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Synthesis and biological activity of (γ-arylpyridino)-dibenzoaza-14-crown-4 ethers

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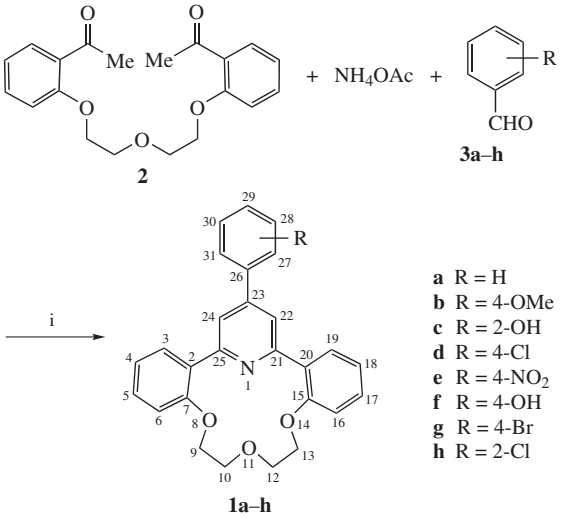
Eight novel aza-14-crown-4 compounds incorporating γ-arylpyridine moiety and possessing high inhibitory activity towards cancer cell lines were synthesized in one step from 1,5-bis(2-acetylphenoxy)-3-oxapentane, aromatic aldehyde and ammonium acetate.

Nitrogen atoms impart many interesting properties to azacrown ethers, for example, increasing ability for metal-ion complexation, and enabling them to function as efficient ion transport agents and as phase-transfer catalysts in some transformations.[1,2] Introduction of bioactive azacyclic subunits into crown ethers shows tremendous effects on bioactivity of thus prepared compounds.[3] We have previously synthesized a series of bis(benzo)azino-14-crown-4 compounds having a crown ether moiety and an aza ring as a subunit, such as piperidone, perhydrodiazine and perhydrotriazines.

As part of our on-going research, in this study, we synthesized novel aza-14-crown-4 ethers with a γ-arylpyridine subunit **1a–h** *via* the domino-type condensation of three components: 1,5-bis-(2-acetylphenoxy)-3-oxapentane **2**, ammonium acetate and an aromatic aldehyde **3a–h** (Scheme 1). The motivation for this synthesis was the role of γ-arylpyridine as a probable pharmacophoric fragment in influencing the biological activities of many drug molecules.[4–6] All azacrown ethers **1a–h** are new and their structures were confirmed by ^{1}H NMR, IR, and LCMS (ionization or electron impact) analyses.†

Apparently, mechanistic pathway for the assembling of the reactants into pyridines **1** should be analogous to that accepted for the Hantsch synthesis.

According to the bioactivity prediction using PASS,[7] compounds **1a–h** are expected to possess cardioprotective, antineurotoxic and antineoplastic activities. Therefore, we tested them (for the exception of compound **1e**) for *in vitro* cytotoxicity in human uterine (FL), human breast adenocarcinoma (MCF7),



Scheme 1 *Reagents and conditions*: i, 1.0 equiv. **2**, 2.6 equiv. NH_4OAc, 1.0 equiv. benzaldehyde **3**, AcOH, 120 °C, 6 h.

† *Synthesis of bis(benzo)(γ-arylpyridino)aza-14-crown-4 ethers* **1a–h** *(general procedure)*. Equimolar amounts of diketone **2** (1.71 g, 5.00 mmol), aromatic aldehyde **3a–h** (5.00 mmol) and ammonium acetate (10 g, 13 mmol) were refluxed in acetic acid (50 ml). The reaction was monitored by TLC and was complete in 6 h. The mixture was allowed to cool to room temperature and neutralized with sodium carbonate solution; then, the product was extracted with ethyl acetate (3×50 ml). The solvent was evaporated *in vacuo*; the residue was purified by column chromatography and recrystallized from ethanol to obtain the pure crown ether product.

23-Phenyl-8,11,14-trioxa-25-azatetracyclo[19.3.1.0^{2,7}.0^{15,20}]pentacosa-2,4,6,15(20),16,18,21(25),22,24-nonaene **1a**. Yield 42%, mp 160–162 °C. IR (KBr, ν/cm^{-1}): 1592, 1249. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ: 3.74 (m, 4H, H-9, H-13), 4.06 (m, 4H, H-10, H-12), 7.00 (td, 2H, H-4, H-18, ^3J 7.5 Hz, ^5J 1.0 Hz), 7.04 (d, 2H, H-6, H-16, ^3J 8.0 Hz), 7.35 (d, 2H, H-3, H-19, ^3J 7.5 Hz), 7.38 (t, 2H, H-5, H-17, ^3J 7.5 Hz, ^5J 1.5 Hz), 7.36 (m, 2H, H-31, H-27), 7.48 (m, 1H, H-29), 7.54 (m, 2H, H-30, H-28), 7.59 (s, 2H, H-22, H-24). MS, *m*/*z*: 410 [M+H]$^+$. Found (%): C, 79.17; H, 5.58; N, 3.46. Calc. for $C_{27}H_{23}NO_3$ (%): C, 79.20; H, 5.66; N, 3.42.

23-(4-Methoxyphenyl-8,11,14-trioxa-25-azatetracyclo[19.3.1.0^{2,7}.0^{15,20}]pentacosa-2,4,6,15(20),16,18,21(25),22,24-nonaene **1b**. Yield 40%, mp 110–111°C. IR (KBr, ν/cm^{-1}): 1608, 1256, 1248. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ: 3.87 (s, 3H, Me), 3.84 (m, 4H, H-9, H-13), 4.13 (m, 4H, H-10, H-12), 6.95 (d, 2H, H-6, H-16, ^3J 8.5 Hz), 6.99–7.01 (m, 4H, H-4, H-18, H-3, H-19), 7.32 (m, 2H, H-5, H-17), 7.49 (s, 2H, H-22, H-24), 7.69 (dt, 2H, H-30, H-28, ^3J 8.5 Hz, ^5J 2.0 Hz), 7.34 (dt, 2H, H-31, H-27, ^3J 7.5 Hz, ^5J 2.0 Hz). MS, *m*/*z*: 440 [M+H]$^+$. Found (%): C, 76.55; H, 5.69; N, 3.16. Calc. for $C_{28}H_{25}NO_4$ (%): C, 76.52; H, 5.73; N, 3.19.

23-(2-Hydroxyphenyl-8,11,14-trioxa-25-azatetracyclo[19.3.1.0^{2,7}.0^{15,20}]pentacosa-2,4,6,15(20),16,18,21(25),22,24-nonaene **1c**. Yield 37%, mp 225–226 °C. IR (KBr, ν/cm^{-1}): 3481, 3060, 1593, 1255. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ: 3.70 (m, 4H, H-9, H-13), 4.02 (m, 4H, H-10, H-12), 6.80 (d, 2H, H-6, H-16, ^3J 8.0 Hz), 6.91 (t, 2H, H-4, H-18, ^3J 7.5 Hz), 7.22–7.30 (m, 4H, H-3, H-19, H-5, H-17), 7.48 (s, 2H, H-22, H-24), 6.68 (d, 1H, H-31, ^3J 8.0 Hz), 6.83 (t, 1H, H-29, ^3J 7.5 Hz), 7.04 (t, 1H, H-28, ^3J 7.0 Hz), 7.22–7.30 (1H, H-30). MS, *m*/*z*: 426 [M+H]$^+$. Found (%): C, 76.18; H, 5.42; N, 3.33. Calc. for $C_{27}H_{23}NO_4$ (%): C, 76.22; H, 5.45; N, 3.29.

Table 1 Cytotoxicity tests performed on compounds **1a–d**,**f–h** (5 μg ml^{-1}) in five cancer cell lines.

Entry	Compound	Cell line, cell survival (%)					Conclusion
		HepG2	MCF7	RD	FL	Lu	
1	DMSO	100.0	100.0	100.0	100.0	100.0	
2	Colchicine (+)	0.7	1.5	1.1	2.5	2.8	Positive
3	**1a**	98.5	97.5	99.2	96.3	99.7	Negative
4	**1b**	71.5	87.6	71.6	76.7	94.5	Negative
5	**1c**	56.5	90.8	26.8	74.1	N/A	Positive with RD
6	**1d**	7.1	42.5	0.0	17.8	92.7	Positive with 04 cell lines
7	**1f**	87.8	91.2	68.8	99.5	N/A	Negative
8	**1g**	70.5	87.2	90.7	90.2	99.5	Negative
9	**1h**	90.7	91.5	96.3	97.3	98.8	Negative

Table 2 Results of IC_{50} tests of compounds **1c**,**d**.

Entry	Compound	Cell line, IC_{50}/μg ml^{-1}				Conclusion
		HepG2	MCF7	RD	FL	
1	Colchicine (+)	0.25	0.31	0.22	0.18	Positive
2	**1c**	>5	>5	1.89	>5	Positive with RD cell line
3	**1d**	2.79	4.56	1.46	1.51	Positive with 04 cell lines

23-(4-Chlorophenyl-8,11,14-trioxa-25-azatetracyclo[19.3.1.0^{2,7}.0^{15,20}]-pentacosa-2,4,6,15(20),16,18,21(25),22,24-nonaene **1d**. Yield 42%, mp 138–140 °C. IR (KBr, ν/cm^{-1}): 1590, 1250. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ: 3.85 (m, 4H, H-9, H-13), 4.15 (m, 4H, H-10, H-12), 6.95 (d, 2H, H-6, H-16, ^3J 8.0 Hz), 7.01 (t, 2H, H-4, H-18, ^3J 7.0 Hz), 7.36 (t, 2H, H-5, H-17, ^3J 7.5 Hz), 7.33 (d, 2H, H-3, H-19, ^3J 7.5 Hz), 7.52 (s, 2H, H-22, H-24), 7.66 (d, 2H, H-30, H-28, ^3J 8.5 Hz), 7.45 (d, 2H, H-31, H-27, ^3J 8.5 Hz). MS, *m/z*: 444 $[M+H]^+$. Found (%): C, 73.02; H, 5.05; N, 3.19. Calc. for $C_{27}H_{22}ClNO_3$ (%): C, 73.05; H, 5.00; N, 3.16.

23-(4-Nitrophenyl-8,11,14-trioxa-25-azatetracyclo[19.3.1.0^{2,7}.0^{15,20}]-pentacosa-2,4,6,15(20),16,18,21(25),22,24-nonaene **1e**. Yield 40%, mp 252–253 °C. IR (KBr, ν/cm^{-1}): 1598, 1251. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ: 3.72 (m, 4H, H-9, H-13), 4.06 (m, 4H, H-10, H-12), 7.79 (dt, 2H, H-3, H-19, ^3J 8.5 Hz, ^5J 1.5 Hz), 6.98 (d, 2H, H-6, H-16, ^3J 7.0 Hz), 7.01 (td, 2H, H-4, H-18, ^3J 8.0 Hz, ^5J 0.5 Hz), 7.52 (s, 2H, H-22, H-24), 7.03 (d, 2H, H-30, H-28, ^3J 8.0 Hz), 7.35 (dd, 2H, H-31, H-27, ^3J 7.5 Hz). MS, *m/z*: 408 $[M-NO_2]^+$. Found (%): C, 71.31; H, 4.93; N, 6.20. Calc. for. $C_{27}H_{22}N_2O_5$ (%): C, 71.35; H, 4.88; N, 6.16.

23-(4-Hydroxyphenyl-8,11,14-trioxa-25-azatetracyclo[19.3.1.0^{2,7}.0^{15,20}]pentacosa-2,4,6,15(20),16,18,21(25),22,24-nonaene **1f**. Yield 40%, mp 211–212 °C. IR (KBr, ν/cm^{-1}): 3420, 1598, 1248. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ: 3.83 (m, 4H, H-9, H-13), 4.11 (m, 4H, H-10, H-12), 6.93 (d, 2H, H-6, H-16, ^3J 8.5 Hz), 7.02 (t, 2H, H-4, H-18, ^3J 7.5 Hz), 7.33 (dd, 2H, H-3, H-19, ^3J 7.5 Hz, ^5J 1.5 Hz), 7.37 (td, 2H, H-5, H-17, ^3J 8.0 Hz, ^5J 1.5 Hz), 7.50 (s, 2H, H-22, H-24), 7.61 (dt, 2H, H-30, H-28, ^3J 8.5 Hz, ^5J 2.0 Hz), 6.92 (dt, 2H, H-31, H-27, ^3J 9.0 Hz, ^5J 2.0 Hz). MS, *m/z*: 426 $[M+H]^+$. Found (%): C, 76.25; H, 5.48; N, 3.31. Calc. for $C_{27}H_{23}NO_4$ (%): C, 76.22; H, 5.45; N, 3.29.

human rhabdomyosarcoma (RD), human hepatocellular carcinoma (HepG2), and lung (Lu) cell lines. The results (Tables 1 and 2) showed that **1c** inhibited the RD cell line and **1d** inhibited the FL, MCF7, RD, and HepG2 cell lines. In particular, the viability of the RD cell line decreased to 0% when incubated with 5 μg ml^{-1} of **1d**. However, **1a** and **1e** exhibited no notable free radical scavenging ability when tested with a previously reported method.[8]

In conclusion, we successfully synthesized eight (γ-aryl-pyridino)dibenzoaza-14-crown-4 ethers by multicomponent cascade reactions of three available compounds. *In vitro* cytotoxicity tests revealed that some of the obtained substances could inhibit the RD, RL, MCF7, RD, and HepG2 lines.

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23-(4-Bromophenyl-8,11,14-trioxa-25-azatetracyclo[19.3.1.0^{2,7}.0^{15,20}]-pentacosa-2,4,6,15(20),16,18,21(25),22,24-nonaene **1g**. Yield 45%, mp 182–184 °C. IR (KBr, ν/cm^{-1}): 1593, 1252. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ: 3.92 (m, 4H, H-9, H-13), 4.22 (m, 4H, H-10, H-12), 6.99 (d, 2H, H-6, H-16, ^3J 8.5 Hz), 7.03 (t, 2H, H-4, H-18, ^3J 7.5 Hz), 7.40 (t, 2H, H-5, H-17, ^3J 7.5 Hz), 7.36 (dd, 2H, H-3, H-19, ^3J 7.5 Hz, ^5J 1.0 Hz), 7.60 (s, 2H, H-22, H-24), 7.61–7.66 (m, 4H, H-27, H-28, H-30, H-31). MS, *m/z*: 488 $[M(^{79}Br)+H]^+$, 490 $[M(^{81}Br)+H]^+$. Found (%): C, 66.44; H, 4.58; N, 2.82. Calc. for $C_{27}H_{22}BrNO_4$ (%): C, 66.40; H, 4.54; N, 2.87.

23-(2-Chlorophenyl-8,11,14-trioxa-25-azatetracyclo[19.3.1.0^{2,7}.0^{15,20}]pentacosa-2,4,6,15(20),16,18,21(25),22,24-nonaene **1h**. Yield 43%, mp 172–174 °C. IR (KBr, ν/cm^{-1}): 1596, 1249. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ: 3.88 (m, 4H, H-9, H-13), 4.16 (m, 4H, H-10, H-12), 6.95 (d, 2H, H-6, H-16, ^3J 8.5 Hz), 7.00 (t, 2H, H-4, H-18, ^3J 7.5 Hz), 7.33–7.38 (m, 4H, H-3, H-19, H-5, H-17), 7.46 (s, 2H, H-22, H-24), 7.52 (m, 1H, H-30), 7.47 (m, 1H, H-29), 7.33–7.38 (m, 2H, H-30, H-28). MS, *m/z*: 444 $[M+H]^+$, 466 $[M+Na]^+$. Found (%): C, 73.08; H, 5.06; N, 3.12. Calc. for $C_{27}H_{22}ClNO_3$ (%): C, 73.05; H, 5.00; N, 3.16.