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Synthesis and Antibacterial Assay of Some New Pyrenyl Pyridine Candidates

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Absract—Novel polycyclic compounds, 1-pyrene-based pyridone derivatives, are synthesized by treatment of pyrenyl acetohydtazide with several arylidenemalononitriles and acetylacetone. Intramolecular cyclization furnishes the functionalized substituted pyridine-2-ones with high yields. Structures of the products are elucidated from the spectral data. Tests on antibacterial activity of the products reveal their high antibacterial effect.

Keywords: pyrenes, 2-pyridone derivatives, antibacterial agents, synthesis

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In our earlier studies, a variety of synthesized 2-pyridones linked pyrene scaffold were tested for their anti-HIV-1 and anti-HSV-1 virus activities [1]. According to literature survey 2-pyridone scaffolds demonstrated multifunctional medicinal and pharmaceutical activities, including HBV inhibiting [2], antiproliferative [3, 4], HIV-1 reverse transcriptase inhibiting [5], and some more.

In continuation of our prior studies of polycyclic hetero-systems [6–8], herein we present synthesized of a series of novel-pyridones incorporated pyrene moieties and their antibacterial activity.

RESULTS AND DISCUSSION

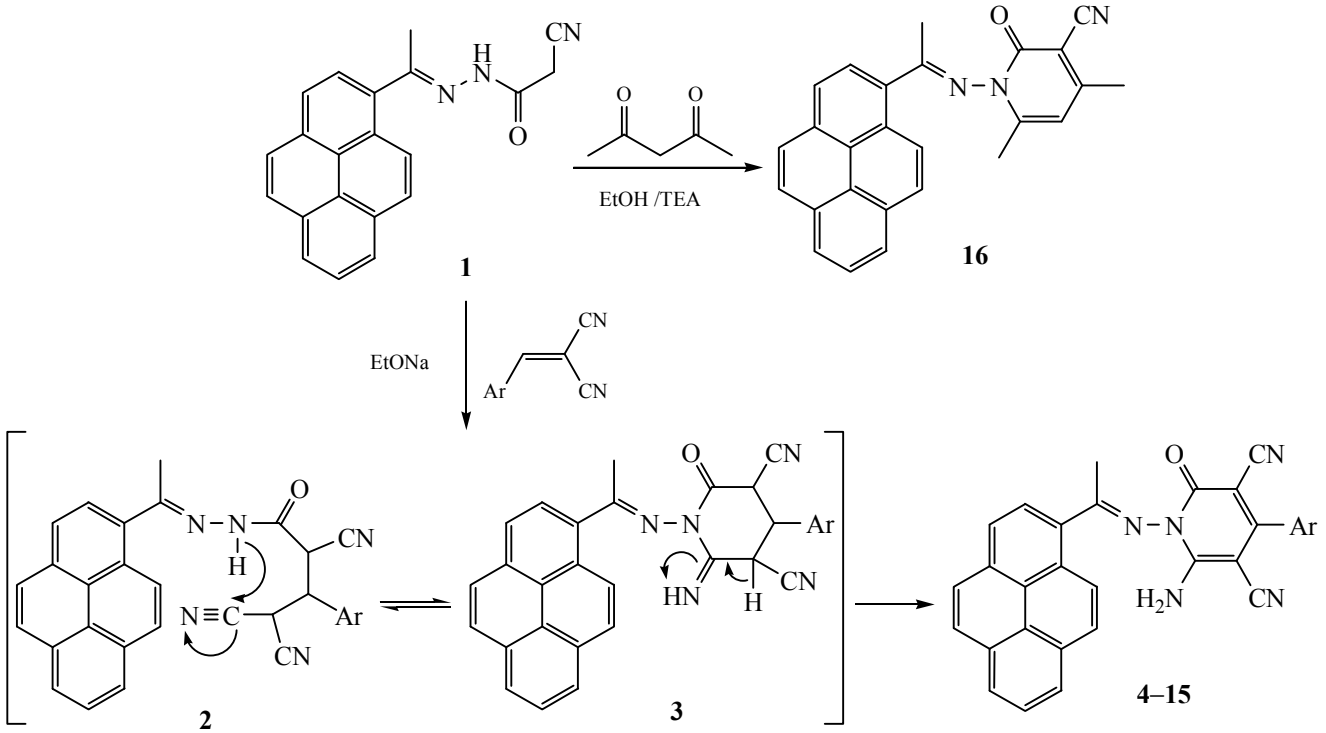
According to the presented below method (Scheme 1), the starting compound pyrenyl acetohydtazide (**1**) [8] reacted with a number of arylidenemalononitrile derivatives giving the Michael adducts of the general formula **2.** Their intramolecular cyclization into the intermediates **3** followed by isomerization led to 2-pyridone derivatives **4–15**. Spectral data of the products supported their structures. In their IR spectra the characteristic bands of the amino, cyano and carbonyl groups were recorded. The initial compound **1** reacted with acetylacetone giving the functionalized 2-pyridone derivative **16**. The structure of compound **16** was confirmed by the bands of the cyano and carbonyl groups at 2219 and 1660 cm^{-1} in its IR spectrum. Four singlets attributed to protons of three methyl groups and pyridine-H^5 recorded in the ^1H NMR spectrum were measured at 1.23, 1.61, 1.87, and 6.45 ppm, respectively.

Antimicrobial activity. Agar-well diffusion assay was used for screening antibacterial activity of the products on Mueller-Hinton agar medium conducted against *S. aureus*; *S. pneumoniae* species as gram (+ve) strains and *E. coli*; *P. aeruginosa* species as gram (–ve) strains at concentration of 100 μg/mL using imipenem as a standard antibiotic. The accumulated data (see the table) indicated the pronounced antibacterial activity of the synthesized compounds **4–16**. The most significant activity was determined for the compound **16**, which was very close to that of the standard.

EXPERIMENTAL

A Griffin apparatus with open capillary tubes was used for recording melting points (uncorrected). IR spectra (KBr disks) were recorded on a Schimadzu 435 IR spectrophotometer. ^1H and ^{13}C NMR spectra were

Scheme 1.



Ar = C_6H_5 (**4**); 4-FC_6H_4 (**5**); 4-$CH_3C_6H_4$ (**6**); 4-$OCH_3C_6H_4$ (**7**); 4-NO_2-C_6H_4 (**8**); 4-$N(CH_3)_2C_6H_4$ (**9**); 4-$CH(CH_3)_2C_6H_4$ (**10**); 4-$(OH)C_6H_4$ (**11**); 3,5-$(Cl)_2C_6H_3$ (**12**); 2,5-$(OCH_3)_2C_6H_3$ (**13**); thiophen-2-yl (**14**); benzo[*d*][1,3]dioxol-5-yl (**15**).

measured on a Varian Gemini 500 MHz Spectrometer using DMSO-d_6 as a solvent and TMS as an internal standard. Mass spectra were measured on a Hewlett Packard 5988 Spectrometer (70 eV).

6-Amino-1-{[(1*E*)-1-(pyren-3-yl)ethylidene]amino}-2-oxo-4-arylpyridine-3,5-dicarbonitrile (4–15). In dry ethanol, EtONa (0.003 mol) was added (5 ml) to a blend in pyrenyl acetohydtazide **1** and an arylidene-malonitrile (0.003 mol). It flowed for 5–8 h, and then filled into crushed ice with diluted HCl neutralized. The solid was precipitated to provide the corresponding products with methanol purification.

6-Amino-1-{[(1*E*)-1-(pyren-3-yl)ethylidene]-amino}-2-oxo-4-phenylpyridine-3,5- dicarbonitrile (4). Yield 73%, mp 147–149°C. IR spectrum, ν, cm^{-1}: 3412, 3334 (NH_2), 2219 (CN), 1665 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.23 s (3H, CH_3), 6.20 s (2H, NH_2), 7.12–8.38 m (14H, Ar-H). ^{13}C NMR spectrum, δ_C, ppm: 13.76, 104.51, 113.24, 114.45, 114.58, 124.87, 125.01, 125.59, 126.18, 126.34, 126.42, 126.63, 127.79, 127.95, 128.15, 128.36, 128.64, 129.06, 130.98, 132.26, 132.89, 157.46, 162.04, 167.82, 168.45. MS: *m/z:* 477 $[M]^+$.

6-Amino-1-{[(1*E*)-1-(pyren-3-yl)ethylidene]amino}-2-oxo-4-(4-fluorophenyl)pyridine-3,5-dicarbonitrile (5). Yield 69%, mp 136–138°C. IR spectrum, ν, cm^{-1}: 3428, 3320 (NH_2), 2215 (CN), 1661 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.20 s (3H, CH_3), 5.82 s (2H, NH_2), 7.12–8.40 m (13H, Ar-H). ^{13}C NMR spectrum, δ_C, ppm: 13.82, 104.55, 113.38, 114.48, 114.52, 115.27, 124.75, 125.01, 125.63, 126.18, 126.55, 126.60, 127.84, 127.99, 128.09, 128.23, 128.42, 129.10, 131.01, 132.96, 157.40, 161.96, 162.13, 167.86, 168.53. MS: *m/z*: 495 $[M]^+$.

6-Amino-1-{[(1*E*)-1-(pyren-3-yl)ethylidene]amino}-2-oxo-4-*p*-tolylpyridine-3,5-dicarbonitrile (6). Yield 71%, mp 121–123°C. IR spectrum, ν, cm^{-1}: 3417, 3310 (NH_2), 2217 (CN), 1668 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.21 s (3H, CH_3), 2.30 s (3H, CH_3), 4.65 s (2H, NH_2), 7.10–8.41 m (13H, Ar-H). ^{13}C NMR spectrum, δ_C, ppm: 13.80, 23.65, 104.50, 113.35, 114.48,

Antibacterial screening of the products **4–16**

Compound	Inhibition zone, mm			
	gram (+ve) bacteria		gram (–ve) bacteria	
	S. aureus	*S. pneumoniae*	*E. coli*	*P. aeruginosa*
4	17±0.3	15±0.1	18±0.2	17±0.1
5	15±0.2	18±0.3	14±0.2	10±0.3
6	10±0.3	16±0.1	15±0.1	18±0.1
7	19±0.1	17±0.3	18±0.3	15±0.2
8	16±0.3	17±0.3	17±0.2	12±0.2
9	14±0.2	14±0.2	15±0.1	15±0.1
10	17±0.3	19±0.1	19±0.2	18±0.2
11	12±0.1	16±0.2	19±0.3	14±0.3
12	14±0.2	19±0.3	12±0.1	17±0.3
13	18±0.2	12±0.3	16±0.3	17±0.1
14	16±0.1	16±0.1	18±0.3	15±0.2
15	15±0.3	19±0.2	19±0.3	17±0.1
16	21±0.2	19±0.3	20±0.1	19±0.3
Imipenem	22	20	22	20

114.57, 124.67, 125.01, 125.45, 126.08, 126.32, 126.38, 126.52, 127.91, 128.14, 128.35, 128.96, 129.04, 129.46, 131.01, 133.16, 137.54, 157.62, 161.98, 167.79, 168.53. MS: *m/z*: 491 $[M]^+$.

6-Amino-1-{[(1*E*)-1-(pyren-3-yl)ethylidene]amino}-2-oxo-4-(*p*-methoxyphenyl)pyridine-3,5-dicarbonitrile (7). Yield 76%, mp 152–154°C. IR spectrum, ν, cm^{-1}: 3446, 3328 (NH_2), 2212 (CN), 1660 (C=O). ^1H NMR spectrum, δ, ppm: 1.23 s (3H, CH_3), 3.81 s (3H, OCH_3), 6.34 s (2H, NH_2), 7.14–8.36 m (13H, Ar-H). ^{13}C NMR spectrum, δ_C, ppm: 13.74, 56.01, 104.46, 113.44, 113.85, 114.43, 114.51, 124.62, 124.79, 125.01, 125.49, 126.13, 126.43, 126.58, 127.36, 127.90, 128.10, 128.19, 129.01, 130.95, 133.21, 157.75, 158.98, 162.02, 167.86, 168.82. MS: *m/z*: 507 $[M]^+$.

6-Amino-1-{[(1*E*)-1-(pyren-3-yl)ethylidene]amino}-2-oxo-4-(*p*-nitrophenyl)pyridine-3,5-dicarbonitrile (8). Yield 72%, mp 168–169°C. IR spectrum, ν, cm^{-1}: 3426, 3319 (NH_2), 2210 (CN), 1664 (C=O). ^1H NMR spectrum, δ, ppm: 1.23 s (3H, CH_3), 5.80 s (2H, NH_2), 7.45–8.40 m (13H, Ar-H). ^{13}C NMR spectrum, δ_C, ppm: 13.70, 104.55, 113.37, 114.49, 114.59, 120.87, 124.57, 125.01, 125.46, 126.09, 126.40, 126.63, 127.31, 127.83, 128.08, 128.15, 128.89, 131.05, 132.99, 137.94, 147.58, 157.86, 162.01, 167.89, 168.85. MS: *m/z*: 522 $[M]^+$.

6-Amino-1-{[(1*E*)-1-(pyren-3-yl)ethylidene]amino}-2-oxo-4-(*p*-dimethylaminophenyl)pyridine-3,5-dicarbonitrile (9). Yield 65%, mp 127–129°C. IR spectrum, ν, cm^{-1}: 3415, 3364 (NH_2), 2217 (CN), 1667 (C=O). ^1H NMR spectrum, δ, ppm: 1.23 s (3H, CH_3), 2.73 s (6H, $2NCH_3$), 6.48 s (2H, NH_2), 7.01–8.38 m (13H, Ar-H). ^{13}C NMR spectrum, δ_C, ppm: 13.67, 38.85, 104.46, 113.31, 113.98, 114.51, 114.59, 121.90, 124.63, 125.01, 125.57, 126.04, 126.58, 126.65, 127.34, 127.78, 128.10, 128.17, 128.94, 131.01, 133.02, 147.82, 157.80, 162.01, 167.79, 168.88. MS: *m/z*: 520 $[M]^+$.

6-Amino-1-{[(1*E*)-1-(pyren-3-yl)ethylidene]amino}-2-oxo-4-(*p*-isopropylphenyl)pyridine-3,5-dicarbonitrile (10). Yield 75%, mp 138–140°C. IR spectrum, ν, cm^{-1}: 3427, 3346 (NH_2), 2221 (CN), 1663 (C=O). ^1H NMR spectrum, δ, ppm: 1.21 s (3H, CH_3), 1.32 d (6H, $2CH_3$), 3.27 m (1H, CH), 6.25 s (2H, NH_2), 7.05–8.41 m (13H, Ar-H). ^{13}C NMR spectrum, δ_C, ppm: 13.70, 23.76, 36.48, 104.56, 113.30, 114.46, 114.62,

124.57, 125.01, 125.52, 126.01, 126.03, 126.18, 126.58, 126.74, 127.81, 128.12, 128.23, 128.89, 129.77, 131.01, 132.99, 147.79, 157.87, 162.01, 167.84, 168.73. MS: *m/z*: 519 $[M]^+$.

6-Amino-1-{[(1*E*)-1-(pyren-3-yl)ethylidene]amino}-2-oxo-4-(*p*-hydroxyphenyl)pyridine-3,5-dicarbonitrile (11). Yield 61%, mp 182–184°C. IR spectrum, ν, cm^{-1}: 3385 (OH), 3420, 3317 (NH_2), 2217 (CN), 1658 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.21 s (3H, CH_3), 4.85 s (2H, NH_2), 7.00–8.42 m (13H, Ar-H), 10.26 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 13.68, 104.54, 113.27, 114.35, 114.67, 115.67, 124.66, 125.01, 125.16, 125.67, 126.10, 126.51, 126.82, 127.58, 127.89, 128.09, 128.18, 128.78, 131.01, 132.95, 157.90, 158.04, 162.01, 167.84, 168.59. MS: *m/z*: 493 $[M]^+$.

6-Amino-1-{[(1*E*)-1-(pyren-3-yl)ethylidene]amino}-2-oxo-4-(3,5-dichlorophenyl)pyridine-3,5-dicarbonitrile (12). Yield 63%, mp 117–119°C. IR spectrum, ν, cm^{-1}: 3445, 3328 (NH_2), 2215 (CN), 1661 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.20 s (3H, CH_3), 5.65 s (2H, NH_2), 7.12–8.40 m (12H, Ar-H). ^{13}C NMR spectrum, δ_C, ppm: 13.65, 104.50, 113.34, 114.42, 114.56, 124.57, 124.61, 125.01, 125.73, 126.08, 126.49, 126.68, 127.94, 128.13, 128.23, 128.84, 129.62, 131.01, 132.90, 134.99, 135.72, 157.87, 162.01, 167.75, 168.76. MS: *m/z*: 546 $[M]^+$.

6-Amino-1-{[(1*E*)-1-(pyren-3-yl)ethylidene]amino}-2-oxo-4-(2,5-dimethoxyphenyl)pyridine-3,5-dicarbonitrile (13). Yield 71%, mp 143–145°C. IR spectrum, ν, cm^{-1}: 3445, 3316 (NH_2), 2220 (CN), 1667 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.23 s (3H, CH_3), 3.79, 3.81 2s (6H, $2OCH_3$), 6.28 s (2H, NH_2), 6.90–8.41 m (12H, Ar-H). ^{13}C NMR spectrum, δ_C, ppm: 13.68, 56.64, 56.82, 104.54, 112.42, 113.40, 114.35, 114.49, 114.58, 115.24, 120.97, 124.51, 125.01, 125.81, 126.02, 126.45, 126.73, 128.03, 128.10, 128.32, 129.01, 130.94, 132.98, 149.85, 153.04, 157.87, 162.01, 167.75, 168.76. MS: *m/z*: 537 $[M]^+$.

6-Amino-1-{[(1*E*)-1-(pyren-3-yl)ethylidene]amino}-2-oxo-4-(2-thiophenyl)pyridine-3,5-dicarbonitrile (14). Yield 68%, mp 161–163°C. IR spectrum, ν, cm^{-1}: 3436, 3310 (NH_2), 2227 (CN), 1663 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.23 s (3H, CH_3), 5.65 s (2H, NH_2), 6.95–8.40 m (12H, Ar-H). ^{13}C NMR spectrum, δ_C, ppm: 13.68, 104.58, 113.38, 114.43, 114.60, 124.47, 125.01, 125.90, 126.01, 126. 39, 126.67, 127.12, 127.96, 128.03, 128.14, 128. 26, 129.01, 129.98, 131.02, 133.14, 136.44, 157.87, 162.01, 167.75, 168.76. MS: *m/z*: 483 $[M]^+$.

6-Amino-1-{[(1*E*)-1-(pyren-3-yl)ethylidene]amino}-2-oxo-4-(benzo[d][1,3]dioxol-6-yl)pyridine-3,5-dicarbonitrile (15). Yield 73%, mp 151–153°C. IR spectrum, ν, cm^{-1}: 3446, 3334 (NH_2), 2223 (CN), 1661 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.21 s (3H, CH_3), 6.12 s (2H, CH_2), 6.45 s (2H, NH_2), 6.90–8.39 m (12H, Ar-H). ^{13}C NMR spectrum, δ_C, ppm: 13.70, 102.45, 104.55, 112.04, 113.41, 114.49, 114.63, 115.18, 119.66, 124.59, 125.01, 125.78, 125.89, 126.01, 126.42, 126.60, 127.99, 128.10, 128.31, 128.96, 131.01, 133.04, 147.86, 148.52, 157.85, 162.01, 167.73, 168.83. MS: *m/z*: 521 $[M]^+$.

4,6-Dimethyl-1-{[(1*E*)-1-(pyren-3-yl)ethylidene]-amino}-2-oxopyridine-3-carbonitrile (16). To a mixture of 2-cyano-*N*'-[1-(pyren-3-yl)ethylidene] acetohydrazide (**1**) (0.003 mol) with acetylacetone (0.003 mol) in absolute ethanol (50 mL) was added TEA (0.5 mL), and the mixture was refluxed for 12 h. The residue produced after pouring into ice-water and HCl neutralization was washed with water and purified in ethanol. Yield 72%, mp 189–191°C. IR spectrum, ν, cm^{-1}: 2219 (CN), 1660 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.23 s (3H, CH_3), 1.61, 1.87 2s (6H, $2CH_3$), 6.45 s (1H, H-5 pyridone), 7.60–8.43 m (9H, Ar-H). ^{13}C NMR spec-trum, δ_C, ppm: 13.65, 14.82, 17.91, 98.10, 101.79, 112.37, 124.60, 125.01, 125.84, 126.01, 126.38, 126.56, 127.95, 128.09, 128.34, 129.02, 131.01, 132.99, 160.39, 160.67, 162.25, 167.81, 169.01. MS: *m/z*: 390 $[M + H]^+$.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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