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ARTICLE

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Synthesis of fused tetracyclic benzo[4,5]furo[3,2-d] pyrimidin-4(3H)-ones derivatives containing thiadiazole/ oxazolidine/triazole/triazinanone moieties

Shengjie He[1,2] | **Junkai Ma**[1,2] | **Fei Li**[1,2] | **Yanggen Hu**[1,2]

[1]School of Pharmaceutical Sciences, Hubei University of Medicine, Shiyan, China

[2]Hubei Key Laboratory of Wudang Local Chinese Medicine Research and Institute of Medicinal Chemistry, Hubei University of Medicine, Shiyan, China

Correspondence
Yanggen Hu, School of Pharmaceutical Sciences, Hubei University of Medicine, Shiyan, China.
Email: huyg@hbmu.edu.cn

Fei Li, School of Pharmaceutical Sciences, Hubei University of Medicine, Shiyan, China.
Email: piaopodexinlifei@163.com

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Abstract

In an attempt to design and synthesize new heterocycles with improved their biological properties, some of fused tetracyclic benzo[4,5]furo[3,2-d]pyrimidin-4(3H)-ones bearing 1,2,4-triazole, 1,3,4-thiadiazole, 1,2,4-triazinanone, and oxazolidine systems have been prepared by the aza-Wittig reactions from readily available starting material under mild conditions. The structure of synthesized compounds was elucidated by ^{1}H NMR, ^{13}C NMR, MS, IR, and elemental analysis.

1 | INTRODUCTION

As it is known, fused pyrimidinone rings, which display a variety of pharmacological properties,[1,2] have recently attracted considerable attention. Some of them show anti-inflammatory, good analgesic, and anti-microbial activities.[3,4] In addition, furopyrimidine as a fused ring with other heterocyclic moieties show prime antitumor activity through inhibition of EGFR tyrosine kinase enzyme.[5] On the other hand, several heterocycle containing triazinanone, thiadiazole, oxazolidine, and triazole have a wide range of medicinal properties, for example, insecticidal, bactericidal, fungicidal, anti-inflammatory, and antitumor agents.[6–10] To introduce these hetercyclic ring in the fused furopyrimidinone system is expected to improve the biological activities. So far, the known methods could not be used to generate diversified fused tetracyclic pyrimidinone derivatives.

Over the past 10 years, considerable interest has been focused on the strategy to design and synthesize new N-heterocycle via aza-Wittig reaction with mild reaction conditions.[11–15] Herein, we report our efforts

aiming to the preparation of fused tetracyclic benzo [4,5]furo[3,2-d]pyrimidin-4(3H)-one derivatives containing 1,3,4-thiadiazole/1,2,4-triazole/1,2,4-triazinanone/oxazolidine moieties via aza-Wittig reactions.

2 | RESULTS AND DISCUSSION

2.1 | Preparation of fused tetracyclic benzo[4,5]furo[3,2-d]pyrimidin-4(3H)-ones containing 1,3,4- thiadiazole/oxazolidine moieties 5a and 5b

As shown in Scheme 1, the preparation of iminophosphorane **2** has been reported earlier.[16] **2** reacted first with excess carbon disulfide to give **3** in satisfactory yields. **3** further reacts with hydrazine hydrate and amino ethanol, respectively, to produce **4a** and **4b**, which were no need to purify and used directly. The methods and strategies used here provide highly efficient synthesis of **3** and **4a**, **4b** without using the highly toxic thiophosgene.

4a reacted with triphenylphosphine and hexachloroethane, Et_3N, and butyl isocyanates to give fused tetracyclic pyrimidinone derivative containing 1,3,4-thiadiazole **5a**. In the presence of K_2CO_3, unexpectedly, when the reaction of S-alkylation of **4b** with methyl 3-(2-(bromomethyl) phenyl)-3-methoxyacrylate generated fused tetracyclic pyrimidinone containing oxazolidine moiety **5b** at 50°C. The direct reaction of **4b** did not cyclize using a catalytic amount of sodium ethoxide at 20°C-25°C, or in dry N,N-dimethy-formamide even temperature exceed 100°C, **4b** did not produce **5b** under the same catalytic conditions. The reaction mechanism of **5b** can be explained by an initial S-alkylation of **4b** to give **5s**, which undergoes further intramolecular nucleophilic substitution reaction more quickly to yield **5b** (Scheme 2).

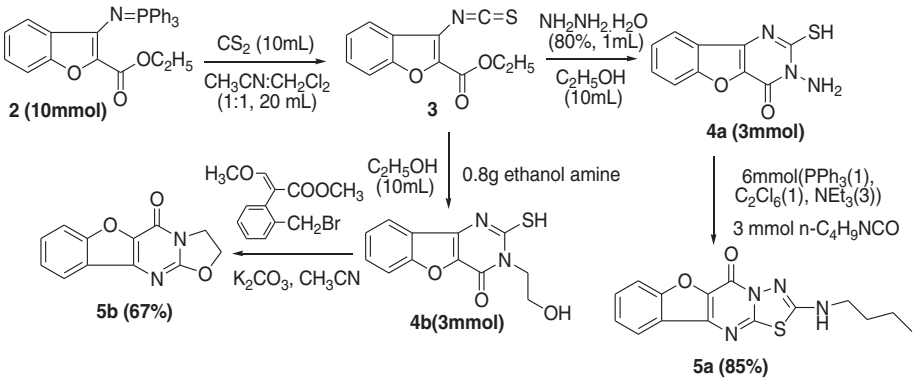
2.2 | Preparation of fused tetracyclic benzo[4,5]furo[3,2-d]pyrimidin-4(3H)-ones containing triazole/triazinanone 7, 9a-9b, and 11

Carbodiimides **6a**, formed by reaction of **2** with phenyl isocyanate, reacts with butyrohydrazide to provide guanidine intermediates **6s**, and then 6s was easily converted to fused tetracyclic benzo[4,5]furo[3,2-d]pyrimidin-4 (3H)-ones containing 1,2,4-triazole moieties **7** with catalytic EtONa (Scheme 3).

In order to obtain various fused tetracyclic pyrimidinone derivatives, the reaction of carbodiimides **6a** and **6b** with hydrazine hydrate gives intermediate **8a** and **8b**. And then **8a** and **8b** with ethyl bromoacetate in the presence of anhydrous K_2CO_3 provided only fused tetracyclic benzo[4,5]furo[3,2-d]pyrimidin-4(3H)-one derivatives containing 1,2,4-triazinanone moieties **9a** and **9b**, respectively. Most worthy of mention is that, from the reaction system after recrystallization, we obtained only **9a** and **9b**, one of the possible regioisomers; the other isomers **9a′** and **9b′** were not found by ^1H NMR analysis of the reaction mixture (Scheme 4). The result may be due to the differences of diversity and nucleophilicity of three different amino groups, which shows that the ammonolysis reaction of intramolecular ester group was easier.

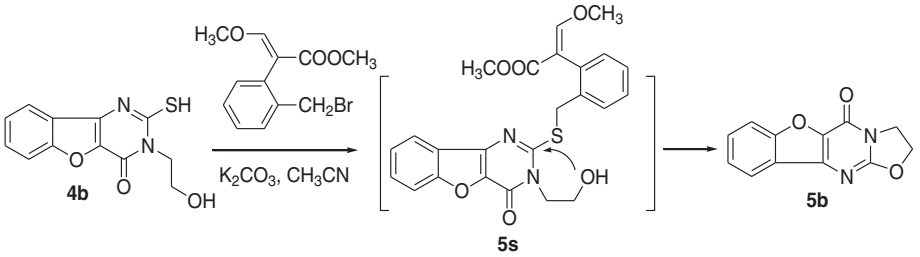
To further extend the method for preparation of diverse tetracyclic pyrimidinones, functionalized iminophosphoranes **10**, converted using compounds **8b** reaction with triphenylphosphine, C_2Cl_6, and $N(C_2H_5)_3$, reacted with phenyl isocyanate to produce carbodiimide intermediate, and then intramolecular cyclization easily gives new fused tetracyclic benzo[4,5]furo[3,2-d] pyrimidin-4(3H)-ones containing 1,2,4-triazole moieties **11** in good yields. The protocols are shown in Scheme 5.

The structures of all the products were confirmed by NMR, IR, MS, and elemental analysis. And the proposed structures are consistent with all the data.

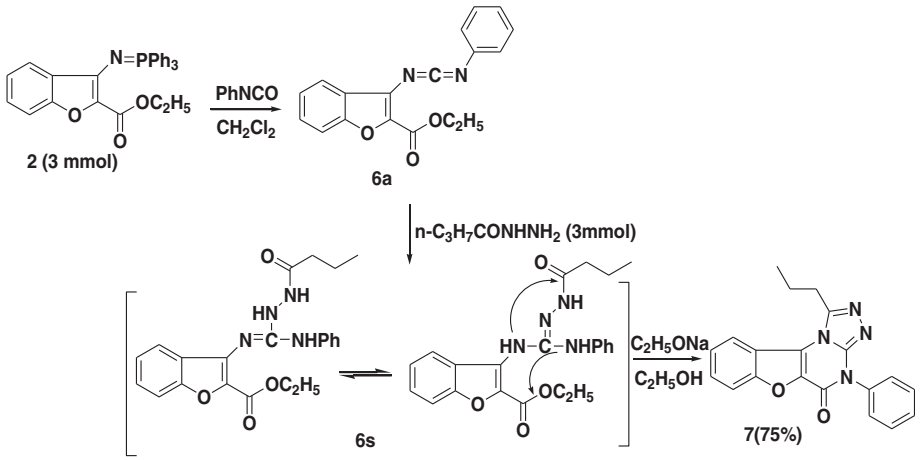


SCHEME 1 Preparation of fused tetracyclic benzo[4,5]furo[3,2-d] pyrimidin-4(3H)-ones containing thiadiazole/oxazolidine moieties **5a** and **5b**

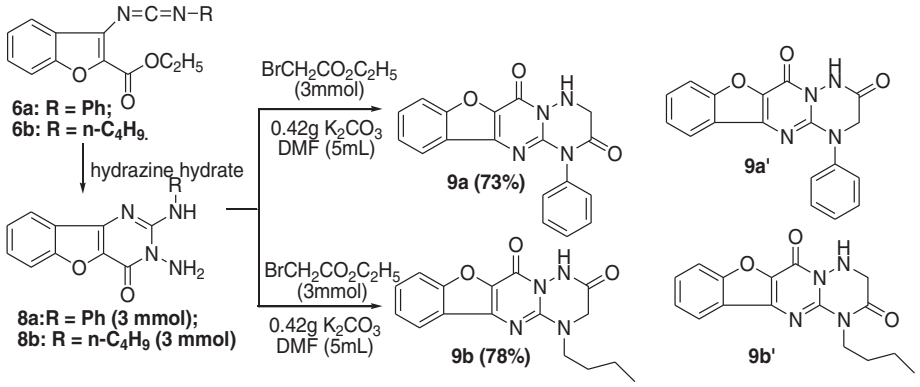
SCHEME 2



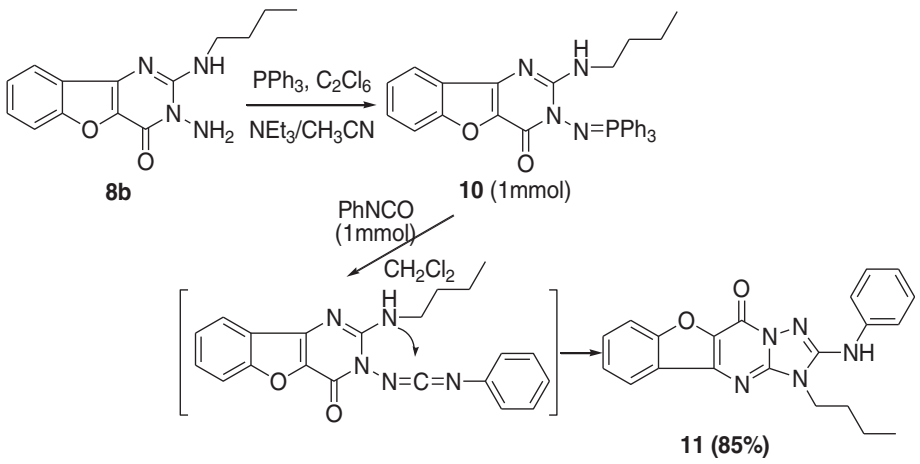
SCHEME 3 Preparation of fused tetracyclic benzo[4,5]furo[3,2-d] pyrimidin-4(3H)-one containing 1,2,4-triazole moieties **7**



SCHEME 4 Preparation of fused tetracyclic benzo[4,5]furo[3,2-d] pyrimidin-4(3H)-ones containing triazinanone moieties **9a**, **9b**



SCHEME 5 Preparation of fused tetracyclic benzo[4,5]furo[3,2-d] pyrimidin-4(3H)-ones containing 1,2,4-triazole moieties **11**



3 | EXPERIMENTAL

3.1 | General

All chemicals were commercially available and analytically pure, and used without further purification. Melting points were recorded using an uncorrected X-4 digital melting point apparatus. MS were measured by using a Finnigan Trace MS spectrometer. IR were recorded on a PE-983 infrared spectrometer as KBr pellets with absorptions in cm^{-1}. NMR were recorded in $CDCl_3$ (or DMSO-d_6) using a Varian Mercury 400 spectrometer with resonances relative to tetramethylsilane (TMS) as an internal standard. Elemental analyses were recorded on a PerkinElmer CHN 2400 instrument. TLC analysis was carried out on silica gel plates GF254 (Wuhan, Geao Co.).

3.2 | General method for the synthesis of fused tetracyclic benzo[4,5]furo[3,2-d] pyrimidin-4(3H)-ones 5a and 5b

The intermediates **4a** and **4b** can be obtained according to a published method.[3] To a solution of iminophosphorane (4.65 g) and carbon disulfide (10 mL) in anhydrous CH_2Cl_2 and CH_3CN (20 mL, v/v = 1:1) was refluxed for 30 hours at 40°C-45°C, and then removed triphenylphosphine sulfide, further reaction with equimolar hydrazine hydrate or amino-ethanol in 20 mL ethanol to give **4a** and **4b**, respectively, which was used directly without further purification.

To a mixture of **4a** (2 mmol) 5 mmol Ph_3P (1.31 g) and 5 mmol C_2Cl_6(1.20 g) in dry CH_3CN (15 mL) was added dropwise $N(C_2H_5)_3$ (1.4 mL, 10 mmol), after the reaction was over (monitored with TLC), n-C_4H_9NCO (2 mmol) was added, and then stirred 4 hours at 25°C-30°C to give fused tetracyclic pyrimidinone containing 1,3,4-thia- diazole **5a**.

A mixture of compound **4b** (2 mmol), methyl 3-(2-(bromomethyl)phenyl)-3- methoxyacrylate (2 mmol), and K_2CO_3 (0.2 g) in dry 5 mL DMF was stirred for 5 hours at 50°C to give fused tetracyclic pyrimidinone containing dihydrooxazole moieties **5b**, and the purity was recrystallized from dichloromethane/alcohol.

Compound **5a** white solid, yield: 0.53 g, 85%, m. p. > 250°C. ^{1}H NMR (400 MHz, DMSO-d6) δ: 8.22(s, 1H, Ar-H), 8.02-8.00(s, 1H, Ar-H), 7.82-7.80(s, 1H, Ar-H), 7.68-7.66(s, 1H, Ar-H), 7.50-7.47(s, 1H, Ar-H), 3.33-3.31 (m, 2H, CH_2), 1.63-1.37(m, 4H, CH_2CH_2) 0.93(t, J = 8.0, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-*d6*) δ: 156.5, 156.3, 156.2, 147.8, 141.4, 136.0, 129.7, 124.2, 121.7, 121.1, 112.9, 43.2, 30.2, 19.5, 13.6. MS (70 eV) m/z (%):314(M^+, 100); Anal. calcd for $C_{15}H_{14}N_4O_2S$ (314.0): C, 57.31; H, 4.49; N, 17.82; found: C, 57.24; H, 4.41; N, 17.70.

Compound **5b** white solid, yield: 0.31 g, 67%, m. p. > 250°C. ^{1}H NMR (600 MHz, DMSO-*d6*) δ: 7.96-7.94(m, 1H, Ar-H), 7.78-7.76(m, 1H, Ar-H), 7.66-7.62(m, 1H, Ar-H), 7.47-7.43(m, 1H, Ar-H), 4.85-4.81(m, 2H, CH_2), 4.34-4.29(m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-*d6*) δ: 157.8, 156.5, 151.0, 143.9, 134.7, 129.7, 124.0, 122.1, 121.2, 112.9, 67.9, 42.8. IR (KBr) 1714(C=O), 1598, 1402, 1255 cm^{-1}. MS (70 eV) m/z (%): 228(M^+, 100), 186(97), 173(16), 130(69), 102(70), 88(9), 75(27). Anal. calcd for $C_{12}H_8N_2O_3$(228.0): C, 63.16; H, 3.53; N, 12.28; found: C, 63.07; H, 3.48; N, 12.15.

3.2.1 | Preparation of fused tetracyclic benzo[4,5]furo[3,2-d]pyrimidin-4(3H)-one derivative 7

Carbodiimide **6**, daminozide (3 mmol), and 15 mL dichloromethane were added into 50 mL round bottom flasks in turn and stirred for 4 hours at 20°C-25°C, and several drops of EtONa (10%) in EtOH (5 mL) was added. The reaction was followed by TLC, after completion of the reaction, the solvent was evaporated, and the residual was recrystallized to give compound **7** as white solid 0.75 g, 75%, m. p. > 250°C; ^{1}H NMR (400 MHz, DMSO-d6) δ: 7.96-7.94(m, 1H, Ar-H), 7.82-7.80(m, 1H, Ar-H), 7.74-7.65(m, 7H, Ar-H), 7.43-7.40(m, 1H, Ar-H), 2.69-2.67 (m, 2H, CH_2), 1.72-1.66(m, 2H, CH_2), 0.93(t, J = 8.0, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-*d6*) δ: 169.0, 157.2, 154.6, 148.9, 147.5, 144.4, 133.8, 132.3, 130.8, 130.5, 128.7, 124.3, 122.6, 122.1, 113.4, 27.6, 19.0, 13.9. MS (70 eV) m/z (%): 344(M^+, 100); Anal. calcd for $C_{29}H_{16}N_4O_2$ (344.13): C, 69.76; H, 4.68; N, 16.27; found: C, 69.65; H, 4.57; N, 16.16.

3.2.2 | Preparation of fused tetracyclic benzo[4,5]furo[3,2-d]pyrimidin-4(3H)-ones containing 1,2,4-triazinanone moieties 9a and 9b

A mixture of 3 mmol **8** (**8a**: 0.87 g, **8b**: 0.81 g) and 3 mmol ethyl 2-bromoacetate (0.50 g) in N,N-dimethyl formamide (5 mL), anhydrous potassium carbonate (0.41 g) were stirred at 50°C-60°C for 6-8 hours. The mixture was poured into ice water and recrystallized from CH_2Cl_2/C_2H_5OH (v/v = 1:1) to give fused tetracyclic benzo[4,5]furo[3,2-d]pyrimidin-4(3H)-ones containing 1,2,4-triazinanone moieties **9a** and **9b**, respectively.

Compound **9a** yield: 0.72 g (73%) m. p. > 250°C. ^{1}H NMR δ: (400 MHz, DMSO-*d6*) 9.46(s, 1H), 8.01-7.95(m, 3H, Ar-H), 7.77-7.76(m, 1H, Ar-H), 7.65-7.63(m, 1H, Ar-H), 7.47-7.38(m, 3H, Ar-H and N-H), 7.12-7.10(m, 1H), 5.85(s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-*d6*) δ: 156.9, 153.3, 150.7, 142.1, 139.0, 132.2, 130.0, 129.1, 124.2, 123.5, 122.9, 121.8, 121.0, 113.3, 110.0, 40.5. MS (70 eV) m/z (%) = 332(M^+, 100); Anal. calcd for $C_{18}H_{12}N_4O_3$ (322.1): C, 65.06; H, 3.64; N, 16.86; found: C, 64.92; H, 3.48; N, 16.75.

Compound **9b** yield: 0.70 g, 78%; m. p. > 250°C. ^{1}H NMR δ: (400 MHz, DMSO-*d6*) 7.92-7.91(m, 1H, Ar-H), 7.70-7.69(m, 1H, Ar-H), 7.61-7.58(m, 1H, Ar-H), 7.42-7.39 (m, 2H, Ar-H and N-H), 5.57(s, 2H, CH_2), 3.47-3.44(m, 2H, CH_2), 1.63-1.60(m, 2H, CH_2), 1.39-1.36(m, 2H, CH_2), 0.94 (t, J = 8.0, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-*d6*) δ: 156.8, 153.9, 153.4, 142.2, 131.9, 129.7, 123.8, 123.2, 121.7, 113.2, 110.0, 40.9, 40.5, 31.4, 20.0, 14.2. MS (70 eV) m/z (%): 312(M^+, 100); Anal. calcd for $C_{16}H_{16}N_4O_3$ (312.3): C, 61.53; H, 5.16; N, 17.94; found: C, 61.40; H, 5.02; N, 17.76.

3.2.3 | Preparation of fused tetracyclic benzo[4,5]furo[3,2-d]pyrimidin-4(3H)-one containing 1,2,4-triazole Moieties 11

General Procedure for the Preparation of 10 as described in detail previously.[17,18] To a solution of 1 mmol iminophosphorane **10** (0.54 g) in dry CH_2Cl_2 (5 mL) was added different isocyanate (1 mmol) under nitrogen and then stirred for 6-8 hours at 25°C-30°C, and then filtered under vacuum to obtain a crude product and recrystallized from CH_2Cl_2/ethanol (v/v = 2:1) to give tetracyclic benzo[4,5]furo[3,2-d]pyrimidin- 4(3H)-ones containing 1,2,4-triazole moieties **11** as white solid 0.30 g (85%); m. p. > 250°C; ^{1}H NMR (400 MHz, DMSO-d6) δ: 9.42(bs, 1H, N-H), 8.07-8.06(m, 1H, Ar-H), 7.80-7.77(m, 3H, Ar-H), 7.68-7.65(m, 1H, Ar-H), 7.49-7.42(m, 3H, Ar-H), 7.13-7.10 (m, 1H, Ar-H), 4.30-2.27(m, 2H, CH_2), 1.83-1.81(m, 2H, CH_2), 1.43-1.39(m, 2H, CH_2), 0.96(t, J = 8.0, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d6) δ: 156.9, 152.3, 148.4, 146.9, 142.9, 139.3, 134.0, 131.5, 130.0, 129.4, 124.2, 123.3, 121.7, 119.6, 113.3, 42.0, 30.1, 19.7, 14.1. IR (KBr, cm^{-1}): 3286 (NH), 1702 (C=O), 1576, 1397. MS (70 eV) m/z (%): 373 (M^+, 100). Anal. calcd for $C_{21}H_{19}N_5O_2$ (373.15): C, 67.55; H, 5.13; N, 18.76; found: C, 67.36; H, 5.25; N, 18.61.

4 | CONCLUSION

In summary, we have developed a diversity-oriented synthesis of fused tetracyclic system via aza-Wittig reaction from easily available starting materials under mild reaction conditions. This versatile approach is expected to be a new technology for the synthesis of pharmacologically important fused tetracyclic benzo [4,5]furo[3,2-d]pyrimidin-4(3H)-one derivatives containing 1,3,4-thiadiazole/ 1,3,4-triazinanone/oxazolidine/ 1,2,4-triazole/ moieties.

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ORCID

Yanggen Hu https://orcid.org/0000-0001-7704-4632

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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