Article

Synthesis of Novel Lipophilic Polyamines via Ugi Reaction and Evaluation of Their Anticancer Activity

Artemiy Nichugovskiy 1,*, Varvara Maksimova 2, Ekaterina Trapeznikova 3, Elizaveta Eshtukova-Shcheglova 1, Igor Ivanov 1, Marianna Yakubovskaya 2, Kirill Kirsanov 2,4, Dmitry Cheshkov 5, Gian Cesare Tron 6 and Mikhail Maslov 1,*

1 Lomonosov Institute of Fine Chemical Technologies, MIREA—Russian Technological University, 86 Vernadsky Ave., 119571 Moscow, Russia
2 N.N. Blokhin National Medical Research Center of Oncology, 23 Kashirskoe Sh., 115478 Moscow, Russia
3 I.M. Sechenov First Moscow State Medical University, 8-2 Trubetskaya Str., 119991 Moscow, Russia
4 Institute of Medicine, Peoples’ Friendship University of Russia, 6 Miklukho-Maklaya Str., 117198 Moscow, Russia
5 State Scientific Research Institute of Chemistry and Technology of Organoelement Compounds, 38 Shosse Entuziastov, 105118 Moscow, Russia
6 Dipartimento di Scienza del Farmaco, Università del Piemonte Orientale, 2 Largo Donegani, 28100 Novara, Italy
* Correspondence: nichugovskij@mirea.ru (A.N.); mamaslov@mail.ru (M.M.)

Abstract: Natural polyamines (PAs) are involved in the processes of proliferation and differentiation of cancer cells. Lipophilic synthetic polyamines (LPAs) induce the cell death of various cancer cell lines. In the current paper, we have demonstrated a new method for synthesis of LPAs via the multicomponent Ugi reaction and subsequent reduction of amide groups by PhSiH₃. The anticancer activity of the obtained compounds was evaluated in the A-549, MCF7, and HCT116 cancer cell lines. For the first time, it was shown that the anticancer activity of LPAs with piperazine fragments is comparable with that of aliphatic LPAs. The presence of a diglyceride fragment in the structure of LPAs appears to be a key factor for the manifestation of high anticancer activity. The findings of the study strongly support further research in the field of LPAs and their derivatives.

Keywords: polyamines; multicomponent Ugi reaction; lipophilic polyamines; anticancer activity

1. Introduction

According to the latest statistics, about 19.3 million cancer cases and 10 million cancer-associated deaths are annually reported worldwide [1]. Currently, the search for new chemotherapeutic agents inhibiting invasion and metastasis faces the problem of resistance of cancer cells due to their somatic changes [2,3]. In this regard, modern biomedical approaches require new therapeutic strategies and development of anticancer agents to overcome these challenges.

Natural polyamines (PAs) putrescine, spermidine, and spermine that are present in significant amounts in all eukaryotic cells are essential for various underlying cellular processes such as proliferation, differentiation, and apoptosis [4]. They are formed inside the cell but can also be obtained from exogenous sources. Exogenous PAs penetrate into the cell by active transport and, once inside, are distributed in all cellular compartments due to their high solubility [5]. In eukaryotic cells, the intracellular concentration of PAs is strictly controlled by the mechanisms of their biosynthesis, catabolism, transport, and excretion. Uptake and biosynthesis of PAs grows up in response to proliferation stimuli. At the same time, catabolism and secretion of PAs, as well as inhibition of their biosynthesis and transport, are induced when higher PA concentrations are reached in the cell [6]. The levels of PAs in cancer cells are higher than in normal cells, and this phenomenon is associated
with a high rate of cell proliferation, decreased level of apoptosis, and overexpression of
genes that affect cancer invasion and metastasis [7].

The first synthesis of the norspermine derivatives 1, 2 (Figure 1) that inhibit the
growth of cancer cells was carried out in 1993 [8]. At present, dozens of PA derivatives with
potential anticancer activity have been developed [9]. Although some of them (3–5) have
been tested at different stages of clinical trials, none of them have been approved so far for
medical use due to their low selectivity against cancer cells [4]. The lack of selectivity of
anticancer agents based on PA structures stimulates further search for novel PA
derivatives with improved properties for potential chemotherapeutic application.

The lipophilic PA may effectively inhibit PA transport into the cell due to its effective
incorporation into the transmembrane channel located on the cell membrane. These data
have been previously reported for AMXT-1501 with the palmitic acid residue [13]. In
addition, we have previously shown that lipophilic PAs, where the lipophilic part is
presented by a diglyceride fragment, also exhibit high anticancer activity [10]. Considering
the results of the mentioned above studies, conjugation of PAs with the diglyceride fragment
may have beneficial pharmacological potential.

The multicomponent Ugi reaction [14] can be used as an effective tool for the rapid
preparation of modified PAs. One of the modifications of this reaction (N-split-Ugi [15,16])
is based on the interaction of a secondary diamine, a carbonyl compound, a carboxylic acid,
and an isocyanide, which together form an α-acylaminoamide, whose amide groups can be
further reduced to form a PA. This modification makes it possible to obtain PAs of different
structures in two steps from simple compounds [17].
In this work, we implemented the multicomponent N-split Ugi reaction for the synthesis of novel alkylated PAs containing aliphatic and cyclic diamines and evaluated their anticancer activity.

2. Results and Discussion

The synthesis of lipophilic PAs using the N-split Ugi reaction is usually carried out in two steps. On the first step, α-acylaminoamide is formed by the condensation of four components. On the second step, the reduction of amide groups is carried out followed by the removal of protective groups. In this work, the commercially available tert-butyl isocyanide (7a) or the previously obtained octadecyl isocyanide (7b) [18] were used as isocyanide components, glacial acetic acid (8a) or N-acetylglycine (8b) as the carboxylic component, and N,N'-dibenzylalkanediamine (9a–c) as the diamine component, while paraformaldehyde (10) was used as the carbonyl component. The reaction was refluxed in methanol in an equimolar ratio of starting reagents for 16 h (Scheme 1). Usually the N-split Ugi reaction proceeds under room conditions, but we used refluxing to dissolve the lipophilic isocyanide and to break paraformaldehyde completely.

\[
\text{RNC} + \text{R}^1\text{COOH} + \text{Bn}_2\text{HN}_N\text{R}^2 + \text{CH}_2\text{O}(10^\circ) \rightarrow \text{R}^1\text{N}^c_\text{Bn} \text{R}^2_\text{N}^c_\text{Bn} \text{R}^3_\text{R}^4\text{N}\text{COH}.
\]

Scheme 1. Synthesis of α-acylaminoamides based on aliphatic diamines.

A noticeably increased yield of the N-split Ugi reaction from 10–11% to 35–48% was observed when the length of the methylene linker between the central nitrogen atoms of diamines was increased from two (compounds 11a,b) to three carbon atoms (compounds 11c,d). On the contrary, further increase in its length to one additional methylene group decreases the yield of α-acylaminoamide 11e to 30%. The obtained yields correlated with the previously published data [15]. In the NMR spectra of the α-acylaminoamides 11a–e, appearance of double sets of signals which correlate with the formation of rotamers around the amide bonds was detected [19].

Piperazine is one of the widely used structural fragments in numerous biologically active compounds. Various piperazine derivatives demonstrated a high antiproliferative activity against different cancer cell lines [20–24]. The replacement of aliphatic diamines with piperazine results in increased conformational rigidity and lipophilicity, altering the proteolytic [25,26] and biological activity of PAs. Compounds 12a–e with a piperazine fragment were obtained as described above for compounds 11a–e. The replacement of aliphatic diamines 9a–c with piperazine (9d) increases the yields of α-acylaminoamides 12a–e and reduces the reaction time from 16 to 12 h (Scheme 2).
Molecules 2022, 27, 6218

Scheme 2. Synthesis of α-acylaminoamides based on piperazine.

The highest yield (compound 12b) was achieved using octadecyl isocyanide (7b) and acetic acid (8a). Although the four-component N-split-Ugi reaction seems to be insensitive to steric hindrances [27], the yields of compounds 12c,d obtained from the diglyceride 7c were significantly lower, suggesting that steric hindrance caused by the ethyl substituent at the C(2) atom of glycerol might be the reason for the observed effect. Additionally, the low yield of compounds 12c,d can be linked with lower stability of isocyanide 7c and its partial transformation into formamide, as evidenced by the presence of the corresponding signal in the C(13) NMR spectra. Apparently, the intermolecular exchange of amide protons led to the strong broadening of the corresponding NH-proton was detected in the 1H NMR spectra. To avoid those problems, the spectra of compounds 12c,d were recorded in DMSO-d6, a solvent that somewhat suppresses the exchange of mobile protons.

In the 13C NMR spectra of compounds 12c,d, no signal of carbonyl carbon at the diglyceride fragment was observed when CDCl3 was used as a solvent. At the same time, a strongly broadened signal of the corresponding NH-proton was detected in the 1H NMR spectra. Apparently, the intermolecular exchange of amide protons led to the strong broadening of the 13C signal of the corresponding carbonyl atom and its merging with the base line of the spectrum. To avoid those problems, the spectra of compounds 12c,d were recorded in DMSO-d6, a solvent that somewhat suppresses the exchange of mobile protons.

Since cancer cells generally overexpress carbohydrate receptors, we attempted to prepare PAs that contain a diglyceride moiety at one terminal nitrogen atom and a carbohydrate moiety at the other via a two-step strategy using 2-(hydroxymethyl)benzoic acid [29]. This approach allows to prepare aminodiimide, which acts as one of the components in the N-split Ugi reaction. Isonitrile 7c reacted with equimolar amounts of 2-(hydroxymethyl)benzoic acid (8c), piperazine (9d), and formaldehyde (10) (Scheme 3) to give monosubstituted aminoamide 13a in a 35% yield. The low yield of the desired product 13a was due to the formation of the symmetrical adduct of aminodiimide 13b with 22% yield. Subsequent treatment of 13a with isocyanide 14a–c, 2-(hydroxymethyl)benzoic acid (8c), and formaldehyde (10) led to formation of the disubstituted piperazines 15a–c in 75%, 80%, and 30% yields, respectively. The low yield of D-glucose containing compound 15c is supposedly associated with a partial deacetylation during reflux.
As reported previously [34], the utilization of benzamide-type substrates is one of the key limitations for the most nickel-catalyzed amide reduction reactions. Indeed, using the abovementioned strategy, benzylamide-derivative 16a was obtained in a good yield of 66%, whereas the yields of piperazyl derivatives 16b–f were significantly lower (Scheme 4).

Treatment of carbohydrate containing aminoamide 15c with phenylsilane did not provide the formation of the desired amine (Scheme 5) due to partial deacetylation of the D-glucose. To overcome this problem, the acetyl groups of aminoamide 15c were initially removed by sodium methoxide in methanol to yield compound 17 (80%). The following reduction of the amide 17 was unsuccessful, and the desired amine was not isolated from the reaction mixture. Thus, the reduction of the amide groups of aminodiamide 15c containing D-glucose requires additional efforts to find alternative synthetic approaches.

Given the fact that Pas with a piperazyl domain have never been reported before, we chose piperazyl derivatives 16b and 16c–f with different hydrophobic domain structures; with short-chain substituents (ethyl (16c), isopropyl (16e), and pentyl (16f)) and different...
numbers of amino groups. To evaluate the effect of lipophilic PA structure on its anticancer activity, other aliphatic lipophilic PAs, which were obtained in this study in much lower yields, were not considered for further evaluation. Aminoamide 17 was used as the negative control.

The cytotoxicity of the lipophilic PAs 16a–f was determined using the MTT-test (see Supplementary Materials) in breast cancer (MCF7), human lung adenocarcinoma (A549), colon cancer (HCT116) cell lines (Table 1). The cytotoxicity data showed that the presence of a diglyceride fragment as a hydrophobic domain (PAs 16c–f) increases their anticancer activity compared with the octadecyl substituent (PA 16b).

### Table 1. Values of cell viability after PA (16b–f) treatment *

| Compounds/Cell Lines | IC₅₀ (µM) | Avg IC₅₀ (µM) |
|----------------------|-----------|---------------|
|                      | A-549     | MCF7          | HCT116        |
| 16b                  | 19.0 ± 0.7| 12.0 ± 1.5    | 20.0 ± 3.0    | 18.5          |
| 16c                  | 5.1 ± 1.3 | 3.5 ± 0.6     | 5 ± 1.5       | 4.3           |
| 16d                  | 3.0 ± 0.4 | 1.0 ± 0.14    | 3.8 ± 0.5     | 2.3           |
| 16e                  | 5.9 ± 0.6 | 3.7 ± 0.5     | 3 ± 0.8       | 4.1           |
| 16f                  | 5.9 ± 0.5 | 4.6 ± 0.9     | 4.3 ± 1.2     | 4.8           |
| 17                   | >100      | >100          | >100          | >100          |
| 3 (BENSpm)           | 0.5       | 1             | n/d           |
| Cisplatin            | 29.0 ± 10 | 14 ± 7        | 7.5           | 16.8          |

* Data represent the mean ± standard deviation from 3 independent experiments; each drug concentration was tested in triplicate. n/d—no data.

Compound 16d with three amino groups showed the highest anticancer activity within all cell lines tested. Compounds with four amino groups 16c,e,f revealed similar anticancer activity. BENSpm (3) and the widely used anticancer agent cisplatin were selected as a positive control. Their IC₅₀ values obtained in this study were close to or of the same value as those obtained in previous reports [35–37]. Comparison of IC₅₀ values obtained suggests that new lipophilic PAs 16c–f have a cytotoxicity that is comparable to that of BENSpm, and several times higher than that of cisplatin.

### 3. Conclusions

Lipophilic Pas manifest excellent preliminary biological activity in cancer cell lines. However, the chemical synthesis of such compounds is complicated. In this paper, we demonstrated the efficient approach for the synthesis of new LPAs, which were obtained using the N-split Ugi multicomponent reaction. The application of this method allowed us to decrease the synthetic steps and to increase the total yield of LPAs from 7% to 28%. The application of PhSiH₃ and NiCl₂(dme) effectively permitted us to reduce several amide groups in the PA precursors and has proven to be a very reliable and efficient method.

The obtained results demonstrate that the biological activity of the novel LPAs is several times higher than that of cisplatin, which is used in medical practice. At the same time, comparison with the clinically tested BENSpm showed similar cytotoxicity, which makes LPAs promising targets for further studies. More detailed biological evaluation will be carried out in the follow up study.

### 4. Materials and Methods

#### 4.1. General

Commercially available solvents were used in this study. All the experiments were carried out under argon atmosphere with the use of the HPLC grade methanol. The reactions were monitored by thin-layer chromatography (TLC) on Silica gel 60 F₂₅₄ plates (Merck, Germany). The substances were identified in UV light (254 nm) by the treatment with Dragendorff’s reagent, or by treatment with a solution of phosphomolybdic acid–cerium sulfate (IV) with subsequent heating. Column chromatography was performed...
on Kieselgel 60 silica gel (0.040–0.063 or 0.063–0.200 mm, Merck, Germany). The $^1$H and $^{13}$C NMR spectra were recorded on Bruker DPX-300, Bruker Avance II 400, or Bruker Avance II 600 Fourier spectrometers (Bruker, Germany) in CDCl$_3$, DMSO-d$_6$ or acetone-d$_6$. Chemical shifts (δ) were expressed in ppm relative to the peak of the residual proton of the solvent. The spin–spin interaction constants (J) are reported in Hz. The high-resolution mass spectra were recorded on a LCQ Deca XP Plus mass spectrometer with ESI ionization (Thermo Finnigan, San Jose, CA, USA) or FT ICR Apex Ultra 7 T (Bruker, Germany), mass spectra were recorded on the Agilent spectrometer. LCMS spectra were recorded on the LC Agilent Infinity 1260 II (Agilent, Beijing, China) and MSD Agilent IQ (Agilent, Singapore). Column Poroshell 120 EC-C18, 100 mm × 4.6 mm × 3 μm, constant flow 800 μL/min, linear gradient from 90% water + 0.1% FA—0–2 min to 90% ACN + 0.1% FA—15–25 min, voltage of ion capillary 3500 V, fragmenter 100 V.

2-Hydroxymethylbenzoic acid (8e) was prepared as described previously [29]. The synthesis of isonitrile derivatives both of diglyceride (7e) and D-glucose was performed according to [18]. The synthesis of PhSiH$_3$ was described in reference [38].

To eliminate minor impurities compounds 16b–f that have been evaluated in cell models were additionally purified prior to use on silica gel and their purity (≥96%) was confirmed by LCMS method.

4.2. Synthetic Methods

4.2.1. General Procedure for the Synthesis for Compounds 11a–e, 12a–e

Isocyanide 7 (1 eq), carboxylic acid 8 (1 eq), and diamine 9 (1 eq) were added sequentially to a solution of paraformaldehyde 10 (1 eq) in methanol (0.5 M). The reaction mixture was at refluxed for 12–16 h. The solvent was evaporated, and the crude reaction mixture was purified by column chromatography.

1,8-Diamino-$^8$N-$^8$Acetyl-$^1$-Tert-Butyl-1,7-Dioxo-$^3$N-$^6$-Dibenzyl-3,6-Diazaoctane (11a)

Yield: 11%, colorless oil. Eluent: CHCl$_3$-MeOH (10:1). $^1$H NMR (600 MHz, acetone-d$_6$, main rotamer) δ 1.31 (s, 9H, (CH$_3$)$_3$), 1.93 (s, 3H, COCH$_3$), 2.62 (br. s, 2H, CH$_2$NCH$_3$), 3.05 (s, 2H, COCH$_2$N), 3.50 (s, 2H, CH$_2$NCO), 3.60 (s, 2H, COCH$_2$NH), 4.05 (d, 2H, J = 4.8 Hz, PhCH$_2$), 4.37 (s, 2H, PhCH$_2$NCO), 7.07–7.46 (m, 12H, 2 Ph, 2 NH). $^{13}$C NMR (150 MHz, acetone-d$_6$, main rotamer) δ 22.7, 29.0, 42.0, 44.4, 50.4, 52.1, 59.5, 60.0, 127.6, 128.3, 128.7, 129.4, 129.9, 132.7, 137.7, 138.7, 169.6, 170.2, 170.4. HRMS ESI m/z: [M + H]$^+$ calcd for C$_{28}$H$_{37}$N$_{4}$O$_{3}$ 453.2860, found: 453.2860.

1,8-Diamino-$^8$N-$^8$Acetyl-$^1$-Octadecyl-1,7-Dioxo-$^3$N-$^6$-Dibenzyl-3,6-Diazaoctane (11b)

Yield: 10%, colorless oil. Eluent: CHCl$_3$-MeOH (10:1). $^1$H NMR (300 MHz, CDC$_1$$_3$, main rotamer) δ 0.88 (t, 3H, J = 7.0 Hz, (CH$_2$)$_{15}$CH$_3$), 1.25 (br. s, 30H, (CH$_2$)$_{15}$CH$_3$), 1.39–1.57 (m, 2H, CH$_2$CH$_2$(CH$_2$)$_{15}$), 2.05 (s, 3H, COCH$_3$), 2.59 (t, 2H, J = 6.5 Hz, COCH$_2$NCH$_2$), 3.16 (s, 2H, COCH$_2$N), 3.20–3.35 (m, 2H, CH$_2$CH$_2$(CH$_2$)$_{15}$), 3.47 (t, 2H, J = 6.5 Hz, CONH$_2$), 3.57 (s, 2H, COCH$_2$NH), 4.04 (s, 2H, PhCH$_2$), 4.14 (s, 2H, PhCH$_2$NCO), 6.51 (s, 1H, NHCOCH$_2$), 6.97–7.50 (m, 11H, 2 Ph, CH$_3$CONH). $^{13}$C NMR (75 MHz, CDC$_1$$_3$, main rotamer) δ 14.1, 22.7, 29.3, 29.4, 29.6, 29.7, 29.7, 29.8, 31.9, 39.1, 41.6, 43.9, 49.6, 51.2, 59.0, 59.8, 125.3, 126.3, 128.2, 128.6, 129.0, 129.1, 135.0, 138.1, 168.8, 169.9, 170.6. HRMS ESI m/z: [M + H]$^+$ calcd for C$_{40}$H$_{60}$N$_{4}$O$_{3}$ 649.5051, found: 649.5051.

1,9-Diamino-$^9$N-$^9$Acetyl-$^1$-Octadecyl-1,8-Dioxo-$^3$N-$^7$-Dibenzyl-3,7-Diazaanone (11c)

Yield: 48%, colorless oil. Eluent: EA-MeOH (9:1). $^1$H NMR (400 MHz, CDC$_1$$_3$, COSY, HSQC, HMBC) δ 0.87 (t, 3H, J = 6.9 Hz, (CH$_2$)$_{15}$CH$_3$), 1.25 (br. s, 30H, (CH$_2$)$_{15}$CH$_3$), 1.38–1.52 (m, 2H, CH$_2$CH$_2$(CH$_2$)$_{15}$), 1.64–1.80 (m, 2H, NCH$_2$CH$_2$CH$_2$N), 2.04 (s, 3H, COCH$_3$), 2.36–2.58 (m, 2H, PhCH$_2$NCH$_2$), 3.06 (s, 2H, COCH$_2$N), 3.09–3.31 (m, 3H, CH$_2$CH$_2$(CH$_2$)$_{15}$, PhCH$_2$N(CO)CH$_2$), 3.39 (t, 1H, J = 7.3 Hz, PhCH$_2$N(CO)CH$_2$), 3.57 (s, 2H, COCH$_2$NH), 4.05 (d, 2H, J = 3.9 Hz, PhCH$_2$), 4.41 (s, 2H, PhCH$_2$NCO), 6.57 (s, 1H, NHCOCH$_2$), 6.84–7.54 (m, 11H, 2 Ph, CH$_3$CONH). $^{13}$C NMR (101 MHz, CDC$_1$$_3$) δ 14.1, 22.7, 29.3, 29.4, 29.6, 29.7, 29.8, 31.9, 39.1, 41.6, 43.9, 49.6, 51.2, 59.0, 59.8, 125.3, 126.3, 128.2, 128.6, 129.0, 129.1, 135.0, 138.1, 168.8, 169.9, 170.6. HRMS ESI m/z: [M + H]$^+$ calcd for C$_{50}$H$_{70}$N$_{4}$O$_{2}$ 777.5444, found: 777.5447.
1,6-Diamino-N^1-Acetyl-N^6-Octadecyl-6-Oxo-N^3,N^3-Dibenzyl-4-Azaahexane (11d)

Yield: 35%, colorless oil. Eluent: PE-EA (4:6). \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 0.80 (t, 3H, \(J = 6.6\ \text{Hz}, \ (\text{CH}_2)_3\text{C}_6\text{H}_5\)), 1.18 (br. s, 30H, \((\text{CH}_2)_3\text{C}_6\text{H}_5\)), 1.29–1.41 (m, 2H, CH\(_2\text{CH}_2\text{CH}_2\text{CH}_3\)), 1.68 (m, 2H, NCH\(_2\text{CH}_2\text{CH}_2\text{CH}_3\)), 2.11 (s, 3H, COCH\(_3\)), 2.31–2.34 (m, 2H, PhCH\(_2\text{NCH}_2\)), 2.67 (s, 2H, COCH\(_3\)), 4.22 (s, 2H, PhCH\(_2\)), 4.32–5.22 (m, 4H, NCH\(_2\text{CH}_2\text{CH}_2\text{CH}_3\)), 7.06 (br. s, 1H, NH). HRMS ESIM / M / Z calcd for C\(_{41}\)H\(_{60}\)N\(_2\)O\(_3\) 663.5208, found: 663.5196. HRMS ESIM / M / Z: [M + Na]\(^+\) calcd for C\(_{41}\)H\(_{66}\)Na\(_2\)N\(_2\)O\(_3\) 868.5033, found: 868.5001.

1,7-Diamino-N^1-Acetyl-N^7-Octadecyl-7-Oxo-N^3,N^3-Dibenzyl-5-Azaheptane (11e)

Yield: 30%, colorless oil. Eluent: EA. \(^1^H\) NMR (300 MHz, main rotator, CDCl\(_3\)) \(\delta\) 0.71 (t, 3H, \(J = 6.7\ \text{Hz}, \ (\text{CH}_2)_3\text{C}_6\text{H}_5\)), 1.12 (br. s, 30H, \((\text{CH}_2)_3\text{C}_6\text{H}_5\)), 1.19–1.41 (m, 6H, \(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3\)), 1.93 (s, 3H, COCH\(_3\)), 2.21–2.36 (m, 2H, PhCH\(_2\text{NCH}_2\)), 2.88 (s, 2H, NCH\(_2\text{CO}\)), 3.16–3.22 (m, 4H, COCH\(_3\)), 3.40 (s, 2H, PhCH\(_2\)), 4.32 (s, 2H, PhCH\(_2\text{NCO}\)), 6.78–7.31 (m, 2 Ph, NH, 1H). HRMS FTICR / M / Z: [M + H]\(^+\) calcd for C\(_{40}\)H\(_{63}\)N\(_3\)O\(_2\) 620.5136, found: 620.5136.

N^1-(N-Acetylglucyl)-N^4-[N-Octadecyl]AminocarbonylMethylpiperazin (12a)

Yield: 60%, colorless oil. Eluent: DCM-DeOMe (20:1). \(^1^H\) NMR (300 MHz, CDCl\(_3\)) \(\delta\) 0.84 (d, 3H, \(J = 6.9\ \text{Hz}, \ (\text{CH}_2)_3\text{C}_6\text{H}_5\)), 1.22 (br. s, 30H, \((\text{CH}_2)_3\text{C}_6\text{H}_5\)), 1.41–1.54 (m, 2H, \(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3\)), 2.01 (s, 3H, COCH\(_3\)), 2.47–2.55 (m, 4H, 2 COCH\(_2\text{NCH}_2\)), 3.00 (s, 2H, COCH\(_3\)), 3.19–3.29 (m, 2H, \(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3\)), 3.38–3.46 (m, 2H, 2 CONH\(_2\)), 3.60–3.66 (m, 2H, 2 CONH\(_2\)), 4.02 (d, 2H, \(J = 4.1\ \text{Hz}, \ \text{COCH}_2\text{NH}\)), 6.61 (t, 1H, \(J = 4.1\ \text{Hz}, \ \text{NHCOCH}_3\)), 6.92 (t, 1H, \(J = 5.5\ \text{Hz}, \ \text{CH}_2\text{CONH}\)). \(^1^C\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 14.1, 22.6, 22.9, 27.0, 29.2, 29.3, 29.5, 29.6, 29.7, 29.7, 31.9, 39.0, 41.2, 42.0, 44.4, 53.0, 53.2, 61.5, 166.6, 169.0, 170.1. HRMS FTICR / M / Z: [M + H]\(^+\) calcd for C\(_{28}\)H\(_{55}\)N\(_2\)O\(_3\) 495.4269, found: 495.4269.

N^1-Acetyl-N^4-[N-Octadecyl]AminocarbonylMethylpiperazin (12b)

Yield: 80%, colorless oil. Eluent: DCM-DeOMe (30:1). \(^1^H\) NMR (300 MHz, CDCl\(_3\)) \(\delta\) 0.90 (t, 3H, \(J = 7.0\ \text{Hz}, \ (\text{CH}_2)_3\text{C}_6\text{H}_5\)), 1.26 (br. s, 30H, \((\text{CH}_2)_3\text{C}_6\text{H}_5\)), 1.48–1.61 (m, 2H, \(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3\)), 2.11 (s, 3H, COCH\(_3\)), 2.49–2.59 (m, 4H, 2 COCH\(_2\text{NCH}_2\)), 3.05 (s, 2H, COCH\(_3\)), 3.20–3.37 (m, 2H, \(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3\)), 3.46–3.54 (m, 2H, 2 CONH\(_2\)), 3.63–3.69 (m, 2H, 2 CONH\(_2\)), 7.06 (br. s, 1H, NH). \(^1^C\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 14.1, 21.3, 22.7, 26.9, 29.2, 29.3, 29.5, 29.6, 29.7, 31.9, 39.0, 41.3, 46.2, 53.1, 53.5, 61.5, 169.0, 169.1. HRMS FTICR / M / Z: [M + H]\(^+\) calcd for C\(_{29}\)H\(_{55}\)N\(_2\)O\(_3\) 438.4054, found: 438.4054.

N^1-(N-Acetylglucyl)-N^4-[N-(rac-1-Decyloxy-2-Ethoxyprop-3-yl]AminocarbonylMethylpiperazin (12c)

Yield: 47%, colorless oil. Eluent: DCM-DeOMe (15:1). \(^1^H\) NMR (600 MHz, DMSO-d6, COSY, HSQC, HMBC) \(\delta\) 0.85 (t, 3H, \(J = 6.9\ \text{Hz}, \ (\text{CH}_2)_2\text{CH}_3\)), 1.09 (t, 3H, \(J = 7.0\ \text{Hz}, \ \text{OCH}_2\text{CH}_3\)), 1.24 (br. s, 14H, \(\text{CH}_2\text{CH}_3\)), 1.43–1.51 (m, 2H, \(\text{OCH}_2\text{CH}_3\)), 1.86 (s, 3H, COCH\(_3\)), 2.34–2.42 (m, 2H, 2 COCH\(_2\text{NCH}_2\)), 2.42–2.48 (m, 2H, 2 COCH\(_2\text{NCH}_2\)), 2.93 (d, \(J = 15.5\ \text{Hz}, 1\text{H}, \text{COCH}_2\text{H}_2\text{N}\)), 2.96 (d, \(J = 15.5\ \text{Hz}, 1\text{H}, \text{COCH}_2\text{H}_2\text{N}\)), 3.07–3.13
(m, 1H, CONHCH₃), 3.25–3.32 (m, 1H, NHCH₂H₅CH), 3.33–3.40 (m, 4H, CH₂OCH₂), 3.40–3.52 (m, 6H, CHOCH₂NHCH₂CH₃, 2 CONCH₂Pip), 3.52–3.59 (m, 1H, OCH₂H₅CH₃), 3.92 (d, 2H, J = 5.5 Hz, COCH₃NH), 7.63–7.70 (m, 1H, CH₂CH₂NH), 7.91 (t, 1H, J = 5.5 Hz, COCH₂NH). ¹³C NMR (151 MHz, DMSO-d₆) δ 13.9, 15.5, 22.0, 22.4, 25.6, 28.7, 28.8, 29.0, 29.0, 29.0, 29.1, 31.3, 39.6, 40.3, 41.3, 44.0, 52.4, 52.7, 60.9, 64.4, 70.6, 71.1, 71.6, 167.0, 168.8, 169.2. HRMS FTICR m/z: [M + H]+ calcd for C₂₅H₃₅N₆O₅ 513.4010, found: 513.4010.

N¹-Acetyl-N⁴-[N-(rac-1-Decyloxy-2-Ethoxyprop-3-yl)Aminocarbonyl]Methylpiperazin (12d)

Yield: 54%, colorless oil. Eluent: DCM-MeOH (30:1). ¹H NMR (600 MHz, DMSO-d₆, HSQC, HMQC) δ 0.85 (t, 3H, J = 7.0 Hz, (CH₃)₂CH₂), 1.09 (t, 3H, J = 7.0 Hz, OCH₂CH₃), 1.24 (br, s, 14H, (CH₂)₂CH₂), 1.44–1.51 (m, 2H, OCH₂CH₃), 1.98 (s, 3H, COCH₃), 2.35–2.39 (m, 2H, 2 COCH₂NCH₂H₅Pip), 2.43–2.45 (m, 2H, 2 COCH₂NCH₂H₅Pip), 2.93 (d, 1H, J = 15.5 Hz, COCH₂H₅N), 2.96 (d, 1H, J = 15.5 Hz, COCH₂H₅N), 3.05–3.13 (m, 1H, CONHCH₂H₅), 3.29 (dd, 1H, J = 13.4, 6.3, 5.1 Hz, CONHCH₂H₅), 3.32–3.39 (m, 4H, CH₂OCH₃), 3.40–3.52 (m, 6H, CH₂OCH₂H₅CH₃, 2 CONCH₂Pip), 3.52–3.59 (m, 1H, CH₂OCH₂H₅CH₃), 7.63–7.68 (m, 1H, NH). ¹³C NMR (151 MHz, DMSO-d₆, DEPT-135) δ 13.8, 15.5, 22.0, 25.6, 28.7, 28.8, 29.0, 29.0, 29.0, 29.0, 31.3, 39.6, 40.7, 45.6, 52.4, 52.9, 60.9, 64.4, 64.4, 70.6, 71.1, 71.6, 168.0, 168.8. HRMS FTICR m/z: [M + H]+ calcd for C₂₅H₃₅N₆O₅ 456.3796, found: 456.3796.

N¹-Acetyl-N⁴-[N-(Cyclohexyl)Aminocarbonyl]Methylpiperazin (12e)

Yield: 75%, colorless oil. Eluent: EA-MeOH (4:1). ¹H NMR (300 MHz, CDCl₃) δ 1.04–1.25 (m, 3H, 2 CH₂CH₂H₅H₃, CHCH₂CH₂H₅H₃), 1.25–1.45 (m, 2H, 2 CH₂CH₂H₅H₃), 1.61 (m, 3H, 2 NHCH₂CH₂H₅H₃, CHCH₂CH₂CH₂H₅H₃), 1.77–1.90 (m, 2H, 2 NHCH₂CH₂H₅H₃), 2.04 (s, 3H, COCH₃), 2.35–2.57 (m, 4H, 2 COCH₂NCH₂H₅Pip), 2.96 (s, 2H, COCH₂N), 3.39–3.50 (m, 2H, 2 CONHCH₂H₅Pip), 3.54–3.64 (m, 2H, 2 CONHCH₂H₅Pip), 3.65–3.86 (m, 1H, CONHCH₂), 6.88 (d, 1H, J = 8.2 Hz, NH). ¹³C NMR (75 MHz, CDCl₃) δ 21.3, 24.7, 25.5, 33.1, 41.4, 46.3, 47.5, 53.1, 53.5, 61.6, 61.8, 169.0. HRMS ESI m/z: [M + H]+ calcd for C₂₄H₂₆N₅O₂ 268.20195, found: 268.20195.

4.2.1.11. Synthesis of Compounds 13a,b

The equimolar solution of isocyanide (7c), 2-(hydroxymethyl)benzoic acid (8e), amine (9d) and paraformaldehyde (10), and in 0.5 M methanol was refluxed for 12 h. The solvent was evaporated, and the crude reaction mixture was purified by column chromatography.

N¹-[N-(rac-1-Decyloxy-2-Ethoxyprop-3-yl)Aminocarbonyl]Methylpiperazin (13a)

Yield: 50%, colorless oil. Eluent: EA-MeOH-NH₃·H₂O (7:3:0.1). ¹H NMR (300 MHz, CDCl₃) δ 0.87 (t, J = 6.3 Hz, 3H, (CH₃)₂CH₂), 1.21 (t, 3H, J = 7.0 Hz, OCH₂CH₃), 1.26 (br, s, 14H, (CH₂)₂CH₂), 1.48–1.63 (m, 2H, OCH₂CH₂), 2.43–2.63 (m, 5H, CH₂NHCH₃Pip), 2.87–2.96 (m, 4H, 2 NCH₂Pip), 2.99 (s, 2H, COCH₂N), 3.17–3.75 (m, 9H, 4H, CH₂OCH₂, CHOCH₂CH₂, CH₂NHC), 7.50 (brs, 1H, CONH). ¹³C NMR (75 MHz, CDCl₃) δ 14.3, 15.8, 22.8, 25.2, 29.5, 29.6, 29.7, 29.8, 40.2, 46.1, 54.7, 62.3, 64.5, 67.5, 71.5, 72.0, 76.9, 170.3. HRMS ESI [M + H]+ calcd for C₂₁H₄₁N₅O₇ 386.3377, found 386.3371.

N¹,N⁴-bis[N-(rac-1-Decyloxy-2-Ethoxyprop-3-yl)Aminocarbonyl]Methylpiperazin (13b)

Yield: 22%, colorless oil. Eluent: EA-MeOH (95:5). ¹H NMR (300 MHz, CDCl₃) δ 0.87 (t, 6H, J = 6.5 Hz, (CH₃)₂CH₂), 1.19 (t, 6H, J = 7.0 Hz, OCH₂CH₃), 1.27 (br, s, 28H, (CH₂)₂CH₂), 1.50–1.63 (m, 4H, OCH₂CH₂), 2.56 (br, s, 8H Pip), 3.01 (s, 4H, COCH₂N), 3.16–3.31 (m, 2H, 2 CH₂NHC), 3.34–3.48 (m, 8H, 2 CHOCH₂CH₂, 2 CH₂NHC), 3.48–3.56 (m, 4H, 2 CH₂OCH₂), 3.56–3.74 (m, 4H, 2 CH₂OCH₂). ¹³C NMR (75 MHz, CDCl₃) δ 14.3, 15.8, 22.8, 26.2, 29.5, 29.6, 29.7, 29.8, 32.0, 40.3, 53.8, 61.7, 65.5, 71.5, 72.0, 76.8, 170.1. HRMS ESI [M + H]+ calcd for C₂₃H₃₇N₈O₈ 685.5838, found 685.5828. HRMS ESI [M + 2H]+ calcd for C₃₉H₇₈N₄O₆ 343.2955, found 343.2954.
4.2.2. General Procedure for the Synthesis of Compounds 15a–c

The equimolar solution of corresponding isocyanide (14a–c), 2-(hydroxymethyl)benzoic acid (8c), amine (13a), and paraformaldehyde (10) in 0.5 M methanol was refluxed for 12 h. The solvent was evaporated, and the crude reaction mixture was purified by column chromatography.

\[ \text{N}^1\text{-[N-(Isopropyl)Aminocarbonyl]Methyl-N}^4\text{-[N-(rac-1-Decyloxy-2-Ethylxyprop-3-yl)Aminocarbonyl]Methylpiperazin} (15a) \]

Yield: 80%, colorless oil. Eluent: EA-MeOH (85:15). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 0.08–0.07 (t, \(J = 7.0\) Hz, 3H, (CH\(_2\))\(_2\)CH\(_3\)), 1.16 (d, \(J = 6.6\) Hz, 6H, CH(CH\(_3\))\(_2\)), 1.20 (t, \(J = 7.0\) Hz, 3H, OCH\(_2\)CH\(_3\)), 1.27 (br.s, 14H, (CH\(_2\))\(_2\)CH\(_3\)), 1.50–1.62 (m, 2H, OCH\(_2\)CH\(_3\)), 2.56 (br.s, 8H Pip protons), 2.97 (s, 2H, CHNH(CH)\(_2\)), 3.03 (d, \(J = 1.6\) Hz, 2H, COCH\(_2\)N), 3.23 (ddd, \(J = 4.8, 6.4, 13.7\) Hz, 1H, CH\(_2\)CH\(_2\)NH), 3.34–3.75 (m, 8H, CHCH\(_2\)H\(_2\)NH, CHOCH\(_2\)CH\(_3\), CH\(_2\)OCH\(_3\)), 4.01–4.16 (m, 1H, CH(CH\(_3\))\(_2\)), 6.86 (br.d, \(J = 8.4\) Hz, 1H, NHCH\(_2\)), 7.44 (br.t, \(J = 5.6\) Hz, 1H, NHCH\(_2\)). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 14.3, 15.8, 22.8, 23.0, 26.3, 29.5, 29.6, 29.7, 29.8, 29.8, 32.0, 40.3, 40.9, 53.7, 53.7, 61.7, 61.7, 65.5, 71.5, 72.0, 76.8, 169.0, 170.0. HRMS ESI [M + H\(^+\)] calcd for C\(_{26}\)H\(_{33}\)N\(_4\)O\(_4\) 485.4061, found 485.4062.

\[ \text{N}^1\text{-[N-(Pentyl)Aminocarbonyl]Methyl-N}^4\text{-[N-(rac-1-Decyloxy-2-Ethylxyprop-3-yl)Aminocarbonyl]Methylpiperazin} (15b) \]

Yield: 75%, colorless oil. Eluent: EA-MeOH (9:1). \(^1\)H NMR (400 MHz, CDCl\(_3\), COSY, HSQC, HMBC) \(\delta\) 0.83–0.94 (m, 6H, (CH\(_2\))\(_2\)CH\(_3\), (CH\(_2\))\(_2\)CH\(_3\)), 1.20 (t, \(J = 7.0\) Hz, OCH\(_2\)CH\(_3\)), 1.23–1.39 (br.s, 18H, (CH\(_2\))\(_2\)CH\(_3\), NHCH\(_2\)CH\(_2\)CH\(_2\)(CH\(_2\)CH\(_3\)), 1.46–1.63 (m, 4H, NHCH\(_2\)CH\(_2\)OCH\(_2\)CH\(_3\)), 1.96, 1.98, 2.0, 2.05 (s, 3H, 4 COCH\(_3\)), 2.46 (m, 4H, CH\(_2\)NCH\(_2\)Pip), 2.58 (br.s, 4H, CH\(_2\)NCH\(_2\)Pip), 2.92 (dd, \(J = 2.3, 16.7\) Hz, 1H, CHNH(OC)(OCH\(_2\)H)), 3.02 (d, \(J = 16.4\) Hz, 1H, CH\(_2\)NH(OC)(OCH\(_2\)H)), 3.09 (dd, \(J = 5.3, 16.7\) Hz, 1H, CHNH(OC)(OCH\(_2\)H)), 3.21 (ddddd, \(J = 4.8, 6.8, 8.0, 13.8\) Hz, 1H, CH\(_2\)NH), 3.34–3.54 (m, 6H, CH(OC)(OCH\(_2\)H), CHOC(OC)(OCH\(_2\)H)), 3.56–3.69 (m, 2H, CH\(_2\)OCH\(_2\)NH, CH\(_2\)OCH\(_2\)H)), 3.80 (ddddd, \(J = 2.2, 4.4, 10.1\) Hz, 1H, H-5), 4.05 (dd, \(J = 2.2, 12.5\) Hz, 1H, H-6), 4.29 (dd, \(J = 4.4, 12.5\) Hz, 1H, H-6), 4.98 (dd, \(J = 9.5, 9.6\) Hz, 1H, H-5), 5.05 (dd, \(J = 9.4, 10.1\) Hz, 1H, H-4), 5.97 (dd, \(J = 9.5, 9.8\) Hz, 1H, H-1), 5.75 (dd, \(J = 9.4, 9.6\) Hz, 1H, H-3), 7.31 (d, \(J = 9.8\) Hz, 1H, CH\(_2\)NH). \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 14.2, 15.7, 20.6, 20.6, 20.6, 20.8, 22.7, 26.2, 29.4, 29.5, 29.6, 29.7, 31.9, 40.2, 40.2, 53.2, 53.7, 61.4, 68.3, 70.5, 71.5, 71.5, 73.0, 73.8, 76.7, 76.7, 76.9, 77.2, 77.4, 77.8, 169.6, 169.9, 170.2, 170.4, 170.6, 171.1. HRMS ESI [M + H\(^+\)] calcd for C\(_{37}\)H\(_{53}\)N\(_4\)O\(_{13}\) 773.4543, found 773.4535.

4.2.3. General Procedure for Synthesis of Compounds 16a–f

NiCl\(_2\)(dme) (0.2 eq) and PhSiH\(_3\) (2 eq for each amide group) were added into a cylindrical pressure vessel with corresponding amide in toluene (1 M). The mixture was flushed with argon, tightly closed, and lowered into a preheated bath to 120 °C and stirred for 24 h. After the mixture was cooled, it was transferred to a separating funnel and organic
products were extracted with 2 M NaOH solution (3 \times 10 \text{ mL}). The combined organic extracts were washed with brine (3 \times 15 \text{ mL}), dried over Na$_2$SO$_4$, filtered, and evaporated in vacuo. The desired product was isolated by column chromatography.

1,9-Diamino-N$^9$-ethyl-N$^1$-Octadeyl-N$^3$N$^7$-dibenzy1-3,7-Diazaanonane (16a)

Yield 410 mg (66\%), colorless oil. Eluent: ACN-NH$_3$:H$_2$O (9:1). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.91 (t, $J$ = 7.0 Hz, 3H, (CH$_2$)$_3$CH$_3$), 0.71 (d, $J$ = 5.6 Hz, 14H, (CH$_2$)$_2$CH$_3$), 1.47–1.60 (m, 2H, CH$_2$CH$_2$(CH$_2$)$_2$), 2.34–2.58 (m, 2H, 4 NHCH$_2$), 3.38–3.46 (m, 4H, CH$_2$OCH$_2$), 3.48–3.54 (m, 2H, CH$_2$OCH$_2$H$_3$), 3.65 (dq, $J$ = 7.0, 9.3 Hz, 3H, NCH$_3$), 5.67–5.74 (m, 1H, Pip protons). $^{13}$C NMR (151 MHz, CD$_2$Cl$_2$) $\delta$ 12.4, 14.3, 16.0, 23.1, 26.6, 29.8, 29.9, 30.0, 30.1, 30.2, 32.4, 47.1, 51.6, 52.6, 53.4, 58.3, 65.6, 72.0, 72.3, 78.3. MS ESI m/z: [M + H]$^+$ calcd for C$_{25}$H$_{55}$N$_4$O$_2$ 443.4, found 443.4. LCMS r/t: 8.31 min.

N$^1$-Ethyl-N$^4$-[1-Octadecy1]Aminoethyl]Piperazin (16b)

Yield: 23\%, colorless oil. Eluent: ACN-NH$_3$:H$_2$O (9:1). $^1$H NMR (600 MHz, CD$_2$Cl$_2$) $\delta$ 0.88 (t, $J$ = 7.0 Hz, 3H, (CH$_2$)$_3$CH$_3$), 1.03 (t, $J$ = 7.2 Hz, 3H, NCH$_2$CH$_3$), 1.16 (t, $J$ = 7.0 Hz, OCH$_2$CH$_3$, 3H), 1.29 (br.s, (CH$_2$)$_2$CH$_3$, 14H), 1.51–1.57 (m, 3H, CH$_2$CH$_2$(CH$_2$)$_2$), 2.35 (q, $J$ = 7.2 Hz, 2H, NHCCH$_3$), 2.37–2.58 (m, 14H, 3CH$_2$NH, Pip protons), 2.58–2.71 (m, 4H, CH$_2$N(CH$_2$)$_2$NCH$_2$). 3.38–3.46 (m, 4H, CH$_2$OCH$_2$), 3.48–3.54 (m, 2H, CH$_2$OCH$_2$H$_3$), 3.65 (dq, $J$ = 7.0, 9.3 Hz, 1H, OCH$_2$H$_3$), 5.67–5.74 (m, 1H, Pip protons). $^{13}$C NMR (151 MHz, CD$_2$Cl$_2$) $\delta$ 12.4, 14.3, 16.0, 23.1, 26.6, 29.8, 29.9, 30.0, 30.1, 30.2, 32.4, 47.1, 51.6, 52.6, 53.4, 58.3, 65.6, 72.0, 72.3, 78.3. MS ESI m/z: [M + H]$^+$ calcd for C$_{25}$H$_{55}$N$_4$O$_2$ 443.4, found 443.4. LCMS r/t: 8.31 min.

N$^1$-Ethyl-N$^4$-[N-(rac-1-Decy1oxy-2-Ethoxyprop-3-yl]Amino]Ethylpiperazin (16d)

Yield 184 mg (38\%), colorless oil. Eluent: EA-MeOH-NH$_3$:H$_2$O (7:3:0.2). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.77–0.94 (t, $J$ = 6.3 Hz, 6H, CH(3H)$_2$), 1.18 (t, $J$ = 7.0 Hz, 3H, OCH$_2$CH$_3$), 1.25 (d, $J$ = 5.6 Hz, 14H, (CH$_2$)$_2$CH$_3$), 1.47–1.60 (m, 2H, CH$_2$CH$_2$(CH$_2$)$_7$), 2.34–2.58 (m, 12H, 2 CH$_2$N and Pip protons), 3.30–3.37 (m, 7H, CH$_2$OCH$_2$, CH$_2$OH). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 14.2, 14.2, 15.8, 22.7, 26.2, 26.2, 29.4, 29.6, 29.7, 29.7, 29.8, 32.0, 43.8, 46.7, 49.2, 51.6, 53.4, 57.7, 65.7, 71.8, 71.9, 77.7.
The optical density of the solution was measured at 540 nm using a Multiskan Sky microplate spectrophotometer (Thermo Scientific, Waltham, MA, USA). The percentage of viable cells was calculated from the absorbance of vehicle control (0.5% DMSO). Each experiment was repeated three times, and each concentration was tested in three replicates (see Supplementary Materials).

### Supplementary Materials

The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/molecules27196218/s1.

### Author Contributions

Conceptualization, A.N. and M.M.; methodology, G.C.T.; software, D.C.; investigation, A.N., V.M. and E.T.; resources, G.C.T., M.M., K.K. and M.Y.; data curation, A.N., V.M. and E.E.-S.; writing—original draft preparation, A.N.; writing—review and editing, M.M. and I.I.; visualization, A.N. and V.M.; supervision, M.M.; funding acquisition, M.M. All authors have read and agreed to the published version of the manuscript.
**Funding:** The reported study was funded by the Russian Foundation for Basic Research (RFBR) (project no. 19-33-90301) and by the Ministry of Science and Higher Education of the Russian Federation (project no. 0706-2020-0019).

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Acknowledgments:** This work was performed using the equipment of the Shared Science and Training Center for Collective Use RTU MIREA and supported by the Ministry of Science and Higher Education of the Russian Federation within the framework of agreement No. 075-15-2021-689 dated 01.09.2021.

**Conflicts of Interest:** The authors declare no conflict of interest.

**References**

1. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J. Clin.* **2021**, *71*, 209–249. [CrossRef] [PubMed]

2. Mansoori, B.; Mohammadi, A.; Davudian, S.; Shirjang, S.; Baradaran, B. The Different Mechanisms of Cancer Drug Resistance: A Brief Review. *Adv. Pharm. Bull.* **2017**, *7*, 339–348. [CrossRef] [PubMed]

3. Germain, N.; Dhayer, M.; Boileau, M.; Fovez, Q.; Kluza, J.; Marchetti, P. Lipid Metabolism and Resistance to Anticancer Treatment. *Biology* **2020**, *9*, 474. [CrossRef] [PubMed]

4. Casero, R.A.; Murray Stewart, T.; Pegg, A.E. Polyamine Metabolism and Cancer: Treatments, Challenges and Opportunities. *Nat. Rev. Cancer* **2018**, *18*, 681–695. [CrossRef]

5. Moinard, C.; Cynober, L.; de Bandt, J.P. Polyamines: Metabolism and Implications in Human Diseases. *Clin. Nutr.* **2005**, *24*, 184–197. [CrossRef]

6. Igarashi, K.; Kashiwagi, K. Polyamines: Mysterious Modulators of Cellular Functions. *Biochem. Biophys. Res. Commun.* **2000**, *271*, 559–564. [CrossRef]

7. Bercovich, Z.; Snapir, Z.; Keren-Paz, A.; Kahana, C. Antizyme Affects Cell Proliferation and Viability Solely through Regulating Cellular Polyamines. *J. Biol. Chem.* **2011**, *286*, 33778–33783. [CrossRef]

8. Saab, N.H.; West, E.E.; Bieszk, N.C.; Preuss, C.V.; Mank, A.R.; Casero, R.A.; Woster, P.M. Synthesis and Evaluation of Unsymmetrically Substituted Polyamine Analogues as Modulators of Human Spermidine/Spermine-N1-Acetyltransferase (SSAT) and as Potential Antitumor Agents. *J. Med. Chem.* **1993**, *36*, 2998–3004. [CrossRef]

9. Nichugovskiy, A.; Tron, G.C.; Maslov, M. Recent Advances in the Synthesis of Polyamine Derivatives and Their Applications. *Molecules* **2021**, *26*, 6579. [CrossRef]

10. Perevoshchikova, K.A.; Nichugovskiy, A.I.; Isagulieva, A.K.; Morozova, N.G.; Ivanov, I.V.; Maslov, M.A.; Shtil, A.A. Synthesis of Novel Lipophilic Tetraamines with Cytotoxic Activity. *Mendeleev Commun.* **2019**, *29*, 616–618. [CrossRef]

11. Varlamova, E.A.; Isagulieva, A.K.; Morozova, N.G.; Sh mendel, E.V.; Maslov, M.A.; Shtil, A.A. Non-Phosphorus Lipids as New Antitumor Drug Prototypes. *Russ. J. Bioorg. Chem.* **2021**, *47*, 965–979. [CrossRef]

12. Li, J.J. Name Reactions: A Collection of Detailed Mechanisms and Synthetic Applications. *Choice Rev. Online* **2014**, *52*, 52–1438. [CrossRef]

13. Khan, A.; Gamble, L.D.; Upton, D.H.; Ung, C.; Yu, D.M.T.; Ehteda, A.; Pandher, R.; Mayoh, C.; Hébert, S.; Jabado, N.; et al. Dual Targeting of Polyamine Synthesis and Uptake in Diffuse Intrinsic Pontine Gliomas. *Nat. Commun.* **2021**, *12*, 971. [CrossRef] [PubMed]

14. Ugi, I. The A-Addition of Immonium Ions and Anions to Isonitriles Accompanied by Secondary Reactions. *Angew. Chem. Int. Ed.* **1962**, *1*, 8–21. [CrossRef]

15. Giovenzana, G.B.; Tron, G.C.; Di Paola, S.; Menegotto, I.G.; Pirali, T. A Mimicry of Primary Amines by Bis-Secondary Diamines as Components in the Ugi Four-Component Reaction. *Angew. Chem.* **2006**, *118*, 1117–1120. [CrossRef]

16. Rabelo, W.F.; Echemendia, R. Synthesis of Novel 1,4 Naphthoquinone-Based Molecules by an Ugi-Type Four-Component Reaction. *Synth. Commun.* **2019**, *49*, 515–521. [CrossRef]

17. Pirali, T.; Callipari, G.; Ercolano, E.; Genazzani, A.A.; Giovenzana, G.B.; Tron, G.C. A Concise Entry into Nonsymmetrical Alkyl Polymamines. *Org. Lett.* **2008**, *10*, 4199–4202. [CrossRef]

18. Nichugovskiy, A.I.; Khrulev, A.A.; Perevoshchikova, K.A.; Cheshkov, D.A.; Morozova, N.G.; Maslov, M.A. Synthesis of Isonitrile Derivatives of Diglycerides and Carbohydrates as Intermediates for Multicomponent Ugi Reaction. *Russ. J. Bioorg. Chem.* **2021**, *47*, 929–938. [CrossRef]

19. Pretsch, E.; Bühmann, P.; Badertscher, M. *Structure Determination of Organic Compounds*; Springer: Berlin/Heidelberg, Germany, 2020; ISBN 978-3-662-62438-8.
20. She, E.X.; Hao, Z. A Novel Piperazine Derivative Potently Induces Caspase-Dependent Apoptosis of Cancer Cells via Inhibition of Multiple Cancer Signaling Pathways. *Am. J. Transl. Res.* 2013, 5, 622–633.

21. Tuncbilek, M.; Bilget Guven, E.; Onder, T.; Cetin Atalay, R. Synthesis of Novel 6-(4-Substituted Piperazine-1-Yl)-9-(β-D-Ribofuranosyl)Purine Derivatives, Which Lead to Senescence-Induced Cell Death in Liver Cancer Cells. *J. Med. Chem.* 2012, 55, 3058–3065. [CrossRef]

22. Sarı, C.; Nalçaoğlu, A.; Değirmencioğlu, I.; Celep Eyüpoğlu, F. Tumor-Selective New Piperazine-Fragmented Silicon Phthalocyanines Initiate Cell Death in Breast Cancer Cell Lines. *J. Photochem. Photobiol. B Biol.* 2021, 216, 112143. [CrossRef] [PubMed]

23. İbiş, K.; Nalbat, E.; Çalışkan, B.; Kahraman, D.C.; Cetin-Atalay, R.; Banoglu, E. Synthesis and Biological Evaluation of Novel Isoxazole-Piperazine Hybrids as Potential Anti-Cancer Agents with Inhibitory Effect on Liver Cancer Stem Cells. *Eur. J. Med. Chem.* 2021, 221, 113489. [CrossRef]

24. Saab, A.M.; Dobmeier, M.; Koenig, B.; Fabri, E.; Finotti, A.; Borgatti, M.; Lampronti, I.; Bernardi, F.; Efferth, T.; Gambari, R. Antiproliferative and Erythroid Differentiation of Piperazine and Triphenyl Derivatives against K-562 Human Chronic Myelogenous Leukemia. *Anticancer Res.* 2013, 33, 3027–3032. [PubMed]

25. Olsen, C.A.; Witt, M.; Jaroszewski, J.W.; Franzyk, H. Solid-Phase Polyamine Synthesis Using Piperazine and Piperidine Building Blocks. *Org. Lett.* 2003, 5, 4183–4185. [CrossRef] [PubMed]

26. Bałczewski, P.; Zurawiński, R.; Mikina, M.; Dudziński, B. Synthesis of Polyamino Nitriles, En Route to Acylpolyamine Neurotoxins, via the Regioselective Michael Cyanoethylation of Unprotected Polyamines. Unusual Behaviour of 1-(2-Aminoethyl)Piperazine. *Tetrahedron* 2009, 65, 8727–8732. [CrossRef]

27. Dömling, A.; Ugi, I. Multicomponent Reactions with Isocyanides. *Angew. Chem. Int. Ed.* 2000, 39, 3168–3210. [CrossRef]

28. Mumm, O. Umsetzung von Säureimidchloriden Mit Salzen Organischer Säuren Und Mit Cyankalium. *Ber. Dtsch. Chem. Ges.* 1910, 43, 886–893. [CrossRef]

29. La Spisa, F.; Feo, A.; Mossetti, R.; Tron, G.C. An Efficient Synthesis of Symmetric and Unsymmetric Bis-(β-Aminoamides) via Ugi Multicomponent Reaction. *Org. Lett.* 2012, 14, 6044–6047. [CrossRef]

30. Volkov, A.; Tinnis, F.; Slagbrand, T.; Trillo, P.; Adolfsson, H. Chemoselective Reduction of Carboxamides. *Chem. Soc. Rev.* 2016, 45, 6685–6697. [CrossRef]

31. Abdel-Magid, A.F. Reduction of C=O to CHOH by Metal Hydrides. In *Comprehensive Organic Synthesis*, 2nd ed.; Elsevier: Amsterdam, The Netherlands, 2014; Volume 8, ISBN 9780080977430.

32. Itsuno, S. Boron Hydride Reduction. *ACS Symp. Ser.* 2016, 1236, 241–274. [CrossRef]

33. Simmons, B.J.; Hoffmann, M.; Hwang, J.; Jackl, M.K.; Garg, N.K. Nickel-Catalyzed Reduction of Secondary and Tertiary Amides. *Org. Lett.* 2017, 19, 1910–1913. [CrossRef]

34. Hie, L.; Fine Nathel, N.F.; Shah, T.K.; Baker, E.L.; Hong, X.; Yang, Y.F.; Liu, P.; Houk, K.N.; Garg, N.K. Conversion of Amides to Esters by the Nickel-Catalysed Activation of Amide C-N Bonds. *Nature* 2015, 524, 79–83. [CrossRef] [PubMed]

35. Huang, Y.; Hager, E.R.; Phillips, D.L.; Dunn, V.R.; Hacker, A.; Frydman, B.; Kink, J.A.; Valasinas, A.L.; Reddy, V.K.; Marton, L.J.; et al. A Novel Polyamine Analog Inhibits Growth and Induces Apoptosis in Human Breast Cancer Cells. *Clin. Cancer Res.* 2003, 9, 2769–2777. [PubMed]

36. Nosova, Y.N.; Zenin, I.V.; Maximova, V.P.; Zhidkova, E.M.; Kirsanov, K.I.; Lesovaya, E.A.; Lobas, A.A.; Gorshkov, M.V.; Kovaleva, O.N.; Milaeva, E.R.; et al. Influence of the Number of Axial Bexarotene Ligands on the Cytotoxicity of Pt(IV) Analogs of Oxpaliplatin. *Bioinorg. Chem. Appl.* 2017, 2017, 4736321. [CrossRef] [PubMed]

37. Koch, J.; Mönch, D.; Maaß, A.; Görg, M.; Hehr, T.; Leibold, T.; Schlitt, H.J.; Dahlke, M.H.; Renner, P. Three Dimensional Cultivation Increases Chemo- and Radioreistance of Colorectal Cancer Cell Lines. *PLoS ONE* 2021, 16, e0244513. [CrossRef] [PubMed]

38. Armarego, W.L.F.; Perrin, D.D. *Purification of Laboratory Chemicals Eighth Edition*; Butterworth-Heinemann: Oxford, UK, 2017; ISBN 978-0-12-805457-4.