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# Template-directed approach to solid-phase combinatorial synthesis of furan-based libraries☆

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**Abstract**—A novel furan based scaffold 5-hydroxymethylfurfural has been identified for the generation of combinatorial libraries using template directed approach on solid phase. This scaffold has been utilized to afford furan-based bi-heterocyclic structures with extensive chemical diversity using cycloaddition, multicomponent and cyclization reactions. © 2002 Elsevier Science Ltd. All rights reserved.

The design and synthesis of structurally diverse multifunctional libraries of small organic molecules on solid support has been the central claim of combinatorial chemistry. Molecular diversity may be derived from chemical laboratory synthesis, from natural products or from biological systems by genetic engineering/manipulation. In the creation of molecular diversity by synthesis, the synthetic strategy and reaction employed are therefore of critical importance. It may be useful to have an important pharmacophore, as a central core nucleus, with a polyfunctional reactivity so that the diverse types of chemical structures can be built on and around the nucleus.[2] The synthetic reaction used to build the structures on this nucleus should be short-path, convergent, high yielding, and amenable to be carried out under mild conditions, so that a diverse variety of prototype molecules and their analogues and homologues can be conveniently prepared. Furthermore, libraries comprising millions of molecules with extensive chemical diversity can be easily clustered into subsets and screening through in vitro ADME tests and may provide high quality data for building, testing and refining predictive models.[3]

In continuation of our interest in the solid-phase synthesis of libraries based on peptides,[4,5] small organic molecules (heterocyclic and acyclic structures)[6–10] and natural products[11,12] we have now targeted the synthesis of libraries with extensive chemical diversity based on heterocyclic compounds. Among the various classes of heterocyclic compounds, furan ring systems form an important component of pharmacologically active compounds, as they are associated with a wide spectrum of biological activities ranging from antifungal,[13] antitrypanosomal[14] and gastrointestinal motility activity[15] to farnesyl transferase[16] and phosphodiestrase inhibitory activity.[17] Despite being an interesting pharmacophore, there are very few reports dealing with the polymer-supported synthesis of libraries based on furan. The libraries reported so far have limited diversity, as furan rings were generated through cyclative cleavage strategy on solid-phase in three to five steps. Gallop et al.[18] presented a traceless solid-phase synthesis of furans via 1,3 dipolar cycloaddition reaction of isomunchones. Whereas Whitehouse et al.[19] have reported a rhodium (II)-mediated solid phase 1,3-dipolar cycloaddition for the synthesis of furan scaffolds.

However, these furan-based scaffolds generated on solid support cannot be subjected to further diversification, resulting in libraries with a low degree of structural diversity. The template-directed approach on solid support using a suitably functionalized furan could be a good alternative for obtaining structurally diverse furan-based libraries.

Using this strategy one can immobilize an appropriately functionalized furan-based scaffold on a solid support and then proceed with the design and synthesis of library in a manner so that the template does not remain the sole structure in the library, instead molecular diversity is introduced by way of generating a series of biheterocyclic structures. In our efforts towards exploring the chemistry of furans on solid phase, we observed that 5-hydroxymethylfurfural could serve as a good scaffold for obtaining structurally di-substituted derivatives of furan. One of the functional groups present on the scaffold can be selectively used for linking the scaffold on to the solid support whereas the second functional group can be readily derivatized using cycloaddition, multicomponent, and cyclization reactions to obtain an array of compounds based on the scaffold. The details of our findings are presented in this paper.

☆ See ref. 1.

*Keywords*: combinatorial chemistry; 5-hydroxymethylfurfural; SPOS.

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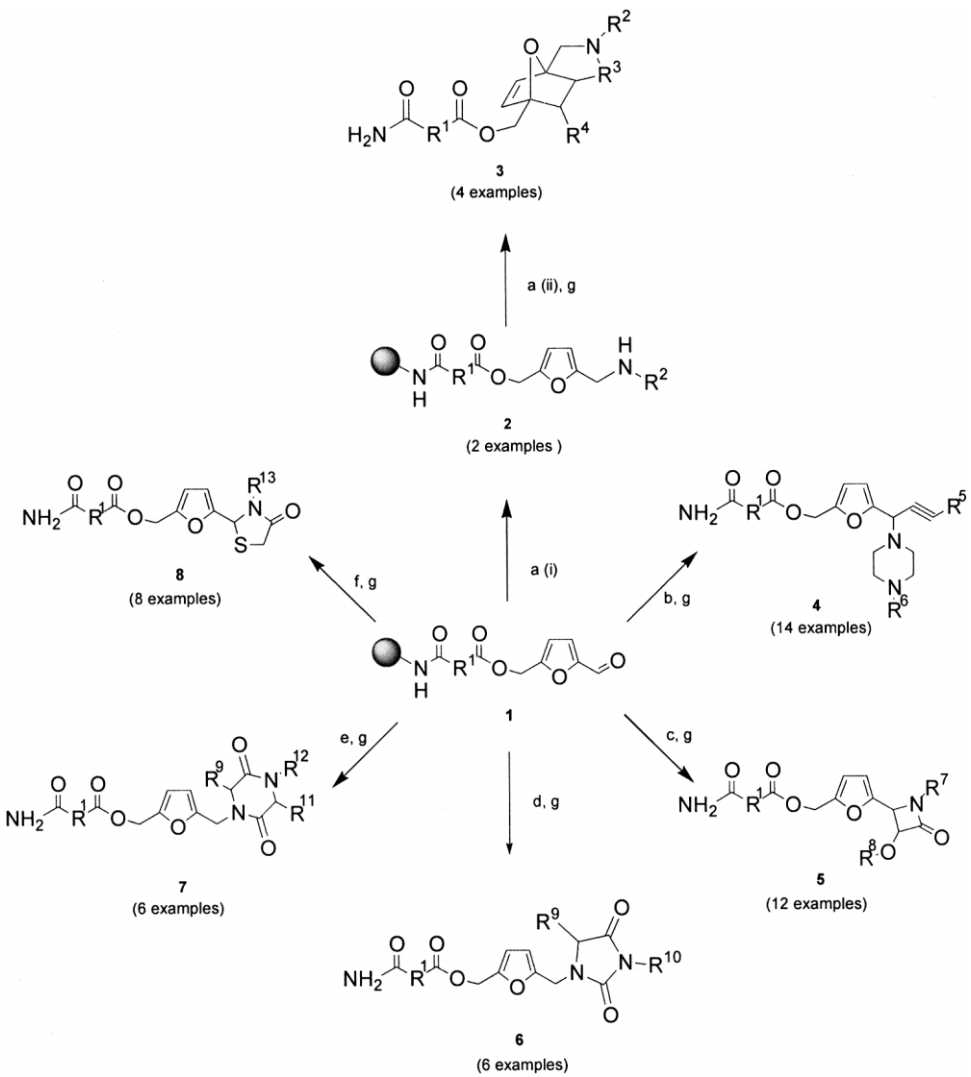


**Scheme 1.** (a) (i) $R^2NH_2$, Tmof, 3 h, $Na(CN)BH_3$, 2 h, rt; (ii) maleic anhydride, pyridine/DMF, 24 h, rt. (b) *N*-substituted piperazine ($R^6$), $CH{\equiv}CR^5$, CuCl, dioxane, 85°C, 6 h. (c) (i) $NH_2R^7$, Tmof, overnight, rt; (ii) $R^8OCH_2COCl$, $Et_3N$, DCM, overnight. (d) (i) $NH_2CHR^9COOMe$, Tmof, 3 h, $Na(CN)BH_3$, 2 h, rt; (ii) $R^{10}NCO$, DCM, rt, overnight; (iii) 1% DIPEA in DCM, 12 h, rt. (e) (i) $NH_2CHR^9COOEt$, Tmof, 3 h, $Na(CN)BH_3$, 2 h, rt; (ii) $HOOCCHR^{11}NR^{12}Fmoc$, HOBt, DIC, DMF, 30% piperidine in DMF, rt, 25 min; (iii) 50% DIPEA in DCM, overnight. (f) $R^{13}NH_2$, Tmof, 12 h, mercaptoacetic acid, $Et_3N$, THF, 60°C, 16 h. (g) 1% TFA in DCM, 15 min.

## 1. Results and discussion

The solid-phase synthesis of various furan based derivatives using 5-hydroxymethylfurfural as a novel scaffold is outlined in Scheme 1. In the first step of our synthesis Sieber amide resin (0.62 mmol/g) was loaded with aliphatic dicarboxylic acid anhydride in pyridine in DMF at room temperature for 12 h. The completion of reaction was monitored by a negative ninhydrin test. This was followed by the coupling of 5-hydroxymethyl furfural to the carboxyl function on the resin using DIC/HOBt/DMAP procedure to get **1** and the completion of the reaction was monitored by the negative carboxyl group test.[20] The widely popular DIC/DMAP procedure used for the esterification resulted in the formation of a significant amount of *N*-acylurea as evident by NMR.[21] Next, the resin bound furfuraldehyde was subjected to Diels–Alder reaction in two steps: reductive alkylation using primary amine followed by treatment with dienophile to get bicyclic Diels–Alder adduct **3** in quantitative yield and high purity. Further, to investigate the scope and limitations of the polymer linked scaffold, we carried out a Mannich reaction using alkyne and secondary amine, β-lactam formation using an amine and an acid chloride, hydantoin formation using an amino acid ester and an isocyanate, diketopiperazine formation using an amino acid ester and a Fmoc amino acid and thiazolidinone formation using a primary amine and mercaptoacetic acid to get **4**, **5**, **6**, **7** and **8**, respectively. The final compounds were cleaved from the solid support using 1% TFA–DCM for 15 min and residues obtained after the evaporation of the cleavage mixture were lyophilized by dissolving in 4:1 $^tBuOH-H_2O$ to get the desired compounds. They were obtained in purities ranging from 70–92% based on analytical HPLC. The compounds were purified by high throughput HPLC-MS and characterized by $^1H$ NMR.

Fifty-two single compounds based on structures **2**–**8** were synthesized using three dicarboxylic aliphatic acids, three dienophiles, four primary and three secondary amines, three alkynes, two isocyanates, two amino acid esters and two

**Table 1**. Molecular weight and HPLC purity of compounds based on **1**–**8**

| Comp. no. | $R^1$ | R | R | ESMS | Yield[a] (%) | Purity[b] (%) |
|---|---|---|---|---|---|---|
| **1a** | $(CH_2)_2$ | – | – | 248.33 ($M+Na^+$) | 70 | 92 |
| **2a** | $(CH_2)_2$ | $R^2$=Cyclohexyl | – | 309.00 ($M+H^+$) | 59 | 92 |
| **2b** | $(CH_2)_2$ | $R^2$=$CH_2$Ph | – | 316.80 ($M+H^+$) | 55 | 90 |
| **3a** | $(CH_2)_2$ | $R^2$=Cyclohexyl | $R^3$=CO, $R^4$=COOH | 429.80 ($M+Na^+$) | 45 | 82 |
| **3b** | $(CH_2)_2$ | $R^2$=$CH_2$Ph | $R^3$=CO, $R^4$=COOH | 436.98 ($M+Na^+$) | 40 | 84 |
| **3c** | $(CH_2)_2$ | $R^2$=Cyclohexyl | $R^3$=CO, $R^4$=$CH_3$ | 377.93 ($M+H^+$) | 47 | 80 |
| **3d** | $(CH_2)_2$ | $R^2$=$CH_2$Ph | $R^3$=CO, $R^4$=$CH_3$ | 384.93 ($M+H^+$) | 42 | 81 |
| **4a** | $(CH_2)_2$ | $R^5$=$(CH_2)_2CH_3$ | $R^6$=$CH(Ph)_2$ | 527.80 ($M+H^+$) | 50 | 77 |
| **4b** | $(CH_2)_2$ | $R^5$=$CH_2OH$ | $R^6$=Ph | 448.00 ($M+Na^+$) | 52 | 82 |
| **4c** | $(CH_2)_2$ | $R^5$=Ph | $R^6$=$CH(Ph)_2$ | 563.07 ($M+H^+$) | 46 | 85 |
| **4d** | $(CH_2)_2$ | $R^5$=$CH_2OH$ | $R^6$=$CH_3$ | 364.07 ($M+H^+$) | 40 | 70 |
| **4e** | $(CH_2)_4$ | $R^5$=Ph | $R^6$=$CH(Ph)_2$ | 590.93 ($M+H^+$) | 51 | 90 |
| **4f** | $(CH_2)_4$ | $R^5$=$CH_2OH$ | $R^6$=Ph | 454.67 ($M+H^+$) | 41 | 85 |
| **4g** | $(CH_2)_3$ | $R^5$=$CH_2OH$ | $R^6$=Ph | 461.73 ($M+H^+$) | 46 | 82 |
| **4h** | $(CH_2)_3$ | $R^5$=Ph | $R^6$=$CH(Ph)_2$ | 576.23 ($M+H^+$) | 49 | 81 |
| **4i** | $(CH_2)_3$ | $R^5$=$(CH_2)_2CH_3$ | $R^6$=$CH(Ph)_2$ | 541.93 ($M+H^+$) | 47 | 89 |
| **4j** | $(CH_2)_4$ | $R^5$=$(CH_2)_2CH_3$ | $R^6$=$CH(Ph)_2$ | 556.20 ($M+H^+$) | 43 | 86 |
| **4k** | $(CH_2)_2$ | $R^5$=$(CH_2)_2CH_3$ | $R^6$=Ph | 428.87 ($M+H^+$) | 45 | 74 |
| **4l** | $(CH_2)_3$ | $R^5$=$(CH_2)_2CH_3$ | $R^6$=Ph | 452.20 ($M+H^+$) | 49 | 81 |
| **4m** | $(CH_2)_2$ | $R^5$=Ph | $R^6$=$CH_3$ | 409.93 ($M+H^+$) | 41 | 77 |
| **4n** | $(CH_2)_3$ | $R^5$=Ph | $R^6$=$CH_3$ | 424.20 ($M+H^+$) | 50 | 83 |
| **5a** | $(CH_2)_2$ | $R^7$=Cyclohexyl | $R^8$=Ph | 462.93 ($M+Na^+$) | 50 | 85 |
| **5b** | $(CH_2)_2$ | $R^7$=$CH_2$Ph | $R^8$=Ph | 470.80 ($M+Na^+$) | 47 | 82 |
| **5c** | $(CH_2)_2$ | $R^7$=Ethylpyridine | $R^8$=Ph | 463.73 ($M+H^+$) | 43 | 79 |
| **5d** | $(CH_2)_2$ | $R^7$=Furfuryl | $R^8$=Phenyl | 439.40 ($M+H^+$) | 49 | 91 |
| **5e** | $(CH_2)_4$ | $R^7$=$CH_2$Ph | $R^8$=Ph | 477.87 ($M+H^+$) | 52 | 86 |
| **5f** | $(CH_2)_3$ | $R^7$=Cyclohexyl | $R^8$=Ph | 454.73 ($M+H^+$) | 50 | 86 |
| **5g** | $(CH_2)_4$ | $R^7$=Cyclohexyl | $R^8$=Ph | 468.73 ($M+H^+$) | 52 | 85 |
| **5h** | $(CH_2)_3$ | $R^7$=Ethylpyridine | $R^8$=Ph | 477.87 ($M+H^+$) | 47 | 81 |
| **5i** | $(CH_2)_4$ | $R^7$=Ethylpyridine | $R^8$=Ph | 492.03 ($M+H^+$) | 44 | 78 |
| **5j** | $(CH_2)_3$ | $R^7$=$CH_2$Ph | $R^8$=Ph | 463.20 ($M+Na^+$) | 41 | 81 |
| **5k** | $(CH_2)_3$ | $R^7$=Furfuryl | $R^8$=Ph | 475.00 ($M+Na^+$) | 39 | 80 |
| **5l** | $(CH_2)_4$ | $R^7$=Furfuryl | $R^8$=Ph | 467.40 ($M+H^+$) | 42 | 84 |
| **6a** | $(CH_2)_2$ | $R^9$=H | $R^{10}$=*p*-Tolyl | 421.67 ($M+Na^+$) | 42 | 82 |
| **6b** | $(CH_2)_3$ | $R^9$=H | $R^{10}$=*p*-Ethoxy-Ph | 443.93 ($M+H^+$) | 45 | 90 |
| **6c** | $(CH_2)_3$ | $R^9$=H | $R^{10}$=*p*-Tolyl | 413.93 ($M+H^+$) | 40 | 80 |
| **6d** | $(CH_2)_4$ | $R^9$=H | $R^{10}$=*p*-Tolyl | 428.73 ($M+H^+$) | 38 | 83 |
| **6e** | $(CH_2)_2$ | $R^9$=H | $R^{10}$=*p*-Ethoxy-Ph | 430.73 ($M+H^+$) | 41 | 73 |
| **6f** | $(CH_2)_4$ | $R^9$=H | $R^{10}$=*p*-Ethoxy-Ph | 480.67 ($M+Na^+$) | 42 | 71 |
| **7a** | $(CH_2)_2$ | $R^9$=H | $R^{11}$=H, $R^{12}$=H | 324.27 ($M+H^+$) | 40 | 91 |
| **7b** | $(CH_2)_3$ | $R^9$=H | $R^{11}$=H, $R^{12}$=H | 338.07 ($M+H^+$) | 41 | 80 |
| **7c** | $(CH_2)_4$ | $R^9$=H | $R^{11}$=H, $R^{12}$=H | 352.13 ($M+H^+$) | 37 | 76 |
| **7d** | $(CH_2)_2$ | $R^9$=H | $R^{11}$=$CH_3$, $R^{12}$=H | 337.93 ($M+H^+$) | 39 | 78 |
| **7e** | $(CH_2)_3$ | $R^9$=$CH_3$ | $R^{11}$=H, $R^{12}$=H | 352.53 ($M+H^+$) | 44 | 82 |
| **7f** | $(CH_2)_4$ | $R^9$=H | $R^{11}$=$CH_3$, $R^{12}$=H | 366.07 ($M+H^+$) | 40 | 81 |
| **8a** | $(CH_2)_2$ | $R^{13}$=$CH_2$Ph | – | 389.00 ($M+H^+$) | 51 | 82 |
| **8b** | $(CH_2)_2$ | $R^{13}$=Cyclohexyl | – | 402.47 ($M+Na^+$) | 56 | 85 |
| **8c** | $(CH_2)_3$ | $R^{13}$=$CH_2$Ph | – | 402.93 ($M+H^+$) | 49 | 84 |
| **8d** | $(CH_2)_3$ | $R^{13}$=Cyclohexyl | – | 394.93 ($M+H^+$) | 46 | 80 |
| **8e** | $(CH_2)_4$ | $R^{13}$=Cyclohexyl | – | 409.00 ($M+H^+$) | 51 | 79 |
| **8f** | $(CH_2)_4$ | $R^{13}$=$CH_2$Ph | – | 416.73 ($M+H^+$) | 53 | 81 |
| **8g** | $(CH_2)_2$ | $R^{13}$=Furfuryl | – | 379.47 ($M+H^+$) | 48 | 88 |
| **8h** | $(CH_2)_3$ | $R^{13}$=Furfuryl | – | 392.87 ($M+H^+$) | 46 | 83 |

[a] Yield after purification by high throughput HPLC-MS.
[b] Purity of crude material based on analytical HPLC.

Fmoc amino acids. The library was generated using an Advanced Chemtech multiple organic synthesizer MOS 496Ω. The compounds were obtained in moderate yields with purities ranging from 70 to 92% and are presented in Table 1. Representative LC-MS for a compound is presented in Fig. 1(a) and (b). The compounds were purified by high throughput HPLC-MS.

## 2. Conclusion

In summary, we have identified 5-hydroxymethylfurfural as a novel scaffold for the generation of highly functionalized furan based libraries. It can be successfully used for the generation of large libraries of furans using an automated synthesizer.

## 3. Experimental

### 3.1. General

Sieber amide resin (1% divinylbenzene, 100–200 mesh, 0.52 mmol/g substitution) and amino acids were purchased

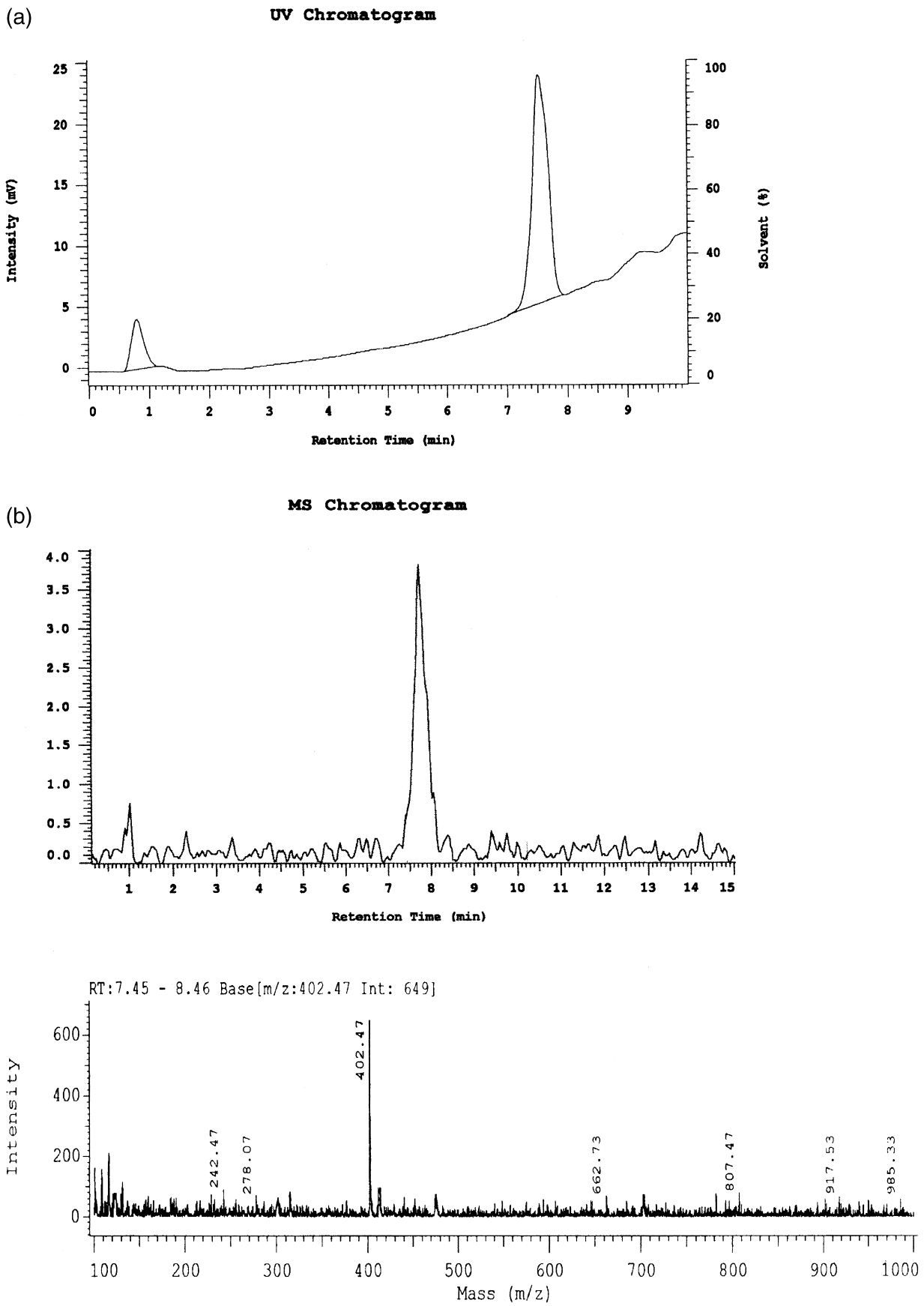


**Figure 1.** (a) UV chromatogram on LC-MS (10×50 mm; $C_{18}$ column) of succinamic acid 5-(3-cyclohexyl-4-oxo-thiazolidin-2-yl)-furan-2-ylmethyl ester (**8b**). (b) MS chromatogram on LC-MS (10×50 mm; $C_{18}$ column) of succinamic acid 5-(3-cyclohexyl-4-oxo-thiazolidin-2-yl)-furan-2-ylmethyl ester (**8b**).

from Novabiochem, Switzerland. *N*-Hydroxybenzotrizaole (HOBT) was purchased from Janseen Chemica, Belgium. 5-Hydroxy methyl furfural, *N*,*N*′-diisopropylcarbodiimide, piperidine and trifluoroacetic acid were purchased from Aldrich.

Analytical reverse high-pressure chromatography (RP-HPLC) was carried out on Shimadzu LC 10 AS/SPD 6A liquid chromatograph instrument, using reversed-phase $C_{18}$ column (4.8×150 mm) with a linear gradient of 10–100% MeOH–water (v/v) over 45 min, flow rate 0.5 ml/min and UV detection at 254 nm. Compounds were purified by automated high-throughput LC-MS system (Lachrom with MS 8000) using reversed-phase $C_{18}$ column (10×50 mm, 5 μm) with a linear gradient 10–100% MeOH–water (v/v) over 12 min. and flow rate 6 ml/min. NMR spectra were recorded on Brucker 300 MHz.

**3.1.1. Succinyl furfural.** Sieber amide (100 mg) resin purchased from Novabiochem (loading capacity 0.63 mmol/g) was deblocked by 30% piperidine in DMF two times (5 min. and 25 min.) and washed with dry DMF (12×3 ml). To this was added succinic anhydride (10 equiv., 63 mg, 0.63 mmol) in 1:1 pyridine/DMF (1 ml) and the reaction was stirred for 12 h. Thereafter, the resin was washed with 0.1 M acetic acid in DCM, DMF, DCM, ether (5×3 ml) and dried. To the resin loaded with succinic anhydride (100 mg) in DMF (1 ml) was added 5-hydroxy methyl furfural (6 equiv., 32 μl, 0.378 mmol), DIC (6 equiv., 48 μl, 0.378 mmol), HOBt (6 equiv., 56 mg, 0.378 mmol) and DMAP (2 equiv., 12 mg, 0.126 mmol) and the reaction was shaken for 24 h. Thereafter, the resin was sequentially washed with DMF, MeOH, DCM, ether (5×3 ml) and dried. The resin bound compound was cleaved with 1% TFA in DCM for 15 min. After the evaporation of the cleavage mixture, *tert*-butanol–water mixture (4:1, v/v) was added to the residue and freeze dried to obtain the desired product based on structure **1**. Succinamic acid 4-formyl-cyclopenta-1, 3-dienyl ester **1a**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 2.55 (t, $J$=6.6 Hz, 2H), 2.73 (t, $J$=6.5 Hz, 2H), 5.16 (s, 2H), 6.59 (d, $J$=3.0 Hz, 1H), 7.21 (d, $J$=3.3 Hz, 1H), 9.63 (s, 1H).

**3.1.2. Diels–Alder reaction.** To the resin bound aldehyde **1** (50 mg) in TMOF (1 ml) was added primary amine (5 equiv., 0.157 mmol) and the reaction was shaken for 3 h. After 3 h, sodium cyanoborohydride (10 equiv., 19.84 mg, 0.315 mmol) and a 40% solution of acetic acid in THF (40 μl) was added and the reaction was shaken for an additional 2 h at room temperature. Thereafter, the resin was washed with DMF, MeOH, DCM, ether (5×3 ml) and dried to get compound **2**. The resin so obtained was treated with maleic anhydride (5 equiv., 15.4 mg, 0.157 mmol) in pyridine/DMF mixture (1:1) and the reaction was shaken at room temperature for overnight. The solvent was drained and resin was washed with DMF, MeOH, DCM and ether (5×3 ml) and dried in vacuo. Finally, the resin was treated with 1% TFA in DCM for 15 min. and freeze-dried to get compound **3**. 7-(3-Carbamoyl-propionyloxymethyl)-3-cyclohexyl-4-oxo-10-oxa-3-aza-tricyclo [5.2.1.01,5] dec-8-ene-6-carboxylic acid (**3a**): $^1$H NMR (300 MHz, DMSO-$d_6$), $\delta$: 1.11–1.46 (m, 6H), 1.56–1.71 (m, 4H), 2.30 (t, $J$=7.2 Hz, 2H), 2.35 (t, $J$=7.2 Hz, 2H), 2.75 (d, $J$=10.5 Hz, 1H), 2.84 (d, $J$=10.5 Hz, 1H), 3.58 (s, 2H), 3.70 (m, 1H), 4.52 (s, 2H), 6.79 (s, 2H).

**3.1.3. Mannich reaction.** Resin bound furfural **1** (50 mg) was treated with an alkyne (8 equiv., 0.252 mmol), substituted piperazine (8 equiv., 0.252 mmol) and cuprous chloride (2 equiv., 8.57 mg, 0.063 mmol) in dioxane and the reaction was shaken at 85°C for 6 h. The resin was filtered, washed with dioxane, DMF, 1 M ammonia solution, DMF, MeOH, THF and DCM (3×3 ml). Finally, the resin was treated with 1% TFA in DCM and the residue obtained after the evaporation of the cleavage mixture under nitrogen was freeze dried by dissolving in *tert*-butanol–water mixture to get the desired compound **4**. Succinamic acid 4-[4-hydroxy-1-(4-phenyl-piperazin-1-yl)-but-2-ynyl]-cyclopenta-1,3-dienylmethyl ester (**4b**): $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 2.30 (t, $J$=7.2 Hz, 2H), 2.38 (t, $J$=6.9 Hz, 2H), 2.52 (t, $J$=3.3 Hz, 4H), 3.33 (t, $J$=3.6 Hz, 4H), 4.20 (s, 2H), 5.03 (s, 2H), 5.29 (s, 2H), 6.32 (d, $J$=3.3 Hz, 1H), 6.54 (d, $J$=3.0 Hz, 1H), 6.7 (d, $J$=4.5 Hz, 2H), 6.8 (d, $J$=4.5 Hz, 1H), 7.1 (m, 2H).

**3.1.4. β-Lactam formation.** This was carried out in two steps. First, resin bound succinyl furfural **1** (50 mg) was treated with an amine (5 equiv., 0.157 mmol) in TMOF for 12 h at room temperature followed by sequential washing of the resin with DMF, DCM and ether (3×3 ml). The resin was then treated with triethylamine (30 equiv., 132 μl, 0.945 mmol) and phenoxy acetyl chloride (20 equiv., 87 μl, 0.63 mmol) in DCM and the reaction mixture was shaken at room temperature for 12 h. The resin was filtered, washed with DMF, MeOH, DCM, and ether and dried. Finally the resin was treated with 1% TFA in DCM and the residue obtained after the evaporation of the cleavage mixture under nitrogen was freeze-dried by dissolving in *tert*-butanol–water mixture to get the desired compound **5**. Succinamic acid 4-[1-cyclohexyl-3-(cyclopenta-1,3-dienyloxy)-4-oxo-azetidin-2-yl]-cyclopenta-1,3-dienylmethyl ester (**5a**): $^1$H NMR (300 MHz, MeOD) $\delta$: 1.2 (m, 10H), 2.51 (t, $J$=6.0 Hz, 2H), 2.53 (t, $J$=5.4 Hz, 2H), 3.3 (m, 1H), 5.02 (s, 2H), 5.2 (d, $J$=4.2 Hz, 1H), 5.5 (d, $J$=4.2 Hz, 1H), 6.1(d, $J$=3.3 Hz, 1H), 6.3 (d, $J$=3.0 Hz, 1H), 6.8 (d, $J$=4.2 Hz, 2H), 6.9 (d, $J$=4.5 Hz, 1H), 7.14 (m, 2H).

**3.1.5. Hydantoin formation.** To the resin bound aldehyde 1 (50 mg) in TMOF (1 ml) was added methyl ester of α-amino acid (5 equiv., 0.157 mmol) and the reaction was shaken for 3 h at room temperature. After 3 h sodium cyanoborohydride (10 equiv., 19.84 mg, 0.315 mmol) and a 40% solution of acetic acid in THF (40 μl) were added and the reaction was shaken for an additional 2 h. Thereafter, the resin was washed with DMF, MeOH, DCM and ether (5×3 ml) and dried, the resin so obtained was treated with isocyanate (10 equiv., 0.315 mmol) in DCM and the reaction mixture was shaken at 50°C for 12 h and then washed with DMF, MeOH, DCM and ether (5×3 ml) and dried. Then resin was shaken with 1% diisopropyl amine in DCM overnight and washed with DCM. Finally, the resin was treated with 1% TFA in DCM and the residue obtained after the evaporation of the cleavage mixture under nitrogen was freeze-dried by dissolving in *tert*-butanol–water mixture to get the desired compound **6**. Succinamic acid 4-(2,4-dioxo-3-p-tolyl-imidazolidin-1-ylmethyl)-cyclopenta-1,

3-dienylmethyl ester (**6a**): $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 2.21 (t, $J$=7.05 Hz, 2H), 2.38 (t, $J$=6.75 Hz, 2H), 2.82 (s, 3H), 4.00 (s, 2H), 4.50 (s, 2H), 4.95 (s, 2H), 6.39 (d, $J$=3.3 Hz, 1H), 6.42 (d, $J$=3.0 Hz, H), 7.19 (m, 2H), 7.23 (m, 2H).

**3.1.6. Diketopiperazine formation.** To the resin bound aldehyde **1** (50 mg) in TMOF (1 ml), was added the methyl ester of α-amino acid (5 equiv., 0.157 mmol) and the reaction was shaken for 3 h. After 3 h sodium cyanoborohydride (10 equiv., 19.84 mg, 0.315 mmol) and a 40% solution of acetic acid in THF (40 μl) were added and the reaction was shaken for 2 h. Thereafter, the resin was washed with DMF, MeOH, DCM, ether (5×3 ml) and dried. The resin so obtained was treated with Fmoc-α-amino acid (3 equiv., 0.094 mmol), HOBT (3 equiv., 14 mg, 0.094 mmol), DIC (3 equiv., 12 mg, 0.094 mmol) in DMF and reaction was allowed to be shaken at room temperature for 12 h. The solvent was drained and the resin was washed with DMF, MeOH, DCM and ether (5×3 ml) and dried. The Fmoc group was deprotected with 30% piperidine in DMF for 25 min and washed with DMF, MeOH, DCM, and ether. Then the reaction was shaken with 50% DIPEA in DCM for overnight and washed with MeOH, DCM and ether (5×3 ml) and dried. Finally the resin was treated with 1% TFA in DCM and the residue obtained after the evaporation of the cleavage mixture under nitrogen was freeze-dried by dissolving in *tert*-butanol–water mixture to get the desired compound **7**. Succinamic acid 4-(2,5-dioxo-piperazin-1-ylmethyl)-cyclopenta-1,3-dienylmethyl ester (**7a**): $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 2.21 (t, $J$=7.05 Hz, 2H), 2.38 (t, $J$=6.75 Hz, 2H), 3.64 (s, 4H), 4.44 (s, 2H), 4.91 (s, 2H), 6.31 (d, $J$=3.0 Hz, 1H), 6.40 (d, $J$=3.3 Hz, 1H).

**3.1.7. Thiazolidinone formation.** To the resin bound aldehyde **1** (50 mg) in TMOF (1 ml) was added primary amine (10 equiv., 0.315 mmol) and the reaction was shaken for 3 h. After that the resin was washed with DMF, DCM and ether (5×3) and dried in vacuo. To this resin in THF was added mercaptoacetic acid (10 equiv., 22 μl, 0.315 mmol) and triethyl amine (15 equiv., 66 μl, 0.472 mmol) and the reaction was shaken at 60°C overnight. Solvent was drained and the resin was washed sequentially with DMF, MeOH, DCM and ether (5×3 ml) and dried. Finally, the resin was treated with 1% TFA in DCM and the residue obtained after the evaporation of the cleavage mixture under nitrogen was freeze-dried by dissolving in *tert*-butanol–water mixture to get the desired compound **8**. Succinamic acid 4-(3-cyclohexyl-2-oxo-thiazolidin-5-ylmethyl)-cyclopenta-1,3-dienylmethyl ester (**8b**): $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 1.31 (m, 6H), 1.62 (m, 4H), 2.40 (t, $J$=6.75 Hz, 2H), 2.47 (t, $J$=6.75 Hz, 2H), 3.64 (s, 2H), 3.88 (m, 1H), 4.91 (s, 2H), 7.37 (d, $J$=3.3 Hz, 1H), 6.53 (s, 1H), 6.8 (d, $J$=3.3 Hz, 1H).

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