Efficient hydrogenation of benzaldoximes and Schiff bases on ceramic high-porosity palladium catalysts

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An efficient catalytic method for the synthesis of benzyl- and dibenzylamines by hydrogenating oximes and Schiff bases was developed on palladium supported high-porosity foamed ceramic block catalyst. The multiple regeneration ability of the foamed ceramic block catalyst can significantly decrease the Pd consumption as compared to the use of the conventional 10%Pd/C catalyst. Owing to a high hardness of the foamed ceramic catalyst, the reaction mixture can rapidly be removed from the reactor without using filtering devices. The structures produced by the reaction are fragments of biologically active and natural molecules. Antiproliferative properties of dibenzylamines revealed on the sea urchin embryo model suggest that these compounds can be considered as promising agents for the design of new anticancer drugs.

Key words: hydrogenation, foamed ceramic Pd catalyst, oximes, benzylamines, polymethoxybenzenes, antiproliferative activity, sea urchin embryo.

Benzylamines (BAs) are the key fragments of many drugs, agrochemicals, and natural molecules and are often used in the modern organic chemistry.[1—5] A new class of psychotropic substances, *viz.*, NBOMes (*N*-benzyloxymethyl derivatives of phenylethylamines), has recently been prepared by the modification of amphetamines by the *N*-benzyl fragment. Three of NBOMes are proposed for application as legal controlled substances in many countries.[6—8]

Diverse methods for the preparation of BAs have been described, but the synthesis often gives a low yield or requires dangerous and expensive reagents. Serious attention is given to the development of selective methods for BAs synthesis. Their efficient synthesis by the reduction of benzonitriles has recently been described.[9] An original selective method for their preparation from benzyl alcohols using the redox process on the polymer resins is known.[10]

The hydrogenation of benzoic acid amines on Rh, Ru, and Pt with hydrogen as well as on Ir with triethylsilane or hydrides of aluminium and boron is also an efficient BA synthetic procedure.[11] An interesting method for the preparation of BAs by the amination of the side chain in alkylquinones has been developed.[12]

Numerous methods are known for the synthesis of BAs from the corresponding oximes (reduction with sodium amalgam, formates, zinc in acid, *etc.*), but the catalytic hydrogenation of benzaldoximes on the 10%Pd/C catalyst seems to be the most convenient and selective method for BAs preparation.[13] However, a substantial drawback of this procedure is a large consumption of Pd (~1 wt.% of the amount of the hydrogenated substrate) and its application for the only one reaction cycle, whereas the processes of Pd isolation and preparation of a new catalysts are fairly laborious.

The development of efficient, ecologically safe, universal, and scalable methods for the synthesis of BAs, which are appropriate for industry, is an urgent task.

Results and Discussion

Palladium containing highly hard support Sibunit is a convenient and efficient catalyst for the hydrogenation of complicated organic molecules. However, this catalyst must be filtered off from the reaction mixture and regenerated in a hydrogen flow before the next experiment.[14—16]

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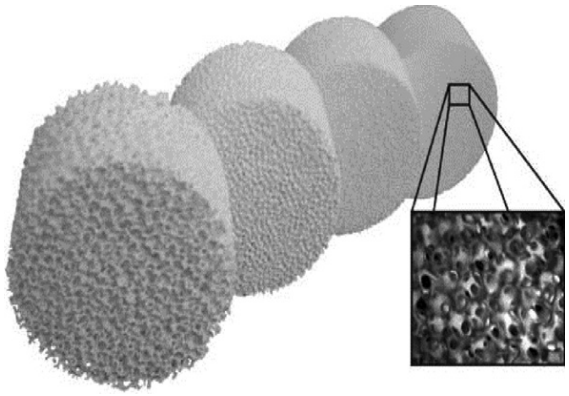


Fig. 1. High-porosity block foamed ceramic catalysts with the pore diameter to 1 mm.

The high-porosity foamed ceramic block catalysts with supported Pd turned out to be efficient catalytic systems for the hydrogenation of benzaldehyde oximes (Fig. 1). High-porosity ceramic catalysts become more and more popular owing to a wide choice of the structure and sizes, high surface, low hydraulic resistance, and high thermal and mechanical stability. Block foamed ceramic catalysts with the cellular structure (block-cellular) are promising systems in various liquid-phase catalytic syntheses of many organic compounds.[17—21]

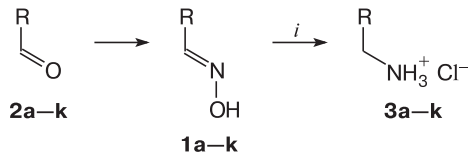
A block-cellular catalyst of this type can withstand multiple (up to 30—40 times) regenerations directly in the reactor at 400 °C after each procedure of hydrogenation without a significant activity loss. The reaction mixture can rapidly be removed from the reactor without using filtering devices due to a high porosity and hardness of the catalyst.

In this work, we first of all selected for hydrogenation benzaldehyde oximes (**1a**—**k**) with two to four methoxy groups in the benzene ring, namely, the fragments observed in numerous natural products (Scheme 1).

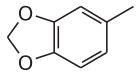
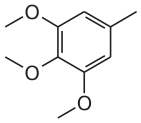
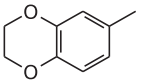
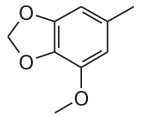
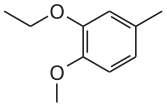
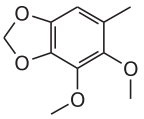
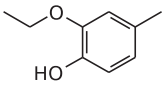
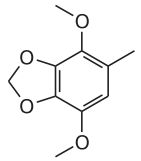
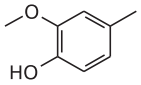
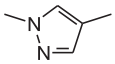
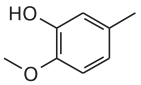
The oximes were almost quantitatively obtained from the corresponding benzaldehydes (**2a**—**k**) and hydroxylamine, and then they were selectively hydrogenated to BAs in methyl or isopropyl alcohol with the addition of aqueous HCl at ~20 °C and a pressure of 10 atm for 3—4 h under mild conditions. In the absence of hydrochloric acid, the yields decrease sharply because of the formation of by-products. The optimized yields and physicochemical parameters of the obtained BAs are presented in Table 1. The possibility to conduct 30—40 cycles of regeneration of the block catalyst enabled 150—200-fold reduction of Pd consumption compared to the use of the conventional 10%Pd/C catalyst.

The reaction was well reproduced at different concentrations and loadings of oxime (2—5%, 1—10 g). The change in hydrochloric acid concentration from 0.5 to 1.5% did not affect the reaction course. Minimum amounts of hydrochloric acid (5 mL of 36% HCl per 100 mL of MeOH) were needed to prepare hygroscopic pyrazolylamine (**3k**) in the crystalline form. Poorly soluble in methanol oximes (**3i**,**j**) were loaded into the reactor as suspensions. Over the reaction time oximes were gradually dissolved without decreasing the yield of the target BAs. For hydrogenation, methanol was successfully replaced by isopropyl alcohol, which was evaporated together with water as an azeotropic mixture.

Scheme 1



i. γ-Al_2O_3(6%)—Pd(2.1—2.4%), 10 atm, ~20 °C, 3—4 h, MeOH—HCl.

Compound **1—3**	R	Compound **1—3**	R
a		**g**	
b		**h**	
c		**i**	
d		**j**	
e		**k**	
f			

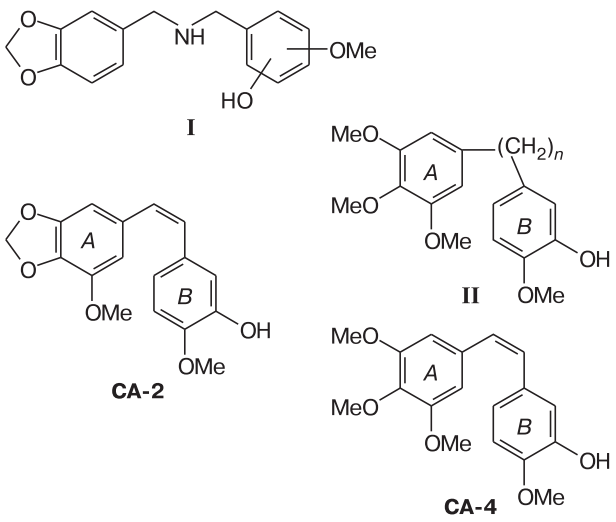
The obtained polymethoxybenzylamines (**3a**,**b**,**g**) can be used for the synthesis of drug analogs, namely, polymethoxydibenzylamines (DBAs) (**4a**—**g**), by hydrogenation on the high-porosity block catalysts. These structures possess diverse biological activity.[26] In particular, they are inhibitors of calcium channels[27] and suppress cell division.[28]

The simplified derivatives of alkaloid chelerythrine (**I**) were recently[29] obtained by the modification of the chelerythrine structure. They are shown to induce the dose-dependent arrest the cell cycle in the G0/G1 phase on the A549 and NCI-H1299 human cancer cells exhibiting a good therapeutic window compared to the initial alkaloid.

Table 1. Physicochemical parameters of benzylamines **3**

Compound	Yield (%)	M.p.*/°C	^{1}H NMR (δ, *J*/Hz)			
			NH_3^+	CH_2N^+	H_{Ar}	OAlk
3a	94	260—261 (260—263)[13]	—	—	—	—
3b	95	149—150 (148—150)[13]	—	—	—	—
3c	97	230—232	8.28 (br.s, 3 H)	3.76 (m, 2 H)	6.79—6.84 (m, 2 H); 7.06 (d, 1 H, *J* = 1.5)	1.19 (t, 3 H, CH_3, *J* = 7); 3.75 (s, 3 H, OCH_3); 3.88 (q, 2 H, CH_2, *J* = 7)
3d	98	221—223 (222—223)[22]	—	—	—	—
3e	76	221—222 (220—221)[23]	—	—	—	—
3f	96	190—191 (190—192)[24]	—	—	—	—
3g	99	209—212 (209—211)[24]	8.54 (br.s, 3 H)	3.94 (q, 2 H, *J* = 5.6)	6.93 (s, 2 H)	3.79 (s, 6 H, 2 OMe); 3.65 (s, 3 H, OMe)
3h	95	222—224 (222)[25]	8.49 (br.s, 3 H)	3.90 (br.s, 2 H)	6.79 (d, 1 H, *J* = 1.4); 6.92 (d, 1 H, *J* = 1.4)	3.83 (s, 3 H); 6.01 (s, 2 H, OCH_2O)
3i	93	145—150	8.32 (br.s, 3 H)	3.75 (s, 2 H)	6.81 (s, 1 H)	3.75 (s, 3 H); 3.94 (s, 3 H); 6.02 (s, 2 H, OCH_2O)
3j	92	237—238	8.27 (s, 3 H)	3.90 (s, 2 H)	6.86 (s, 1 H)	3.79 (s, 3 H); 3.90 (s, 3 H); 6.04 (s, 2 H, OCH_2O)
3k	81	173—177 (decomp.)	8.35 (s, 3 H)	3.87 (m, 2 H)	7.53 (s, 1 H); 7.80 (s, 1 H)	3.83 (s, 3 H, NCH_3)

* Literature data are given in parentheses.



Dibenzylamines **4a**—**g** can be considered as analogs of natural antimitotics combretastatins (**CA-2** and **CA-4**) with the triatomic binding unit between rings *A* and *B*. The replacement of the ethylene bridge in combretastatins by linkers of various length (one to four carbon atoms) (**II**) was reported. One of these compounds showed cytotoxicity comparable with that of natural combretastatin.[30]

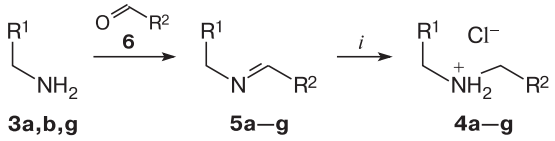
The syntheses of DBAs were carried out *via* the standard scheme by the condensation of BAs with benzaldehydes followed by hydrogenation (Scheme 2).[29] Intermediate Schiff bases (**5a**—**g**) were easily obtained by reflux of polymethoxybenzylamines (**3a**,**b**,**g**) and the corresponding benzaldehydes (**6**) in toluene with the simultaneous removal of water and without further purification were hydrogenated on the block high-porosity catalysts to DBAs **4a**—**g**. The yields and physicochemical parameters of the synthesized DBAs are presented in Table 2.

Unlike oxime hydrogenation, the addition of HCl to the reaction solution (Scheme 2) was not needed. The hydrogenation proceeded smoothly in both methanol and DMF. Usually the yields of DBA **4** in DMF were higher, as a rule, due to a higher solubility of the initial Schiff bases (**5**).

Biological assays. The ability of DBA **4** to suppress cell division was studied on a sea urchin *Paracentrotus lividus* embryo model according to the previously developed assay.[31] The assay provides rapid and simple evaluation of the antiproliferative activity of the tested molecules due to feasible artificial fertilization, rearing, and observation, as well as high permeability of eggs and embryos to various compounds. The frequent synchronous cell division, with the first mitotic cycle completion in 70—75 min post fertilization followed by blastomere cleavage every 35—40 min, makes it possible to monitor a test molecule effect during several successive cell cycles. The obtained effect-inducing threshold concentration, *C*/μmol L^{-1}, is presented below.

Compound	**4a**	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	**CA-2**	**CA-4**
*C**	4	>4	4	1	2	4	2	0.002	0.002

Scheme 2



i. γ-Al_2O_3(6%)—Pd(2.1—2.4%), 10 atm, ~20 °C, 2 h.

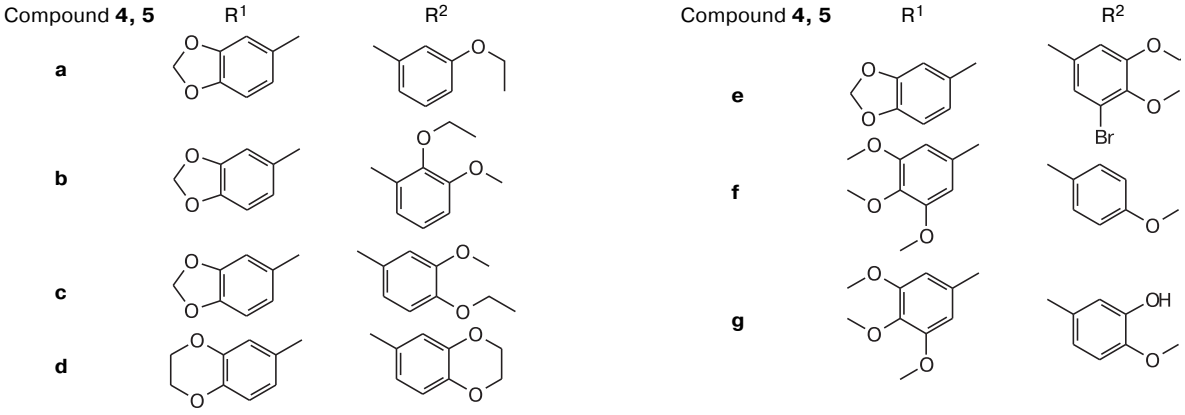


Table 2. Physicochemical parameters of dibenzylamines **4**

Compound	Yield (%)	M.p./°C	^{1}H NMR (δ, *J*/Hz)			
			NH_2^+	CH_2N^+	H_{Ar}	OAlk
4a	93	155—160	9.79 (br.s, 2 H)	3.99—4.06 (m, 4 H)	6.93—6.96 (m, 2 H); 7.02—7.03 (dd, 1 H, *J* = 2.7); 7.07(d, 1 H, *J* = 7.7); 7.22 (m, 2 H); 7.31 (t, 1 H, *J* = 8.0)	1.32 (t, 3 H, CH_3, *J* = 7.0); 4.02 (q, 2 H, CH_2, *J* = 7.0); 6.06 (s, 2 H, OCH_2O)
4b	87	143—147	9.58 (s, 2 H)	4.00 (br.s, 2 H); 4.07 (s, 2 H)	6.97—6.98 (m, 2 H); 7.08—7.12 (m, 2 H); 7.19—7.22 (m, 2 H)	1.14 (t, 3 H, CH_3, *J* = 7.0); 3.80 (s, 3 H, OCH_3); 3.93 (q, 2 H, CH_2, *J* = 7.0); 6.05 (s, 2 H, OCH_2O)
4s	88	166—171	9.71 (br.s, 2 H)	3.99—4.03 (m, 4 H)	6.93—6.95 (m, 2 H); 6.99—7.02 (m, 2 H); 7.22—7.32 (m, 2 H)	1.31 (t, 3 H, CH_3, *J* = 7.0); 3.78 (s, 3 H, OCH_3); 4.02 (q, 2 H, CH_2, *J* = 7.0); 6.05 (s, 2 H, OCH_2O)
4d	87	232—235	9.41 (br.s, 2 H)	3.98 (t, 4 H, *J* = 5)	6.89 (d, 2 H, *J* = 8); 6.95—6.97 (dd, 2 H, J_1 = 8.3, J_2 = 1.5); 7.08 (d, 2 H, *J* = 1.5)	4.25 (s, 8 H, OCH_2CH_2O)
4e	59	184—186	9.68 (s, 2 H)	4.05 (s, 4 H)	6.95 (d, 1 H, *J* = 8.0); 7.01 (d, 1 H, *J* = 8.0); 7.20 (s, 1 H); 7.35 (br.s, 1 H); 7.40 (br.s, 1 H)	3.74 (s, 3 H, OCH_3); 3.85 (s, 3 H, OCH_3); 6.05 (s, 2 H, OCH_2O)
4f	44	164—167	9.68 (br.s, 2 H)	4.03—4.06 (m, 4 H)	6.93 (s, 2 H); 6.98 (d, 2 H, *J* = 8.5); 7.49 (d, 2 H, *J* = 8.5)	3.66 (s, 3 H, OCH_3); 3.77 (s, 3 H, OCH_3); 3.79 (s, 6 H, 2 OCH_3);
4g	98	172—175	8.82 (s, 2 H)	3.73 (br.s, 4 H)	6.64 (s, 2 H); 6.70—6.84 (m, 3 H)	3.76 (s, 6 H, 2 OCH_3); 3.63 (s, 3 H, OCH_3); 3.58 (s, 3 H, OCH_3)

Thus, benzyl- and dibenzylamines can readily be obtained in large amounts by the hydrogenation of oximes and Schiff bases on the block high-porosity ceramic palladium catalysts. They possess antiproliferative properties and could be of interest for the development of new antitumor drugs.

Experimental

^{1}H NMR spectra were recorded on a Bruker DRX-500 spectrometer (working frequency 500.13 Hz, DMSO-d_6, Me_4Si as an internal standard). Mass spectra were detected on a Finnigan MAT INCOS 50 quadrupole mass spectrometer (direct injection, ionization energy 70 eV). Elemental analysis was carried out on a Perkin—Elmer 2400 automated C,H,N microanalyzer. TLC studies were conducted on the Merck $60F_{254}$ plates. Silica gel Acros 0.035-0.070 mm 60A was used for preparative chromatography. Melting points were determined on a Boetius heating stage and were not corrected.

Oximes of aromatic aldehydes **1a—k** were prepared according to earlier described procedures from the corresponding aldehydes and hydroxylamine, Compound **1a**, m.p. 104—105 °C (*cf.* Ref. 32: m.p. 106—107 °C); **1b**, m.p. 97—99 °C (*cf.* Ref. 32: m.p. 98—99 °C); **1c**, m.p. 97—98 °C *cf.* Ref. 33: m.p. 98 °C); **1d**, m.p. 104—106 °C (*cf.* Ref. 34: m.p. 106 °C); **1e**, m.p. 122—123 °C (*cf.* Ref. 35: m.p. 123—124 °C); **1f**, m.p. 140—141 °C (*cf.* Ref. 36: m.p. 142 °C); **1g**, m.p. 92—93 °C (*cf.* Ref. 37: m.p. 94—95 °C); **1h**, m.p. 158—159 °C (*cf.* Ref. 25: m.p. 159—160 °C); **1j**, m.p. 157—158 °C (*cf.* Ref. 38: m.p. 160 °C); **1k**, m.p. 78—80 °C (*cf.* Ref. 39: m.p. 80—81 °C).

3,4-Methylenedioxy-2,5-dimethoxybenzaldehyde oxime (1i). A 50% solution of NaCl (250 mmol) was rapidly added dropwise with stirring to a mixture of aldehyde (100 mmol), water (25 mL), ethanol (5 mL), ice (40 g), and hydroxylamine hydrosulfate (110 mmol). The temperature of the mixture was maintained within 20—25 °C by adding ice. The reaction mixture was stirred for 1 h, and then extracted with dichloromethane (2×100 mL). The aqueous layer was acidified to pH 6 by dropwise addition of concentrated HCl. The precipitated crystals were filtered off on a Büchner funnel, washed with distilled water (3×30 mL), and dried to a constant weight. The yield was 93%. M.p. 166—168 °C. Found (%): C, 56.83; H, 6.21; N, 6.65; O, 30.31. $C_{10}H_{13}NO_4$. Calculated (%): C, 56.86; H, 6.20; N, 6.63; O, 30.30. ^{1}H NMR, δ: 3.79 (s, 3 H, OMe); 3.84 (s, 3 H, OMe); 6.08 (s, 2 H, OCH_2O); 6.91 (s, H_{Ar}); 8.14 (m, 1 H, CHN); 11.11 (s, 1 H, NOH).

Hydrogenation in the liquid phase was conducted in a steel autoclave with the fluoroplastic bush in which the commercially available[40] block-cellular high-porosity catalyst was placed. A foamed ceramic material (α-Al_2O_3) coated with the γ-Al_2O_3 sol (porosity 70—95%) was used as a support. The support was impregnated with a $Pd(NO_3)_2$ solution and heated to 450 °C to coat the support with oxide PdO. Prior to hydrogenation, the catalyst was reduced to metallic Pd with hydrogen at 50—55 °C in an autoclave with the aim to obtain the 2.4%Pd/6%γ-Al_2O_3 catalyst. A such block of the catalyst can be regenerated with hydrogen 30—40 times without activity loss.

A block of the high-porosity block-cellular catalyst (2—4%Pd/6%γ-Al_2O_3, diameter 40 mm, height 50 mm, average pore diameter ~2 mm, block weight 31.6 g, porosity 70—95%) was fixed at the center of a cylindrical autoclave (internal diameter 50 mm) equipped with a thermocouple, an inlet tube for hydrogen supply, and heating jacket. The autoclave with the reaction mixture was stirred using a platform shaking device (capacity of 120—160 min^{-1}).

Hydrogenation of oximes 1a—k (general procedure). A solution of oxime **1a—k** (23 mmol) in isopropyl alcohol (100 mL) was loaded into the autoclave with the fluoroplastic bush, concentrated HCl (10.5 mL) was added, and a block of the regenerated catalyst was fixed. Hydrogenation was conducted for 3—5 h at ~20 °C and a hydrogen pressure of 10 atm, which was maintained at this level during the reaction. The reaction course was monitored by TLC. After the initial oxime disappeared completely, the reaction solution was poured out of the autoclave, the catalyst block was washed with methanol (3×30 mL), and the combined solutions were filtered from mechanical impurities. The solvent was evaporated, and analytically pure aromatic benzylamines **3a—k** were obtained.

When hydrogenation was conducted in methanol (100 mL), solvent removal was followed by drying residue using azeotropic distillation with isopropyl alcohol (2×50 mL). For the hydrogenation of compound **1k**, the reaction mixture was additionally purified by reflux with active carbon for 1 h. The block catalyst was regenerated directly in the reactor at 400 °C in a hydrogen flow and further used in the next hydrogenation procedure.

3,4-Methylenedioxybenzylamine hydrochloride (3a). The yield was 94%. M.p. 260—261 °C (*cf.* Ref. 13: m.p. 260—263 °C). Found (%): C, 51.26; H, 5.36; Cl, 18.86; N, 7.48; O, 17.03. $C_8H_{10}ClNO_2$. Calculated (%): C, 51.21; H, 5.37; Cl, 18.90; N, 7.47; O, 17.05.

3,4-Ethylenedioxybenzylamine hydrochloride (3b). The yield was 95%. M.p. 149—150 °C (*cf.* Ref. 13: m.p.148—150 °C). Found (%): C, 53.66; H, 5.99; Cl, 17.56; N, 6.94; O, 15.85. $C_9H_{12}ClNO_2$. Calculated (%): C, 53.61; H, 6.00; Cl, 17.58; N, 6.95; O, 15.87.

4-Methoxy-3-ethoxybenzylamine hydrochloride (3c). The yield was 97%. M.p. 230—232 °C. Found (%): C, 55.11; H, 7.42; Cl, 16.30; N, 6.44; O, 14.73. $C_{10}H_{16}ClNO_2$. Calculated (%): C, 55.17; H, 7.41; Cl, 16.29; N, 6.43; O, 14.70.

4-Hydroxy-3-ethoxybenzylamine hydrochloride (3d). The yield was 98%. M.p. 221—223 °C (*cf.* Ref. 22: m.p. 222—223 °C). Found (%): C, 53.02; H, 6.94; Cl, 17.43; N, 6.89; O, 15.72. $C_9H_{14}ClNO_2$. Calculated (%): C, 53.08; H, 6.93; Cl, 17.41; N, 6.88; O, 15.71.

4-Hydroxy-3-methoxybenzylamine hydrochloride (3e). The yield was 76%. M.p. 221—222 °C (*cf.* Ref. 23: m.p. 220—221 °C). Found (%): C, 50.72; H, 6.37; Cl, 18.67; N, 7.38; O, 16.86. $C_8H_{12}ClNO_2$. Calculated (%): C, 50.67; H, 6.38; Cl, 18.69; N, 7.39; O, 16.87.

3-Hydroxy-4-methoxybenzylamine hydrochloride (3f). The yield was 96%. M.p. 190—191 °C (*cf.* Ref. 24: m.p. 190—192 °C). Found (%): C, 50.72; H, 6.37; Cl, 18.67; N, 7.38; O, 16.86. $C_8H_{12}ClNO_2$. Calculated (%): C, 50.67; H, 6.38; Cl, 18.69; N, 7.39; O, 16.87.

3,4,5-Trimethoxybenzylamine hydrochloride (3g). The yield was 99%. M.p. 209—211 °C (*cf.* Ref. 24: m.p. 209—211 °C). Found (%): C, 51.45; H, 6.89; Cl, 15.15; N, 5.98; O, 20.53. $C_{10}H_{16}ClNO_3$. Calculated (%): C, 51.40; H, 6.90; Cl, 15.17; N, 5.99; O, 20.54.

3-Methoxy-4,5-methylenedioxybenzylamine hydrochloride (3h). The yield was 95%. M.p. 222—224 °C (*cf.* Ref. 25: m.p. 222 °C). Found (%): C, 49.62; H, 5.57; Cl, 16.31; N, 6.43;

O, 22.06. $C_9H_{12}ClNO_3$. Calculated (%): C, 49.67; H, 5.56; Cl, 16.29; N, 6.44; O, 22.05.

2,3-Dimethoxy-4,5-methylenedioxybenzylamine hydrochloride (3i). The yield was 93%. M.p. 145—150 °C. Found (%): C, 48.52; H, 5.65; Cl, 14.33; N, 5.65; O, 25.84. $C_{10}H_{14}ClNO_4$. Calculated (%): C, 48.48; H, 5.66; Cl, 14.34; N, 5.66; O, 25.86.

2,5-Dimethoxy-3,4-methylenedioxybenzylamine hydrochloride (3j). The yield was 92%. M.p. 237—238 °C. Found (%): C, 48.44; H, 5.71; Cl, 14.33; N, 5.65; O, 25.85. $C_{10}H_{14}ClNO_4$. Calculated (%): C, 48.49; H, 5.70; Cl, 14.31; N, 5.66; O, 25.84.

(1*N*-Methylpyrazol-4-yl)methanamine (3k) was purified additionally with active carbon. The yield was 71%. M.p. 173—177 °C (with decomp.). Found (%): C, 54.14; H, 8.08; N, 37.76. $C_5H_9N_3$. Calculated (%): C, 54.03; H, 8.16; N, 37.81.

Synthesis of Schiff bases (5a—g) from benzylamines (3a,b,g) and benzaldehydes (general procedure). A solution of benzylamine **3a,b,g** (4 mmol) and the corresponding aldehyde (4 mmol) in toluene (50 mL) was refluxed under argon in a flask with a drying column filled with sodium sulfate. The solvent was evaporated on a rotary evaporator, and the residue was kept for 14 h in a refrigerator. The precipitated crystals (or yellow oil) were washed with hexane and then hydrogenated without further purification.

Synthesis of dibenzylamines (4a—g) (general procedure). A solution of the Schiff base (2.6 mmol) in DMF (85 mL) and the catalyst block were loaded into an autoclave with the fluoroplastic bush. Hydrogenation was carried out for 3—5 h at ~20 °C and a hydrogen pressure of 10 atm, which was maintained during the reaction. The reaction course was monitored by TLC. After the complete disappearance of the initial Schiff base, the reaction solution was poured out of the autoclave, the catalyst block was washed with DMF (3×30 mL), the combined solutions were filtered from mechanical impurities, and the solvent was evaporated on a rotary evaporator.

***N*-(3-Ethoxybenzyl)-3,4-methylenedioxybenzylamine hydrochloride (4a).** The yield was 93%. M.p. 155—160 °C. Found (%): C, 63.49; H, 6.25; Cl, 11.01; N, 4.34; O, 14.91. $C_{17}H_{20}ClNO_3$. Calculated (%): C, 63.45; H, 6.26; Cl, 11.02; N, 4.35; O, 14.92. MS, m/z (I_{rel} (%)): 285 $[M]^+$ (6), 151 (10), 150 (100), 137 (9), 136 (90), 135 (83), 108 (26), 107 (15), 106 (7), 105 (6), 91 (5).

***N*-(3-Methoxy-2-ethoxybenzyl)-3,4-methylenedioxybenzylamine hydrochloride (4b).** The yield was 87%. M.p. 143—147 °C. Found (%): C, 61.38; H, 6.31; Cl, 10.11; N, 3.99; O, 18.20. $C_{18}H_{22}ClNO_4$. Calculated (%): C, 61.45; H, 6.30; Cl, 10.08; N, 3.98; O, 18.19. MS, m/z (I_{rel} (%)): 315 $[M]^+$ (6), 180 (22), 166 (20), 165 (7), 164 (7), 152 (10), 151 (9), 150 (79), 149 (11), 137 (19), 136 (22), 135 (100), 122 (15), 121 (8), 107 (6), 106 (7), 105 (8), 93 (6), 91 (6).

***N*-(3-Methoxy-4-ethoxybenzyl)-3,4-methylenedioxybenzylamine hydrochloride (4c).** The yield was 88%. M.p. 166—171 °C. Found (%): C, 61.51; H, 6.29; Cl, 10.06; N, 3.97; O, 18.17. $C_{18}H_{22}ClNO_4$. Calculated (%): C, 61.45; H, 6.30; Cl, 10.08; N, 3.98; O, 18.19. MS, m/z (I_{rel} (%)): 315 $[M]^+$ (10), 180 (40), 166 (42), 165 (16), 162 (8), 152 (6), 151 (9), 150 (55), 138 (15), 137 (49), 136 (37), 135 (100), 123 (7), 122 (10), 121 (6), 106 (10), 105 (9), 94 (6), 93 (6).

***N*-(3,4-Ethylenedioxy)-3,4-ethylenedioxybenzylamine hydrochloride (4d).** The yield was 87%. M.p. 231—235 °C. Found (%): C, 61.76; H, 5.77; Cl, 10.14; N, 4.01; O, 18.32. $C_{18}H_{20}ClNO_4$. Calculated (%): C, 61.80; H, 5.76; Cl, 10.13; N, 4.00; O, 18.30. MS, m/z (I_{rel} (%)): 313 $[M]^+$ (27), 312 (14), 311 (31), 176 (63), 165 (29), 164 (100), 163 (13), 162 (9), 161 (8), 151 (23), 150 (61), 149 (66), 137 (23), 136 (11), 135 (10), 134 (10), 123 (85), 121 (11), 119 (5), 109 (12), 108 (18), 107 (14), 106 (19), 105 (48), 101 (6), 95 (10), 94 (46), 93 (15), 92 (8), 91 (15).

N*-(3-Bromo-4,5-dimethoxybenzyl)-3,4- methylenedioxybenzylamine hydrochloride (4e).** The yield was 59%. M.p.184—186 °C. Found (%): C, 49.05; H, 4.59; Br, 19.17; Cl, 8.50; N, 3.35; O, 15.35. $C_{17}H_{19}BrClNO_4$. Calculated (%): C, 49.00; H, 4.60; Br, 19.18; Cl, 8.51; N, 3.36; O, 15.36. MS, m/z (I_{rel} (%)): 381 $[M]^+$ (7), 379 (9), 246 (13), 244 (15), 232 (23), 231 (23), 230 (26), 229 (22), 185 (5), 162 (6), 152 (5), 151 (45), 150 (75), 149 (14), 148 (14), 136 (31), 135 (100), 122 (6), 121 (9), 120 (8), 106 (8), 105 (14), 92 (5).N*-(3,4,5-Trimethoxybenzyl)-4-methoxybenzylamine hydrochloride (4f).** The yield was 44%. M.p. 164—167 °C. Found (%): C, 61.11; H, 6.83; Cl, 10.01; N, 3.97; O, 18.08. $C_{18}H_{24}ClNO_4$. Calculated (%): C, 61.10; H, 6.84; Cl, 10.02; N, 3.96; O, 18.09. MS, m/z (I_{rel} (%)): 317 $[M]^+$ (11), 183 (11), 182 (100), 181 (28), 167 (21), 151 (25), 148 (8), 139 (5), 137 (7), 136 (40), 122 (7), 121 (55).

***N*-(3,4,5-Trimethoxybenzyl)-4-methoxy-3-hydroxybenzylamine hydrochloride (4g).** The yield was 98%. M.p. 172—175 °C. Found (%): C, 58.41; H, 6.55; Cl, 9.60; N, 3.80; O, 21.64. $C_{18}H_{24}ClNO_5$. Calculated (%): C, 58.46; H, 6.54; Cl, 9.59; N, 3.79; O, 21.63. MS, m/z (I_{rel} (%)): 333 $[M]^+$ (39), 316 (8), 210 (5), 197 (5), 196 (26), 182 (100), 181 (46), 168 (5), 167 (18), 166 (8), 153 (6), 152(27), 151 (22), 150 (6), 148 (7), 139 (6), 138 (14), 137 (57), 136 (6), 124 (6), 123 (6), 122 (10), 109 (5), 94 (9).

Study of the antiproliferative activity of compounds on a sea urchin embryo model.[31] Experiments were carried out at the Biological Laboratory of the N. K. Koltzov Institute of Developmental Biology (Russian Academy of Sciences) in Cyprus. Adult sea urchins, *Paracentrotus lividus* L. (Echinidae, Echinodermata), were collected in the coastal area and kept in an aerated seawater tank. Spawning was triggered by intracoelomic injection of 0.5 *M* KCl (1—2 mL). The resulting eggs were washed with seawater filtered through a nylon filter and then fertilized by adding drops of diluted sperm. The embryos (600—2000 unit mL^{-1}) were incubated in filtered seawater at room temperature (18—23 °C) until thew beginning of active feeding (36—40 h, mid-pluteus 2) under gentle agitation with a motor-driven plastic paddle (60 rpm).

The stock solutions of chemical compounds were prepared in DMSO followed by a 10-fold dilution with 96% ethanol. The solubility of the test compounds was monitored using an MBS-10 stereomicroscope. Combretastatins **CA-2** and **CA-4** synthesized according to the described procedure[41] were used as a positive control.

The compounds were tested in six-well cultural plates at 8—14 min post fertilization. An egg suspension (5 mL) was placed in each well, and the corresponding volume of a solution of the test compound was added to achieve the required final concentration. The maximum concentration of the solvent did not exceed the maximum tolerated one (1% for ethanol and 0.05% for DMSO). The two-fold decreasing concentrations of compounds were used until the effect disappeared. The antiproliferative activity of test molecules was assessed by the lowest (threshold) effective concentration altering fertilized eggs cleavage. The observations were carried out with a Biolam LOMO optical microscope (St. Petersburg).

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