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SYNTHESIS AND CYTOTOXICITY OF *N*-(3,4-DIMETHOXYPHENYL)ETHYLAMIDES OF *N*-BENZOYL-α-AMINO ACIDS

D. B. Tukhtaev,[1*] A. Sh. Saidov,[1] M. Alimova,[1]
E. O. Terent′eva,[2] Z. S. Khashimova,[2]
Sh. S. Azimova,[2] and V. I. Vinogradova[2]

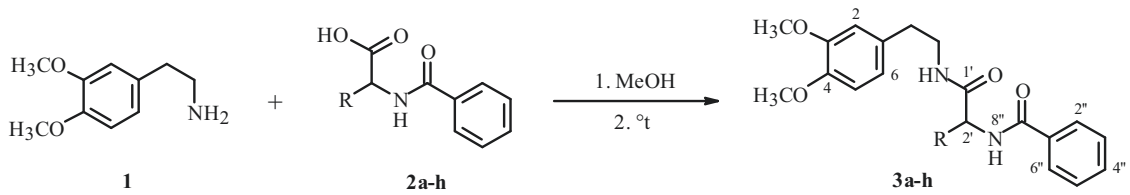
Amides were synthesized from N*-benzoyl aliphatic* α*-amino acids and homoveratrylamine and screened for cytotoxicity.*

Keywords: α-amino acids, Schotten–Baumann method, *N*-benzoyl α-amino acid derivatives, homoveratrylamine, amides, cytotoxicity.

The development of efficient approaches to the design of biologically active compounds is a high-priority problem for medicinal chemistry. Amino acids are highly interesting in the search for potential medicines [1].

Amino acids are bifunctional compounds with relatively low toxicities and convenient starting materials for synthesizing a variety of derivatives from the amine and carboxylic acid. They are used for introduction of pharmacophores into synthetic molecules [2–8] and total synthesis of heterocycles, which create novel promising medicines [9].

Amides are fundamental chemical structural units, are used widely in synthesis to form amines, and have important applications [10]. It seemed interesting to us to use *N*-[2-(3,4-dimethoxypheny)ethyl]amides of α-amino-acid benzoyl derivatives as synthons for various heterocyclic compounds. Therefore, the reactions of 3,4-dimethoxyphenylethylamine (**1**, homoveratrylamine) and *N*-substituted α-amino acids **2a**–**h** were studied.



1 **2a-h** **3a-h**

R = H (**a**); CH_3 (**b**) CH_2CH_3 (**c**); $CH_2CH_2CH_3$ (**d**); $CH(CH_3)CH_3$ (**e**); $CH_2(CH_2)_2CH_3$ (**f**); $CH(CH_3)CH_2CH_3$ (**g**); $CH_2CH(CH_3)_2$ (**h**)

Simple and inexpensive methods for synthesizing amides over broad scales in addition to methods for producing amides of amino acids requiring further activation of the carboxylic acids [11, 12] or the use of catalysts [13] were developed. However, they had certain limitations because of side reactions at high temperatures [14]. Problems associated with possible transformation upon heating of α-amino acids into diketopiperazines by formation of intra-amide bonds were eliminated by producing α-amino-acid *N*-benzoyl derivatives **2a**–**h** using the Schotten–Baumann method [15–18].

A distinctive feature of the previous condensation of **1** with mono- and dibasic carboxylic acids [19, 20] was the heating of not a mixture of compounds but of a salt prepared beforehand in one pot. The high yields of amides and simplicity of this method were reproduced in reactions of **1** with α-amino-acid *N*-benzoyl derivatives **2a**–**h** to afford amides **3a**–**h** in 69–88% yields.

1) Samarkand State University, Samarkand, Uzbekistan, e-mail: davlatuzb@mail.ru; 2) S. Yu. Yunusov Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan. Translated from *Khimiya Prirodnykh Soedinenii*, No. 4, July–August, 2019, pp. 597–600. Original article submitted January 28, 2019.

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TABLE 1. Cytotoxicity of Amides **3a**–**h** 24 h After Administration

Compound	Cell growth inhibition, %			
	HeLa (n=8)		HEp-2 (n=4)	
	100 μM	10 μM	100 μM	10 μM
Cisplatin	90.2 ± 5.6	34.7 ± 3.4	74.4 ± 4.1	17.9 ± 2.0
3a	21.2 ± 1.2	19.1 ± 1.3	38.6 ± 3.4	17.4 ± 2.0
3c	8.8 ± 0.8	0.0 ± 0.0	15.4 ± 2.1	4.5 ± 1.1
3d	12.1 ± 2.3	4.0 ± 0.2	36.8 ± 5.2	19.5 ± 2.6
3e	40.7 ± 2.8	0.0 ± 0.0	24.6 ± 3.7	6.1 ± 0.6
3f	9.8 ± 0.6	0.0 ± 0.0	48.7 ± 3.6	27.7 ± 3.4
3g	15.4 ± 1.2	0.0 ± 0.0	24.1 ± 1.8	16.3 ± 0.9
3h	13.0 ± 0.9	9.5 ± 0.7	47.9 ± 3.8	31.3 ± 3.1

The structures of the synthesized amides were studied using IR and PMR spectroscopy. IR spectra of the products exhibited absorption bands at 1651–1666 cm^{-1} and 1628–1635 cm^{-1} for two carbonyl $\nu_{C=O}$ groups, the intensity of which was greater than that of aromatic-ring absorption bands at 1566–1611 cm^{-1}, and strong N–H bands at 3328–3430 and 3229–3305 cm^{-1}.

PMR spectra of amides **3a**–**h** showed that the α-methylene resonances appeared as a 2H triplet at δ 2.68–2.71 ppm; β-methylene, as 1H multiplets 3.39 and 3.53. Methoxyl protons resonated as singlets at 3.74–3.76 and 3.76–3.78 ppm. The aromatic region had three resonances characteristic of a 1,3,4-substituted aromatic ring. Thus, H-6 was observed as a doublet of doublets at δ 6.64–6.68 ppm; H-2 and H-5, as doublets at 6.61–6.67 and 6.65–6.73. Also, resonances of the benzoyl aromatic ring and characteristic resonances of NH-β and NH-groups of amino acids appeared at 6.25–6.67 and 6.69–7.21 ppm.

Doubled resonances of H-2′ [δ 4.36 (0.46H, dd, J = 1.2, 7.4), 4.47 (0.51H, dd, J = 2.5, 6.2)] and amino-acid NH [δ 6.77 (0.51H, d, J = 8.4), 6.83 (0.49H, d, J = 8.3)] were obtained in **3g** with two asymmetric C atoms (C-2′ and C-3′).

The PASS program predicted that **3a**–**h** would probably exhibit ataractic activity and stimulate serotonin release and could be used to treat muscular dystrophy and to prevent precancerous conditions.

Cytotoxicity studies of **3a** and **3c**–**h** showed that human epithelial type 2 (HEp-2) laryngeal adenocarcinoma cells were more sensitive to the amides than HeLa cervical carcinoma cells (Table 1). Amides **3f** and **3h** at 100 μM were most active and inhibited growth of HEp-2 cells by 48.7 ± 3.6% and 47.9 ± 3.8% vs. the control. The inhibitory effects of these compounds fell to 27.7 ± 3.4% and 31.3 ± 3.1% if the concentration was reduced to 10 μM. However, they were greater than that of the reference drug cisplatin, which inhibited growth of HEp-2 cells by only 17.9 ± 2.0% under analogous conditions.

Amide **3e** at 100 μM was the only compound exhibiting cytotoxicity against HeLa cells (40.7 ± 2.8%). However, the value against HEp-2 cells was only 24.6 ± 3.7%.

Thus, heating salts of *N*-benzoyl-α-aliphatic amino acids and homoveratrylamine prepared beforehand in one pot gave in 69–88% yields amides **3a**–**h**, which inhibited growth of HEp-2 cells to various degrees.

EXPERIMENTAL

IR spectra were recorded from KBr pellets on a System 2000 FTIR instrument (PerkinElmer). PMR spectra were recorded in $CDCl_3$ with HMDS internal standard on a Unity-400+ Varian spectrometer (400 MHz). R_f values were determined on LSL_{254} silica gel plates (5/40 μm) using $CHCl_3$–MeOH (8:1). Melting points of synthesized compounds were determined on a Stuart SMP10 Melting Point Apparatus.

Benzoyl derivatives of amino acids were prepared by the literature method [15–18] to afford *N*-benzoyl-DL-glycine (**2a**), mp 186–188°C (lit. mp 192°C [15] and 188–191°C [16]); *N*-benzoyl-DL-alanine (**2b**), mp 139–142°C; *N*-benzoyl-α-aminobutyric acid (**2c**); *N*-benzoyl-DL-norvaline (**2d**), mp 154–156°C (lit. mp 152–154°C [15]); *N*-benzoyl-L-valine (**2e**), mp 130–132°C (lit. mp 132–134°C [15]); *N*-benzoyl-DL-norleucine (**2f**), mp 136–137°C [15]; *N*-benzoyl-DL-leucine (**2g**), mp 135–137°C (lit. mp 138°C [18]); and *N*-benzoyl-DL-isoleucine (**2h**), mp 127–129°C (lit. mp 35–136°C [16]).

General Method for Synthesizing Amides 3a–h. Equimolar amounts of homoveratrylamine (**1**) and *N*-benzoylamino acids (**2a**–**h**) were dissolved in a sufficient volume (1–2 mL) of MeOH to complete salt formation. The resulting salt was

heated at 175–178°C on a glycerin bath for 2–4 h. The course of the reaction was monitored using TLC. The mixture was dissolved in $CHCl_3$, extracted with HCl (3%) and NaOH (2%), washed with distilled H_2O until neutral, and evaporated. The solid was worked up with Me_2CO. The resulting precipitate was filtered off.

α-Benzoylamino-*N*-[2-(3,4-dimethoxyphenyl)ethyl]acetamide (3a), $C_{19}H_{22}N_2O_4$, was prepared from homoveratrylamine (0.4 g, 2.2 mmol) and 2-benzamidoethanoic acid (0.4 g, 2.23 mmol). Yield 88% (0.66 g), mp 92–94°C (Me_2CO), R_f 0.64. IR spectrum (ν, cm^{-1}): 3323, 3297 (NH), 3075, 2932, 2835 (Ar-CH), 1672, 1633 (N-C=O), 1547, 1517. ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.71 (2H, t, J = 7.1, H-α), 3.46 (2H, q, J = 7, H-β), 3.7 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.01 (2H, d, J = 5.1, H-2′), 6.56 (1H, t, J = 5.7, NH-β), 6.62–6.67 (3H, m, Ar-2, 5, 6), 7.21 (1H, t, J = 4.7, NH-8″), 7.37 (2H, t, J = 7.7, H-3″, 5″), 7.46 (1H, tt, J = 2.2, 7.5, H-4″), 7.74 (2H, dd, J = 1.4, 7.0, H-2″, 6″). ^1H NMR spectrum (400 MHz, CD_3OD, δ, ppm, J/Hz): 2.67 (2H, t, J = 7.3, H-α), 3.36 (2H, t, J = 7.4, H-β), 3.69 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.92 (2H, s, H-2′), 6.67 (1H, dd, J = 1.9, 8.1, H-6), 6.73 (1H, d, J = 8.1, H-5), 6.77 (1H, d, J = 1.9, H-2), 7.41 (2H, t, J = 7.7, H-3″, 5″), 7.49 (1H, tt, J = 2.1, 7.8, H-4″), 7.80 (2H, dd, J = 1.4, 7.7, H-2″, 6″). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 35.35 (C-α), 41.08 (C-β), 44.03 (C-2′), 55.00 (OCH_3), 56.03 (OCH_3), 111.42 (C-2), 111.96 (C-5), 120.83 (C-6), 127.31 (C-2″, 6″), 128.82 (C-3″, 5″), 131.22 (C-4), 132.13 (C-4″), 133.56 (C-1″), 147.84 (C-4), 149.17 (C-4), 167.96, 169.17 (C=O).

α-Benzoylamino-*N*-[2-(3,4-dimethoxyphenyl)ethyl]propionamide (3b), $C_{20}H_{24}N_2O_4$, was prepared from homoveratrylamine (0.5 g, 2.76 mmol) and 2-benzamidopropanoic acid (0.54 g, 2.8 mmol). Yield 71.5% (0.703 g), mp 121–123°C (Me_2CO), R_f 0.69. IR spectrum (ν, cm^{-1}): 3417, 3317 (NH), 3070, 2931, 2834 (Ar-CH), 1662, 1634 (N-C=O), 1547, 1519. ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.39 (3H, d, J = 6.9, H-3′), 2.70 (2H, t, J = 7.1, H-α), 3.44 (2H, m, H-β), 3.74 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.62 (1H, td, J = 1.7, 7.2, H-2′), 6.61 (1H, d, J = 1.7, H-2), 6.63 (1H, dd, J = 1.8, 7.9, H-6), 6.65 (1H, d, J = 8, H-5), 6.66 (1H, br.s, NH-β), 6.96 (1H, d, J = 7.3, NH-8″), 7.36 (2H, t, J = 8.2, H-3″, 5″), 7.45 (1H, tt, J = 2, 7.5, H-4″), 7.71 (2H, dt, J = 1.4, 8.2, H-2″, 6″).

α-Benzoylamino-*N*-[2-(3,4-dimethoxyphenyl)ethyl]butyramide (3c), $C_{21}H_{26}N_2O_4$, was prepared from homoveratrylamine (0.7 g, 3.86 mmol) and 2-benzamidobutanoic acid (0.801 g, 3.87 mmol). Yield 75.5% (1.08 g), mp 132–134°C (Me_2CO), R_f 0.79. IR spectrum (ν, cm^{-1}): 3468, 3414, 3296 (NH), 3072, 2927, 2871 (Ar-CH), 1652, 1628 (N-C=O), 1544, 1529. ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.86 (3H, t, J = 7.4, H-4′), 1.67 (1H, m, H-3′a), 1.87 (1H, m, H-3′b), 2.70 (2H, t, J = 7.2, H-α), 3.39 (1H, m, H-β), 3.50 (1H, m, H-β), 3.74 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 4.55 (1H, q, J = 7.7, H-2′), 6.62 (1H, d, J = 1.9, H-2), 6.64 (1H, d, J = 7.4, H-5), 6.66 (1H, dd, J = 1.8, 7.4, H-6), 6.89 (1H, t, J = 6.3, NH-β), 7.10 (1H, d, J = 8, NH-8″), 7.35 (2H, t, J = 7.2, H-3″, 5″), 7.43 (1H, tt, J = 1.3, 7.5, H-4″), 7.73 (2H, dd, J = 1.4, 7.2, H-2″, 6″).

α-Benzoylamino-*N*-[2-(3,4-dimethoxyphenyl)ethyl]valeramide (3d), $C_{22}H_{28}N_2O_4$, was prepared from homoveratrylamine (0.6 g, 3.3 mmol) and 2-benzamidopentanoic acid (0.734 g, 3.3 mmol). Yield 77.4% (0.986 g), mp 107–110°C (Me_2CO), R_f 0.74. IR spectrum (ν, cm^{-1}): 3305 (NH), 3076, 2924, 2870 (Ar-CH), 1653, 1629 (N-C=O), 1549, 1529. ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.84 (3H, t, J = 7.4, H-5′), 1.28 (2H, q, J = 8, H-4′), 1.61 (1H, m, H-3′), 1.80 (1H, m, H-3′), 2.70 (2H, t, J = 7, H-α), 3.41 (1H, m, H-β), 3.50 (1H, m, H-β), 3.76 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 4.52 (1H, q, J = 7.5, H-2′), 6.41 (1H, br.s, NH-β), 6.62 (1H, d, J = 1.8, H-2), 6.65 (1H, d, J = 8.0, H-5), 6.67 (1H, dd, J = 8.7, 1.8, H-6), 6.81 (1H, d, J = 8, NH-8″), 7.37 (2H, t, J = 7.6, H-3″, 5″), 7.45 (1H, tt, J = 2.1, 7.4, H-4″), 7.71 (2H, dt, J = 7.1, 1.5, H-2″, 6″).

α-Benzoylamino-β-methyl-*N*-[2-(3,4-dimethoxyphenyl)ethyl]butyramide (3e), $C_{22}H_{28}N_2O_4$, was prepared from homoveratrylamine (0.65 g, 3.6 mmol) and 2-benzamido-3-methylbutanoic acid (0.8 g, 3.6 mmol). Yield 80% (1.1 g), mp 164–166°C (Me_2CO), R_f 0.77. IR spectrum (ν, cm^{-1}): 3304 (NH), 3073, 2959, 2862 (Ar-CH), 1652, 1631 (N-C=O), 1545, 1523. ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.90 (6H, dd, J = 1.8, 6.7, H-4′, 5′), 2.10 (1H, m, H-3′), 2.70 (2H, t, J = 7.1, H-α), 3.40 (1H, m, H-β), 3.53 (1H, m, H-β), 3.76 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 4.34 (1H, dd, J = 1.4, 7.3, H-2′), 6.41 (1H, t, J = 6, NH-β), 6.63 (1H, d, J = 2.0, H-2), 6.67 (1H, dd, J = 2.0, 8.3, H-6), 6.68 (1H, d, J = 8.6, H-5), 6.89 (1H, d, J = 8.7, NH-8″), 7.37 (2H, tt, J = 1.2, 7.6, H-3″, 5″), 7.45 (1H, dt, J = 7.4, 1.4, H-4″), 7.73 (2H, dt, J = 1.4, 7.0, H-2″, 6″).

α-Benzoylamino-*N*-[2-(3,4-dimethoxyphenyl)ethyl]caproamide (3f), $C_{23}H_{30}N_2O_4$, was prepared from homoveratrylamine (0.8 g, 4.4 mmol) and 2-benzamidohexanoic acid (1 g, 4.4 mmol). Yield 73% (1.28 g), mp 131–133°C (Me_2CO), R_f 0.76. IR spectrum (ν, cm^{-1}): 3361, 3272 (NH), 3107, 2931, 2859 (Ar-CH), 1657, 1634 (N-C=O), 1577, 1537. ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.81 (3H, t, J = 7.1, H-6′), 1.24 (4H, m, H-4′, 5′), 1.62 (2H, m, H-3′), 2.71 (2H, t, J = 7, H-α), 3.42 and 3.49 (1H each, m, H-β), 3.76 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 4.48 (1H, q, J = 6.8, H-2′), 6.33 (1H, t, J = 7.2, NH-β), 6.63–6.68 (3H, m, H-2, 5, 6), 6.76 (1H, d, J = 7.4, NH-8″), 7.37 (2H, tt, J = 1.3, 7.3, H-3″, 5″), 7.46 (1H, tt,

J = 1.5, 7.4, H-4″), 7.71 (2H, dt, J = 1.5, 7.0, H-2″, 6″). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 14.12 (C-6′), 22.69 (C-5′), 27.87 (C-4′), 32.59 (C-3′), 35.42 (C-α), 40.97 (C-β), 53.81 (C-2′), 56.00 (OCH_3), 56.04 (OCH_3), 111.37 (C-2), 111.88 (C-5), 120.82 (C-6), 127.23 (C-2″, 6″), 128.82 (C-3″, 5″), 131.20 (C-1), 132.03 (C-4″), 133.97 (C-1″), 147.85 (C-4), 149.19 (C-3), 167.35, 171.82 (C=O).

α-Benzoylamino-β-methyl-*N*-[2-(3,4-dimethoxyphenyl)ethyl]valeramide (3g), $C_{23}H_{30}N_2O_4$, was prepared from homoveratrylamine (0.9 g, 4.97 mmol) and 2-benzamido-3-methylpentanoic acid (1.17 g, 4.97 mmol). Yield 76% (1.5 g), mp 156–158°C (Me_2CO), R_f 0.79. IR spectrum (ν, cm^{-1}): 3430, 3304 (NH), 3071, 2927, 2873 (Ar-CH), 1651, 1630 (N-C=O), 1547, 1523. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.85 (6H, m, $2CH_3$), 1.07 (1H, m, H-4′), 1.45 (1H, m, H-4′), 1.86 (1H, m, H-3′), 2.70 (2H, t, J = 7.1, H-α), 3.40, 3.53 (1H each, m, H-β), 3.76 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 4.36 (0.46H, dd, J = 1.0, 7.4, H-2′), 4.47 (0.51H, dd, J = 2.5, 6.2, H-2′), 6.25 (1H, br.s, NH-β), 6.62 (1H, d, J = 1.8, H-2), 6.67 (1H, d, J = 8.6, H-5), 6.69 (1H, dd, J = 1.8, 8.4, H-6), 6.77 (0.51H, d, J = 8.4, NH-8″), 6.83 (0.49H, d, J = 8.3, NH-8″), 7.37 (2H, dt, J = 1.6, 7.7, H-3″, 5″), 7.45 (1H, tt, J = 1.4, 7.1, H-4″), 7.72 (2H, dt, J = 1.4, 7.0, H-2″, 6″).

α-Benzoylamino-γ-methyl-*N*-[2-(3,4-dimethoxyphenyl)ethyl]valeramide (3h), $C_{23}H_{30}N_2O_4$, was prepared from homoveratrylamine (1 g, 5.53 mmol) and 2-benzamido-4-methylpentanoic acid (1.3 g, 5.53 mmol). Yield 69% (1.5 g), mp 119–121°C (Me_2CO), R_f 0.71. IR spectrum (ν, cm^{-1}): 3280 (NH), 3093, 2961, 2928 (Ar-CH), 1666, 1633 (N-C=O), 1562, 1518. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.85 (6H, dd, J = 1.3, 6.1, $2CH_3$), 1.60 (2H, m, H-3′), 2.69 (2H, t, J = 7.1, H-α), 3.38 , 3.48 (1H each, m, H-β), 3.75 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.58 (1H, m, H-2′), 6.56 (1H, br.s, NH-β), 6.61 (1H, d, J = 1.7, H-2), 6.64 (1H, dd, J = 1.6, 7.4, H-6), 6.66 (1H, d, J = 7.4, H-5), 6.81 (1H, d, J = 7.6, NH-8″), 7.37 (2H, t, J = 7.7, H-3″, 5″), 7.44 (1H, tt, J = 2.0, 7.5, H-4″), 7.71 (2H, dd, J = 1.4, 7.0, H-2″, 6″).

Cytotoxicity. HeLa cervical carcinoma and HEp-2 laryngeal adenocarcinoma cells (ATCC:CCL-23) were obtained from the cell culture bank of the Institute of Cytology, RAS. Cells were cultivated in RPMI-1640 media (HiMedia, India) containing antibiotics, L-glutamine (2 mM), and FBS (10%, HiMedia, India) in a CO_2 incubator (Shellab, USA). Versene solution (0.02%) was used to transfer cells.

Cytotoxicity was assayed using the MTT method [21]. Cells were inoculated into 96-well plates with 2,000 cells per well and treated with growth medium (100 μL each). Cells were treated after 24 h with test compounds (100 μM) in DMSO (0.8 vol% of the medium), left in the CO_2 incubator for 1 d, treated with MTT solution (20 μL per well, 5 mg/mL), and left for 3 h. The medium (100 μL) was discarded. The well was treated with DMSO (50 μL) to lyse cells and release formazan into the solvent. Optical density was measured at 620 nm on an EnSpire 2300 spectrophotometer (PerkinElmer, USA). Cell survival was determined from the ratio of living cells treated with test compound to those in the control. The control were cells without compounds. The effect was comparable to that of the cytostatic Kemoplat (Fresenius Kabi, India), which contains cisplatin as the active ingredient.

Results were analyzed and processed statistically using Origin 8.6 software, well-known variance statistics methods with significance evaluation (M ± m) of the parameters, and differences of groups according to the Student *t*-criterion. Results were considered statistically significant for $p \le 0.05$.

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