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Characterization and biological evaluation of some novel pyrazolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-8-ones synthesized *via* the Gewald reaction

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Abstract: The synthesis of substituted pyrazolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-8-ones (**IIIa**–**j**) from 5-amino-3-methyl-1*H*-thieno[3,2-*c*]pyrazole-6-carbonitrile **(II)** is described. The key compound **II** was synthesized from (5-methyl-2,4-dihydro-3*H*-pyrazol-3-ylidene)malononitrile **I** *via* the Gewald reaction. The synthesis of the title compounds **IIIa**–**j** was accomplished by condensation of **II** with different aromatic aldehydes. The newly synthesized heterocyles were characterized by elemental analysis, IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopic investigation. All the newly synthesized compounds were evaluated for antimicrobial activity against a variety of bacterial strains.

Keywords: pyrazolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-8-ones; carbonitrile; Gewald reaction; antimicrobial activity.

INTRODUCTION

Pyrazole-containing compounds have practical applications in medicinal and agrochemical fields and the biological activities of pyrazoles[1,2] and its derivatives are well documented. The pyrazole ring is the basic moiety for a number of dyes, drugs and anaesthetics.[3,4] Substituted pyrazolopyrimidinones are found to be useful as cardiotonic,[5] herbicidal[6] and antiviral[7] agents. A literature survey revealed that substituted pyrazolopyrimidinones are potent and selective inhibitors of type 5 cyclic guanosine-3',5'-monophosphate phosphodiesterase (cGMP) PDE-5[8,9] and, as such, have utility in the treatment of male erectile dysfunction (MED) and female sexual dysfunction (FSD).[10] C-6 substituted pyrimidinone and pyrimidinedione derivatives showed selective antitumour,[11] antiviral,[12] antitubercular[13] and antifungal activity,[14] suggesting the importance of testing this family of compounds as broad-spectrum drugs.

In the search of bioactive molecules and in continuation of previous work on the development of syntheses of polyfunctionally substituted heterocyclic com-

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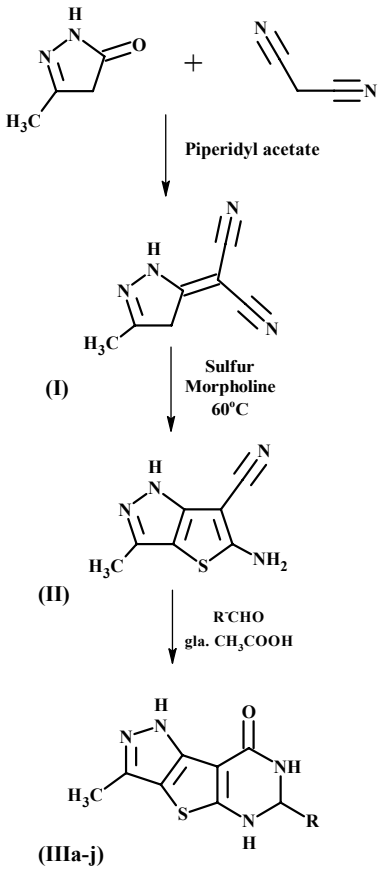
pounds, a novel synthetic approach for the synthesis of 6-aryl-3-methyl-1,5,6,7--tetrahydro-8*H*-pyrazolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-8-ones (**IIIa**–**j**) is reported herein. All the newly synthesized compounds (**IIIa**–**j**) were evaluated for their antibacterial and antifungal activity. The biological activities of the synthesized compounds were compared with reference standard drugs.

RESULTS AND DISCUSSION

Chemistry

The synthesis of 5-amino-3-methyl-1*H*-thieno[3,2-*c*]pyrazole-6-carbonitrile (**II**) was accomplished by refluxing (5-methyl-2,4-dihydro-3*H*-pyrazol-3-ylidene)malononitrile (**I**) and sulphur in the presence of morpholine for 6 h using the Gewald reaction.[15–20] Compound **II** on reaction with different aromatic ketones in glacial acetic acid furnished the title compounds 6-aryl-3-dimethyl-1,5,6,7--tetrahydro-8*H*-pyrazolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-8-ones (**IIIa**–**h**) in excellent yields (Scheme 1).



R = phenyl;
2-hydroxyphenyl;
4-hydroxyphenyl;
2-chlorophenyl;
3-chlorophenyl;
4-fluorophenyl;
2-nitrophenyl;
3-nitrophenyl;
4-nitrophenyl;
4-methoxyphenyl.

Scheme 1.

The purity of the compounds was controlled by TLC. The spectral data of all the newly synthesized compounds, given below, were in full agreement with the proposed structures.

*(5-Methyl-2,4-dihydro-3*H*-pyrazol-3-ylidene)malononitrile* ***(I)***. Yield 52 %; m.p.190–192 °C. Anal. Calcd. for $C_7H_6N_4$: C, 57.53; H, 4.14; N, 38.34. Found: C, 57.31; H, 4.02; N, 38.16. IR (KBr, cm^{-1}): 3226 (−NH), 2210 (−CN), 1658 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 0.9 (3H, *s*, $-CH_3$), 1.9 (2H, *s*, $-CH_2$), 7.1 (1H, *s*, −NH); ^{13}C-NMR (75 MHz, DMSO-d_6, δ, ppm): 19.5, 35.1, 61.8, 113.9, 153.5, 181.3. MS (*m*/*z*): 146.

*5-Amino-3-methyl-1*H*-thieno[3,2-*c*]pyrazole-6-carbonitrile* ***(II)***. Yield 58 %; m.p. 206 °C. Anal. Calcd. for $C_7H_6N_4S$: C, 47.18; H, 3.39; N, 31.44; S, 17.99. Found: C, 46.95; H, 3.19; N, 31.23; S, 17.75. IR (KBr, cm^{-1}): 3420–3305 ($-NH_2$), 2234 (−CN), 1645 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 2.68 (3H, *s*, $-CH_3$), 4.00 (2H, *s,* $-NH_2$). ^{13}C-NMR (75 MHz, DMSO-d_6, δ, ppm): 14.6, 105.8, 110.8, 114, 135, 136.5, 144. MS (*m*/*z*): 178.

*3-Methyl-6-phenyl-1,5,6,7-tetrahydro-8*H*-pyrazolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-8-one* ***(IIIa)***. Yield 42 %; m.p. 215 °C. Anal. Calcd. for $C_{14}H_{12}N_4OS$: C, 59.14; H, 4.25; N, 19.70; O, 5.63; S, 11.28. Found: C, 59.14; H, 4.25; N, 19.57; O, 5.50; S, 11.13. IR (KBr, cm^{-1}): 3327 (−NH), 3105 (−CH, aromatic), 2970 ($-CH_3$), 1680 (C=O), 681 (C−S−C). ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 2.23 (3H, *s*, $-CH_3$), 5.90 (1H, *s*, −CH), 7.24–7.72 (4H, *s*, Ar−H). ^{13}C-NMR (75 MHz, DMSO-d_6, δ, ppm): 14.6, 70.6, 106.4, 127.2, 127.4, 128.9, 136.4, 142.7, 144.9, 163.4, 166.0. MS (*m*/*z*): 284.

*6-(2-Hydroxyphenyl)-3-methyl-1,5,6,7-tetrahydro-8*H*-pyrazolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-8-one* ***(IIIb)***: Yield 40 %; m.p. 208 °C. Anal. Calcd. for $C_{14}H_{12}N_4O_2S$: C, 59.14; H, 4.25; N, 19.70; O, 5.63; S, 11.28. Found: C, 58.98; H, 4.11; N, 19.56; O, 5.49; S, 11.15. IR (KBr, cm^{-1}): 3400–3100 (−OH), 3125 (−CH, aromatic), 2975 ($-CH_3$), 1682 (C=O), 680 (C−S−C). ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 2.32 (3H, *s*, $-CH_3$), 6.01 (1H, *s*, −CH), 6.93–7.24 (4H, *s*, Ar−H), 5.02 (1H, *s*, −OH). ^{13}C-NMR (75 MHz, DMSO-d_6, δ, ppm): 14.7, 60.2, 106.6, 116.2, 122.3, 125.9, 128.6, 129.1, 136.6, 143.1, 145.2, 155.2, 163.2, 165.9. MS (*m*/*z*): 300.

*6-(4-Hydroxyphenyl)-3-methyl-1,5,6,7-tetrahydro-8*H*-pyrazolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-8-one* ***(IIIc)***. Yield 45 %; m.p. 202 °C. Anal. Calcd. for $C_{14}H_{12}N_4O_2S$: C, 59.14; H, 4.25; N, 19.70; O, 5.63; S, 11.28. Found: C, 59.01; H, 4.13; N, 19.58; O, 5.50; S, 11.16. IR (KBr, cm^{-1}): 3450–3100 (−OH), 3110 (−C−H, aromatic), 2970 ($-CH_3$), 1685 (C=O), 685 (C−S−C). ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 2.22 (3H, *s*, $-CH_3$), 5.91 (1H, *s*, −CH), 6.93–7.14 (4H, *s*, Ar−H), 5.01 (1H, *s*, −OH). ^{13}C-NMR (75 MHz, DMSO-d_6, δ, ppm): 14.6, 70.4, 106.2, 116.4, 129.1, 136.2 , 137.4, 143.1, 145.4, 157.3, 163.6, 166.7. MS (*m*/*z*): 300.

*6-(2-Chlorophenyl)-3-methyl-1,5,6,7-tetrahydro-8*H*-pyrazolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-8-one (**IIId**)*: Yield 48 %; m.p. 238 °C. Anal. Calcd. for $C_{14}H_{11}ClN_4OS$: C, 52.75; H, 3.48; Cl, 11.12; N, 17.58; O, 5.02; S, 10.06. Found: C, 52.62; H, 3.37; Cl, 11.01; N, 17.42; O, 4.89; S, 9.91. IR (KBr, cm^{-1}): 3327 (–NH), 3105 (–CH, aromatic), 2970 ($–CH_3$), 1680 (C=O), 730 (C–Cl), 683 (C–S–C). ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 2.36 (3H, *s*, $–CH_3$), 6.01 (1H, *s*, –CH), 7.24–7.42 (4H, *s*, Ar–H), 8.12 (1H, *s*, –NH). ^{13}C-NMR (75 MHz, DMSO-d_6, δ, ppm): 14.9, 61.3, 106.4, 126.9, 128.4, 128.7, 128.9, 133.4, 136.4, 143.2, 145.4, 163.4, 166.6. MS (*m*/*z*): 318.

*6-(3-Chlorophenyl)-3-methyl-1,5,6,7-tetrahydro-8*H*-pyrazolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-8-one (**IIIe**)*. Yield 52 %; m.p. 246 °C. Anal. Calcd. for $C_{14}H_{11}ClN_4OS$: C, 52.75; H, 3.48; Cl, 11.12; N, 17.58; O, 5.02; S, 10.06. Found: C, 52.61; H, 3.35; Cl, 10.99; N, 17.42; O, 5.02; S, 10.06. IR (KBr, cm^{-1}): 3340 (−NH), 3115 (−CH, aromatic), 2975 ($−CH_3$), 1683 (C=O), 750 (C−Cl), 685 (C−S−C). ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 2.39 (3H, *s*, $−CH_3$), 6.02 (1H, *s*, −CH), 7.04–7.22 (4H, *s*, Ar−H). ^{13}C-NMR (75 MHz, DMSO-d_6, δ, ppm): 14.8, 70.1, 106.3, 125.6, 127.4, 127.9, 131.0, 134.6, 136.9, 142.7, 145.2, 146.6, 163.4, 166.0. MS (*m*/*z*): 318.

*6-(4-Fluorophenyl)-3-methyl-1,5,6,7-tetrahydro-8*H*-pyrazolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-8-one (**IIIf**)*. Yield 40 %; m.p. 258 °C. Anal. Calcd. for $C_{14}H_{11}FN_4OS$: C, 55.62; H, 3.67; F, 6.28; N, 18.53; O, 5.29; S, 10.61. Found: C, 55.51; H, 3.54; F, 6.13; N, 18.39; O, 5.16; S, 10.48. IR (KBr, cm^{-1}): 3335 (−NH), 3120 (−CH, aromatic), 2975 ($−CH_3$), 1685 (C=O), 710 (C−F), 689 (C−S−C). ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 2.45 (3H, *s*, $−CH_3$), 5.90 (1H, *s*, −CH), 7.03–7.11 (4H, *s*, Ar–H). ^{13}C-NMR (75 MHz, DMSO-d_6, δ, ppm): 14.1, 69.6, 106.1, 115.6, 129.0, 136.1, 140.9, 141.9, 145.0, 161.3, 164.4, 166.3. MS (*m*/*z*): 302.

*3-Methyl-6-(2-nitrophenyl)-1,5,6,7-tetrahydro-8*H*-pyrazolo[3',4':4,5]thieno-[2,3-*d*]pyrimidin-8-one (**IIIg**)*. Yield 38 %; m.p. 282 °C. Anal. Calcd. for $C_{14}H_{11}N_5O_3S$: C, 51.06; H, 3.37; N, 21.27; O, 14.57; S, 9.74. Found: C, 50.93; H, 3.25; N, 21.14; O, 14.46; S, 9.60. IR (KBr, cm^{-1}): 3350 (−NH), 3112 (−CH, aromatic), 2970 ($−CH_3$), 1680 (C=O), 691 (C−S−C). ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 2.35 (3H, *s*, $−CH_3$), 6.01 (1H, *s*, −CH), 7.87–7.43 (4H, *s*, Ar−H). ^{13}C-NMR (75 MHz, DMSO-d_6, δ, ppm): 14.8, 61.2, 106.1, 121.3, 128.0, 128.4, 134.9, 136.0, 137.9, 142.8, 145.4, 147.8, 163.6, 166.4. MS (*m*/*z*): 329.

*3-Methyl-6-(3-nitrophenyl)-1,5,6,7-tetrahydro-8*H*-pyrazolo[3',4':4,5]thieno-[2,3-*d*]pyrimidin-8-one (**IIIh**)*. Yield 35 %; m.p. 275 °C; Anal. Calcd. for $C_{14}H_{11}N_5O_3S$: C, 51.06; H, 3.37; N, 21.27; O, 14.57; S, 9.74. Found: C, 50.96; H, 3.24; N, 21.13; O, 14.45; S, 9.63. IR (KBr, cm^{-1}): 3350 (−NH), 3105 (−CH, aromatic), 2970 ($−CH_3$), 1682 (C=O), 687 (C−S−C). ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 2.32 (3H, *s*, $−CH_3$), 6.01 (1H, *s*, −CH), 7.35–7.97 (4H, *s*, Ar−H). ^{13}C-NMR

(75 MHz, DMSO-d_6, δ, ppm): 14.6, 69.9, 106.2, 120.4, 122.7, 130.2, 133.6, 142.7, 145.2, 149.6, 163.6, 166.7. MS (*m*/*z*): 329.

*3-Methyl-6-(4-nitrophenyl)-1,5,6,7-tetrahydro-8*H-*pyrazolo[3',4':4,5]thieno-[2,3-*d*]pyrimidin-8-one (**IIIi**)*. Yield 45 %; m.p. 280 °C. Anal. Calcd. for $C_{14}H_{11}N_5O_3S$: C, 51.06; H, 3.37; N, 21.27; O, 14.57; S, 9.74. Found: C, 50.94; H, 3.26; N, 21.15; O, 14.44; S, 9.62. IR (KBr, cm^{-1}): 3340 (−NH), 3114 (−CH, aromatic), 2969 ($-CH_3$), 1682 (C=O), 687 (C−S−C). ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 2.32 (3H, *s*, $-CH_3$), 5.91 (1H, *s*, −CH), 7.05–7.24 (4H, *s*, Ar−H). ^{13}C-NMR (75 MHz, DMSO-d_6, δ, ppm): 14.5, 70.7, 106.6, 121.8, 128.6, 136.6, 142.7, 144.9, 147.5, 151.9, 163.4, 166.0. MS (*m*/*z*): 329.

*3-Methyl-6-(4-methoxyphenyl)-1,5,6,7-tetrahydro-8*H-*pyrazolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-8-one (**IIIj**)*. Yield 55 %; m.p. 210 °C. Anal. Calcd. for $C_{15}H_{14}N_4O_2S$: C, 57.31; H, 4.49; N, 17.82; O, 10.18; S, 10.20. Found: C, 57.19; H, 4.36; N, 17.69; O, 10.03; S, 10.08. IR (KBr, cm^{-1}): 3327 (−NH), 3105 (−CH, aromatic), 2968 ($-CH_3$), 1685 (C=O), 692 (C−S−C), 1286 (C−O−C). ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 2.12 (3H, *s*, $-CH_3$), 3.98 (3H, *s*, $-OCH_3$), 5.89 (1H, *s*, −CH), 7.25–7.87 (4H, *s*, Ar−H), 8.58 (1H, *s*,–NH). ^{13}C-NMR (75 MHz, DMSO-d_6, δ, ppm): 14.7, 56.6, 70.4, 106.2, 115.2, 128.6, 136.6, 137.9, 142.6, 145.2, 159.4, 163.6, 166.6. MS (*m*/*z*): 314.

Biological screening

Microbiology. The compounds **IIIa–j** were evaluated for their antimicrobial activity against *Streptococcus pyogenes, Staphylococcus aureus, Escherichia coli, Bacillus subtillis* and antifungal activity against *Candida albicans* and *Aspergillus niger* at a concentration of 50 μg ml^{-1} in DMF using the cup-plate method.[21,22] After 24 h of incubation at 37 °C, the zones of inhibition were measured in mm. The activities were compared with those of some known antibiotics, such as ampicillin, chloramphenicol, norfloxacin and ciprofloxacin, as well as griseofulvin at the same concentration. The results are summarized in Table I.

TABLE I. Antimicrobial activity (zones of inhibition, mm) of 6-aryl-3-methyl-1,5,6,7-tetrahydropyrazolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-8-ones

Compound	Antibacterial activity				Antifungal activity	
	S. pyogenes	*S. aureus*	*E. coli*	*B. subtilis*	*C. albicans*	*A. niger*
IIIa	12	12	10	9	12	11
IIIb	11	14	12	12	13	12
IIIc	12	11	13	11	12	13
IIId	11	11	12	11	11	12
IIIe	9	12	10	10	12	12
IIIf	12	12	11	11	12	11
IIIg	12	11	13	13	11	13
IIIh	10	12	12	12	12	12
IIIi	12	9	10	10	10	10
IIIj	13	14	10	10	10	10

TABLE I. Continued

Compund	Antibacterial activity				Antifungal activity	
	S. pyogenes	*S. aureus*	*E. coli*	*B. subtilis*	*C. albicans*	*A. niger*
Ampicillin	16	18	16	18	–	–
Chloramphenicol	18	16	19	16	–	–
Ciprofloxacin	23	17	20	19	–	–
Norfloxacin	22	20	22	22	–	–
Griseofluvin	–	–	–	–	20	19

EXPERIMENTAL

Melting points were determined routinely in open capillaries and are uncorrected. The formation and purity of the compounds were routinely checked by TLC using silica gel-G. The spots were located under iodine vapour or UV light. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ on a Brucker DRX-300 at 300 MHz using TMS as the internal standard. The mass spectra were scanned on a GCMS-QP2010 instrument.

*Preparation of (5-methyl-2,4-dihydro-3*H*-pyrazol-3-ylidene)malononitrile (**I**)*

An equimolar mixture of 5-methyl-2,4-dihydro-3*H*-pyrazol-3-one and malononitrile was refluxed in the presence of piperidyl acetate (2–3 drops) for 6 h. The product obtained by pouring the reaction mixture into ice-cold water was filtered, dried and recrystallized from 95 % ethanol.

*Preparation of 5-amino-3-methyl-1*H*-thieno[3,2-*c*]pyrazole-6-carbonitrile (**II**)*

(5-Methyl-2,4-dihydro-3*H*-pyrazol-3-ylidene)malononitrile (**I**) and sulphur were refluxed in the presence of morpholine (3.0 ml) for 6 h. The product obtained by pouring the reaction mixture into ice-cold water was filtered, dried and recrystallized from 95 % ethanol.

*General procedure for synthesis of 6-aryl-3-methyl-1,5,6,7-tetrahydro-8*H*-pyrazolo[3',4':4,5]-thieno[2,3-*d*]pyrimidin-8-ones (**IIIa**–**j**)*

An equimolar mixture of 5-amino-3-methyl-1*H*-thieno[3,2-*c*]pyrazole-6-carbonitrile (**II**) and an appropriate aldehyde in glacial acetic acid (20 ml) was refluxed for 6 h. The product was isolated and recrystallized from 95 % ethanol.

Antibacterial activity

The purified compounds **IIIa**–**j** were screened for their antibacterial activity. The nutrient agar, prepared in the usual manner, was inoculated specially with 0.50 ml of 24 h old subcultures of *Streptococcus pyogenes*, *Staphylococcus aureus*, *Bacillus subtilius* and *Escherichia coli*, taken in separate conical flasks at 40–50 °C, and mixed well by gentle shaking. About 25 ml of the contents of the flask were poured and evenly spread in a Petri dish (13 mm in diameter) and allowed to settle down for 2 h. The cups (10 mm in diameter) were formed with the help of a borer in the agar medium and filled with 40 µl (40 µg ml^{-1}) solution of a sample in DMF. The plates were incubated at 37 °C for 24 h and the control was maintained with 40 µl of DMF in a similar manner. The zones of inhibition of bacterial growth were measured in mm. The antibacterial activity of the compounds **IIIa**–**j** was compared with known standard reference drugs, such as ampicillin, chloramphenicol, norfloxacin, ciprofloxacin at same concentration.

Antifungal activity

Aspergillus niger and *Candida albicans* were employed for testing the fungicidal activity using the cup plate method. The cultures were maintained on Sabouraud's agar slants. Sterilized Sabouraud's agar medium was inoculated with 0.50 ml of a 72 h old suspension of fun-

gal spores from a separate flask. About 25 ml of the inoculated medium was evenly spread in a sterilized Petri dish and allowed to settle down for 2 h. The cups (10 mm in diameter) were punched in the Petri dish and loaded with 4 μl (40 μg ml^{-1}) of solution of a sample in DMF. The plates were incubated at room temperature (30 °C) for 48 h. After completion of the incubation period, the zones of inhibition of growth by compounds **IIIa**–**j** were measured as the diameter in mm. Together with the test solution, one cup in each Petri dish was filled with solvent, which acted as the control. The antifungal activities of compounds **IIIa**–**j** were compared with the known standard drug griseofulvin.

CONCLUSIONS

To summarize, a new class of 6-aryl-3,6-dimethyl-1,5,6,7-tetrahydro-8*H*-pyrazolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-8-ones (**IIIa**–**h**), were synthesized. The newly synthesized heterocycles exhibited moderate to promising antimicrobial activity against standard strains. These results make them interesting lead molecules for further synthetic and biological evaluation. It can be concluded that this class of compounds certainly hold great promise towards the pursuit of discovering novel classes of antimicrobial agents. Further studies to acquire more information concerning structure–activity relationships are in progress.

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И З В О Д

КАРАКТЕРИЗАЦИЈА И БИОЛОШКО ТЕСТИРАЊЕ НОВИХ ПИРАЗОЛО[3',4':4,5]ТИЈЕНО[2,3-*d*] ПИРИМИДИН-8-ОНА ДОБИЈЕНИХ ПРИМЕНОМ GEWALD-ОВЕ РЕАКЦИЈЕ

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Описана је синтеза супституисаних пиразоло[3',4':4,5]тијено[2,3-*d*]пиримидин-8-она (**IIIa**–**j**) из 5-амино-3-метил-1*H*-тијено[3,2-*c*]пиразол-6-карбонитрила (**II**). Кључно једињење **II** синтетизовано је из (5-метил-2,4-дихидро-3*H*-пиразол-3-илиден)малононитрила (**I**) применом Gewald-ове реакције. Синтеза једињења **IIIa**–**j** извршена је кондензацијом једињења **II** са различитим ароматичним алдехидима. Ново-добијена хетероциклична једињења окарактерисана су помоћу елементалне анализе и IR, ^{1}H-NMR, ^{13}C-NMR и MS спектралних података. Сва једињења тестирана су на антимикробну активност према различитим бактеријским сојевима.

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REFERENCES

1. W. E. Kirkpatrick, T. Okabe, I. W. Hillyard, R. K. Robins, A. T. Dren, T. Novinson, *J. Med Chem*. **20** (1977) 386
2. A. A. Elagamy, F. M. A. El-Taweel, F. A. Amer, H. H. Zoorob, *Arch. Pharm.* **246** (1987) 320
3. (a) A. N. Kost, I. I. Grandberg, in *Advances in Heterocyclic Chemistry*, A. R. Katritzky Ed., Academic Press, New York, 1996, p. 347; (b) H. B. Nihset, *J. Chem. Soc*. **12** (1938) 1568
4. G. W. Raiziss, L. W. Clemence, M. Friefelder, *J. Am. Chem. Soc*. **63** (1941) 2739

5. Warner-Lambert Co., Jpn. Kokai Tokkyo Koho Jp., 61, 236, 778, 1986
6. S. D. Lindell, B. A. Moloney, B. D. Hewitt, C. G. Earnhaw, P. J. Philip, J. E. Dancer, *Bioorg. Med. Chem. Lett*. **9** (1999) 1985
7. Y. S. Sanghvi, S. B. Larson, D. F. Smee, G. R. Revankar, R. K. Robins, *Nucleosides, Nucleotides* **10** (1991) 1417
8. M. K Bunnage, J. P. Mathias, S. D. A. Street, A. Wood, PCT Int. Appl. WO, 14, 333, 487, 1999
9. A. S. Bell, N. K. Terrett, Eur. Pat. EP 526, 004, 1993
10. P. C. Doherty, Jr., V. A. Place, W. L. Smith, PCT Int. Appl. 9, 921, 558, 1999
11. (a) G. M. Szczech, P. Furman, G. R. Painter, D. W. Barry, K. Borroto-Esoda, T. B. Grizzle, M. R. Blum, J. P. Sommadossi, R. Endoh, T. Niwa, M. Yamamoto, C. Moxham, *Antimicrob. Agents Chemother.* **44** (2000) 123; (b) F. J. Giles, E. J. Feldman, G. J. Roboz, R. A. Larson, S. W. Mamus, J. E. Cortes, S. Verstovsek, S. Federl, M. Talpaz, M. Beran, M. Albitar, S. M. O'Brien, H. M. Kantarjian, *Leuk. Res.* **27** (2003) 1091; (c) F. J. Giles, *Expert Rev. Anticancer Ther.* **2** (2002) 261; (d) J. Toyohara, A. Hayashi, M. Sato, A. Gogami, H. Tanaka, K. Haraguchi, Y. Yoshimura, H. Kumamoto, Y. Yonekura, Y. Fujibayashi, *Nucl. Med. Biol.* **30** (2003) 687; (e) T. J. Mangner, R. W. Klecker, L. Anderson, A. F. Shields, *Nucl. Med. Biol.* **30** (2003) 215; (f) J. Toyohara, Y. Fujibayashi, *Nucl. Med. Biol.* **30** (2003) 681; (g) F. Dieterle, S. Müller-Hagedon, H. M. Liebich, G. Gauglitz, *Artif. Intell. Med.* **28 (**2003) 265
12. (a) D. C. Rowley, M. S. T. Hansen, D. Rhodes, C. A. Striffer, H. Ni, J. A. McCammon, F. D. Bushman, W. Fenical, *Bioorg. Med. Chem.* **10** (2002) 3619; (b) A. Arnaud, L. Fontana, A. J. Angulo, Á. Gil, J. M. López-Pedrosa, *Clin. Nutr.* **22** (2003) 391; (c) J. E. Gallant, *J. Clin. Virol.* **25** (2002) 317
13. (a) P. Molina, E. Aller, A. Lorenzo, P. Lopez-Cremades, I. Rioja, A. Ubeda, M. C. Terencio, M. J. Alcaraz, *J. Med. Chem.* **44** (2001) 1011; (b) A. Kumar, S. P. Sinha, M. S. Chauhan, *Bioorg. Med. Chem. Lett.* **12** (2002) 667
14. (a) J. B. Bher, T. Gourlain, A. Helimi, G. Guillerm, *Bioorg. Med. Chem. Lett.* **13 (**2003) 1713; (b) H. P. De Koning, M. I. Al-Salabi, A. M. Cohen, G. H. Coombs, J. M. Wastling, *Int. J. Parasitol.* **33** (2003) 821
15. K. Gewald, *Chem. Heterocycl. Compd*. *Engl.Transl.* **12** (1976) 1077
16. E. C. Taglor, G. Berger, *J. Org. Chem.* **32** (1967) 2376
17. V. P. Arya, S. J. Shenoy, *Indian J. Chem.* **10** (1972) 815
18. A. Rosoasky, K. K. N. Chen, M. Lin. *J. Med. Chem*. **16** (1973) 191
19. L. G. Sharanina, S. N. Barana, *Chem. Heterocycl. Compd. Engl. Transl.* **10** (1974) 171
20. S. A. Swelam, M. E. A. Abdel Salam, O. L. Zaki, *Indian J. Heterocycl. Chem*. **8** (1999) 257
21. A. L. Barry, in *The Antimicrobic Susceptibility Test: Principles and Practices*, A. L. Barry Ed., Lea and Febiger, Philadelphia, PA, 1976, p. 180
22. *Manual of Clinical microbiology*, 6th Ed., P. R. Murray, E. J. Baron, M. A. Pfaller, F. C. Tenover, H. R. Yolken, Eds., ASM Press, Washington DC, 1995, p. 15.