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Studies on Synthesis and Biological Activities of 2,7-Diamino Substituted Thienopyrimidinone Derivatives

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Abstract

Thienopyrimidinone derivatives have wide application prospect in the field of medicine and agricultural chemical due to their good biological and pharmacological activities. 12 new compounds which have not been reported in the literature were synthesized in 54% - 64% yields via aza-Wittig reaction of 3,4-diethoxy-2,5-bis(triphenylphosphine)phosphinimine thiophene with aromatic iso-cyanate and nucleophile amine or hydrazine hydrate; the new compounds were confirmed by IR, ^{1}H NMR, LC-MS. Their antibacterial activities were tested and some of the compounds showed good antibacterial activity to gibberella of tea and phoma of tea.

Keywords

Thienopyrimidinone Derivatives, Aza-Wittig Reaction, Synthesis, Antibacterial Activity

2,7-二氨基取代噻吩并嘧啶酮衍生物的合成与生物活性研究

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摘　要

噻吩并嘧啶酮类衍生物由于其良好的生物活性和药理活性，在医学和农用化学领域有很广阔的应用前景。利用三组分aza-Wittig反应，用3,4-二乙氧羰基-2,5-双三苯基膦亚胺噻吩、芳基异氰酸酯、亲核试剂胺或水合肼以54%~64%的收率合成了12个未见文献报道的化合物，通过IR，^{1}H NMR，LC-MS对化合物进行了表征。进一步探究了化合物的抑菌活性，结果表明部分化合物对茶树生赤霉菌和茶树生茎点霉有良好的抑菌活性。

关键词

噻吩并嘧啶酮衍生物，Aza-Wittig反应，合成，抑菌活性

1. 引言

作为一类具有广谱高效低毒的生物活性的稠环化合物，含氮杂环化合物因其在杀菌、杀虫、除草、消炎、抗病毒、抗肿瘤等方面都有很好的活性[1] [2] [3] [4] [5]，从而引起了人们对此类杂环化合物的重视。而大多数含氮杂环化合物对病菌和害虫具有高选择性的杀灭作用，相对来说，对温血动物、鸟类、鱼类的毒性较低[6] [7] [8]，由于这些特性使得含氮杂环化合物在医学和农药学领域的应用日渐广泛。含嘧啶类氮杂环化合物是氮杂环大家庭中的重要一个成员，自然界内许多重要的生物碱、天然产物的骨架结构均为嘧啶环类衍生物，这类衍生物在动植物体内的新陈代谢过程中起着重要作用[9] [10]，而噻吩并嘧啶衍生物是一类将噻吩环嵌入到嘧啶环上得到的稠环化合物，从噻吩并嘧啶酮的构造上来分析，噻吩并嘧啶酮与人体中 DNA，RNA 的基本构成物嘌呤构造相似，从而有可能成为人体核酸代谢拮抗物的替代物，相关文献也证明了此类化合物具有杀虫、杀菌、抗病毒、抗肿瘤、除草等生物活性[11]-[16]，近年来利用原料易得、反应条件温和、产率较高的 aza-Wittig 反应来合成取代含氮杂环和稠杂环成为热门，另外，该方法易于在环上变换官能团，有利于对药物的构效关系研究[17] [18] [19]。本文致力于利用三组分串联 aza-Wittig 反应设计和合成新型噻吩并嘧啶酮衍生物，对所合成的物质进行生物活性测试，并希望能找到具有研究前的化合物。合成路线见图 1 和表 1。

2. 结果与讨论

2.1. 结构表征

目标化合物的 IR 图谱中，所有特征基团均有明显的吸收，氨基峰在 3481 cm^{-1}~3411 cm^{-1} 有较为明显的伸缩振动，芳环在 2854 cm^{-1}~2952 cm^{-1} 有明显的伸缩振动，羰基峰在 1710 cm^{-1} 附近有明显的伸缩振动，C=N 双键的振动峰出现在 1500 cm^{-1} 左右出现的强伸缩振动峰，在 1350 cm^{-1}~1550 cm^{-1} 出现的强弱不等的伸缩振动峰为 C=C 双键的振动峰。化合物的 ^{1}H NMR 图谱，化合物的各个出峰均得到了验证。两个芳环在 δ7.42 ppm~6.96 ppm 表现为一组多峰，六位与七位的仲胺和伯胺两个活泼氢分别在 δ8.56 ppm 左右和 δ4.83 ppm 左右表现出一组单峰，有时伯胺的氢无法顺利出峰，当为吗啡啉取代基的 4 组氢表现

为两组峰，与 O 相连的两组 CH_2 在 δ3.37 ppm 左右表现为一组三重峰，与 N 相连的两组 δCH_2 在 3.00 ppm 左右表现为一组三重峰；若为哌啶取代基 5 组 CH_2 表现为三组峰，与 N 相连的两组 δCH_2 在 3.00 左右表现为一组三重峰，其余三组 CH_2 在 1.43 ppm~1.19 ppm 表现出两组多峰；若为二乙胺取代 4 组 CH_2 变现为两组峰，与 N 相连的两组 CH_2 在 δ3.00 ppm 左右表现为一组四重峰，另外两组 CH_2 在 δ0.76 ppm 左右表现出一组三重峰。目标化合物的 LC-MS 图中所有目标化合物都出现[M + H]峰，部分化合物出现[M + Na]和[2M + H]峰。

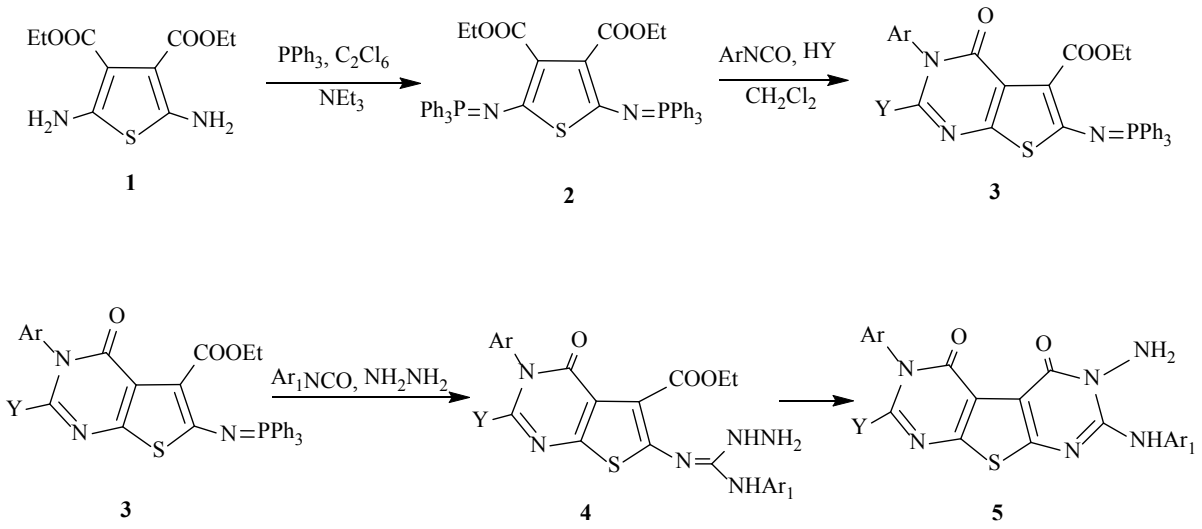

Figure 1. The synthetic route of compound **5**
图 1. 化合物 **5** 的合成路径

Table 1. Synthesis of Compound **5**
表 1. 化合物 **5** 的合成

Product	Ar	Y	Ar_1	Yield/%
5a	Ph	morpholin-4-yl	4-Me-Ph	54
5b	Ph	piperidin-1-yl	4-Me-Ph	62
5c	Ph	NEt_2	Ph	59
5d	Ph	NEt_2	4-Me-Ph	56
5e	Ph	NEt_2	4-CF_3O-Ph	60
5f	Ph	NEt_2	4-CF_3-Ph	58
5g	4-Me-Ph	morpholin-4-yl	Ph	54
5h	4-Me-Ph	morpholin-4-yl	4-Me-Ph	59
5i	4-Me-Ph	morpholin-4-yl	4-Me-O-Ph	62
5j	4-Me-Ph	morpholin-4-yl	4-Cl-Ph	64
5k	4-Me-Ph	piperidin-1-yl	4-Me-Ph	62
5l	4-Me-Ph	NEt_2	4-CF_3CO-Ph	59

2.2. 化合物的抑菌活性

菌种茶树生赤霉菌(*Pyrenomycctes*)、蔷薇生链格孢(*Alternariaalternata*)、茶树炭疽菌(*Gloeosporiumtheaesinensis miyake*)和茶树生芝点霉(*Phomaadianticola*)四种菌由华中农业大学植物科学技术学院提供。

抑菌活性试验采用含毒介质法。在 PDA 培养基中按 100 mg/L (有效含量)加入定量乳化剂吐温−80，待培养基冷却后接种直径为 5 mm 的供试菌片，菌丝面朝下，置于培养箱(25˚C)培养，48 h 后调查抑制率。结果见表 2。从表中数据来看，有如下规律：1) 大多数化合物对四种受试菌种的抑菌效果在 41%~89%之间，对茶树生赤霉菌和茶树生芝点霉的抑制活性较好；2) 其中化合物 **5h** 对茶树生赤霉菌和茶树生芝点霉的抑制活性分别为 80%和 81%，**5i** 对茶树生芝点霉属的抑制活性为 80%，**5j** 对茶树生赤霉菌和茶树生芝点霉的抑制活性分别为 89%和 83%的，**5a** 对蔷薇生链格孢和茶树炭疽菌的抑制活性为 71%；3) 从表中可以看出化合物 **5h**，**5i**，**5j** 的活性较高，而化合物 **5h**，**5i**，**5j** 七位均为吗啡啉取代，六位为 Ph-Me-P 取代，活性高于七，六位的其他取代基团，说明二位引入吗啡啉环，六位引入 Ph-Me-P 比引入其他取代基更加有利于化合物的杀菌活性。

Table 2. Antibacterial activity of compounds **5** (Inhibition at 100 mg/L%)
表 2. 化合物 **5** 的抑菌活性(抑制率%)

化合物	茶树生赤霉菌	蔷薇生链格孢	茶树炭疽菌	茶树生芝点霉
5a	72	71	71	58
5b	50	59	62	47
5c	41	74	58	46
5d	33	53	42	37
5e	51	52	46	35
5f	62	50	66	50
5g	39	64	73	69
5h	80	47	52	81
5i	32	56	42	80
5j	89	70	46	83
5k	32	54	69	77
5l	63	50	62	54

3. 结论

利用 aza-Wittig 反应设计并合成了一系列新型噻吩并双嘧啶二酮衍生物，通过 IR，^{1}H NMR，LC-MS 等方法对所合成化合物进行了结构表征，采用含毒介质离体平皿法对茶树生赤霉菌，蔷薇生链格孢，茶树炭疽菌，茶树生芝点霉等 4 种菌进行了初步的杀菌活性测试。目标化合物对测试的 4 种菌均有一定的杀菌活性，特别是对茶树生赤霉菌和茶树生芝点霉属的抑制活性较高，其中 5h，5i，5j 的活性相对较好。

4. 实验部分

4.1. 仪器与试剂

RY-2 型熔点仪(天津市分析仪器厂)；AM-600MHz 氢核磁共振潜仪(德国 Bruker 公司)；AVAIAR330

型红外光谱仪(美国 Nieolet 公司)；紫外灯(波长 254 nm，ZF-7)；Agilent 6100 系列单四极杆质谱仪(美国 Agilent 公司)。

异氰酸酯购自于安耐吉药业有限公司，氘代试剂购自于百灵威试剂有限公司，其他试剂购置于国药集团化学试剂有限公司。溶剂都需要经过严格的干燥处理，乙腈、三乙胺加入活化的 4A 分子筛除水，无水乙醚加入钠丝干燥，二氯甲烷加入干燥的氯化钙干燥，乙醇重蒸。

4.2. 中间体 1，2，3 的制备

中间体 1，2，3 的制备参见文献[20] [21] [22] [23]。

4.3. 目标化合物 5 的制备

称取干燥膦亚胺 **3** 2 mmol 加入到 100mL 圆底烧瓶，加入 10 mL 二氯甲烷溶解，用注射器称取 2 mmol 芳基异氰酸酯快速注入烧瓶中密闭于 0~5˚C 密闭 8 h~12 h，减压脱去大部分溶剂，加入 V (乙醚)：V (石油醚) = 2:1 (20 mL)过滤以除去三苯氧磷，滤液脱去溶剂加入无水乙醇溶解，将其转入另一个干燥的 100 mL 圆底烧瓶中并配备磁力搅拌，向其中滴加两当量的水合肼的乙醇溶液，滴完，继续搅拌 1 h，过程中会析出大量白色沉淀，过滤，柱层析分离得白色固体。

2-(4-甲苯氨基)-3-氨基-6-苯基-7-(吗啡啉-4-基)噻吩并[2,3-d:5,4-d’]双嘧啶-4,5(3H,6H)-二酮(**5a**)

White crystals (yield 57%). m.p. 277˚C~278˚C. 1H NMR ($CDCl_3$, 400 MHZ) δ (ppm) 8.56 (s, 1H, N-H), 7.42~6.96 (m, 9H, Ar-H), 4.83 (s, 2H, NH_2), 3.36 (t, J = 4.8Hz, 4H, $2OCH_2$), 3.01 (t, J = 4.4Hz, 4H, $2NCH_2$), 2.41 (s, 3H, CH_3). IR (KBr) 3487, 3408 (NH_2), 1701 (C=O), 1536, 1486, 1359, 950 cm^{-1}. LC-MS m/z 502.1 [M + 1].

2-(4-甲苯氨基)-3-氨基-6-苯基-7-(哌啶-1-基) 噻吩并[2,3-d:5,4-d’]双嘧啶-4,5(3H,6H)-二酮(**5b**)

White crystals (yield 62%). m.p. >300˚C. 1H NMR ($CDCl_3$, 400 MHZ) δ (ppm) 8.47 (s, 1H, N-H), 7.41~7.04 (m, 9H, Ar-H), 4.74 (s, 2H, NH_2), 3.08~2.98 (t, J = 4.8Hz, 4H, $2NCH_2$), 2.36 (s, 3H, CH_3), 1.42~1.40 (m, 2H, CH_2), 1.38~1.17 (m, 4H, $2CH_2$). IR (KBr) 3420, 3311 (NH_2), 1701 (C=O), 1530, 1495, 1468, 944, 753 cm^{-1}. LC-MS m/z 500.1 [M + 1].

2-(苯氨基)-3-氨基-6-苯基-7-(二乙胺)噻吩并[2,3-d:5,4-d’]双嘧啶-4,5(3H,6H)-二酮(**5c**)

White crystals (yield 59%). m.p. 269˚C~271˚C. 1H NMR ($CDCl_3$, 400 MHZ) δ (ppm) 8.59 (s, 1H, N-H), 7.53~7.07 (m, 10H, Ar-H), 4.87 (s, 2H, NH_2), 3.02~2.97 (q, J = 7.2Hz, 4H, $2NCH_2$), 0.79~0.76 (t, J = 6.8Hz, 6H, $2CH_3$). IR (KBr) 3455, 3311 (NH_2), 1704 (C=O), 1539, 1489, 1465, 932 cm^{-1}. LC-MS m/z 474.1 [M + 1].

2-(4-甲苯氨基)-3-氨基-6-苯基-7-(二乙胺)噻吩并[2,3-d:5,4-d’]双嘧啶-4,5(3H,6H)-二酮(**5d**)

White crystals (yield 56%). m.p. 271˚C~273˚C. 1H NMR ($CDCl_3$, 400 MHZ) δ (ppm) 8.50 (s, 1H, N-H), 7.45~7.17 (m, 9H, Ar-H), 4.76 (s, 2H, NH_2), 3.07~3.02 (q, J = 7.2Hz, 4H, $2NCH_2$), 2.35 (s, 3H, CH_3), 0.82~0.78 (t, J = 7.2Hz, 6H, $2CH_3$). IR (KBr) 3414, 3308 (NH_2), 1701 (C=O), 1530, 1468, 1377, 938 cm^{-1}. LC-MS m/z 488.1 [M + 1].

2-(4-三氟甲氧基苯氨基)-3-氨基-6-苯基-7-(二乙胺)噻吩并[2,3-d:5,4-d’]双嘧啶-4,5(3H,6H)-二酮(**5e**)

White crystals (yield 60%). m.p. 274˚C~276˚C. 1H NMR ($CDCl_3$, 400 MHZ) δ (ppm) 8.67 (s, 1H, N-H), 7.59~7.08 (m, 9H, Ar-H), 4.87 (s, 2H, NH_2), 3.05~3.00 (q, J = 7.2Hz, 4H, $2NCH_2$), 0.81~0.77 (t, J = 6.8Hz, 6H, $2CH_3$). IR (KBr) 3487, 3408 (NH2), 1704 (C=O), 1533, 1495, 1468, 1159 cm^{-1}. LC-MS m/z 558.1 [M + 1].

2-(4-三氟甲基-苯氨基)-3-氨基-6-苯基-7-(二乙胺)噻吩并[2,3-d:5,4-d’]双嘧啶-4,5(3H,6H)-二酮(**5f**)

White crystals (yield 58%). m.p. 277˚C~279˚C. 1H NMR ($CDCl_3$, 400 MHZ) δ (ppm) 8.87 (s, 1H, N-H),

7.80~7.22 (m, 9H, Ar-H), 4.83 (s, 2H, NH_2), 3.11~3.06 (q, J = 7.2Hz, 4H, $2NCH_2$), 0.84~0.81 (t, J = 7.2Hz, 6H, $2CH_3$). IR (KBr) 3420, 3340 (NH_2), 1689 (C=O), 1533, 1471, 1324, 943 cm^{-1}. LC-MS m/z 542.1 [M + 1].

2-(苯氨基)-3-氨基-6-(4-甲苯基)-7-(吗啡啉-4-基) 噻吩并[2,3-d:5,4-d']双嘧啶-4,5(3H,6H)-二酮(**5g**)

White crystals (yield 54%). m.p. 263˚C~265˚C. 1H NMR ($CDCl_3$, 400 MHZ) δ (ppm) 8.61 (s, 1H, N-H), 7.54~6.97 (m, 9H, Ar-H), 4.83 (s, 2H, NH_2), 3.38 (t, J = 4.8Hz, 4H, $2OCH_2$), 3.05 (t, J = 4.4Hz, 4H, $2NCH_2$), 2.38 (s, 3H, CH_3). IR (KBr) 3478, 3304 (NH_2), 1709 (C=O), 1542, 1495, 1468, 997 cm^{-1}. LC-MS m/z 502.1 [M + 1].

2-(4-甲苯氨基)-3-氨基-6-(4-甲苯基)-7-(吗啡啉-4-基)噻吩并[2,3-d:5,4-d']双嘧啶-4,5 (3H,6H)-二酮(**5h**)

White crystals (yield 59%).m.p. 258˚C~260˚C. 1H NMR ($CDCl_3$, 400 MHZ) δ (ppm) 8.49 (s, 1H, N-H), 7.38~6.90 (m, 8H, Ar-H), 4.86 (s, 2H, NH_2), 3.36 (t, J = 4.8Hz, 4H, $2OCH_2$), 3.01 (t, J = 4.4Hz, 4H, $2NCH_2$), 2.38 (d, 6H, $2CH_3$). IR (KBr) 3411, 3328 (NH_2), 1704 (C=O), 1540, 1497, 1456, 951 cm^{-1}. LC-MS m/z 516.1 [M + 1].

2-(4-甲氧基-苯氨基)-3-氨基-6-(4-甲苯基)-7-(吗啡啉-4-基)噻吩并[2,3-d:5,4-d']双嘧啶-4,5(3H,6H)-二酮(**5i**)

White crystals (yield 62%). m.p. 262˚C~264˚C. 1H NMR ($CDCl_3$, 400 MHZ) δ (ppm) 8.43 (s, 1H, N-H), 7.46~6.92 (m, 8H, Ar-H), 4.77 (s, 2H, NH_2), 3.83 (s, 3H, OCH_3), 3.38 (t, J = 4.8Hz, 4H, $2OCH_2$), 3.07 (t, J = 4.4Hz, 4H, $2NCH_2$), 2.39 (s, 3H, CH_3). IR (KBr) 3414, 3320 (NH_2), 1701 (C=O), 1562, 1497, 1386, 1109, 753 cm^{-1}. LC-MS m/z 532.1[M + 1].

2-(4-氯苯氨基)-3-氨基-6-(4-甲苯基)-7-(吗啡啉-4-基)噻吩并[2,3-d:5,4-d']双嘧啶-4,5 (3H,6H)-二酮(**5j**)

White crystals (yield 64%). m.p. >300˚C. 1H NMR ($CDCl_3$, 400 MHZ) δ (ppm) 8.63 (s, 1H, N-H), 7.56~7.06 (m, 8H, Ar-H), 4.77 (s, 2H, NH_2), 3.42 (t, J = 4.8Hz, 4H, $2OCH_2$), 3.08 (t, J = 4.8Hz, 4H, $2NCH_2$), 2.39 (s, 3H, CH_3). IR (KBr) 3417, 3325 (NH_2), 1701 (C=O), 1539, 1486, 1439, 950 cm^{-1}. LC-MS m/z 536.1 [M + 1].

2-(4-甲苯氨基)-3-氨基-6-(4-甲苯基)-7-(哌啶-1-基) 噻吩并[2,3-d:5,4-d']双嘧啶-4,5 (3H,6H)-二酮(**5k**)

White crystals (yield 62%). m.p. >300˚C. 1H NMR ($CDCl_3$, 400 MHZ) δ (ppm)：8.47 (s, 1H, N-H), 7.41~6.94 (m, 8H, Ar-H), 4.82 (s, 2H, NH_2), 3.03 (t, J = 5.2Hz, 4H, $2NCH_2$), 2.38 (d, J = 6.8Hz, 6H, $2CH_3$), 1.43~1.18 (m, 6H, $3CH_2$). IR (KBr) 3467, 3304 (NH_2), 1701 (C=O), 1530, 1495, 1368, 944 cm^{-1}. LC-MS m/z 514.1 [M + 1].

2-(4-三氟甲氧基-苯氨基)-3-氨基-6-(4-甲苯基)-7-(二乙胺)噻吩并[2,3-d:5,4-d']双嘧啶-4,5(3H,6H)-二酮(**5l**)

White crystals (yield 59%). m.p. >300˚C. 1H NMR ($CDCl_3$, 400 MHZ) δ (ppm) 8.67 (s, 1H, N-H), 7.66~7.04 (m, 8H, Ar-H), 4.81 (s, 2H, NH_2), 3.09-3.04 (q, J = 7.2Hz, 4H, $2NCH_2$), 2.38 (s, 3H, CH_3), 0.85~0.81 (t, J = 6.8Hz, 6H, $2CH_3$). IR (KBr) 3484, 3414 (NH_2), 1704 (C=O), 1533, 1506, 1471, 935 cm^{-1}. LC-MS m/z 572.1 [M + 1].

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参考文献

[1] Tinney, F.J., Cetenko, W.A., Kerbleski, J.J., Connor, D.T., Sorenson, R.J. and Herzig, D.J. (1981) Synthesis and Anti-

allergy Activity of 4-oxo-4H-pyrido[1,2-a]thieno[2,3-d]pyrimidines. *Journal of Medicinal Chemistry*, **24**, 878-882. https://doi.org/10.1021/jm00139a021

[2] Harald, W. and Birgit, F. (2000) Fungicidal Combination Comprising Thieno[2,3-d]pyrimidine-4-one. WO0027200.

[3] Ivachtohenko, A., Kovalenko, S. and Tkachenko, O.V. (2004) Synthesis of Substituted Thienopyrimidine-4-ones. *ACS Combinatorial Science*, 573-583. https://doi.org/10.1021/cc0499461

[4] Molina, P., Arques, A. and Vinader, M.V. (1990) Iminophosphorane-Mediated Synthesis of 2H-Indazole Derivatives: Preparation of 2,3-diamino-2H-Indazoles by Intramolecular Trapping of Phosphazides and 1H-1,2,4-triazolo[2,3-b]indazoles by a Tandem Aza-Wittig/Heterocumulene-Mediated Strategy. *The Journal of Organic Chemistry*, 4724-4731. https://doi.org/10.1021/jo00302a045

[5] Xia, G.X., Wang, Q., Ge, H., Liao, X.M., Huo, G.Y., Zhai, X., Shi, C., Duan, L.J., Mao, Y. and Liu, Y.J. (2018) Nitrogen-Containing Fused Heterocyclic Compound, Preparation Method Therefor, and Intermediate, Composition, and Application Thereof. WO 2018121766.

[6] 柏再苏, 王大翔. 杂环、基因工程和二十一世纪的农药[J]. 农药, 1998(37): 2-6.

[7] Ahankar, H., Ramazani, A., Amini, I., Ahmadi, Y. and Souldozi, A. (2011) The Reaction of (N-isocyanimino) Triphenylphosphorane with (E)-3-aryl-2-propenoic Acid Derivatives: One-Pot Synthesis of 2-[(E)-2-aryl-1-ethenyl]-1,3,4-oxadiazoles via Intramolecular Aza-Wittig Reaction. *Heteroatom Chemistry*, **22**, 612-616.

[8] El-Kashef, H., Farghaly, A.R., Al-Hazmi, A., Terme, T. and Vanelle, P. (2010) Pyridine-Based Heterocycles. Synthesis of New Pyrido [4',3':4,5]thieno[2,3-d]pyrimidines and Related Heterocycles. *Molecules*, **15**, 2651-2666. https://doi.org/10.3390/molecules15042651

[9] Eguehi, S., Suzuki, T., Okawa, T. and Matsushita, Y. (1996) Synthesis of Optically Active Vasicinone Based on Intramolecular Aza-Wittig Reaction and Asymmetric Oxidation[1]. *The Journal of Organic Chemistry*, 7316-7319. https://doi.org/10.1021/jo9609283

[10] O'Neil, I.A., Murray, C.L., Potter, A.J. and Kalindjian, S.B. (1997) The Synthesis of a Novel Benzodiazocine via an Intramolecular Staudinger/Aza-Wittig Cyclization. *Tetrahedron Letters*, **38**, 3609-3610. https://doi.org/10.1016/S0040-4039(97)00680-1

[11] Chambhare, R.V., Khadse, B.G., Bobde, A.S. and Bahekar, R.H. (2003) Synthesis and Preliminary Evaluation of Some N-[5-(2-furanyl)-2-methyl-4-oxo-4H-thieno[2,3-d]pyrimidin-3-yl]-carboxamide and 3-substituted-5-(2-furanyl)-2-methyl-3H-thieno[2,3-d]pyrimidin-4-ones as Antimicrobial Agents. *European Journal of Medicinal Chemistry*, **38**, 89-100. https://doi.org/10.1016/S0223-5234(02)01442-3

[12] Dewal, M.B., Wani, A.S., Vidaillac, C., Oupický, D., Rybak, M.J. and Firestine, S.M. (2012) Thieno[2,3-d]pyrimidinedione Derivatives as Antibacterial Agents. *European Journal of Medicinal Chemistry*, **51**, 145-153. https://doi.org/10.1016/j.ejmech.2012.02.035

[13] Ekkati, A.R., Madiyan, V., Ravin-dranathan, K.P., Bae, J.H., Schlessinger, J. and Jorgensen, W.L. (2011) Aryl Extensions of Thienopyrimidinones as Fibroblast Growth Factor Receptor 1 Kinase Inhibitors. *Tetrahedron Letters*, **52**, 2228-2231. https://doi.org/10.1016/j.tetlet.2010.12.081

[14] Janssens, F.E., Torremans, J.G. and Hens, J.F. (1984) Bicyclic Heteroeyelyl Containing N-(Bicyclic Heterocyclyl)-4-piperidinamines. EP0144101.

[15] Kanawade, S.B., Toche, R.B. and Rajani, D.P. (2013) Synthetic Tactics of New Class of 4-aminothieno[2,3-d]pyrimidine-6-carbonitrile Derivatives Acting as Antimicrobial Agents. *European Journal of Medicinal Chemistry*, **64**, 314-320. https://doi.org/10.1016/j.ejmech.2013.03.039

[16] Lambert, P.H., Vaultier, M. and Carrie, R. (1985) Application of the Intramolecular Aza-Wittig Reaction to the Synthesis of Vinylogous Urethanes and Amides. *The Journal of Organic Chemistry*, **50**, 5352-5356. https://doi.org/10.1021/jo00225a066

[17] Kobayashi, K., Matsumoto, N., Naga-shima, M. and Inouchi, H. (2015) One-Pot Synthesis of 3-Acetyl-2-aryl-3,4-dihydroquinazolines from N-[2-(Azidomethyl)phenyl]benzamides Utilizing Intramolecular Aza-*Wittig* Reaction. *Helvetica Chimica Acta*, **98**, 184-189. https://doi.org/10.1002/hlca.201400316

[18] Kurita, J., Iwata, T., Yasuike, S. and Tsuchiya, T. (1992) A New Route to 1,3-benzoxazepines and 1,3-benzodiazepines via Intramolecular Aza-*Wittig* Reaction. *Chemical Communications*, **2**, 81-82. https://doi.org/10.1039/c39920000081

[19] He, H.W., Ding, M.W. and Huang, N.Y. (2005) New Efficient Synthesis of 6,7,8,9-tetrahydro-benzothieno[2,3-d] 1,2,4-triazolo[1,5-a]pyrimidin-10(3h)-ones via a Tandem Aza-*Wittig*/Heterocumulene-Mediated Annulation. *Synthesis*, No. 10, 1601-1604.

[20] Cao, M.H., Xu, S.Z. and Chen, C.S. (2011) An Efficient Route for Synthesis of 2-alkylaminobenzo[b]thieno[3,2-d]pyrimidin-4(3H)-one. *Chinese Chemical Letters*, **22**, 443-446. https://doi.org/10.1016/j.cclet.2010.11.015

[21] Xu, S.Z., Cao, M.H., Chen, C.S. and Ding, M.W. (2009) Efficient Synthesis of Benzothieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-5(1h)-onesviaatandem Aza-*Wittig*/Heterocumulene-Mediated Annulation. *Journal of Heterocyclic Chemistry*, **46**, 903-908. https://doi.org/10.1002/jhet.158

[22] Ding, M.W., Xu, S.Z. and Zhao, J.F. (2004) Application of Bis(iminophosphorane) in Heterocyclic Synthesis: New Entries to Symmetrically or Unsymmetrically Substituted Thieno[2,3-d:5,4-d']dipyrimidine-4,5(3H,6H)-diones. *The Journal of Organic Chemistry*, **69**, 8366-8371. https://doi.org/10.1021/jo048691v

[23] Xu, S.Z., Hu, Y.G. and Ding, M.W. (2006) New Efficient Synthesis of 2-Substituted Benzothieno[3,2-d]pyrimidin-4(3H)-one via a Tandem Aza-*Wittig* Reaction. *Synthesis*, **24**, 4180-4186.