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Synthesis of thio- and furan-fused heterocycles: furopyranone, furopyrrolone, and thienopyrrolone derivatives

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ABSTRACT

We report herein the synthesis of a novel class of compounds, ethyl 4-oxo-4*H*-furo[3,2-*c*]pyran-6-yl carbonate, (7*E*)-7-[(dimethylamino)methylene]-4*H*-furo[3,2-*c*]pyran-4,6(7*H*)-dione, 5-oxo-*N*-phenyl-2,5-dihydro-4*H*-furo[3,2-*b*]pyrrole-4-carboxamide, and 5-oxo-*N*-phenyl-5,6-dihydro-4*H*-thieno[3,2-*b*]pyrrole-4-carboxamide starting from the corresponding acid derivatives. Intramolecular cyclization in the presence of thionyl chloride formed the target fused ring systems. Additional transformation was seen in the cyclization of furan-fused heterocycle. A mechanism was proposed based on experimental and computational findings.

1. Introduction

Furan and thiophene derivatives are of great importance due to their crucial role in synthetic organic chemistry.[1–6] They have been proven to exhibit a wide range of biological activities and so they exist in a number of commercially available pharmaceuticals such as furazolidone (**1**),[7] ranitidine (**2**),[8] and tioconazole (**3**) (Fig. 1).[9]

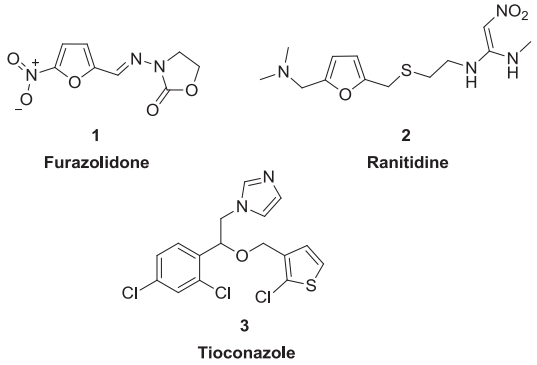

Fig. 1. Structures of some commercially available drugs containg furan or thiophene ring.

Fusing furan rings with other heterocycles results in new characteristics. Furopyranones (**4**) and furopyrrolones (**5**) are key examples of furan-fused heterocyclic systems that have crucial roles (Fig. 2).[10–14] For instance neo-tanshinlactone (**6**), a furopyranone derivative, is reported to be 20 times more selective than anti-estrogenic tomoxifen citrate, which is clinically used in breast cancer therapies.[15]

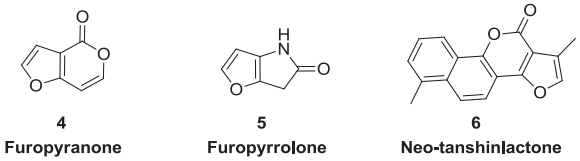

Fig. 2. Structures of some furan-fused heterocycles.

Based on known examples,[9,16] thio- and furan-fused heterocycles have the potential to possess biological activities.

Therefore we were inspired to work on the development of new synthetic methodologies for thio- and furan-fused heterocycles. Starting from diacid **7**, we aimed here to prepare of the furopyranone **8** and furopyrrolone **9** derivatives (Scheme 1).

2. Results and discussion

The starting compounds **12** and **13** were synthesized using previous methodologies in which commercially available dimethyl

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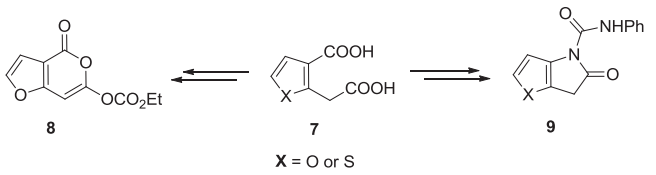
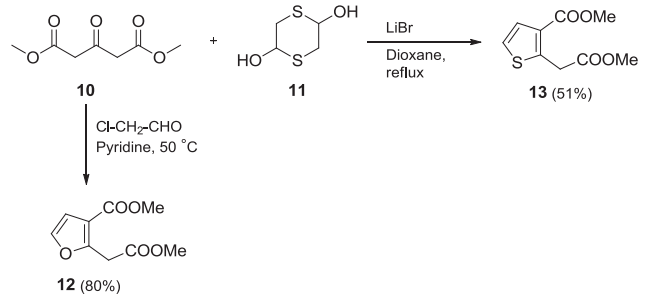


8 7 9

Scheme 1. The synthetic strategy for furopyranone **8** and furopyrrolone **9** derivatives.

1,3-acetonedicarboxylate (**10**) was reacted with chloroacetaldehyde in pyridine to yield furan diester **12**,[17] and with 2,5-dihydroxy-1,4-dithiane (**11**) and lithium bromide in dioxane to yield thiophene diester **13**[18] (Scheme 2).[19]

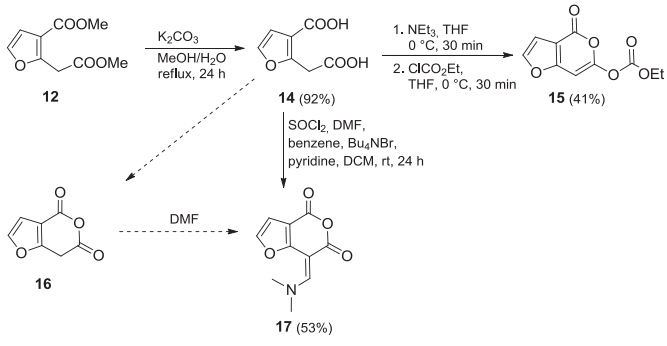


10 **11** **13** (51%)

12 (80%)

Scheme 2. Synthesis of furan and thiophene diesters **12** and **13**.

For the synthesis of furopyranone derivatives, the key compound was the furan diacid **14**. A previously published method by Balci et al.[20] was applied to the furan diacid **14**, which was obtained by the reaction of furan diester **12** with potassium carbonate in a methanol/water mixture.[21] According to this method, furan diacid **14** was then treated with triethylamine and then with ethyl chloroformate, which yielded the cyclization product furopyranone **15**. For the synthesis of further furopyranone derivatives, a modified Vilsmeier–Haack reaction was applied to diacid **14**. Treatment of furan diacid **14** with thionyl chloride, dimethyformamide, pyridine and tetrabutylammonium bromide as a catalyst in dichloromethane resulted in the formation of **17** (Scheme 3). We assume that the diacid **14** first undergoes a cyclization reaction to form the anhydride **16** followed by a condensation reaction of the methylene functionality in **16** with the dimethyl formamide to give **17**. The confirmation of the structure of furopyrandione **17** was achieved by X-ray analysis (Fig. 3).



12 **14** (92%) **15** (41%)

16 **17** (53%)

Scheme 3. Synthesis of furopyranone **15** and furopyrandione **17**.

After the synthesis of furopyranone **15** and furopyrandione **17**, we turned our attention to furo- and thienopyrrolone **9** framework construction, starting from diacid **7**, for which a nitrogen atom must be inserted into the molecule.

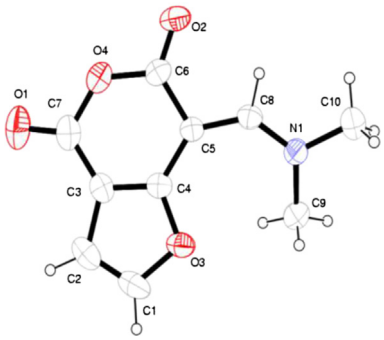
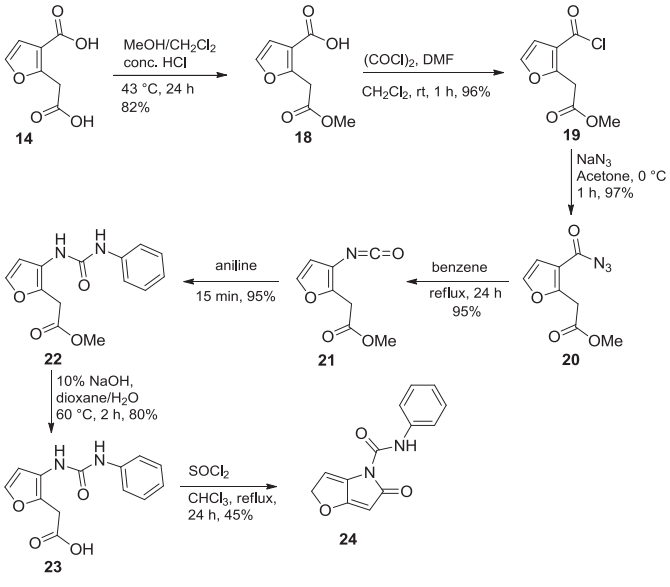


Fig. 3. ORTEP drawing of furopyrandione **17**. Thermal ellipsoids are shown at 40% probability level.

In order to achieve this goal, furan diacid **14** was reacted with concentrated HCl in dichloromethane from which the carboxylic acid group connected to the methylene group in **14** was selectively converted to ester functionality to form monoester **18**.[22,23] The monoester **18** was then reacted with oxalyl chloride in dichloromethane to give the acyl chloride **19**. To introduce the nitrogen atom into the molecule, Curtius rearrangement,[24–28] one of the most convenient methods to generate urea and urethane derivatives, was performed on acyl azide **20** in benzene, which was generated by the reaction of acyl chloride **19** with sodium azide in acetone. The isocyanate **21** formed by the Curtius rearrangement, was mixed with aniline to yield the corresponding urea ester **22**. Then the ester functionality of the molecule **22** was hydrolyzed with 10% NaOH in a dioxane/water mixture to give urea acid **23**. Finally the intramolecular cyclization of the molecule **23** was achieved by adding thionyl chloride in chloroform forming the rearranged product **24** (Scheme 4). The structure of **24** was established by ^{1}H and ^{13}C NMR spectra. Finally X-ray diffraction analysis of **24** confirmed unambiguously the proposed structure (Fig. 4).



14 **18** **19** **20** **21** **22** **23** **24**

Scheme 4. Attempt to synthesize target furopyrrolone derivative **9**.

After the characterization of the unexpected product **24**, we also aimed to apply the same methodology to synthesize the corresponding thienopyrrolone derivative starting from thiophene diacid **25**. For regiospecific formation of the monoester **26**, diacid **25** was treated with HCl in methanol at 40 °C (Scheme 5).[29] The

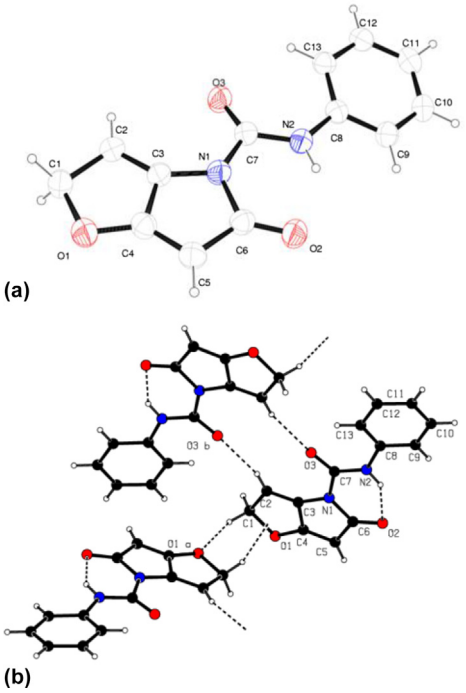
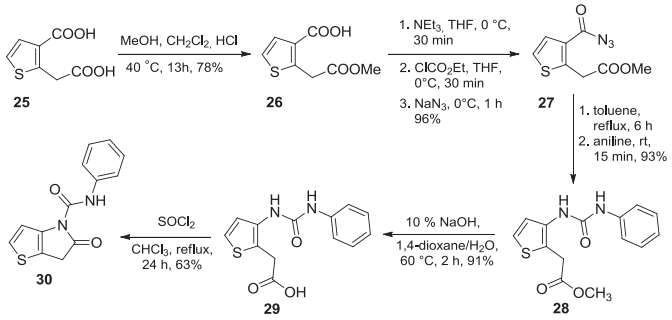


Fig. 4. (a) ORTEP drawing of furopyrrolone **24**. Thermal ellipsoids are shown at 40% probability level. (b) Dimeric structure with the *H*-bonding geometry.



Scheme 5. Synthesis of thienopyrrolone **30**.

monoester **26** was reacted with triethylamine and ethyl chloroformate in dichloromethane, followed by sodium azide addition to yield acyl azide **27**.

The application of the Curtius rearrangement to **27** followed by the addition of aniline in toluene yielded the urea-ester **28**, which was then hydrolyzed by 10% NaOH in a dioxane/water mixture to form urea acid **29**.

Finally the intramolecular cyclization reaction was achieved by adding thionyl chloride in chloroform to urea-acid **29** to give the thienopyrrolone derivative **30**.

The results of the cyclization reactions vary considerably, depending on the heteroatoms. The thiophene structure in **30** was preserved, but the furan structure in **24** was isomerized to a conjugated dienone structure. Accordingly, we conclude that the aromaticity of the five-membered ring should play an important role in this transformation. It is well known that the aromaticity of the two five-membered rings increases in the order of furan<<thiophene.[30]

In order to address this question we carried out geometry optimization calculations at the B3LYP/6-31G* levels of theory on **24**, **30**, **31**, and **33**. Relative free enthalpy comparison of the resulting geometries showed that rearranged isomers of the furopyrrolone **24** and thienopyrrolone **32** derivatives are more stable by 4.1 kcal mol^{-1} and 0.2 kcal mol^{-1} than the nonrearranged isomers **31** and **30**, respectively (Fig. 5). Additional computational efforts in determining single-point energies at B3LYP/6-311G(2df,2p) levels of theory gave a similar outcome for the furopyrrolone derivative **24**. Single point solvation calculations with the polarized continuum model (PCM) were carried out with chloroform since it was used as solvent in experimental studies. The rearranged isomer **24** was found to be more stable by 4.9 kcal mol^{-1}. However, it was found that thienopyrrolone **30** derivative was more stable compared to its isomer by 0.4 kcal mol^{-1}, which is in agreement with the experimental results.[31]

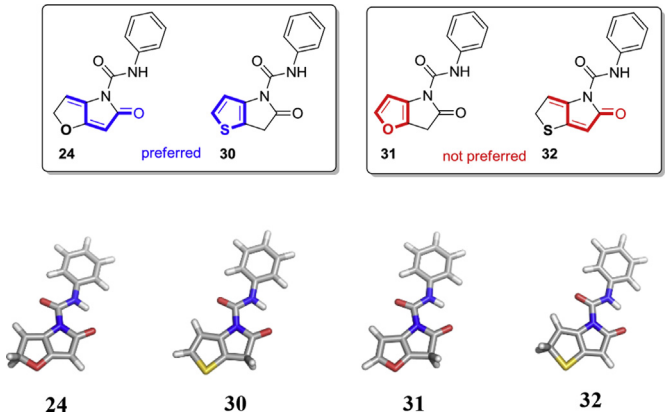
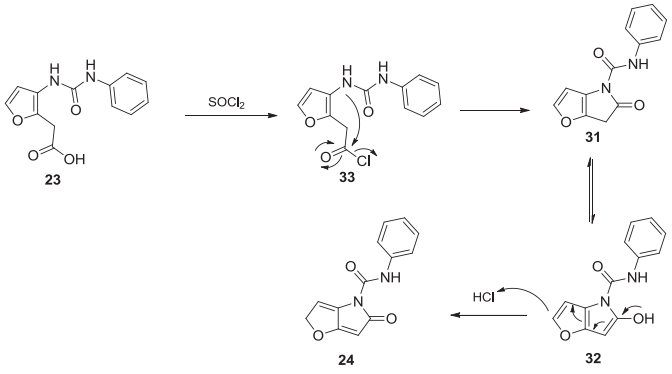


Fig. 5. At B3LYP/6-31G* level (PCM solvation in $CHCl_3$) geometry optimized structures for **24**, **30**, **31**, and **32**.

Based on experimental and computational results, we proposed a mechanism outlined in Scheme 6 for the formation of compound **24**. The first step is in situ acyl chloride formation from urea-acid **23**. Acyl chloride **33** may undergo cyclization via intramolecular nucleophilic attack from the NH group directly connected to the furan ring. This transformation was also supported by the isolation of the thienopyrrolone derivative **30** without further reaction. Keto–enol tautomerism of **31** and protonation give compound **24** as the sole product.



Scheme 6. Proposed mechanism for the synthesis of compound **24**.

3. Conclusion

The presented results show the importance of acyl azide based cyclizations for the formation of valuable heterocyclic systems. We have developed a method for the construction of furo- and thienopyrrolone derivatives starting from furan and thiophene dicarboxylic acids. The method developed here can be applied to the

synthesis of further heterocycles as well as introduction of further substituents.

4. Experimental section

4.1. General

Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were recorded on a Bruker Instrument Avance Series-Spectrospin DPX-400 Ultrashield instrument in acetone-d_6, $CDCl_3$, CD_3OD, and DMSO-d_6 with TMS as internal reference. Chemical shifts (δ) were expressed in units parts per million (ppm). Spin multiplicities were given as singlet (s), doublet (d), doublet of doublets (dd), triplet (t) and quartet (q) and coupling constants (J) were reported in Hertz (Hz). IR spectra were recorded on a Perkin Elmer 980 spectrometer. Elemental analysis were determined on a Leco CHNS-932 instrument (Ataturk University). Melting points were determined on a Thomas-Hoover capillary melting point apparatus. 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 aluminum plates.

*4.1.1. Synthesis of methyl 2-(2-methoxy-2-oxoethyl)-3-furoate (**12**).*[17] A solution of chloroacetaldehyde (26.5 mL, 45%) in water was added dropwise to a solution of dimethyl 1,3-acetonedicarboxylate (**10**) (25.0 g, 143.5 mmol) in pyridine (50 mL) with stirring. Stirring was continued for 24 h at 50 °C. Then the reaction mixture was extracted with water and ethyl acetate. The organic layer was washed successively with 2 M HCl, 5% $NaHCO_3$, 10% NaOH and brine, and then dried over $MgSO_4$. The solvent was evaporated and the product was purified by silica gel column chromatography eluting with hexane/ethyl acetate (3:1) gave **12** as a colorless liquid (22.8 g, 80%). R_f=0.43; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, $J_{5,4}$=2.0 Hz, 1H, H-5), 6.67 (d, $J_{4,5}$=2.0 Hz, 1H, H-4), 4.05 (s, 2H, CH_2), 3.79 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 163.9, 154.2, 141.9, 115.5, 110.8, 52.4, 51.6, 33.5.

*4.1.2. 2-(Carboxymethyl)-3-furoic acid (**14**).* To a solution of diester 12 (5.0 g, 25.2 mmol) in 60 mL solution of 1:1 CH_3OH/H_2O was added K_2CO_3 (10.0 g, 72.4 mmol). The solution was refluxed for 24 h. Then the reaction mixture was acidified with concentrated HCl (15 mL) and extracted with ethyl acetate (3×50 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to give diacid **14**[26] as white powder (3.97 g, 23.3 mmol) in 92% yield, mp 210–212 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.67 (br s, 2H, –OH), 7.65 (d, $J_{4,5}$=2.0 Hz, 1H, H-5), 6.66 (d, $J_{5,4}$=2.0 Hz, 1H, H-4), 3.97 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.9, 164.4, 154.8, 142.3, 115.6, 110.9 and 33.4.

*4.1.3. Ethyl 4-oxo-4H-furo[3,2-c]pyran-6-yl carbonate (**15**).* To a solution of diacid **14** (1.50 g, 8.8 mmol) in 10 mL of THF at 0 °C, triethylamine (1.80 mL, 13.2 mmol) in 6 mL THF was added dropwise and the mixture was stirred for 30 min. This was followed by slow addition of a cooled solution of ethyl chloroformate (1.65 mL, 17.6 mmol) in 6 mL of THF and the reaction mixture was stirred at the same temperature for 30 min. The mixture was extracted with ethyl acetate (2×15 mL) and water (20 mL) and the organic phase was washed with saturated $NaHCO_3$ solution (3×40 mL) and with water (2×25 mL). Then organic layer was dried over $MgSO_4$. After that, compound **15** (0.81 g, 3.6 mmol) was obtained and purified on silica gel column chromatography using hexane/ethyl acetate as eluent (3:1) in 41% yield as white crystals, mp 82–83 °C. R_f=0.44; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, $J_{2,3}$=2.1 Hz, 1H, H-2), 6.88 (dd, $J_{3,2}$=2.1 Hz, $J_{3,7}$=0.8 Hz, 1H, H-3), 6.43 (d, $J_{7,3}$=0.8 Hz, 1H, H-7), 4.36 (q, J=7.2 Hz, 2H, CH_2), 1.39 (t, J=7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 156.0, 154.3, 150.6, 144.8, 108.6, 107.8, 86.2, 66.7, 14.1; ν_{max} (ATR) 1774, 1623, 1565, 1232, 1167, 1065 cm^{-1} [found: C, 53.78; H, 3.61. $C_{10}H_8O_6$ requires C, 53.58; H, 3.60, O. 42.82]; HRMS calcd for $C_{10}H_8O_6$ $(M+Na)^+$: 247.02131, found: 247.02467.

*4.1.4. Synthesis of (7E)-7-[(dimethylamino)methylene]-4H-furo[3,2-c]pyran-4,6(7H)-dione (**17**).* Benzene (7 mL), dimethyl formamide (2.8 mL) and thionyl chloride (2.3 mL) were mixed in a dropping funnel and two separate layers were formed in 5 min. The lower layer was added to a mixture of diacid **14** (2.36 g 13.9 mmol), tetrabutylammonium bromide (0.6 g, 1.9 mmol), and pyridine (3.2 mL) in 100 mL dichloromethane. The solution was kept stirring at room temperature overnight. Then the solution was washed with saturated $NaHCO_3$ solution (3×50 mL) and the combined organic extracts were washed with 1 M HCl solution (3×50 mL) and with water (2×25 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated under vacuum. The residue was then purified by column chromatography (SiO_2, 120 g) eluting with ethyl acetate to yield the compound **17** (1.53 g, 7.4 mmol) in 53% yield as pale yellow solid, mp 154–155 °C. R_f=0.18; ^{1}H NMR (400 MHz, CD_3OD) δ 8.07 (s, 1H, H-1′), 7.50 (d, $J_{2,3}$=2.2 Hz, 1H, H-2), 6.76 (d, $J_{3,2}$=2.2 Hz, 1H, H-3), 3.48 (s, 3H, NCH_3), 3.47 (s, 3H, NCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 159.4, 157.9, 154.8, 141.8, 108.1, 104.0, 85.6, 49.1, 43.0; ν_{max} (ATR) 1752, 1694, 1608, 1529, 1476, 1432, 1391, 1312, 1271, 1116, 1082, 1051; HRMS calcd for $C_{10}H_9NO_4$ $(M+H)^+$: 208.06043, found: 208.06348.

*4.1.5. 2-(2-Methoxy-2-oxoethyl)-3-furoic acid (**18**).* To a stirred solution of diacid **14** (3.5 g, 20.6 mmol) in 90 mL of dichloromethane/methanol (2:1) mixture, 15 drops of concentrated HCl were added. This mixture was kept stirring at 42 °C for 24 h. After the completion of the reaction, the solvent was evaporated to give the crude product, which was then separated by column chromatography (160 g, SiO_2, hexane/EtOAc, 3:1). The first fraction was identified as diester **12** (0.450 g, 11%), and the second fraction was the monoester **18** (3.10 g, 82%), white solid, mp 81–83 °C. R_f=0.21; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, $J_{5,4}$=2.0 Hz, 1H, H-5), 6.75 (d, $J_{4,5}$=2.0 Hz, 1H, H-4), 4.11 (s, 2H, CH_2), 3.74 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 169.0, 155.6, 142.3, 115.3, 111.2, 52.6, 33.7; ν_{max} (ATR) 3149, 3127, 2957, 2685, 2614, 1728, 1681, 1324, 1280, 1246, 1166 cm^{-1} [found: C, 52.41; H, 4.17. $C_8H_8O_5$ requires C, 52.18; H, 4.38].

*4.1.6. Synthesis of methyl [3-(chlorocarbonyl)-2-furyl]acetate (**19**).* Oxalyl chloride (1.7 mL, 19.8 mmol) was added to a stirred solution of monoester **18** (3.10 g, 16.8 mmol) in 40 mL dichloromethane, followed by addition of dimethyl formamide (5 drops) as catalyst. After stirring this mixture for 1 h at room temperature, the solvent was evaporated to give acyl chloride **19** (3.27 g, 96%), which was used without purification for the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, $J_{5,4}$=2.1 Hz, 1H, H-5), 6.79 (d, $J_{4,5}$=2.1 Hz, 1H, H-4), 4.03 (s, 2H, CH_2), 3.71 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 162.1, 156.2, 142.4, 120.5, 112.7, 52.7, 33.8; ν_{max} (ATR) 3135, 2955, 1750, 1574, 1436, 1338, 1251, 1171 cm^{-1}.

*4.1.7. Synthesis of 1-[2-(2-methoxy-2-oxoethyl)-3-furoyl]triaza-1,2-dien-2-ium (**20**).*[20] To a solution of acyl chloride **19** (3.07 g, 15.2 mmol) in 40 mL of acetone, NaN_3 (1.47 g, 22.6 mmol) in 8 mL of chilled water was added dropwise at 0 °C. This mixture was stirred for 1 h at 0 °C. Then, 100 mL water was added and the mixture was extracted with ethyl acetate (2×100 mL). The combined organic extracts were dried over $MgSO_4$, and then concentrated to give the acyl azide **20** (3.07 g, 97%) as colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, $J_{5,4}$=2.0 Hz, 1H, H-5), 6.63 (d, $J_{4,5}$=2.0 Hz, 1H, H-4),

4.06 (s, 2H, CH_2), 3.68 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 168.2, 155.4, 142.2, 116.9, 110.5, 52.5, 33.7; ν_{max} (ATR) 2955, 2154, 2133, 1742, 1686, 1601, 1420, 1299, 1133 cm^{-1}.

*4.1.8. Synthesis of methyl (3-isocyanato-2-furyl)acetate (**21**).* A solution of acyl azide **20** (3.05 g, 14.6 mmol) in 35 mL of dry benzene was stirred at reflux temperature for 24 h. Then, solvent was evaporated under vacuum to give the isocyanate **21** as yellowish liquid (2.51 g, 95%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, $J_{5,4}$=2.1 Hz, 1H, H-5), 6.19 (d, $J_{4,5}$=2.1 Hz, 1H, H-4), 3.63 (s, 2H, CH_2), 3.56 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 141.7, 140.2, 128.3, 116.9, 109.4, 52.4, 31.3; ν_{max} (ATR) 2272, 1742, 907, 730 cm^{-1}.

*4.1.9. Synthesis of methyl {3-[(anilinocarbonyl)amino]-2-furyl}acetate (**22**).* To a solution of isocyanate **21** (2.51 g 13.9 mmol) in 40 mL dichloromethane, 1.5 mL (16.4 mmol) aniline was added at room temperature. Then this mixture was kept stirring at room temperature for 15 min. After evaporation of the solvent the crude product was purified by silica gel column chromatography (SiO_2, 90 g) eluting with hexane/ethyl acetate mixture (1:1) to give urea-ester as **22** a white powder (3.61 g, 95%), mp 142–143 °C. R_f=0.36; ^1H NMR (400 MHz, CD_3OD) δ 7.39 (dd, $J_{2',3'}=J_{6',5'}$=8.7 Hz, $J_{2',4'}=J_{6',4'}$=1.2 Hz, 2H, H-2′, H-6′), 7.36 (d, $J_{5,4}$=2.0 Hz, 1H, H-5), 7.29 (quasi t, $J_{3',2'}=J_{3',4'}=J_{5',6'}=J_{5',4'}$=7.2 Hz, 2H, H-3′, 5′), 7.01 (tt, $J_{4',3'}=J_{4',5'}$=7.2 Hz, $J_{4',2''}=J_{4',6'}$=1.2 Hz, 1H, H-4′), 6.62 (d, 1H, $J_{4,5}$=2.0 Hz, H-4), 3.74 (s, 2H, CH_2), 3.70 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 154.8, 141.9, 138.5, 129.1, 128.5, 123.6, 121.8, 120.2, 110.3, 52.7, 31.8; ν_{max} (ATR) 3288, 1739, 1557, 1495, 1340, 1221, 1163, 1095 cm^{-1}; [found: C, 61.59; H, 5.03; N, 10.06. $C_{14}H_{14}N_2O_4$ requires C, 61.31; H, 5.14; N, 10.21].

*4.1.10. Synthesis of {3-[(anilinocarbonyl)amino]-2-furyl}acetic acid (**23**).* To a stirred solution of urea-ester **22** (3.81 g, 13.9 mmol) in 60 mL dioxane/water mixture (2:1) was added 4 mL of 10% NaOH solution at room temperature. Then this mixture was kept stirring at 60 °C for 2 h. Then, concentrated HCl (15 mL) was added dropwise to the reaction mixture. The resulting mixture was extracted with ethyl acetate (2×100 mL) and the organic layer was dried over $MgSO_4$. Finally, the acid **23** was obtained by evaporating the solvent under vacuum as a white solid (2.89 g, 80%), mp 201–202 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 12.58 (br s, 1H, COOH), 8.60 (s, 1H, NH), 8.10 (s, 1H, NH), 7.46 (d, $J_{5,4}$=2.0 Hz, 1H, H-5), 7.42 (bd, $J_{2',3'}=J_{6',5'}$=7.9 Hz, 2H, H-2′ and H-6′), 7.26 (bt, $J_{3',2'}=J_{5',6'}=J_{3',4'}=J_{5',4'}$=7.9 Hz, 2H, H-3′ and H-5′), 6.95 (bt, $J_{4',3'}=J_{4',5'}$=7.9 Hz, 1H, H-4′) 6.73 (d, $J_{4,5}$=2.0 Hz, 1H, H-4), 3.64 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.6, 152.6, 140.6, 139.8, 136.0, 128.8, 122.3, 121.7, 118.0, 108.3 and 31.8; ν_{max} (ATR) 3292, 3145, 1703, 1598, 1559, 1445, 1430, 1289, 1245 cm^{-1}; HRMS calcd for $C_{13}H_{12}N_2O_4$ $(M+H)^+$: 261.08698, found: 261.08817.

*4.1.11. Synthesis of 5-oxo-N-phenyl-2,5-dihydro-4H-furo[3,2-b]pyrrole-4-carboxamide (**24**).* To a stirred solution of acid **23** (0.5 g, 1.9 mmol) in 20 mL of $CHCl_3$ (ethanol free), 0.2 mL thionyl chloride was added at room temperature. Then this mixture was heated to reflux temperature and kept stirring for 24 h. The solvent was evaporated to give of the crude product, which was then purified by column chromatography (21.0 g SiO_2; hexane/ethyl acetate 3:1) to give compound **24** as white crystals from $CHCl_3$/*n*-hexane (3:1) (0.21 g, 45%), mp 155–157 °C. R_f=0.33; ^1H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 1H, NH), 7.56 (dd, $J_{2,3'}=J_{6',5'}$=8.6 Hz, $J_{2',4'}=J_{6',4'}$=1.2 Hz, 2H, H-2′ and H- 6′), 7.30–7.40 (m, 2H, H-3′ and H-5′), 7.13 (tt, $J_{4',3'}=J_{4',5'}$=7.4 Hz, $J_{4',2'}=J_{4',6'}$=1.2 Hz, 1H, H-4′), 6.58 (dt, $J_{3,2}$=2.0 Hz, $J_{3,6}$=1.6 Hz, 1H, H-3), 5.46 (dd, $J_{2,3}$=2.0 Hz, $J_{6,2}$=1.1 Hz, 2H, H-2), 5.07 (dt, $J_{6,3}$=1.6 Hz, $J_{6,2}$=1.1 Hz, 1H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 175.2, 148.4, 137.2, 133.5, 129.2, 124.4, 120.2, 112.6, 86.5 and 84.1. ν_{max} (ATR) 3108, 1717, 1666, 1596, 1556, 1500, 1448, 1355, 1290, 1236, 1108, 1084 cm^{-1}; HRMS calcd for $C_{13}H_{10}N_2O_3$ $(M-H)^-$: 241.06187, found: 241.06241.

*4.1.12. Synthesis of methyl [3-(azidocarbonyl)thiophen-2-yl]acetate (**27**).* To a solution of acid **26**[29] (50.0 mg, 0.25 mmol) in 5 mL THF, NEt_3 (53 μL, 0.38 mmol) was added at 0 °C and stirred for 30 min. Then, ethyl chloroformate (55 μL, 0.58 mmol) was added and stirred at 0 °C for 30 min. After addition of NaN_3 (33.0 mg, 0.50 mmol), the reaction mixture was stirred for 1 h at 0 °C. Later, 10 mL water was added and the mixture was extracted with Et_2O (2×25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The product was purified with column chromatography on silica gel (10 g) eluting with diethyl ether to give pale yellow solid **27** (54.0 mg, 96%). R_f=0.83; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J=5.4 Hz, 1H), 7.16 (d, J=5.4 Hz, 1H), 4.24 (s, 2H, CH_2), 3.74 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 168.2, 146.2, 130.3, 129.0, 123.8, 52.5, 34.6; ν_{max} (ATR) 3116, 2952, 2139, 1719, 1663, 1524, 1437, 1232, 1173, 1070, 1006, 933, 846, 715 cm^{-1}.

*4.1.13. Synthesis of methyl {3-[(phenylcarbamoyl)-amino]thiophen-2-yl}acetate (**28**).* A solution of acyl azide **27** (0.15 g, 0.67 mmol) in 5 mL of dry toluene was stirred at reflux temperature for 6 h. Then, aniline (70 μL, 0.80 mmol) was added at rt and the resulting mixture was stirred for 15 min. After removal of the solvent, the crude product was purified by column chromatography on SiO_2 (20 g) eluting with hexane/EtOAc (5:1, 3:1) and urea-ester **28** was recrystallized from chloroform under petroleum ether atmosphere to give white powder (180.0 mg, 93%), mp 158–160 °C. R_f=0.16 (hexane/EtOAc 3:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (br d, J=8.0 Hz, 2H, benzene), 7.28 (br t, J=7.6 Hz, 2H, benzene) 7.21 (s, 2H, thiophene), 7.06 (br t, J=7.3 Hz, 1H, benzene), 6.98 (br s, 2H, NH), 3.77 (s, 2H, CH_2), 3.66 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 154.3, 138.4, 134.3, 129.1, 125.7, 123.7, 123.6, 120.5, 52.7, 32.5. ν_{max} (ATR) 278, 2950, 2920, 1735, 1639, 1583, 1549, 1446, 1240, 1206, 743, 693, 664, 631 cm^{-1}; HRMS calcd for $C_{14}H_{14}N_2O_3S$ $(M+Na)^+$: 313.06173, found: 313.06410.

*4.1.14. Synthesis of {3-[(phenylcarbamoyl)amino]thiophen-2-yl}acetic acid (**29**).* To a stirred solution of urea-ester **28** (100.0 mg, 0.34 mmol) in 15 mL dioxane/water mixture (2:1) was added 0.1 mL of 10% NaOH at room temperature. Then, this mixture was kept stirring at 60 °C for 2 h. Then concentrated HCl (2 mL) was added to the reaction mixture and the resulting mixture was extracted with ethyl acetate (4×20 mL) and the organic layer was dried over $MgSO_4$. Finally, the urea-acid **29** was obtained by evaporating the solvent. The compound was recrystallized from chloroform under petroleum ether atmosphere to give white crystals (87.0 mg, 91%), mp 179–181 °C. ^1H NMR (400 MHz, acetone-d_6) δ 8.49 (br s, 1H, NH), 7.86 (br s, 1H, NH), 7.53 (dd, J=8.7, 0.9 Hz, 2H, benzene), 7.41 (d, J=5.4 Hz, 1H, thiophene), 7.31–7.19 (m, 3H), 6.97 (tt, J=7.4, 1.0 Hz, 1H, benzene), 3.77 (s, 2H, CH_2); ^{13}C NMR: (100 MHz, acetone-d_6) δ 172.1, 154.0, 140.9, 135.8, 129.5, 125.4, 123.1, 122.9, 119.4, 32.9. ν_{max} (ATR) 3282, 2909, 1696, 1640, 1579, 1545, 1444, 1294, 1238, 897, 744, 655, 629; HRMS calcd for $C_{13}H_{12}N_2O_3S$ $(M+Na)^+$: 299.04608, found: 299.04890.

*4.1.15. Synthesis of 5-oxo-N-phenyl-5,6-dihydro-4H-thieno[3,2-b]pyrrole-4-carboxamide (**30**).* To a stirred solution of urea-acid **29** (45.0 mg, 0.16 mmol) in 20 mL $CHCl_3$ (ethanol free), 50 μL $SOCl_2$ was added at room temperature. Then, the reaction mixture was heated to reflux temperature and kept stirring for 24 h. The solvent was evaporated to give crude product, which was purified by column chromatography on silica gel (10 g) eluting with hexane/EtOAc (2:1) to give purple solid **30** (26.5 mg, 63%), mp 111–113 °C. R_f=0.55; ^1H NMR (400 MHz, $CDCl_3$) δ 10.23 (br s, 1H), 7.54–7.63 (m, 3H, benzene and thiophene), 7.36 (t, J=7.9 Hz, 2H, benzene), 7.30 (d, J=5.1 Hz, 1H, thiophene), 7.14 (t, J=7.4 Hz, 1H, benzene), 3.86 (s, 2H,

CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0, 148.2, 142.8, 137.2, 129.2, 126.8, 124.6, 120.5, 117.7, 115.5, 37.3. ν_{max} (ATR) 3242, 3095, 2910, 1726, 1701, 1599, 1553, 1499, 1448, 1291, 1227, 1191, 1076, 696; HRMS calcd for $C_{14}H_{14}N_2O_3S$ $(M-H)^-$: 257.03902, found: 257.04081.

4.2. X-ray crystal structure analysis of 17 and 24

For the crystal structure determination, single-crystals of the compounds **17** and **24** were used for data collection on a four-circle Rigaku R-AXIS RAPID-S diffractometer (equipped with a two-dimensional area IP detector). Graphite-monochromated Mo-K_α radiation (λ=0.71073 Å) and oscillation scans technique with Δw=5° for one image were used for data collection. The lattice parameters were determined by the least-squares methods on the basis of all reflections with $F^2>2\sigma(F^2)$. Integration of the intensities, correction for Lorentz and polarization effects and cell refinement was performed using CrystalClear (Rigaku/MSC Inc., 2005) software.[32] The structures were solved by direct methods using SHELXS-97[33] and refined by a full-matrix least-squares procedure using the program SHELXL-97.[33] All the non-hydrogen atoms were located from the Fourier maps and were refined anisotropically. All H atoms were refined isotropically, with the isotropic vibration parameters related to the non-H atom to which they are bonded. The final difference Fourier maps showed no peaks of chemical significance.

*4.2.1. Crystal data for (**17**).* $C_{10}H_9NO_4$, crystal system, space group: monoclinic, $P2_1/n$; (no: 14); unit cell dimensions: a=7.0237(4), b=12.2539(6), c=11.0368(37) Å, α=90, β=939.712(3), γ=90 Å; volume: 936.30(9) $Å^3$; Z=4; calculated density: 1.470 g/cm^3; absorption coefficient: 0.115 mm^{-1}; F(000): 432; θ-range for data collection 2.5–26.4°; refinement method: full matrix least-square on F^2; data/parameters: 1281/139; goodness-of-fit on F^2: 1.102; final R-indices [$I>2\sigma$(I)]: R_1=0.064, wR_2=0.166; largest diff. peak and hole: 0.187 and −0.290 e $Å^{-3}$.

*4.2.2. Crystal data for (**24**).* $C_{13}H_{10}N_2O_3$, crystal system, space group: monoclinic, C2/c; (no:15); unit cell dimensions: a=27.7731(8), b=5.2110(1), c=15.4807(4) Å, α=90, β=92.951(2), γ=90 Å; volume: 2237.61(10) $Å^3$; Z=8; calculated density: 1.438 g/cm^3; absorption coefficient: 0.105 mm^{-1}; F(000): 1008; θ-range for data collection 2.6–26.7°; refinement method: full matrix least-square on F^2; data/parameters: 1809/164; goodness-of-fit on F^2: 1.075; final R-indices [$I>2\sigma(I)$]: R_1=0.096, wR_2=0.239; largest diff. peak and hole: 0.444 and −0.284 e $Å^{-3}$.

CCDC-988941 (**17**) and 989578 (**24**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Supplementary data

These data include the ^1H and ^{13}C NMR spectra of compounds (24 pages). Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.05.071.

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