.9 Hz, 1H), 6.65 (d, J=2.0 Hz, 1H), 4.88 (d, J=6.0 Hz, 2H), 4.76 (s, 2H), 3.89 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 168.2, 165.0, 163.7, 157.4, 153.2, 149.3, 141.7, 120.6, 114.9, 110.9, 106.0, 51.7, 45.0, 36.2.

*4.1.16. 2-({[(4-Oxo-4,6-dihydro-5H-thieno[2,3-c]pyrrol-5-yl)carbonyl]amino}methyl)-3-thienoic acid (**22a**).* H_2O (1 mL) was added to a stirred solution of the acyl chloride **20a** (250 mg, 0.73 mmol) in THF (25 mL) and stirred at 60 °C for 2 h. The solvent and excess H_2O were evaporated. The crude product was purified by column chromatography eluting with ethyl acetate to give carboxylic acid **22a** as a white solid (170 mg, 72%), mp 250–251 °C; [Found: C, 48.49; H, 3.30; N, 8.31. $C_{13}H_{10}N_2O_4S_2$ requires C, 48.44; H, 3.13; N, 8.69%]; R_f (5% MeOH/EtOAc) 0.73; ν_{max} (ATR) 3290, 3094, 3078, 2979, 2579, 1696, 1631, 1526, 1465, 1441, 1419, 1395, 1359, 1263, 1236, 1183, 1137, 1092, 1027 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 12.95 (br s, 1H), 9.04 (t, J=6.2 Hz, 1H), 7.74 (d, J=5.0 Hz, 1H), 7.40 (d, J=5.3 Hz, 1H), 7.35 (d, J=5.3 Hz, 1H), 7.29 (d, J=5.0 Hz, 1H), 4.89 (s, 2H), 4.88 (d, J=6.2 Hz, 2H); δ_C (100.6 MHz, DMSO-d_6) 164.9, 164.3, 154.0, 152.3, 151.3, 137.8, 132.8, 129.5, 129.2, 123.6, 119.9, 48.0, 38.0.

*4.1.17. 2-({[(4-Oxo-4,6-dihydro-5H-furo[2,3-c]pyrrol-5-yl)carbonyl]amino}methyl)-3-furoic acid (**22b**).* The same procedure was used as described above using acyl chloride **20b** (400 mg, 1.30 mmol) and crystallized from ethanol to give carboxylic acid **22b** as a white solid (260 mg, 70%), mp 206–207 °C; [Found: C, 53.80; H, 3.51; N 9.51. $C_{13}H_{10}N_2O_6$ requires C, 53.80; H, 3.47; N, 9.65%]; R_f (5% MeOH/EtOAc) 0.60; ν_{max} (ATR) 3332, 3157, 3132, 1698, 1660, 1538, 1512, 1461, 1320, 1267, 1255, 1156, 1076 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 12.87 (br s, 1H), 8.74 (t, J=5.9 Hz, 1H), 8.01 (d, J=1.8 Hz, 1H), 7.67 (d, J=1.9 Hz, 1H), 6.86 (d, J=1.9 Hz, 1H), 6.69 (d, J=1.8 Hz, 1H), 4.81 (s, 2H), 4.76 (d, J=5.9 Hz, 2H); δ_C (100.6 MHz, DMSO-d_6) 169.5, 165.2, 164.7, 157.8, 152.8, 150.9, 142.7, 119.9, 115.3, 111.4, 106.1, 45.4, 36.3.

*4.1.18. 5,5′-Carbonyl-bis(5,6-dihydro-4H-thieno[2,3-c]pyrrol-4-one) (**6a**).* The acyl chloride **20a** (400 mg, 1.17 mmol) was dissolved in toluene (25 mL) and heated at reflux for 48 h. After evaporation of solvent the crude product was purified by column chromatography (silica gel, 40 g) eluting with dichloro-methane/ethyl acetate (3:2) to give **6a** as a white solid (175 mg, 49%), mp 260–262 °C; [Found: C, 51.43; H, 2.62; N, 8.93. $C_{13}H_8N_2O_3S_2$ requires C, 51.30; H, 2.65; N, 9.20%]; R_f (50% EtOAc/hexane) 0.53; ν_{max} (ATR) 3120, 3092, 3072, 2980, 1711, 1678, 1525, 1455, 1362, 1315, 1254, 1152, 1123, 1088 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.34 (d, J=5.0 Hz, 2H), 7.20 (d, J=5.0 Hz, 2H), 5.01 (s, 4H); δ_C (100.6 MHz, $CDCl_3$) 161.9, 152.4, 149.2, 138.6, 130.9, 121.1, 47.9; HRMS found $(M+Na)^+$: 326.9846, $C_{13}H_8O_3S_2N_2Na$ requires: 326.9869.

*4.1.19. 5,5′-Carbonyl-bis(5,6-dihydro-4H-furo[2,3-c]pyrrol-4-one) (**6b**).* The same procedure was used as described above using acyl chloride **20b** (100 mg, 0.32 mmol) to give the product **6b** as a white solid (45 mg, 51%), mp 200–202 °C; [Found: C, 57.02; H, 2.85; N, 10.15. $C_{13}H_8N_2O_5$ requires C, 57.36; H, 2.96; N, 10.29%]; R_f (50% EtOH/hexane) 0.47; ν_{max} (ATR) 3154, 3125, 1738, 1662, 1441, 1405, 1308, 1267, 1131 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.50 (d, J=2.0 Hz, 2H), 6.60 (d, J=2.0 Hz, 2H), 4.83 (s, 4H); δ_C (100.6 MHz, $CDCl_3$) 168.1, 161.4, 149.4, 149.3, 120.5, 106.4, 45.5; HRMS found $(M+Na)^+$: 295.0310, $C_{13}H_8O_5N_2Na$ requires: 295.0331.

*4.1.20. 2-({[(4-Oxo-4,6-dihydro-5H-thieno[2,3-c]pyrrol-5-yl)carbonyl]amino}methyl)-3-thienyl azide (**23a**).* A solution of NaN_3 (0.162 g, 2.5 mmol) in H_2O (2 mL) was added to a stirred solution of the acyl chloride **20a** (400 mg, 1.17 mmol) in acetone (30 mL) at 2 °C. Precipitation of inorganic salt was immediately observed. The resulting mixture was stirred for 1 h and then H_2O (100 mL) was added. The mixture was extracted with ethyl acetate (3×50 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by column chromatography eluting with ethyl acetate/dichloromethane/hexane (1:1:1) to give acyl azide **23a** as a white solid (210 mg, 52%), mp 146–147 °C; [Found: C, 45.31; H, 2.76; N, 19.85. $C_{13}H_9N_5O_3S_2$ requires C, 44.95; H, 2.61; N, 20.16%]; R_f (50% EtOAc/hexane) 0.60; ν_{max} (ATR) 3303, 3116, 2960, 2930, 2144, 1712, 1671, 1520, 1470, 1446, 1273, 1248, 1168, 1141, 1070 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.12 (br t, J=6.1 Hz, 1H), 7.35 (d, J=5.0 Hz, 1H), 7.32 (d, J=5.4 Hz, 1H), 7.20 (d, J=5.0 Hz, 1H), 7.06 (d, J=5.4 Hz, 1H), 4.95 (d, J=6.3 Hz, 2H), 4.84 (s, 2H); δ_C (100.6 MHz, $CDCl_3$) 168.1, 165.1, 152.8, 152.4, 138.7, 131.1, 129.2, 124.8, 124.1, 123.3, 120.5, 47.4, 37.9.

*4.1.21. 2-({[(4-Oxo-4,6-dihydro-5H-furo[2,3-c]pyrrol-5-yl)carbonyl]amino}methyl)-3-furoyl azide (**23b**).* A solution of NaN_3 (0.68 g, 10.5 mmol) in H_2O (5 mL) was added to a stirred solution of the acyl chloride **20b** (1.8 g, 5.83 mmol) in acetone (70 mL) at 2 °C. Precipitation of inorganic salt was immediately observed. The resulting mixture was stirred for 1 h and H_2O (100 mL) was added. The mixture was extracted with ethyl acetate (3×150 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by column chromatography eluting with ethyl acetate/dichloromethane/hexane (1:1:1) to give acyl azide **23b** as a white solid (1.72 g, 92%), mp 121–122 °C; [Found: C, 49.68; H, 2.98; N, 21.83. $C_{13}H_9N_5O_5$ requires C, 49.53; H, 2.88; N, 22.22%]; R_f (50% EtOAc/hexane) 0.48; ν_{max} (ATR) 3305, 3126, 2178, 2141, 1717, 1684, 1580, 1535, 1460, 1415, 1308, 1257, 1199, 1133, 1072 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.87 (br t, J=5.5 Hz, 1H), 7.57 (d, J=2.0 Hz, 1H), 7.34 (d, J=2.0 Hz, 1H), 6.67 (d, J=2.0 Hz, 1H), 6.65 (d, J=2.0 Hz, 1H), 4.90 (d, J=6.0 Hz, 2H), 4.76 (s, 2H); δ_C (100.6 MHz, $CDCl_3$) 165.9, 165.7, 162.7, 156.4, 150.8, 150.0, 139.7, 118.2, 113.9, 108.3, 103.6, 42.7, 34.0.

*4.1.22. Methyl 2-({[(4-oxo-4,6-dihydro-5H-thieno[2,3-c]pyrrol-5-yl)carbonyl]amino}-methyl)-3-thienylcarbamate (**25a**).* The acyl azide **23a** (200 mg, 0.58 mmol) was dissolved in dry benzene (30 mL) and heated at reflux for 7 h. To this solution, dry MeOH (2 mL) was added and stirred at 50 °C for 2 h. The solvent and excess MeOH were evaporated. The crude product was purified by column chromatography (silica gel, 30 g) eluting with ethyl acetate/dichloromethane/hexane (1:1:2) to give urethane **25a** as a white solid (150 mg, 74%), mp 211–213 °C; [Found: C, 47.72; H, 3.60; N, 11.67. $C_{14}H_{13}N_3O_4S_2$ requires C, 47.85; H, 3.73; N, 11.96%]; R_f (50% EtOAc/hexane) 0.60; ν_{max} (ATR) 3294, 3105, 3091, 2958, 1743, 1692, 1674, 1581, 1537, 1493, 1437, 1274, 1232, 1148, 1041 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.02 (br s, 1H), 8.92 (br t, J=5.4 Hz, 1H), 7.42 (br s, 1H), 7.35 (d, J=5.0 Hz, 1H), 7.19 (d, J=5.0 Hz, 1H), 7.09 (d, J=5.4 Hz), 4.84 (s, 2H), 4.45 (d, J=6.4 Hz, 2H), 3.73 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 165.1, 154.7, 154.2, 152.5, 138.5, 135.1, 131.2, 123.4, 123.3, 121.9, 120.5, 52.4, 47.5, 35.1.

*4.1.23. Methyl 2-({[(4-oxo-4,6-dihydro-5H-furo[2,3-c]pyrrol-5-yl)carbonyl]amino}-methyl)-3-furylcarbamate (**25b**).* The acyl azide **23b** (500 g, 1.59 mmol) was dissolved in dry benzene (50 mL) and reacted with MeOH as described above. Urethane **25b** was isolated as a white solid (410 g, 81%), mp 210–212 °C; [Found: C, 52.37; H, 4.13; N, 12.85. $C_{14}H_{13}N_3O_6$ requires C, 52.67; H, 4.10; N, 13.16%]; R_f (50% EtOAc/hexane) 0.45; ν_{max} (ATR) 3303, 3158, 3141, 1741, 1713, 1664, 1651, 1530, 1503, 1459, 1317, 1243, 1141, 1070 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.80 (br s, 1H), 8.26 (br s, 1H,), 7.49 (d, J=2.0 Hz, 1H), 7.16 (d, J=2.0 Hz, 1H), 6.77 (br s, 1H), 6.58 (d, J=2.0 Hz, 1H,), 4.67 (s, 2H), 4.30 (d, J=6.0 Hz, 2H), 3.71 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 168.2, 164.9, 154.7, 154.5, 149.4, 141.0, 138.9, 123.1, 120.5, 107.4, 106.0, 52.3, 45.0, 34.5.

*4.1.24. Carbonyl-bis{[3-(amino)-2-furyl]methyl}-4-oxo-4,6-dihydro-5H-furo[2,3-c]pyrrole-5-carboxamide (**26b**).* The acyl azide **23b** (500 mg, 1.59 mmol) was dissolved in dry benzene (50 mL) and heated at reflux for 7 h. Water (2 mL) was added to this solution and

stirred at 50 °C for 4 h. The solvent and excess H_2O were evaporated. The crude product was purified by washing with ethyl acetate/dichloromethane/hexane (1:1:1) to give the product **26b** as a white solid (360 mg, 84%), mp 241–243 °C; [Found: C, 54.35; H, 3.70; N 14.89. $C_{25}H_{20}O_9N_6$ requires C, 54.75; H, 3.68; N, 15.32%]; R_f (EtOAc) 0.51; ν_{max} (ATR) 3314, 3142, 1717, 1664, 1519, 1309, 1259, 11,456, 1072 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 8.62 (t, J=5.6 Hz, 2H,), 8.36 (br s, 2H), 8.00 (d, J=2.0 Hz, 2H), 7.48 (d, J=1.9 Hz, 2H), 6.86 (d, J=2.0 Hz, 2H,), 6.69 (d, J=1.9 Hz, 2H), 4.81 (s, 4H), 4.44 (d, J=5.6 Hz, 4H); δ_C (100.6 MHz, DMSO-d_6) 169.0, 164.6, 152.9, 152.5, 150.4, 140.9, 138.8, 122.5, 119.5, 108.4, 105.7, 45.0, 34.3; HRMS found $(M+Na)^+$: 571.1188, $C_{25}H_{20}O_9N_6Na$ requires: 571.1189.

*4.1.25. Carbonyl-bis{[3-(amino)-2-thienyl]methyl}-4-oxo-4,6-dihydro-5H-thieno[2,3-c]pyrrole-5-carboxamide (**26a**).* The acyl azide **23a** (150 mg, 0.43 mmol) was dissolved in dry benzene (30 mL) and heated at reflux for 7 h. The benzene was evaporated and the residue was dissolved in THF (30 mL). To this solution, H_2O (2 mL) was added, stirred at 50 °C for 1 h and allowed to cool to room temperature. Hexane was added to mixture, filtered and washed with chloroform to give the product **26a** as a white solid (50 mg, 34%), mp 269–271 °C; [Found: C, 48.75; H, 3.16; N, 13.39. $C_{25}H_{20}N_6O_5S_4$ requires C, 49.01; H, 3.29; N, 13.72%]; R_f (EtOAc) 0.65; ν_{max} (ATR) 3290, 3102, 3076, 2924, 1702, 1680, 1634, 1584, 15,378, 1507, 1397, 1354, 1265, 1148, 1032 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 8.84 (t, J=5.8 Hz, 2H), 8.65 (br s, 2H), 7.73 (d, J=5.0 Hz, 2H), 7.34 (d, J=5.4 Hz, 2H), 7.29 (d, J=5.8 Hz, 2H), 7.28 (d, J=5.0 Hz, 4H), 4.91 (s, 4H), 4.55 (d, J=5.8 Hz, 4H,); δ_C (100.6 MHz, DMSO-d_6) 164.6, 153.7, 152.3, 137.7, 136.6, 134.4, 132.6, 124.2, 124.0, 122.9, 119.7, 47.8, 35.4.

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Supplementary data

These data include the ^1H and ^{13}C NMR spectra of 24 compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.09.050.

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