Synthesis and Characterization of Macrocyclic Chiral Tröger’s Base Phenhomazine Candidates as Anticancer Agent

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1,4,7,10-Tetraoxa[10](2,8)trögerophane 5 was synthesized from its corresponding precursors. Heating of 2 with p-nitrophenoxide afforded bis(p-nitrophenyl)ether 3, which was treated with hydrazine hydrate to give bis(p-aminophenyl)ether 4. Treatment of 4 with paraformaldehyde and trifluoroacetic anhydride gave trögerophane 5. Reaction of 5 with trifluoroacetic anhydride afforded phenhomazine derivative 6, which was treated with potassium carbonate to afford tetrahydrophenhomazine 7. Finally, reaction of 7 with phenacylchloride, bromoacetic acid, or ethyl bromoacetate in the presence of triethyl amine under reflux, afforded the corresponding macrocyclic compounds 8, 9 and 10, respectively. The synthesized trögerophane, precursors and its newly synthesized phenhomazines derivatives were screened for anticancer activity. Results revealed that 1,4,7,10-tetraoxa[10](2,8)trögerophane had a promising selectivity towards colon cancer cell line with an IC50 of 92.7 µg/ml.

Keywords: chiral macrocyclic, tröger’s base, trögerophane, phenhomazines, anticancer activity

INTRODUCTION

Tröger’s base, “5,11-methano-2,8-dimethyl-5,6,11,12-tetrahydrodibenzo[b,f][1,5]diazocine” (Figure 1), was first prepared by Julius Tröger in 1887 by condensing dimethoxymethane with p-toluidine in the presence of hydrochloric acid (Tröger, 1887). In 1998, Alhussein et al. have reported a series of macrocyclic Tröger bases and their optical and complexing properties and named them for the first time as Trögerophanes (Ibrahim, et al., 1998; Miyahara, et al., 1999).

Although Tröger base and its analogues have attracted interest of many researcher groups due to their fascinating structures and properties (Yuan, et al., 2011), however, attention has been inadequately focused on these compounds from the biological point of view (Bailly, et al., 2000; Baldeyrou, et al., 2002; Manda, et al., 2014; Yang, et al., 2015). In addition, some of macrocyclic hetero-nitrogen derivatives have been synthesized (Abu-Ghalia, et al., 2012; Amr, et al., 2019; Naglah, et al., 2020) and have shown promising biological activity, i.e. analgesic and anticonvulsant (Amr, 2005),
derivatives and tested their anticancer activities. In continuation of our previous work in biology and pharmacology (Thagfan, et al., 2018), anticancer (Amr et al., 2018), as well as biological activities (Khayyat and Amr, 2014). In view of these observations and in continuation of our previous work in macrocyclic chemistry, we synthesized some new Trögerophane derivatives and tested their anticancer activities.

**MATERIALS AND METHODS**

**Materials**

Triethylene glycol bis(p-aminophenyl) ether 4 was synthesized according to previously reported procedure (Ibrahim, et al., 1998). Paraformaldehyde, methanol, trifluoroacetic acid, hydrazine hydrate, triethyl amine, phenacyl chloride, bromoacetic acid, and paraformaldehyde (0.5 g) was added portion-wise while stirring. To the remaining residue, ethanol (20 ml) was added and the mixture was boiled under atmospheric pressure to get rid of the least traces of the anhydride. The remaining ethanol was removed under vacuum. The resulting colorless viscous liquid was treated with diethyl ether to afford colorless needles of the desired salt according to previously reported procedure (Ibrahim, et al., 1998).

**Synthesis of N-Trifluoroacetamide Phenomazime Trifluoroacetate (6)**

The trögerophane 5 (0.239 g, 0.0065 mol) in trifluoroacetic anhydride (10 ml) was refluxed for 65 h, after which the unreacted anhydride was recovered using a Dean-Stark trap. To the remaining residue, ethanol (20 ml) was added and the mixture was boiled under atmospheric pressure to get rid of the least traces of the anhydride. The remaining ethanol was removed under vacuum. The resulting colorless viscous liquid was treated with diethyl ether to afford colorless needles of the desired salt 6. Yield 92%, m.p. 150–151°C (Dec.). IR (film): ν = 1697 (C=O) cm⁻¹. 1H NMR (300 MHz, CDCl₃): δ = 7.27 (d, 1H, δ = 8.91 Hz, Ar-H), 7.23–7.86 (brs, 2H, N=H, exchangeable with D₂O), 6.94 (d, 1H, J = 16.7 Hz, -CH₂-N), 6.27 (dd, 2H, J = 9.7 Hz, Ar-Ch₂), 6.54 (d, 1H, J = 2.6 Hz, Ar-H), 6.44 (d, 1H, J = 2.97 Hz, Ar-Ch₂), 5.48 (d, 1H, J = 14.5 Hz, Ar-CH₂-N), 4.84 (d, 1H, J = 13.5 Hz, Ar-CH₂-N), 3.95–3.99 (m, 4H, O-CH₂-CH₂), 4.23 (d, 1H, J = 14.9 Hz, Ar-CH₂-N), 4.22 (d, 1H, J = 13.5 Hz, Ar-CH₂-N), 3.68–3.51 (m, 4H, O-CH₂-CH₂), 3.31–3.18 (m, 4H, O-CH₂-CH₂). MS (EI, 70 eV): m/z (%) = 368 (32) [M⁺]. C₂₁H₂₄N₂O₇ (368.43). Calcd: C 68.46; H 6.57; N 7.60; found: C 68.29; H 6.57; N 7.45.

**Synthesis of 1,4,7,10-Tetraoxa[10](2,8)-trögerophane (5)**

To a mixture of triethylene glycol bis(p-aminophenyl) ether 4 (0.368 g, 0.0065 mol) and potassium carbonate (1.01 g) in methanol (15 ml) was stirred at 50 °C for 3 h. The solvent was evaporated under reduced pressure and the residue was treated with chloroform. The undissolved matter was filtered off, and the filtrate was evaporated under vacuum to give the free base as a white solid. The solid was recrystallized from ethanol/methylene chloride. Yield 43%, m.p. 235°C (Lit. mp: 234–235°C [2]). IR (film): ν = 3030, 3000 (C-H aromatic), 2930, 2900 (C-H aliphatic), 1605 (C=C stretching) cm⁻¹. 1H NMR (300 MHz, CDCl₃): δ = 2.53–2.70 (m, 4H, O-CH₂-CH₂), 3.50–3.63 (m, 4H, O-CH₂-CH₂), 3.98 (d, 2H, J = 16.7 Hz, -CH₂-N), 4.09–4.22 (m, 4H, O-CH₂-CH₂), 4.46 (s, 2H, -N-CH₂-N-), 4.57 (d, 2H, J = 16.7 Hz, -CH₂-N), 6.49 (d, 2H, J = 2.97 Hz, Ar-H), 6.83 (dd, 2H, J₁ = 5.94 Hz, J₂ = 2.64 Hz, Ar-H), 7.01 (d, 2H, J = 8.58 Hz, Ar-H). 13C NMR (75 MHz, CDCl₃): δ = 155.41, 141.58, 128.66, 125.07, 118.24, 116.86, 72.78, 69.88, 69.51, 68.40, 60.63 (21 C). MS (EI, 70 eV): m/z (%) = 235 (42) [M⁺]. C₂₅H₂₄N₂O₁₇F₆ (566.45). Calcd: C 50.89; H 4.27; N 4.95; found: C 51.03; H 4.40; N 4.94.

**Synthesis of 1,4,7,10-Tetraoxa[10](2,8)-5,6,11,12-tetraphydrophephonazime (7)**

A mixture of trifluoroacetate salt 6 (0.368 g, 0.0065 mol) and potassium carbonate (1.01 g) in methanol (15 ml) was stirred at 50 °C for 3 h. The solvent was evaporated under reduced pressure and the residue was treated with chloroform. The undissolved matter was filtered off, and the filtrate was evaporated under vacuum to give the free base as a white solid. The solid was recrystallized from ethanol/methylene chloride. Yield 43%, m.p. 235°C (Lit. mp: 234–235°C [2]). IR (film): ν = 3030, 3000 (C-H aromatic), 2930, 2900 (C-H aliphatic), 1605 (C=C stretching) cm⁻¹. 1H NMR (300 MHz, CDCl₃): δ = 2.53–2.70 (m, 4H, O-CH₂-CH₂), 3.50–3.63 (m, 4H, O-CH₂-CH₂), 3.98 (d, 2H, J = 16.7 Hz, -CH₂-N), 4.09–4.22 (m, 4H, O-CH₂-CH₂), 4.46 (s, 2H, -N-CH₂-N-), 4.57 (d, 2H, J = 16.7 Hz, -CH₂-N), 6.49 (d, 2H, J = 2.97 Hz, Ar-H), 6.83 (dd, 2H, J₁ = 5.94 Hz, J₂ = 2.64 Hz, Ar-H), 7.01 (d, 2H, J = 8.58 Hz, Ar-H). 13C NMR (75 MHz, CDCl₃): δ = 155.41, 141.58, 128.66, 125.07, 118.24, 116.86, 72.78, 69.88, 69.51, 68.40, 60.63 (21 C). MS (EI, 70 eV): m/z (%) = 235 (42) [M⁺]. C₂₅H₂₄N₂O₁₇F₆ (566.45). Calcd: C 50.89; H 4.27; N 4.95; found: C 51.03; H 4.40; N 4.94.
powder which could be recrystallized from ethyl acetate to afford 7 as colorless crystals. Yield 79%, m.p. 172–173 °C. IR (film): ν = 3397 (N-H) cm⁻¹. 1H NMR (300 MHz, CDCl₃); δ = 6.68 (d, 1H, J = 2.51 Hz, Ar-H), 6.66 (d, 1H, J = 2.51 Hz, Ar-H), 6.50 (d, 2H, J = 2.51 Hz, Ar-H), 6.49 (d, 1H, J = 2.51 Hz, Ar-H), 4.67 (s, 1H, Ar-H), 4.79 (d, 2H, J = 13.55 Hz, Ar-CH₂-N), 4.29–4.20 (m, 2H, O-CH₂-CH₂), 4.08–3.96 (m, 2H, O-CH₂-CH₂), 3.97 (d, 2H, J = 14.05 Hz, Ar-CH₂-N), 3.96–3.72 (br.s, 2H, N-H, exchangeable with D₂O), 3.69 (d, 2H, J = 13.51 Hz, Ar-CH₂-N), 3.38 (m, 2H, O-CH₂-CH₂), 2.88–2.79 (m, 2H, O-CH₂-CH₂), 2.82 (m, 2H, O-CH₂-CH₂). 13C NMR (75 MHz, CDCl₃); δ = 175.3, 147.2, 145.3, 140.9, 125.9, 113.6, 109.9, 107.5, 68.3, 67.8, 67.1, 62.9 (24 C). MS (EI, 70 eV): m/z (%) = 356 (25) [M⁺], C₂₈H₂₈N₅O₆ (528.25). Calcd: C 67.34; H 6.85; N 7.77.

**Synthesis of N,N’-Diphenacyl Phenomazine (8)**

To a mixture of the tetrahydrophenomazine 7 (0.356 g, 0.001 mol), and phenacyl chloride (0.308 g, 0.002 mol) in ethanol (100 ml), triethylamine (1.0 ml) was added dropwise. The reaction mixture was refluxed for 2 h. The reaction was followed up by TLC. At the end, the reaction mixture was evaporated under vacuum. The solid formed was collected and recrystallized from ethyl acetate to afford 8. Yield 70.3%, m.p. 210 °C. IR (film): ν = 1732, 1729, 1245, 1187 cm⁻¹. 1H NMR (300 MHz, CDCl₃); δ = 6.65 (d, 2H, J = 8.58 Hz, Ar-H), 6.58 (dd, 2H, J = 6.24 Hz, J₂ = 8.58 Hz, Ar-H), 6.40 (d, 2H, J = 6.24 Hz, Ar-H), 5.54 (d, 2H, J = 14 Hz, Ar-CH₂-N), 4.25 (s, 4H, N-CH₂-CO-), 4.36 (d, 2H, J = 14 Hz, Ar-CH₂-N), 4.28–4.20 (m, 2H, O-CH₂-CH₂), 4.10 (q, 4H, J = 8 Hz, CH₃-CH₂-CO-), 4.03–3.95 (m, 2H, O-CH₂-CH₂), 3.62–3.44 (m, 4H, O-CH₂-CH₂), 3.37–3.16 (m, 2H, O-CH₂-CH₂), 2.99–2.82 (m, 2H, O-CH₂-CH₂). 13C NMR (75 MHz, CDCl₃); δ = 170.1, 147.2, 142.1, 125.5, 112.3, 109.3, 107.7, 68.3, 67.8, 67.3, 61.0, 60.6, 58.5, 14.2 (28 C). MS (EI, 70 eV): m/z (%) = 528 (22) [M⁺]. C₃₅H₂₈N₄O₆ (559.52). Calcd: C 63.62; H 6.86; N 5.30; found: C 63.31; H 6.18; N 4.93.

**Anti-Cancer Screening**

The newly synthesized derivatives were assessed against three cancer cell lines; namely hepatocellular carcinoma (HepG-2), breast adenocarcinoma (MCF-7) and Colon Carcinoma (HCT-116) using standard MTT assay (El-Faham, et al., 2014; Elsayed, et al., 2016; Amr, et al., 2018). The assay depends on the mitochondrial reduction of yellow MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) to purple formazan. Briefly, cells were propagated in RPMI-1640 medium supplemented with 1% antibiotic-antimycotic mixture and 1% L-glutamine at 37°C and 5% CO₂. Upon investigation, cells were plated at a concentration of 104 cells/well in 96-well microtiter plates and incubated for 24 h. Accordingly, exhausted medium was aspirated and fresh medium was added. Then cells were treated with different concentrations of the prepared compounds (0.78–100.00 μg/ml), and incubation proceeded for another 48 h. Afterwards, medium was aspirated and 40 μl MTT (2.5 mg/ml/well) was added and the plates were further incubated for 4 h. The reaction was terminated by the addition of 200 μl/well of 10% sodium dodecyl sulfate, and the plates were incubated overnight to dissolve the developed formazan dye. Doxorubicin was used as positive control. DMSO is the vehicle used for dissolution of compounds, and its final concentration on the cells was less than 0.2%. Absorbance was read using a microplate multi-well reader at 595/620 nm. Results were statistically evaluated using an independent t-test and SPSS 11.
program. The percentage inhibition in cell viability was calculated:

\[
\frac{\text{Absorbance}_{\text{extract}}}{\text{Absorbance}_{\text{DMSO}}} - 1 \times 100\%
\]

A probit analysis was carried for IC50 and IC90 determination using the SPSS 11 program.

RESULTS AND DISCUSSION

Synthesis
In the present study, we synthesized some newly phenhomazine derivatives, 6–10, using 1,4,7,10-tetraoxa[10](2,8)trögerophane, 5 as a starting material. The rigidity, V-shape, and the presence of a C2 axis of symmetry, have imparted unique structural features on the molecule. Including crown ether oxygens was thought to provide the macrocycle with many important and interesting characteristics. Accordingly, oxygen atoms can increase the solubility in organic solvents by taking advantage of the flexibility of the ether linkage. Also, crown ether linkage can provide the macrocycle with complexing capabilities. In addition, it can keep the chirality of the molecule unchanged when the endomethylene bridge is removed. Therefore, increasing the energy barrier against inversion of the dibenzodiazocine moiety will produce in one fixed conformation for this macrocycle. Earlier, we have reported the synthesis of this trögerophane 5 (Ibrahim, et al., 1998; Miyahara, et al., 1999). In the reported method, the intramolecular condensation cyclization of 4 to form 5 in 45% yield, was carried out by reaction with 37% formalin in the presence of concentrated hydrochloric acid under moderately dilute conditions in ethanol at room temperature for 13 days. In order to reduce longer reaction time (13 days) as well as higher solvent consumption, a wide variety of reaction conditions were searched by analyzing the products via HPLC. From the modified method, it can be concluded that raising the reaction temperature to 60–70 °C and using TFA with conc. HCl, and replacing formalin with p-formaldehyde, shortens the reaction time to 18 h, as well as decreasing the amount of consumed ethanol without significantly affecting the yields of trögerophane 5 (43%) (Scheme 1).

Treatment of trögerophane 5 with refluxing trifluoroacetic anhydride afforded the N-trifluoroacetamide phenhomazine trifluoroacetate 6, which was stirred with potassium carbonate in methanol for 3 h to afford a good yield of 1,4,7,10-tetraoxa[10](2,8)-5,6,11,12-tetrahydrophenhomazine 7 (Scheme 2). The structures of both 6 and 7 were confirmed on the basis of their elemental and spectral data. The IR spectrum of 7 reveals only one absorption band for the N-H stretching at ν 3398 cm⁻¹ indicating the symmetry of the molecule and the absence of intramolecular hydrogen bonding between the secondary amine protons and the transanular nitrogen. 1H-NMR spectrum showing two N-H protons appearing as broad singlet at δ 3.96–3.72 ppm is consistent with the assumed. Reaction of tetrahydrophenhomazine 7 with active electrophiles, namely phenacyl chloride, bromoacetic acid, and ethyl bromoacetate, in the presence of triethyl amine under reflux, afforded the corresponding bis(p-nitrophenyl)ether 3, which was treated with hydrazine hydrate in the presence of 5% Pd/C as catalyst to give bis(p-aminophenyl)ether 4 (Ibrahim, et al., 1998; Miyahara, et al., 1999). In the reported method, the intramolecular condensation cyclization of 4 to form 5 in 45% yield, was carried out by reaction with 37% formalin in the presence of concentrated hydrochloric acid under moderately dilute conditions in ethanol at room temperature for 13 days. In order to reduce longer reaction time (13 days) as well as higher solvent consumption, a wide variety of reaction conditions were searched by analyzing the products via HPLC. From the modified method, it can be concluded that raising the reaction temperature to 60–70 °C and using TFA with conc. HCl, and replacing formalin with p-formaldehyde, shortens the reaction time to 18 h, as well as decreasing the amount of consumed ethanol without significantly affecting the yields of trögerophane 5 (43%) (Scheme 1).

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corresponding N,N’-disubstituted phenhomazines 8, 9 and 10, respectively (Scheme 2).

The IR spectrum of N, N’-diphenacyl phenhomazine 8 revealed two bands at \( \nu = 1698, 1694 \text{ cm}^{-1} \) indicating the phenacyl C=O bonds. In case of the N,N’-dicarboxymethyl phenhomazine 9, a broad band at \( \nu = 3400–2800 \text{ cm}^{-1} \) was clearly indicating that hydrogen bonded carboxylic O-H, and others at \( \nu = 1710, 1706 \text{ cm}^{-1} \) were due to the C=O of the carboxylic group. Furthermore, N,N’-diethoxycarbonylmethyl phenhomazine 10, gave bands at \( \nu = 1732, 1729 \text{ cm}^{-1} \) which can be related to the ester C=O bonds. In addition to these IR data, the absence of the stretching vibration band of the N-H of the tetrahydrophenhomazine, proved that the electrophilic substitution reaction has occurred as expected. In addition to their 13C-NMR, which were consistent with the proposed structures of 8, 9, and 10, their 1H NMR spectra revealed highly indicative peaks which supported the claimed structures. For example, the singlet at \( \delta = 4.5 \text{ ppm} \) indicated 4 protons of the two methylene groups of the phenacyl moiety. The singlet at \( \delta = 12.5 \text{ ppm} \) in the 1H NMR spectrum of 9 is quiet enough to confirm the presence of the carboxylic protons. Finally, the presence of a quartet at \( \delta = 4.10 \text{ ppm} \), and a triplet at \( \delta = 1.11 \text{ ppm} \) with the same coupling constant (\( J = 8 \text{ Hz} \)), proved the presence of the ethyl group protons in the structure of 10.
Anticancer Activity
The cytotoxic potentials of the prepared compounds 2–10 against the investigated human tumor cell lines HCT-116, HepG-2 and MCF-7) were investigated using standard MTT assay with doxorubicin as the reference drug. DMSO was used as the negative control. Cells were exposed to different concentrations of the prepared compounds (0.78–100.00 μg/ml). Results presented in Figure 2 show that only trögerophane 5 had promising cytotoxic effects against HCT-116 carcinoma cell, where the obtained with IC50 recorded 92.7 μg/ml. Other tested compounds showed some sort of weak cytotoxicity, however, the investigated concentration range was not appropriate to obtain IC50 values for these compounds. Results also revealed that the obtained IC50 value for the most potent compound, 5, against HCT-116, was almost similar to that obtained by the tested positive drug, doxorubicin (85.3 μg/ml).

Results showed that different synthesized derivative reacted differently towards various cell lines. This is expected, since different cell types react differently towards affecting compounds due to their inherent differences in membrane structures and functions (Kaplánek et al., 2015; Elsayed, et al., 2016; Amr, et al., 2018). Furthermore, our results revealed that the prepared trögerophane 5 had showed the most promising cytotoxic effect against colon cancer cell line. This is in good agreement with those results published earlier, where Gaslonde et al. (2011) reported the cytotoxic potentials of their prepared trögerophanes against L1210 leukemia and KB-3-1 solid tumor cell lines. They also found that the prepared trögerophane were more potent than their corresponding parent molecules. Furthermore, Kaplánek et al. (2015) synthesized and evaluated the anticancer potentials of different hydrazone derivatives prepared based on tröger’s base structure. They also reported promising cytotoxic potentials against various cancer cell lines ranging from 0.05 to >100 μM. However, it is difficult to compare our obtained IC50 values with those previously reported in the literature against the same cell line due to different descriptors of activities, i.e IC50, EC50, GI50, etc.), different structures, as well as different experimental conditions.

DATA AVAILABILITY STATEMENT
The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS
The listed authors contributed to this work as described in the following: AI, KA, NH, and ME gave the concepts of the work, interpretation of the results, the experimental part and prepared the manuscript, HH, and AA cooperated in the preparation of the manuscript and performed the revision before submission. KM and EE contributed to the anticancer activity. All authors have read and agreed to the published version of the manuscript.

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REFERENCES

Abu-Ghalia, M. H., Abd El-Hamid, M., Zweel, M. A., Amr, A. E., and Moafi, S. A. (2012). Synthesis and reactions of new chiral linear and macrocyclic tetra- and penta-peptide candidates. Z. Naturforsch. 67b, 806–818. doi:10.5560/ZNB.2012-0116

Al Thagafi, S. S., Fayed, A. A., Bahshwan, S. A., Amr, A. E., Aljuhani, N., Al-Omar, M. A., et al. (2018). Pharmacological activities of some synthesized chiral macrocyclic pentapeptide Schiff base candidates. Biomedical Research 29, 3605–3609. doi:10.4066/biomedicalresearch.29-18-1058

Alanazi, M. M., Amr, A. E., Naglah, A. M., Abdel-Mageid, R. E., and Elsayed, E. A. (2020). Anti-proliferate activity and 5α-reductase inhibitors of chiral macrocyclic (na-di-nicotinoyl)[1-phenylalaninyl-l-leucinyl]pentapeptide candidates against Incap and pc-3 prostate cancer cell lines. J. Sci. Ind. Res. 79, 60–65. Available at: http://nopr.niscair.res.in/handle/123456789/53460

Amr, A. E., Abo-Ghalia, M. H., and Abdalla, M. M. (2006). Synthesis of novel macrocyclic peptido-calix[4]arenes and peptidopyridines as precursors for potential molecular metallacages, chemosensors and biologically active candidates. Z. Naturforsch. 61b, 1335–1345. doi:10.1515/znb-2006-1104

Amr, A. E., Abo-Ghalia, M. H., Moustafa, G. O., Al-Omar, M. A., Nossir, E., and Elsayed, E. A. (2018). Design, synthesis and docking studies of novel macrocyclic pentapeptides as anticancer multi-targeted kinase inhibitor. Molecules 23, 2416. doi:10.3390/molecules23102416

Amr, A. E., El-Naggar, M., Al-Omar, M. A., Elsayed, E. A., and Abdalla, M. M. (2018). In Vitro and in Vivo anti-breast cancer activities of some synthesized pyrazolinyl-estradi-17-one candidates. Molecules 23, 1572. doi:10.3390/molecules23071572

Amr, A. E., Naglah, A. M., Sabry, N. M., Ibrahim, A. A., Elsayed, E. A., and Attar, A. (2019). Synthesis and investigation of 3,5-bis-linear and macrocyclic tripeptidopyridine candidates by using l-valine, N,N′-(3,5-pyridinediylidicarboxyl)bis-dimethyl ester as synthon. Z. Naturforsch. B Chem. Sci. 74b, 473–478. doi:10.1515/znb-2019-0006

Amr, A. E. (2005). Synthesis of some new linear and chiral macrocyclic pyridine carbazides as analgesic and anticonvulsant agents. Z. Naturforsch. 60b, 990–998. doi:10.1515/znb-2005-0914

Arab, M. E., Fléfé, E. M., Sabry, N. M., and Amr, A. E. (2016). Synthesis and antimicrobial activity of some linear dipptide pyridine and macrocyclic pentaaazapyrindyl candidates. Z. Naturforsch. 71, 803–810. doi:10.1515/znb-2016-0018

Baillie, C., Laine, W., Demeunynck, M., and Lhomme, J. (2000). Enantiospecific recognition of DNA sequences by a proflavine Tröger base. Biochem. Biophys. Res. Commun. 273, 681–685. doi:10.1006/bbrc.2000.2997

Baldeyrou, B., Tardy, C., Bailly, C., Colson, P., Houssier, C., Charmantray, F., et al. (2002). Synthesis and DNA interaction of a mixed proflavine-phenanthroline Tröger base. Eur. J. Med. Chem. 37, 315–322. doi:10.1016/S0223-5234(02)01356-9

El-Faham, A., Elzatahry, A., Al-Othman, Z., and Elsayed, E. A. (2014). Facile directed to the corresponding author.
Ibrahim, A. A., Matsumoto, M., Miyahara, Y., Izumi, K., Suenaga, M., Shimizu, N., et al. (1998). Synthesis and properties of a new series of trögerophanes. *J. Heterocycl. Chem.* 35, 209–215. doi:10.1002/jhet.5570350139

Johnson, R. A., Gorman, R. R., Wnuk, R. J., Crittenden, N. J., and Aiken, J. W. (1993). Tröger's base. An alternate synthesis and a structural analog with thromboxane A2 synthetase inhibitory activity. *J. Med. Chem.* 36, 3202–3206. doi:10.1021/jm00073a023

Kaplánek, R., Havlík, M., Dolenský, B., Rak, J., Džubák, P., Konečný, P., et al. (2015). Synthesis and biological activity evaluation of hydrazone derivatives based on a Tröger's base skeleton. *Bioorg. Med. Chem.* 23, 1651–1659. doi:10.1016/j.bmc.2015.01.029

Khayyat, S., and Amr, Ael-G. (2014). Synthesis and biological activities of some new (Nα-dinicotinoyl)-bis-L-leucyl linear and macrocyclic peptides. *Molecules* 19, 10698–10716. doi:10.3390/molecules190810698

Manda, B. R., Alla, M., Ganji, R. J., and Addlagatta, A. (2014). Discovery of Tröger's base analogues as selective inhibitors against human breast cancer cell line: design, synthesis and cytotoxic evaluation. *Eur. J. Med. Chem.* 86, 39–47. doi:10.1016/j.ejmech.2014.08.044

Miyahara, Y., Izumi, K., Ibrahim, A. A., and Inazu, T. (1999). Novel C2 chiral diamine ligands derived from cyclic Tröger bases. *Tetrahedron Letters* 40, 1705–1708. doi:10.1016/S0040-4039(99)00032-5

Negah, A. M., Amr, A. E., Abdel-Mageid, R. E., Al-Omar, M. A., and Abd El-Salam, O. I. (2020). Synthesis of chiral 3,5-bis(1-phenylalaninyl-l-leucinyl)pyridine Schiff base and their macrocyclic carboxamidate derivatives using 3,5-bis(1-phenylalaninyl)-pyridine methyl ester. *Z. Naturforsch. B Chem.* 75b, 251–258. doi:10.1515/znb-2019-0146

Paul, A., Maji, B., Misra, S. K., Jain, A. K., Munisippa, K., and Bhattacharya, S. (2012). Stabilization and structural alteration of the G-quadruplex DNA made from the human telomeric repeat mediated by Tröger’s base based novel benzimidazole derivatives. *J. Med. Chem.* 55, 7460–7471. doi:10.1021/jm300442r

Thirunayanan, G. (2017). Antimicrobial and insect antifeedant activities of some Tröger’s bases. *Arab. J. Chem.* 10, S636–S643. doi:10.1016/j.arabjc.2012.10.025

Tröger, J. (1887). Ueber einige mittelst nascirenden Formaldehydes entstehende Basen. *J. Prakt. Chem.* 36, 225–245. doi:10.1002/prac.18870360123

Yang, Z., Zhang, H., Yu, B., Zhao, Y., Ma, Z., Ji, G., et al. (2015). Azo-functionalized microporous organic polymers: synthesis and applications in CO2 capture and conversion. *Chem Commun (Camb)* 51, 11576–11579. doi:10.1039/c5cc03151f

Yuan, C., Xin, Q., Liu, H., Wang, L., Jiang, M., and Tao, X. (2011). Λ-shaped optoelectronic materials based on Tröger’s base. *Sci. China Chem.* 54, 587–595. doi:10.1007/s11426-011-4224-z

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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