

Fused Pyrimidines. Part II: Synthesis and Antimicrobial activity of Some Furo[3,2-*e*]imidazo[1,2-*c*]pyrimidines and Furo[2,3-*d*]pyrimidines

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2-Amino-4,5-diphenylfuran-3-carbonitrile (**2**) reacted with *N*-[bis(methylthio)methylene]glycine ethyl ester (**1**) to afford a double cyclized product 5-methylthio-8,9-diphenylfuro[3,2-*e*]imidazo[1,2-*c*]pyrimidin-2(3*H*)-one (**3**). Compound **2** also reacts with benzonitrile to give 4-amino-2,5,6-triphenylfuro[2,3-*d*]pyrimidine (**4**). Treatment of **2** with HCONH₂, under reflux, afforded 4-amino-5,6-diphenylfuro[2,3-*d*]pyrimidine (**5**) which was then allowed to react with chloroacetaldehyde to give 8,9-diphenylfuro[3,2-*e*]imidazo[1,2-*c*]pyrimidine (**6**). Reaction of **2** with HCOOH gave 5,6-diphenylfuro[2,3-*d*]pyrimidin-4(3*H*)-one (**7**) which was then converted to its tosyl derivative (**8**). The antimicrobial activity of the synthesized compounds **2–8** was tested.

INTRODUCTION

Pyrimidines, being an integral part of DNA and RNA, exhibit diverse pharmacological properties as effective bactericide, fungicide, viricide, insecticide, medicine.^{1–3} Certain pyrimidines and annulated pyrimidine derivatives are also known to display anticancer, antimalarial, antileishmanial and antifilarial activities.^{4–7} Some furans are shown to be useful for the inhibition of thrombin formation.⁸ Furans have also been extensively investigated for their pharmacological uses. Some heterocyclic systems constructed on furans, possess antihypertensive, antialergic and antidepressant activities.^{9–11} In continuation of our earlier work¹² and the biodynamic properties of these ring systems prompted us to design a system, which combines these two biolabile components in a ring together to give compact structures for screening their antimicrobial activities.

EXPERIMENTAL

General

Melting points were determined on an electrothermal apparatus in an open capillary tube and are uncorrected. The ¹H- and ¹³C-NMR were measured on Bruker AC 200 spectrometer using DMSO-*d*₆ or CDCl₃ as the solvent and chemical shifts were expressed as δ values in ppm against TMS as an internal standard. TLC using silica G routinely checked the purity of the compounds and the spots were exposed in iodine vapour for visualization.

N-[Bis(methylthio)methylen]glycine ethyl ester (**1**)

To a solution of glycine ethyl ester hydrochloride (50 mmol) and carbon disulfide (50 mmol) in chloroform (50 ml) triethylamine (105 mmol) was added dropwise. After 1 h stirring methyl iodide (55 mmol) was added and refluxed the mixture for another 1 h. The resultant mixture was

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washed with water (2 × 20 ml), dried (Na₂SO₄) and evaporated the solvent. The crude oil was dissolved in acetone (30 ml), anhydrous K₂CO₃ (10 g) and methyl iodide (60.2 mmol) were added. The reaction mixture refluxed for 3 h and stirring was continued for overnight at r.t. After evaporation of the solvent, the residue was diluted with ether (20 ml), washed with water (2 × 20 ml), dried (Na₂SO₄) and the solvent was removed by evaporation. The residue was distilled under reduced pressure to furnish **1** (80 %) as colourless syrup, b.p. 96–98 °C, 0.08 mm Hg. ¹H-NMR (CDCl₃) δ/ppm: 4.29 (q, 2H, *J* = 7.09 Hz, OCH₂), 4.24 (s, 2H, CH₂), 2.56 (s, 3H, SCH₃), 2.45 (s, 3H, SCH₃), 1.28 (t, 3H, *J* = 7.09 Hz, CH₃). ¹³C-NMR (CDCl₃) δ/ppm: 169.3, 162.2, 60.1, 53.7, 14.4, 14.0, 13.7.

5-Methylthio-8,9-diphenylfuro[3,2-*e*]imidazo[1,2-*c*]pyrimidin-2(3*H*)-one (**3**)

Equimolar amounts of **1** and **2** in acetic acid were refluxed for 8 h. The reaction mixture was cooled and poured into water. The solid so formed was collected by filtration and crystallized from EtOH to furnish **3** as yellowish crystals (82 %), m.p. > 270 °C. *Analysis Calcd.* for C₂₁H₁₅N₃O₂S (373.44): C 67.54, H 4.05, N 11.25; Found: C 67.49, H 4.11, N 11.21. ¹H-NMR (CDCl₃) δ/ppm: 7.69 (m, 5H, Ar-H), 7.47 (m, 5H, Ar-H), 4.20 (s, 2H, CH₂), 2.70 (s, 3H, SCH₃). ¹³C-NMR (CDCl₃) δ/ppm: 170.14, 166.32, 162.07, 139.63, 137.52, 132.76, 131.14, 130.18, 129.53, 129.11, 128.45, 127.51, 125.41, 121.78, 113.31, 50.43, 13.25.

4-Amino-2,5,6-triphenylfuro[2,3-*d*]pyrimidine (**4**)

A mixture of **2** (1.92 mmol), NaOMe (3.84 mmol) and benzonitrile (1.92 mmol) in 2-propanol (10 ml) was refluxed for 20 h. On cooling the precipitate was filtered off and recrystallized from EtOH to afford **4** (68 %) as brown crystals, m.p. 250–252 °C. *Analysis Calcd.* for C₂₄H₁₇N₃O (363.42): C 79.32, H 4.72, N 11.56; Found: C 79.28, H 4.74, N 11.52. ¹H-NMR (DMSO-*d*₆) δ/ppm: 7.89 (m, 5H, Ar-H), 7.62 (m, 5H, Ar-H), 7.40 (m, 5H, Ar-H), 4.95 (s, 2H, NH₂). ¹³C-NMR (DMSO-*d*₆) δ/ppm: 170.14, 140.26, 131.19, 129.00, 128.60, 128.18, 127.45, 127.26, 127.05, 126.66.

4-Amino-5,6-diphenylfuro[2,3-*d*]pyrimidine (**5**)

A solution of **2** (3.85 mmol) in formamide (5 ml) was refluxed for 2 h. The precipitate that formed on cooling was filtered off and recrystallized from EtOH to give **5** (63 %) as brown crystals, m.p. 252–254 °C. ¹H-NMR (CDCl₃) δ/ppm: 7.16 (s, 1H, CH), 7.02 (m, 10H, 2 × Ph), 6.12 (s, 2H, NH₂). ¹³C-NMR (CDCl₃) δ/ppm: 163.27, 156.25, 151.57, 144.57, 129.93, 127.86, 127.41, 126.83, 124.36, 113.65.

8,9-Diphenylfuro[3,2-*e*]imidazo[1,2-*c*]pyrimidine (**6**)

A mixture of **5** (0.52 mmol), NaOAc (0.1 g) and 40 % chloroacetaldehyde (0.45 ml) in water (1.5 ml) was heated on steam bath for 2 h with stirring. Extraction by chloroform and evaporation of solvent to give **6** (66 %), m.p. > 270 °C. *Analysis Calcd.* for C₂₀H₁₃N₃O (311.35): C 77.16,

H 4.21, N 13.50; Found: C 77.13, H 4.24, N 13.48. ¹H-NMR (CDCl₃) δ/ppm: 8.31 (s, 1H, H-5), 7.60 (d, 1H, *J* = 2.4 Hz, H-2), 7.50 (d, 1H, *J* = 2.4 Hz, H-3), 7.41 (m, 10H, 2 × Ph). ¹³C-NMR (CDCl₃) δ/ppm: 165.34, 157.41, 153.15, 147.67, 134.51, 131.21, 130.21, 129.72, 128.80, 127.13, 126.50, 114.41.

5,6-Diphenylfuro[2,3-*d*]pyrimidin-4(3*H*)-one (**7**)

A suspension of **2** (1.92 mmol) in formic acid (10 ml, 85 %) was refluxed for 4 h. The solid that precipitated was collected and recrystallized from EtOH to give **7** (75.2 %), m.p. 210–212 °C. ¹H-NMR (CDCl₃) δ/ppm: 8.00 (s, 1H, NH), 7.84 (s, 1H, H-2), 7.57 (m, 5H, Ar-H), 7.52 (m, 5H, Ar-H). ¹³C-NMR (CDCl₃) δ/ppm: 187.96, 164.02, 144.82, 139.89, 130.56, 130.18, 129.27, 128.74, 128.30, 126.77.

4-Oxo-5,6-diphenylfuro[2,3-*d*]pyrimidin-3-*p*-toluene sulfonate ester (**8**)

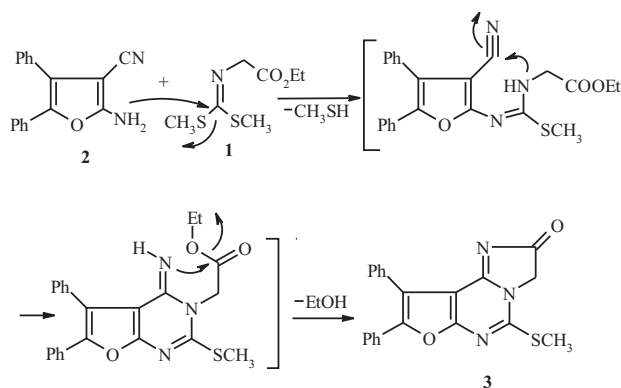
A solution of **7** (0.86 mmol), *p*-TsCl (0.86 mmol) in ether (5 ml) was heated at 30 °C for 5 h. After evaporation of ether, the resulting solid was recrystallized from EtOH to give **8** (66 %) as yellowish crystals, m.p. > 270 °C. *Analysis Calcd.* for C₂₅H₁₈N₂O₄S (442.50): C 67.86, H 4.10, N 6.33; Found: C 67.81, H 4.15, N 6.36. ¹H-NMR (CDCl₃) δ/ppm: 7.62 (s, 1H, H-2), 7.51 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.45 (m, 5H, Ph), 7.32 (m, 5H, Ph), 7.15 (d, 2H, *J* = 8.0 Hz, Ar-H), 2.24 (s, CH₃). ¹³C-NMR (CDCl₃) δ/ppm: 188.14, 183.43, 182.74, 179.50, 160.10, 153.91, 148.48, 144.83, 131.50, 130.55, 129.08, 128.55, 127.60, 118.39, 28.92.

RESULTS AND DISCUSSION

The annelating reagent, *N*-[bis(methylthio)methylene]glycine ethyl ester (**1**) was prepared by reacting glycine ethyl ester hydrochloride with CS₂/Et₃N/MeI and subsequently accomplishing the alkylation of the intermediate thus obtained with MeI/K₂CO₃ as described in the literature.¹³

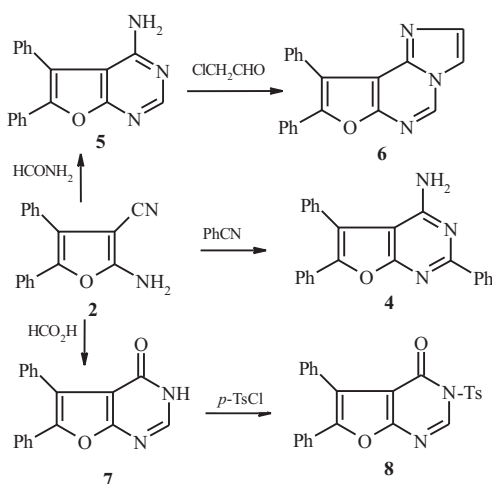
The starting material, 2-amino-4,5-diphenylfuran-3-carbonitrile (**2**) was prepared according to a modified Gewald method.¹⁴

Refluxing an equimolar mixture of **1** and **2** in dry acetic acid allows one-pot annelation yielded in a remarkably easy way and efficient double cyclized product 5-methylthio-8,9-diphenylfuro[3,2-*e*]imidazo[1,2-*c*]pyrimidin-2(3*H*)-one (**3**) in 82 % yield (Scheme 1). The ¹H-NMR spectrum of **3** exhibited a two-proton singlet for CH₂ at δ 4.20 ppm, a three-proton singlet for one SCH₃ at δ 2.70 ppm, two multiplets at δ 7.69 and 7.47 ppm for ten protons of two phenyl groups. No peaks were found for NH₂ (δ 5.10 ppm) and a carboethoxy group (δ 4.29 and 1.28 ppm). The ¹³C-NMR spectrum displayed signals at δ 170.14 ppm for C=O carbon and at δ 50.43 ppm for methylene carbon at position C-3 of the molecule. The rest of the spectrum was in good agreement with the structure **3**.



Scheme 1.

Compound **2** was readily cyclized to the corresponding 4-amino-2,5,6-triphenylfuro[2,3-*d*]pyrimidine (**4**) upon treatment with benzonitrile and NaOMe in refluxing 2-propanol (Scheme 2). Reaction of compound **2** with for-



Scheme 2.

mamide gave the corresponding 4-amino-5,6-diphenylfuro[2,3-*d*]pyrimidine (**5**) which was then allowed to react with chloroacetaldehyde to yield 8,9-diphenylfuro[3,2-*e*]imidazo[1,2-*c*]pyrimidine (**6**). The ¹H-NMR and ¹³C-NMR spectra supported the assigned products **4**, **5** and **6** respectively (see Experimental).

Compound **2** also underwent cyclization with formic acid to afford 5,6-diphenylfuro[2,3-*d*]pyrimidin-4(3*H*)-one (**7**) which was then converted to its tosyl derivative (**8**) with *p*-TsCl. The proposed structures for the products **7** and **8** were supported by their spectral data (see Experimental).

ANTIMICROBIAL SCREENING

Antibacterial activity

Newly synthesized compounds **3–8** were screened *in vitro* for their antimicrobial activities against bacteria *B. cereus*, *S. dysenteriae* and *S. typhi* using disc diffusion

TABLE I. Antibacterial activity of compounds **3–8**.

Comp.	<i>B. cereus</i>	<i>S. dysenteriae</i>	<i>S. typhi</i>
3	14	9	17
4	7	–	–
5	–	–	–
6	6	–	8
7	8	6	–
8	6	–	7
Ampicillin	21	30	24

method.¹⁵ *N,N*-Dimethyl formamide (DMF) was used, as a solvent to prepare desired solution (1 %) of the compounds initially. Proper control was maintained with DMF. The inhibition zones of microbial growth (100 µg/disc) produced by different compounds were measured in millimeters at the end of an incubation period of 48 h at (35±2) °C (Table I). DMF alone showed no inhibition zone. Ampicillin (25 µg/disc) was used as a standard antibiotic for the evaluation of the antimicrobial activity. The screening results indicate that not all compounds exhibited antibacterial activity. Some compounds showed weak to moderate activity against all the organisms tested. Compound **3** showed better activity compared with other synthesized products.

Antifungal activity

Newly synthesized compounds **3–8** were screened for their antifungal against *M. phaseolina*, *F. equiseti*, *A. alternata* and *C. corchori* using poisoned-food technique.¹⁶ DMF (1 %) was used as solvent and the inhibition zones were measured in millimeters at the end of an incubation period of 48 h at (35±2) °C (Table II). Nystatin was used as a reference to evaluate the potency of the tested chemicals.

TABLE II. Antifungal activity of compounds **3–8**.

Comp.	<i>M. phaseolina</i>	<i>F. equiseti</i>	<i>A. alternata</i>	<i>C. corchori</i>
3	65.52	68.75	42.31	22.72
4	29.4	55.0	27.1	35.5
5	42.0	28.35	61.30	33.0
6	25.7	55.0	48.2	20.45
7	31.9	29.0	22.9	22.10
8	50.0	19.2	52.4	26.68
Nystatin	71.78	44.7	51.55	40.51

Amongst the synthesized compounds screened for the antifungal activity, compounds **3**, **4** and **6** showed excellent results against *F. equiseti*, which were also greater than that of the standard antibiotic, Nystatin. Compound **3** also showed better inhibition for other fungi. The other compounds also exhibited moderate to good activity against the tested organisms.

REFERENCES

1. C. C. Cheng, *Prog. Med. Chem.* **6** (1969) 67–75.
2. D. B. Scott McNair, T. L. V. Ulbriant, M. L. Rogers, E. Chu, and C. Rose, *Cancer Res.* **19** (1959) 15–19.
3. Sankyo Co Ltd; Ube Industries Ltd. *Japan Kokai Tokyo Koho JP 59 36,667*; *Chem. Abstr.* **101** (1984) 110939z.
4. J. P. Jonak, S. F. Zakrzewski, and L. H. Mead, *J. Med. Chem.* **15** (1972) 662–64.
5. E. A. Falco, *Br. J. Pharmacol.* **6** (1961) 185–190.
6. V. J. Ram, *Arch. Pharm. (Weinheim, Ger.)*, **323** (1990) 895–899.
7. R. E. Howells, J. Tinsley, E. Devaney, and G. Smith, *Acta Trop.* **38** (1981) 289–305.
8. De Angelis, G. Gerald, and H. J. E. Hess, US Pat (1973) 3755583; *Chem. Abstr.* **79** (1973) 115624e.
9. F. Sauter, J. Frohlich, and A. Z. M. S. Chowdhury, *Sci. Pharm.* **64** (1996) 647–653.
10. V. M. Patil, S. S. Sangapure, and Y. S. Agasimudin, *Indian J. Chem., Sect. B* **23** (1984) 132–135.
11. H. Takashi, S. Kenji, and T. Y. Nakayama, *J. Heterocycl. Chem.* **28** (1991) 263–267.
12. M. M. H. Bhuiyan, K. M. M. Rahman, M. K. Hossain, and M. Fakruddin, *Pakistan J. Sci. Ind. Res.* **47** (2004) 256–258.
13. F. Sauter, J. Frohlich, K. Blasl, and K. Gewalt, *Heterocycles* **40** (1995) 851–866.
14. K. Gewalt, E. Schinke, and H. Bottcher, *Chem. Ber.* **99** (1966) 94–100.
15. A. W. Bauer, W. M. M. Kirby, J. C. Sherris, and M. Turck, *Am. J. Clin. Pathol.* **45** (1966) 493–496.
16. R. K. Grover and J. D. Moore, *Phytopathology* **52** (1962) 876–880.

SAŽETAK

Kondenzirani pirimidini. II dio: Sinteza i antimikrobna aktivnost nekih furo[3,2-*e*]imidazo[1,2-*c*]pirimidina i furo[2,3-*d*]pirimidina

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2-Amino-4,5-difenilfuran-3-karbonitril (**2**) u reakciji s etilnim esterom *N*-[bis(metiltio)metilen]glicina (**1**) daje produkt dvostruke ciklizacije – 5-metiltio-8,9-difenilfuro[3,2-*e*]imidazol[1,2-*c*]pirimidin-2(3*H*)-on (**3**). Također, u reakciji s benzonitrilom spoj **2** daje 4-amino-2,5,6-trifenilfuro[2,3-*d*]pirimidin (**4**). Grijanjem spoja **2** s HCONH₂ dobiven je 4-amino-5,6-difenilfuro[2,3-*d*]pirimidin (**5**), koji reakcijom s kloroacetaldehidom daje 8,9-difenilfuro[2,3-*d*]imidazo[1,2-*c*]pirimidin (**6**). Reakcijom **2** s HCOOH dobiven je 5,6-difenilfuro[2,3-*d*]pirimidin-4(3*H*)-on (**7**), koji je preveden u tozilat (**8**). Spojevima **2-8** ispitana je antimikrobna aktivnost.