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Synthesis of New [γ–(Aryl)pyridino]dibenzo–27,28–Diazacrownophanes Containing Two Pyridine Rings

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*In continuation of developing new cytotoxic compounds, six azacrownophanes containing both 2,4,6-triarylpyridine and 2,6-bis(phenoxymethyl)pyridine moieties were synthesized successfully by one-step domino-condensation of podand 2,6-bis[(2-acetophenyl)oxymethyl]pyridine, arylaldehydes and ammonium acetate according to the conditions of Hantzsch reactions. The compounds **5a-c** were selected for cytotoxicity evaluations against human cell lines (HepG2, Lu1, RD, FL and MCF-7). Compound **5b** showing the highest cytotoxicity is interesting for the development of promising anticancer drugs.*

Keywords: Arylpyridine, cytotoxicity, Hantzsch reaction, azacrownophane.

Синтез новых [γ–(арил)пиридино]дибензо–27,28–диазокраунофанов, содержащих два пиридиновых кольца

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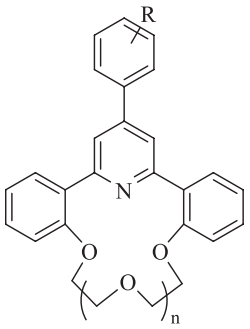
*В продолжение разработки новых цитотоксических соединений были синтезированы шесть азакраунофанов, содержащих остатки 2,4,6-триарилпиридина и 2,6-бис(феноксиметил)пиридина, путем одностадийной доминоконденсации поданда – 2,6-бис[(2-ацетофенил)оксиметил]пиридина, арилальдегидов и ацетата аммония по реакции Ганча. Для соединений **5a-c** была оценена цитотоксичность в отношении клеточных линий человека (HepG2, Lu1, RD, FL и MCF-7). Соединение **5b**, проявляющее наибольшую цитотоксичность, представляет интерес для разработки перспективных противораковых лекарственных средств.*

Ключевые слова: Арилпиридин, цитотоксичность, реакция Ганча, азакраунофаны.

Introduction

Drug development is one of the most attractive tasks in medicinal chemistry. In this connection, pharmacophore approaches have become one of the major tools in drug discovery in the previous century. Now a days, several synthetic methods were designed for the development of new medical drugs. Among them, multicomponent condensation reactions (MCR) are highly applicable and important in synthesis of novel molecules due to their significant cost effectiveness and less reaction time. Recent studies have shown that azacrown ethers incorporating γ-arylpyridine have brought strong cytotoxicity towards human cancer cell lines: Hepatocellular carcinoma (HepG2), Rhabdosarcoma (RD), Human Uterine (FL), Human Breast adenocarcinoma (MCF7), Human Prostate Cancer (PC3) (Table 1).[1–4]



The present research is focused on synthesis of an effective pharmacophores – 2,4,6-triarylpyridine and 2,6-diphenoxymethylpyridine. The combination of polyarylpyridine and azacrownophane is promising to bring a novel class of bioactive compounds. To be specific, novel [(γ-aryl)pyridino]dibenzodiazacrownophanes with a γ-arylpyridine subunit (**5a-f**) were synthesized *via* the domino-type condensation of three components: 2,6-bis[(2-acetophenyl)oxymethyl]pyridine (**3**), ammonium acetate and arylaldehyde derivatives.

The structure of the synthesized compounds was confirmed by the physico-chemical methods, such as IR, ^{1}H NMR, ^{13}C NMR, LCMS and HRMS. The bioactivity of all synthesized compounds was predicted by PASS[5] and some of the selected compounds (**5a-c**) were evaluated *in vitro* for their cytotoxicity against human cancer cell lines.

Experimental

Reagents purchased from commercial sources (Sigma-Aldrich) were used without any additional purification. Melting points were determined in open capillary tubes on a digital Stuart SMP3 apparatus. Elemental analysis was conducted on Euro Vector EA-3000 analyzer. IR spectra were recorded in FTIR Affinity – 1S SHIMADZU. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions at 25 °C, using a BRUKER 500 MHz NMR spectrometer at VNU University of Science and TMS as internal standard and chemical shifts are given in parts per million (δ). Signal of the residual protons of the solvent (7.26 ppm for $CHCl_3$) was used as the reference in ^{1}H NMR spectra, while solvents signals (77.2 ppm for $CDCl_3$) was used as the reference in ^{13}C NMR spectra. Mass spectra were recorded on LTQ Orbitrap XL using electrospray ionization source and on instruments Finnigan MAT 95 XL (EI, ionizing energy 70 eV) at VNU University of Science.

Compound 2,6-bis(tosyloxymethyl)pyridine (**2**) was synthesized based on the method described earlier.[6]

*Synthesis of 2,6-bis[(2-acetophenyl)oxymethyl]pyridine (**3**).* A solution of 1.37 g (3.00 mmol) 2,6-bis(tosyloxymethyl)pyridine (**2**), 1.00 ml (8.30 mmol) 2'-hydroxyacetophenone and 2.00 g (14.50 mmol) K_2CO_3 in 10.00 ml acetonitrile was heated to reflux for 16 h. After that the mixture was cooled at ambient temperature, 500 ml ice water (0–4 °C) was added, then a slightly pink precipitate appeared. The precipitate was filtered by Buchner funnel, dried and recrystallized in ethanol to collect a white crystalline solid (**3**) (1.00 g, 88 %). M.p. 85–87 °C, R_f = 0.33 (*n*-hexane/ethyl acetate = 1/1). Found (%): C 73.83, H 5.34, N 3.53. Calcd. for $C_{23}H_{21}NO_4$ (%): C 73.58, H 5.64, N 3.73. LCMS (*m/z*): 376 $[M+H]^+$, 398 $[M+Na]^+$. IR (KBr) ν_{max} cm^{-1}: 1664 (C=O), 1595 (C=N), 1236 (C-O-C), 1450.47, 1485.19, 1595.13 ($C=C_{aryl}$). ^{1}H NMR (500MHz, $CDCl_3$, TMS) δ_H ppm: 2.67 (s, 6H, 2×CH_3); 5.31 (s, 4H, 2×-OCH_2-); 6.99 (d, 2H, J = 8.0 Hz, H^4, $H^{4'}$); 7.03 (t, 2H, J = 7.5 Hz, H^2, $H^{2'}$); 7.44 (t.d, 2H, J = 8.5 Hz, 2.0 Hz, H^3, $H^{3'}$); 7.74 (d.d, 2H, J = 8.0 Hz, 2.0 Hz, H^1, $H^{1'}$); 7.48 (d, 2H, J = 7.5 Hz, $H^{\beta}_{pyridine}$), 7.81 (t, 1H, J = 8.0 Hz, $H^{\gamma}_{pyridine}$).

*General method for synthesis of [γ-(phenyl)pyridino]dibenzodiazacrownophanes (**5a–f**).* Equimolar amounts of 2,6-bis[(2-acetophenyl)oxymethyl]pyridine (**3**) (0.5 g, 1.30 mmol), aromatic aldehyde (**4a-f**) [1.30 mmol, 0.177 g (**4a**), 0.177 g (**4b**), 0.196 g (**4c**), 0.159 g (**4d**), 0.241 g (**4e**), 0.146 g (**4f**)] and ammonium acetate (5.00 g, 65.00 mmol) were refluxed in acetic acid (10 ml) for 11 hours (the reaction was monitored by TLC). The mixture was allowed to cool to room temperature and neutralized with sodium carbonate solution; then, the product was extracted with ethyl acetate (4×30 ml), dried over Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*; the residue was first purified by column chromatography with a gradient elution of ethyl acetate/*n*-hexane affording the white solid which was then recrystallized from ethanol to obtain the pure azacrownophane product.

Table 1. Cytotoxicity on the human cancer cell lines.

No	R	n	Cell lines (IC_{50} – μg/ml)					
			RD	HepG2	MCF7	FL	PC3	Lu1
1	2-OH	1	1.89	–	–	–	N/A	N/A
2	4-Cl	1	1.46	2.79	4.56	1.51	N/A	N/A
3	3-Br	1	4.11	4.37	1.98	N/A	4.06	–
4	3-NO_2	1	–	–	4.78	N/A	–	–
5	4-Me	2	2.56	2.61	N/A	1.39	N/A	2.66
6	4-OH	2	6.89	7.96	N/A	6.74	N/A	6.95
7	2-OMe	2	7.53	6.59	N/A	–	N/A	7.90

All the compounds **5a-f** are new and their structures were characterized by usual spectroscopic methods.

*a) 25-(4-Methoxyphenyl)-8,16-dioxa-27,28-diazapentacyclo [21.3.1.1^{10,14}.0^{2,7}.0^{17,22}]octacosa-2,4,6,10,12,14,17,19,21,23,25,1(27)-dodecaene (**5a**).* Yield: 0.43 g (70 %), white crystals. M.p. 138–140 °C (from EtOH). R_f = 0.38 (EtOAc:MeOH = 5:1). HRMS (ESI) *m/z*: 473.1865 $[M+H]^+$. Calcd. for $C_{31}H_{25}N_2O_3^+$ *m/z*: 473.1860. IR (KBr) ν_{max} cm^{-1}: 1253 (C-O-C), 1444, 1597 (C=C_{aryl}). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ_H ppm: 3.85 (s, 3H, -OCH_3); 5.12 (s, 4H, 2×-OCH_2-); 6.95 (d, 2H, *J* = 9.0 Hz, H^A, $H^{A'}_{methoxyphenyl}$); 7.03 (d, 2H, *J* = 7.5 Hz, H_6, H_{18}); 7.07 (t.d, 2H, *J* = 7.5 Hz, 0.5 Hz, H_4, H_{20}); 7.16 (d, 2H, *J* = 8.0 Hz, H_5, H_{19}); 7.35–7.40 (m, 4H, H^{β}_{11}, H^{β}_{13}, H_3, H_{21}); 7.45 (s, 2H, H^{β}_{24}, H^{β}_{26}); 7.44 (m, 1H, H^{γ}_{12}); 7.61 (d, 2H, *J* = 8.5 Hz, H^B, $H^{B'}_{methoxyphenyl}$). ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ_c ppm: 55.35, 73.31, 114.31, 116.29, 120.73, 121.75, 121.99, 128.35, 129.40, 130.64, 130.75, 133.76, 136.41, 155.97, 156.64, 157.44.

*b) 25-(2-Methoxylphenyl)-8,16-dioxa-27,28-diazapentacyclo [21.3.1.1^{10,14}.0^{2,7}.0^{17,22}]octacosa-2,4,6,10,12,14,17,19,21,23,25,1(27)-dodecaene (**5b**).* Yield: 0.38 g (62 %), white crystals. M.p. 142–144 °C (from EtOH). R_f = 0.42 (EtOAc:MeOH = 5:1). LCMS *m/z*: 473 $[M+H]^+$. HRMS (ESI) *m/z*: 473.1320 $[M+H]^+$. Calcd. for $C_{31}H_{25}N_2O_3^+$ *m/z*: 473.1860. IR (KBr) ν_{max} cm^{-1}: 1244.09 (C-O-C), 1446.61, 1597.06 (C=C_{aryl}). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ_H ppm: 3.81 (s, 3H, -OCH_3); 5.13 (s, 4H, 2×-OCH_2-); 6.95 (d, 1H, *J* = 8.5 Hz, $H^{3'}_{methoxyphenyl}$); 7.00–7.07 (m, 5H, $H^{5'}_{methoxyphenyl}$, H_4, H_5, H_{19}, H_{20}); 7.15 (d, 2H, *J* = 8.5 Hz, H_6, H_{18}); 7.32–7.37 (m, 3H, H^{β}_{11}, H^{β}_{13}, $H^{4'}_{methoxyphenyl}$); 7.39–7.42 (m, 3H, H_3, H_{21}, $H^{6'}_{methoxyphenyl}$); 7.46 (t, 1H, *J* = 7.5 Hz, H^{γ}_{12}); 7.48 (s, 2H, H^{β}_{24}, H^{β}_{26}). ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ_c ppm: 55.58, 73.10, 111.33, 116.15, 120.93, 121.73, 121.89, 123.86, 128.01, 129.26, 129.75, 130.84, 130.91, 133.85, 136.38, 155.96, 156.55, 156.69.

*c) 25-(3-Nitrophenyl)-8,16-dioxa-27,28-diazapentacyclo [21.3.1.1^{10,14}.0^{2,7}.0^{17,22}]octacosa-2,4,6,10,12,14,17,19,21,23,25,1(27)-dodecaene (**5c**).* Yield: 0.48 g (74 %), white crystals. M.p. 249–250 °C (from EtOH). R_f = 0.50 (EtOAc:MeOH = 5:1). Found (%): C 73.63, H 4.54, N 8.55. Calcd. for $C_{30}H_{21}N_3O_4$ (%): C 73.91, H 4.34, N 8.62. LCMS *m/z*: 488 $[M+H]^+$. IR (KBr) ν_{max} cm^{-1}: 1251 (C-O-C), 1379, 1597 (C=C_{aryl}), 1503, 1398 (C-NO_2). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ_H ppm: 5.12 (s, 4H, 2×-OCH_2-); 7.03 (d, 2H, *J* = 8.0 Hz, H_6, H_{18}); 7.10 (t, 2H, *J* = 7.5 Hz, H_4, H_{20}); 7.20 (d, 2H, *J* = 8.0 Hz, H_5, H_{19}); 7.38–7.42 (m, 4H, H^{β}_{11}, H^{β}_{13}, H_3, H_{21}); 7.45 (t, 1H, *J* = 8.5 Hz, $H^5_{nitrophenyl}$); 7.53 (s, 2H, H^{β}_{24}, H^{β}_{26}); 7.63 (t, 1H, *J* = 8.0 Hz, H^{γ}_{12}), 8.00 (d, 1H, *J* = 7.5Hz, $H^6_{nitrophenyl}$); 8.27 (d, 1H, *J* = 8.0 Hz, $H^4_{nitrophenyl}$); 8.52 (s, 1H, $H^2_{nitrophenyl}$).

*d) 25-(4-Methylphenyl)-8,16-dioxa-27,28-diazapentacyclo [21.3.1.1^{10,14}.0^{2,7}.0^{17,22}]octacosa-2,4,6,10,12,14,17,19,21,23,25,1(27)-dodecaene (**5d**).* Yield: 0.45 g (76 %), white crystals. M.p. 158–160 °C (from EtOH). R_f = 0.24 (EtOAc:Aceton = 5:1). Found (%): C 81.83, H 5.16, N 6.35. Calcd. for $C_{31}H_{24}N_2O_2$ (%): C 81.56, H 5.30, N 6.14. HRMS (ESI) *m/z*: 457.1965 $[M+H]^+$, 479.1317 $[M+Na]^+$. Calc. for $C_{31}H_{25}N_2O_2^+$: 457.1911. IR (KBr) ν_{max} cm^{-1}: 1047, 1249 (C-O-C), 1448, 1597, (C=C_{aryl}). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ_H ppm: 2.32 (s, 3H, -CH_3); 5.05 (s, 4H, 2×-OCH_2-); 6.95–7.70 (m, 14H, H_{arom}); 7.41 (s, 2H, H^{β}_{24}, H^{β}_{26}); 7.90 (m, 1H, H^{γ}_{12}).

*e) 25-(3-Bromophenyl)-8,16-dioxa-27,28-diazapentacyclo [21.3.1.1^{10,14}.0^{2,7}.0^{17,22}]octacosa-2,4,6,10,12,14,17,19,21,23,25,1(27)-dodecaene (**5e**).* Yield: 0.41 g (60 %), white crystals. M.p. 205–207 °C (from EtOH). R_f = 0.36 (EtOAc:MeOH = 5:1). Found (%): C 68.87, H 4.35, N 5.68. Calcd. for $C_{30}H_{21}BrN_2O_2$ (%): C 69.11, H 4.06, N 5.37. LCMS *m/z*: 521 $[M+H]^+_{(Br=79)}$ and 523 $[M+H]^+_{(Br=79)}$. IR (KBr) ν_{max} cm^{-1}: 1051, 1245 (C-O-C), 1450, 1588 (C=C_{aryl}). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ_H ppm: 5.15 (s, 4H, 2×-OCH_2-); 7.07–7.62 (m, 15H, H_{arom}, H^{γ}_{12}); 7.83 (s, 2H, $H^{\beta}_{24,}$ H^{β}_{26}).

*f) 25-(2-Thienyl)-8,16-dioxa-27,28-diazapentacyclo[21.3.1.1^{10,14}.0^{2,7}.0^{17,22}]octacosa-2,4,6,10,12,14,17,19,21,23,25,1(27)-dodecaene (**5f**).* Yield: 0.45 g (77 %), white crystals. M.p. 158–160 °C (from EtOH). R_f = 0.23 (EtOAc). Found (%): C 75.23, H 4.34, N 6.56. Calcd. for $C_{28}H_{20}N_2O_2S$ (%): C 74.98, H 4.49, N 6.25. LCMS *m/z*: 449 $[M+H]^+$. IR (KBr) ν_{max} cm^{-1}: 1161, 1408, 1593 (C=C_{aryl}). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ_H ppm: 5.11 (s, 4H); 7.06 (d, 2H, *J* = 8.0 Hz, H_6, H_{18}); 7.16 (d, 2H, *J* = 8.0 Hz, H_5, H_{19}); 7.04–7.10 (m, 3$H_{thienyl}$); 7.36–7.46 (m, 7H, H_3, H_4, H_{20}, H_{21}, $H^{\beta}_{11,13}$, H^{γ}_{12}), 7.47 (s, 2H, $H^{\beta}_{24,26}$).

Cytotoxicity Assay

Five human cancer cell lines were obtained from the American Type Culture Collection (Manassas, VA) ATCC as FL (human cervix carcinoma), RD (human rhabdomyosarcoma), Lu1 (human lung adenocarcinoma), HepG2 (human hepatocellular carcinoma), MCF-7 (Human breast adenocarcinoma). The cells were grown in DMEM (Dulbecco's Modified Eagle Medium) supplemented with L-glutamine, Sodium pyruvate, $NaHCO_3$, PSF (Penicillin – Streptomycin sulfate – Fungizone); NAA (Non-Essential Amino Acids); 10 % BCS (Bovine Calf Serum). All incubations were performed at 37 °C for 72 hours in a CO_2 (5 %) incubator with the plates capped in the normal fashion.

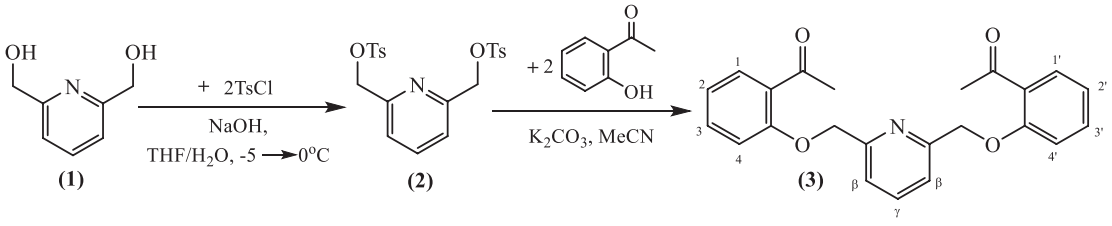
The MTT is based on the protocol described by Skehan & *etc*. (1990)[7] and Likhiwitayawuid & *etc*. (1993).[8] This method has worldwide application and recommended by National Cancer Institute (NCI) and College of Medicine, University of Illinois at Chicago for routine drug screening.

Results and Discussion

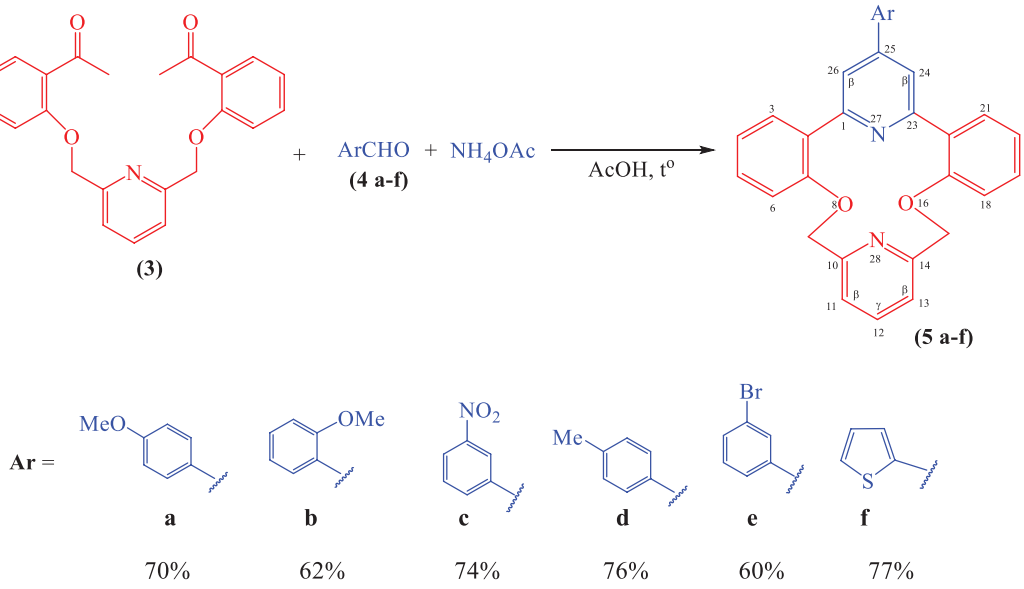
The parent compound (**3**) was effectively prepared from 2'-hydroxyacetophenone and 2,6-bis(tosyloxymethyl) pyridine (**2**) by using a known procedure[6] (Scheme 1).

The structure of 2,6-bis[(2-acetophenyl)oxymethyl] pyridine (**3**) was confirmed by IR and ^{1}H NMR spectra. More precise, IR spectrum showed a strong signal of C=O at 1664.57 cm^{-1}. In ^{1}H NMR spectrum, the product gave two sharp signals assignable to six protons of the methyl group at δ = 2.67 ppm (s, 6H, 2×CH_3) and to four protons of ether group at δ = 5.31 ppm (s, 4H, 2×-OCH_2-). Signals of eight protons of aromatic rings were corresponded to ABCD system at δ = 6.99–7.75 ppm and three signals of pyridine protons at δ = 7.48 ppm (2$H^{\beta}_{pyridine}$) and δ = 7.81 ppm ($H^{\gamma}_{pyridine}$).

In this study, we continue to develop new compounds possessing both the polysubstituted pyridine and ether frag-



Scheme 1. Synthesis of podand 2,6-bis[(2-acetophenyl)oxymethyl]pyridine (**3**).



Scheme 2. Synthesis of new [γ-(aryl)pyridino]dibenzo-27,28-diazacrownophanes (**5a-f**).

ments. The synthesis of novel dibenzodiazacrownophane with two pyridine subunits (**5a-f**), *via* a domino-type condensation of three components – 2,6-bis[(2-acetophenyl) oxymethyl]pyridine (**3**), benzaldehyde derivatives (**4a-f**) and ammonium acetate, is proposed (Scheme 2). The reactions take place with good yields 60–77 % depending on the type of starting benzaldehydes (**4a-f**) used in the reaction.

The structures of all synthesized compounds were confirmed by spectral data (IR, NMR and MS). All [γ-(aryl) pyridino]dibenzo-27,28-diazacrownophanes (**5a-f**) contained charactisitic peaks of singlet signal (4H, 2×-OCH_2-) in δ = 5.05–5.15 ppm region and singlet signal of two *β*-protons (H_{24}, H_{26}) in δ = 7.41–7.83 ppm region of the ^{1}H NMR spectrum. For example, the ^{1}H NMR spectrum of [γ-(4-methoxyphenyl)pyridino]dibenzo-27,28-diazacrownophane (**5a**) showed two singlets at δ = 3.85 ppm and 5.12 ppm which are assigned to the three protons of methyl groups (s, 3H, -OCH_3) and to the four protons of two methylene groups (s, 4H, 2×-OCH_2-), respectivelly. Two *β*-protons of γ-(methoxyphenyl)pyridine subunit (H_{24}, H_{26}) appeared as a singlet signal at 7.45 ppm in the ^{1}H NMR spectrum. The spectrum of ^{13}C NMR and HRMS (473.1865 $[M+H]^+$) also indicated the suitable structure of proposed [γ-(4-methoxyphenyl)pyridino]dibenzo-27,28-diazacrownophane (**5a**) (see Experimental part). Protons of methoxyphenyl fragment appears as two doublets in system AABB at δ = 6.95 ppm and 7.61 ppm.

PASS[6] was used to evaluate the general bioactivity potential of an organic drug-like molecule. Therefore, computer-aided drug discovery program was applied to predict the biological activities of synthesized compounds before *in vitro* testing (Table 2).

The selected synthesized compounds (**5a-c**) were evaluated *in vitro* for their biological activity against five human tumor cell lines: FL (human cervix carcinoma), RD (human rhabdomyosarcoma), Lu1 (human lung adenocarcinoma), HepG2 (human hepatocellular carcinoma) and MCF-7 (human breast adenocarcinoma). The bioactivities of synthesized compounds towards human cancer cell lines are shown in Table 3. Azacrown ether **5a** showed positive results in cytotoxicity test against HepG2, Lu1 and RD cell lines. The similar synthesized compound **5c** exhibited potent cytotoxicity only against HepG2 cell lines. Compound **5b** containing γ-(2-methoxyphenyl)pyridine showed significant activity against four cancer cell lines (HepG2, Lu1, RD and MCF-7). Based on these results,

Table 2. Prediction of several bioactivities of compounds (**5a-f**) by PASS program (Pa > 70 %).

Compound	Predicted activities	Pa (%)
5a	Aspulvinone dimethylallyltransferase inhibitor	87.5
	Gluconate 2-dehydrogenase (acceptor) inhibitor	83.2
	Nitrate reductase (cytochrome) inhibitor	74.7
	Chlordecone reductase inhibitor	72.5
	Taurine dehydrogenase inhibitor	72.2
	4-Nitrophenol 2-monooxygenase inhibitor	71.1
5b	Aspulvinone dimethylallyltransferase inhibitor	82.8
	Gluconate 2-dehydrogenase (acceptor) inhibitor	79.5
5c	Acrocylindropepsin inhibitor	78.9
	Chymosin inhibitor	78.9
	Saccharopepsin inhibitor	78.9
	Ubiquinol-cytochrome-c reductase inhibitor	75.9
	Hyponitrite reductase inhibitor	75.2
	Lysase inhibitor	70.3
5d	Nitrate reductase (cytochrome) inhibitor	84.1
	CYP2B5 substrate	73.6
	Aspulvinone dimethylallyltransferase inhibitor	74.2
	Membrane permeability inhibitor	71.2
5e	Aspulvinone dimethylallyltransferase inhibitor	85.2
5f	CYP2A6 inhibitor	73.5
	Anaphylatoxin receptor antagonist	74.4

Table 3. Cytotoxicity tests performed on compounds **5a-c** in human cancer cell lines.

Entry	Conc. (μg/ml)	Cell line, cell survival (%)					Conclusion
		HepG2	Lu1	RD	FL	MCF-7	
DMSO	0.5%	100	100	100	100	100	
Taxol (+)	5	3.46 ± 0.28	2.14 ± 0.3	3.28 ± 0.31	0	5.01 ± 0.95	
5a	10	48.63 ± 1.47	36.49 ± 1.33	47.21 ± 1.33	N/A	60.83 ± 1.26	+ (03 cell lines)
5b	10	32.23 ± 2.2	30.18 ± 2.24	12.01 ± 2.14	N/A	39.64 ± 2.78	+ (04 cell lines)
5c	10	35.69 ± 0.5	91.01 ± 1.3	51.95 ± 0.4	80.18±0.3	N/A	+ (01 cell lines)

Table 4. Results of IC_{50} test.

Entry	Cell lines IC_{50} (μg/ml)				Conclusion
	HepG2	Lu-1	RD	MCF-7	
Taxol (+)	0.275	0.48	0.25	0.47	+
5a	10.86	3.32	6.92	–	+ (03 cell lines)
5b	1.15	1.41	3.28	2.47	+ (04 cell lines)
5c	8.983	–	–	–	+ (01 cell lines)

[γ-(aryl)pyridino]dibenzo-27,28-diazacrownophanes (**5a-c**) were selected for further evaluation on IC_{50} test.

To investigate the effectiveness of **5a-c** in inhibiting cancer cell lines, inhibitory tests (IC_{50}) were conducted. The synthesized compound **5c** exhibited potent cytotoxicity against the HepG2 cell line with an IC_{50} value of 8.983 μg/ml (equivalent $18.44 \cdot 10^{-3}$ μM). The analogue **5a** inhibited the HepG2, Lu1 and RD cell lines with IC_{50} values of 10.86 μg/ml (equivalent $23.00 \cdot 10^{-3}$ μM), 3.32 μg/ml (equivalent $7.03 \cdot 10^{-3}$ μM), 9.92 μg/ml (equivalent $21.01 \cdot 10^{-3}$ μM), respectively. Azacrownophane **5b** showed the highest activity against all of four human cell lines in IC_{50} test with the value in the 1.15–3.28 μg/ml (equivalent $(2.44–6.95) \cdot 10^{-3}$ μM) (Table 4).

Conclusion

In conclusion, a number of [γ-(aryl)pyridino]dibenzo-27,28-diazacrownophanes containing two pyridine rings have been successfully synthesized through the domino one-pot reaction of a new parent compound 2,6-bis[(2-acetophenyl)oxymethyl]pyridine. Diazacrownophane **5b** showed significant cytotoxic activity against human cancer HepG2, Lu1, RD and MCF-7 cell lines whereas the similar synthesized compound **5a** possessed cytotoxicity against HepG2, Lu1, RD cell lines. Compound **5c** exhibited cytotoxicity only against HepG2 cell line.

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