ACS OMEGA

http://pubs.acs.org/journal/acsodf

Article

Efficient Synthesis of Various Substituted (Thio)Ureas, Semicarbazides, Thiosemicarbazides, Thiazolidones, and Oxadiazole Derived from [2.2]Paracyclophane

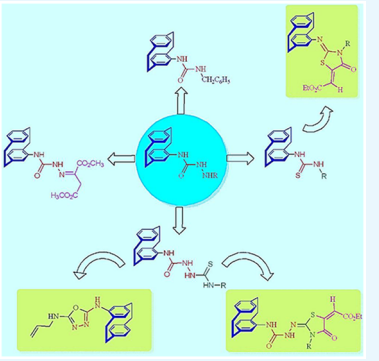
Mohammed B. Alshammari, Ashraf A. Aly,* Stefan Bräse,* Martin Nieger, and Lamiaa E. Abd El-Haleem

Cite This: *ACS Omega* 2022, 7, 12879−12890

Read Online

ACCESS | Metrics & More | Article Recommendations

ABSTRACT: The strategies of the syntheses of various (thio)ureas, semicarbazides, thiosemicarbazides, thiazolidones, and oxadiazole derived from the [2.2]paracyclophane molecule are achieved starting with 4-(2.2]paracyclophanyl)isocyanate. The structures of the obtained products were elucidated by NMR, mass spectrometry, and infrared (IR) spectroscopy in addition to high-resolution mass spectrometry (HRMS). X-ray structure analysis was also used to prove the assigned structure.



1. INTRODUCTION

[2.2]Paracyclophane (PC) chemistry has evolved from the functional molecules to functional materials and from the synthetic curiosity to emerging applications in asymmetric synthesis, energy materials, π-stacked polymers, and functional parylene coatings (i.e. polymer made by polymerization of PC induced by vapor-phase pyrolysis).[1−4] [2.2]Paracyclophane is also described as a rigid molecule within the interior of the conjugated segment with an otherwise similar aspect ratio to the phenylene unit. The intermolecular interactions in PC involving aromatic rings are the key processes in both chemical and biological recognition.[5]

Recently, it has been shown that connecting heterocycles with the PC moiety showed anticancer activity as in the case of paracyclophanyl-dihydronaphtho[2,3-*d*]thiazoles and paracyclophanyl-thiazolium bromides.[6] Among the following three assigned series **I**−**III** of the synthesized paracyclophanyl-heterocycles (Figure 1), series I having 1,4-dihydronaphthoquinone, was found as more active as antiproliferative agents than their naphthalene-containing congeners (series II and III) toward the SK-MEL-5 melanoma cell line.[6]

Previously, we reported the various classes of connection between PC and heterocycle moieties.[7] Aly et al. synthesized heterocycles conjugated to [2.2]paracyclophane such as five-membered rings (i.e., imidazolinone,[8] pyrrole,[9] triazolethiones, and substituted oxadiazoles[10]) together with six-membered rings (i.e., pyridine).[11,12]

It was reported that some marketed drugs had been found to contain the *N*-acylhydrazone motif in their structures, e.g., azumolene, carbazochrome, dantrolene, nitrofurantoin, nitrofurazone, nifuroxazide, and testosterone 17-enanthate 3-benzilic acid hydrazone.[13] More specifically, acylhydrazide-based compounds have shown antioxidant activities.[14] Hydrazides and carbohydrazides have been described as useful building blocks for the assembly of various heterocyclic rings.[15−19] Ureas and thioureas in combination with benzothiazoles were reported that they produced DNA topoisomerase or HIV reverse transcriptase inhibitors.[20−22] 1,3,4-Oxadiazole heterocyclic ring is one of the most important heterocyclic moieties due to its versatile biological actions.[23] Based upon the aforementioned, we are encouraged to incorporate a PC molecule to (thio)urea, semicarbazides, thiosemicarbazide, thiazolidone, and oxadiazole groups.

2. RESULTS AND DISCUSSION

2.1. Synthesis of 1*N*-Benzyl-3-*N*-[2.2]-paracyclophanylurea (6) and *N*-(4′-[2.2]Paracyclophanyl)hydrazinecarboxamides 7a, 7b. The strategy of preparing compounds **6**, **7a**, and **7b** was divided into two parts: First, starting with the parent hydrocarbon **1** as a commercial

Received: January 7, 2022
Accepted: February 23, 2022
Published: April 6, 2022

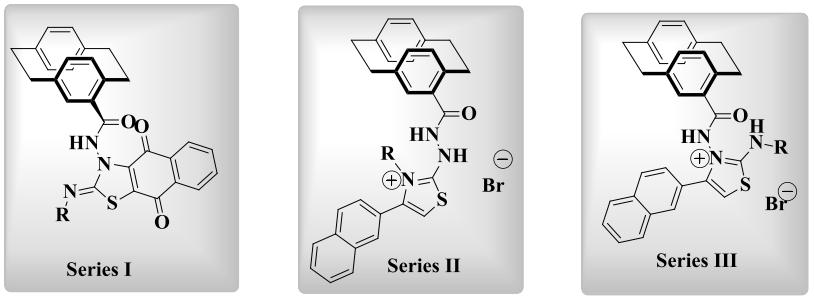
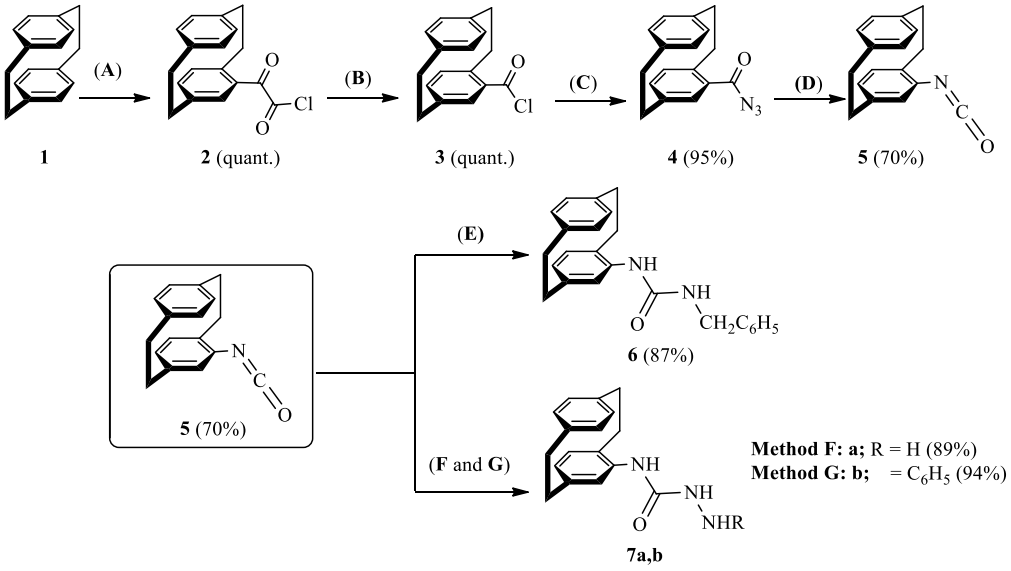


Figure 1. Different series of paracyclophanyl-thiazole derivatives (**I**–**III**) as anticancer agents.

Scheme 1. Synthesis of 1*N*-Benzyl-3-*N*-[2.2]paracyclophanylurea (6) and *N*-(4′-[2.2]Paracyclophanyl)hydrazinecarboxamides 7a and 7b[a]



[a]Reagents and conditions: (A) $(COCl)_2/AlCl_3$, −10 to 5 °C, 20 min; (B) PhCl, Δ, 40 h; (C) NaN_3, acetone/water, r.t., 2 h; (D) toluene, 80 °C, 1 h; (E) $PhCH_2NH_2$/fusion, 100 °C, 10 h; (F) NH_2NH_2 as a solvent, Δ, 20 h; (G) $PhNHNH_2$, toluene, 20 h.

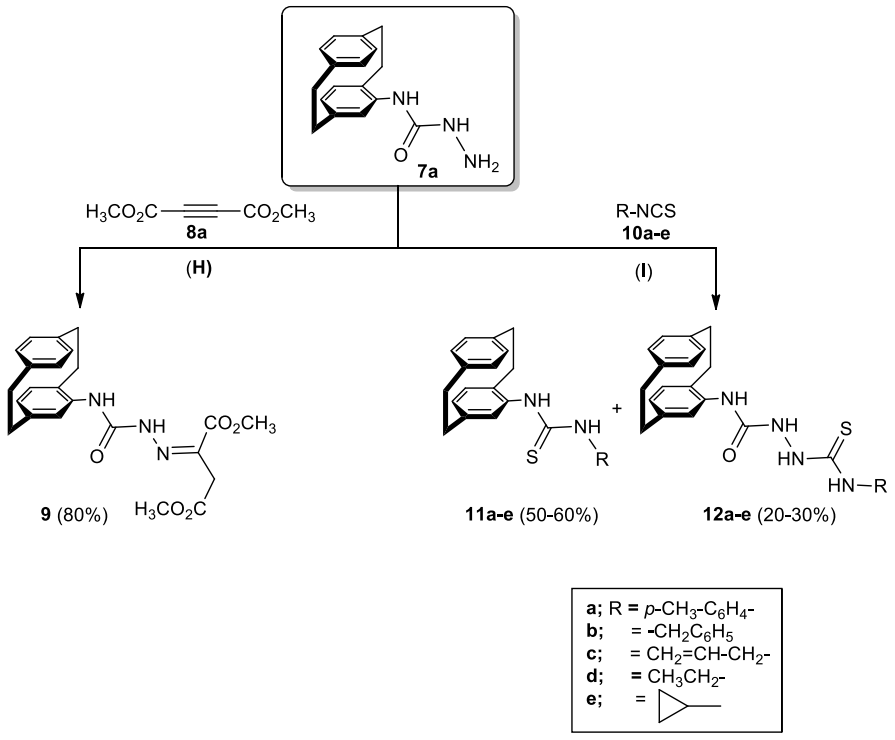
product, which was then converted into the acid chloride derivative **3**[24] by the procedure described in Scheme 1. At the beginning, compound **1** was converted into **2** during reaction with oxalyl chloride/aluminum trichloride. Then, heating **2** in refluxing chlorobenzene caused decarbonylation to give **3**. Subsequently, the resulting acid chloride **3** was subjected toward NaN_3/acetone to give compound **4**[24] (Scheme 1). Heating **4** in toluene at 80 °C provided the corresponding isothionate **5**[24] in 70% yield (Scheme 1). Second, fusion of **5** with benzylamine gave the corresponding urea **6** in 87% yield (Scheme 1). Based on NMR, IR, mass spectra, as well as HRMS, the structure of compound **6** was satisfactorily proved. As the ^{1}H NMR spectrum indicated the appearance of the CH_2 protons of compound **6** as a doublet at δ_H = 4.26 (J = 6.0 Hz). Whereas, the two NH protons appeared as two singlets at δ_H = 7.73 and 6.75 ppm. In ^{13}C NMR, the CH_2 and the carbonyl carbon signals resonated at δ_C = 42.9 and 158.1 ppm, respectively. On subjecting **5** with hydrazines by the procedure mentioned in Scheme 1, *N*-(4′-[2.2]paracyclophanyl)-hydrazinecarboxamides **7a** and **7b** were obtained in very good yields (Scheme 1). The structure of the newly prepared compound **7a** was established by IR, NMR, mass spectra, as well as HRMS. The IR spectrum revealed a diagnostic broad band at $\tilde{\nu}$ = 3352−3214 for NH groups, whereas the carbonyl group appeared at $\tilde{\nu}$ = 1632 cm^{-1}. The ^{1}H NMR spectrum exhibited the NH-2 and NH-1 protons at δ_H = 7.59 and 6.88 ppm, respectively. In addition, the characteristic hydrazine-NH_2 resonated in the ^{1}H NMR spectrum at δ_H = 4.72 ppm. The ^{13}C NMR spectrum displayed the carbonyl-carbon at δ_C = 157.3, whereas the four distinctive CH_2-bridged carbons of PC resonated at δ_C = 35.4, 35.1, 32.9, and 32.3 ppm. HRMS proved the chemical formula of **7a** as $C_{17}H_{19}N_3O$.

For compound **7b**, HRMS confirmed the molecular formula of compound **7b** as $C_{23}H_{23}N_3O$. The ^{1}H NMR spectrum revealed the NH protons as three singlets at δ_H = 8.36 (for NH-2), 7.97 (for NH-1), and 6.60 ppm for (NH-3). The ^{13}C NMR spectrum of compound **7b** revealed the carbonyl carbon at δ_C = 155.8, whereas the carbon signal of C-Ph was observed at δ_C = 149.1 ppm (see the Experimental Section). The four carbon signals of the CH_2−CH_2 appeared at δ_C = 36.4, 36.1, 35.7, and 32.2 ppm.

2.2. Reaction of Compound 7a with Dimethyl Acetylenedicarboxylate (8a) and Substituted Isothiocyanates 10a−10e. In extension to the aforesaid strategy and taking compound **7a**, as an example, in the reaction between **7a** and dimethyl acetylenedicarboxylate (**8a**), the reaction gave compound **9** in 80% yield (Scheme 2). HRMS confirmed the molecular formula of **9** as $C_{23}H_{25}N_3O_5$ indicating the addition reaction of compound **7a** to **8a** proceeded without elimination of a MeOH molecule.

https://doi.org/10.1021/acsomega.2c00141
ACS Omega 2022, 7, 12879−12890

Scheme 2. Strategy of Various Reactions of *N*-(4′-[2.2]Paracyclophanyl)hydrazinecarboxamide (7a)[a]



[a]Reagents and conditions: (H) EtOH, reflux 4 h; (I) oil path EtOH, 70 °C, reflux 4−8 h.

To discriminate between the possible structures **9** and **9′**, we analyzed the NMR spectrum. As, the hydrazano-NH appeared in the ^{1}H NMR spectrum as a singlet at δ_H = 11.01, whereas the PC-NH at δ_H = 8.45. The two methyl-ester protons appeared as two very close singlets at δ_H = 3.90 and 3.75 ppm. The ^{1}H NMR did not reveal any proton for the ethylenic-H, which excluded the formation of the isomeric product **9′** (Figure 2). The CH_2 carbon and its protons attached to the

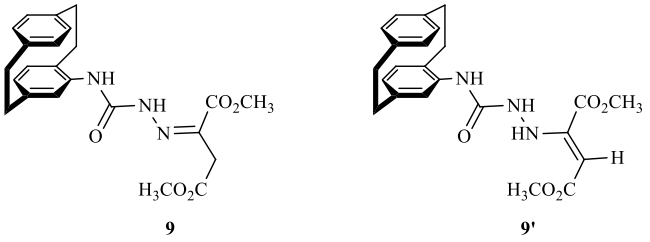


Figure 2. Additive products **9** and **9′** from the reaction between **7a** and **8a**.

ester group resonated at the same region of the ethylenic-CH_2 of PC. The ^{13}C NMR spectrum revealed the two methyl-esters at δ_C = 52.5 and 52.1 ppm (see the Experimental Section). The structure of **9** was unambiguously proved by X-ray structure analysis as shown in Figure 3.

X-ray structure analysis of compound **9** showed different bond lengths of the C−N bonds, as the bond lengths of C16−N17 and C18−N19 are 1.413 and 1.384 Å, respectively. The lengths of the double bonds assigned to the C═O and N═C as in C18−O18 and N20−C21 are 1.225 and 1.272 Å, respectively. Whereas the lengths of the C−C bond assigned to the C21−C22 and C22−C23 are 1.496 and 1.510 Å, respectively.

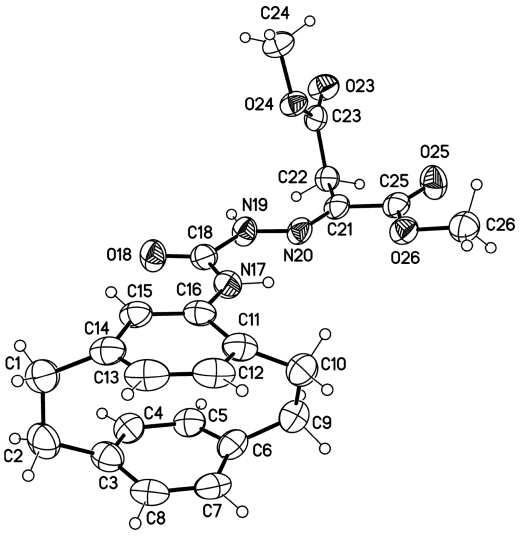


Figure 3. Molecular structure of compound **9** (displacement parameters are drawn at the 50% probability level).

Surprisingly, when compound **7a** was subjected to substituted isothiocyanates **10a−10e**, the unexpected substituted thiourea derivatives **11a−11e** were obtained in 50−60% yields as the major products, whereas the expected products results in the addition reaction of **7a** to **10a−10e** were obtained in 20−30% yields (Scheme 2). Both products were separated by column chromatography using ethyl acetate−hexane, 10:1. The IR spectrum of compound **11d**, as an example, revealed absorptions at $\tilde{\nu}$ = 3296−3206 (NH, s), 3091 (aryl-H), 2925 (aliph.-CH), and 1456 cm^{-1} (C═S). Additionally, the ^{1}H NMR spectrum revealed two singlets at δ_H = 8.99 (NH-1) and 7.50 ppm (NH-3). The ethyl protons

https://doi.org/10.1021/acsomega.2c00141
ACS Omega 2022, 7, 12879−12890

were detected in the ^{1}H NMR spectrum as a quartet at δ_H = 3.61 (for CH_2, J = 7.2 Hz) and as a double-triplet at δ_H = 1.08 ppm (for CH_3, J = 13.2, 7.1 Hz). The ^{13}C NMR spectrum presented the C═S and the ethyl carbon signals at δ_C = 180.2, 56.5 (CH_2-ethyl) and 14.9 ppm (CH_3-ethyl), respectively. HRMS confirmed the molecular formula of **11d** as $C_{19}H_{22}N_2S$. Finally, X-ray structure analysis confirmed the structure of compound **11d** as shown in Figure 4.

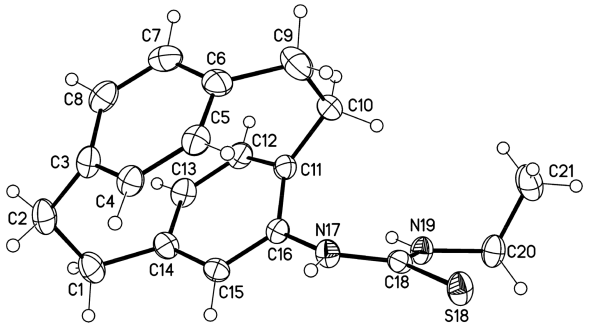


Figure 4. Molecular structure of one of the crystallographic independent molecules of compound **11d** (displacement parameters are drawn at the 50% probability level).

The structures of compounds **12a−12e** were identified as thiamido derivatives of **11a−11e** (Scheme 2). As for example, compound **12d** was proved as *N*-(4′-[2.2]paracyclophanyl)-2-(ethylcarbamothioyl)hydrazine-1-carboxamide. In the ^{1}H NMR spectrum, compound **12d** supported the structure, since four singlets for NH protons appeared at δ_H = 9.29 (NH-3), 8.37 (NH-2), 8.29 (NH-4), and 7.59 ppm (NH-1). The ethyl protons resonated in the ^{1}H NMR spectrum as a quartet at δ_H = 3.61 (CH_2, J = 7.2 Hz) and as a triplet for CH_3 at δ_H = 1.12 ppm (J = 7.1 Hz). The ^{13}C NMR spectrum confirmed the structure of **12d** by the appearance of the C═S carbon signal at δ_C = 182.6, in addition to a signal at δ_C = 155.0 ppm for the carbonyl carbon signal. The ethyl carbon signals were distinguished at δ_C = 39.0 (CH_2-ethyl) and at δ_C = 14.9 ppm (CH_3-ethyl). Mass spectrometry showed the molecular ion peak at m/z (%) = 368 (20). Besides that, HRMS proved the molecular formula of **12d** to be $C_{20}H_{24}N_3OS$.

The mechanism describes the formation of compounds **11a−11e** and **12a−12e** could be explained as due to the addition of the NH lone pair to the electrophilic center in **10a−10d** in the C═S to form compound **11** (Scheme 3). Rearrangement of **11** involved addition of the NH-PC *via* the bond between NH-PC and C═O to the electrophilic carbon of C═S accompanied by the oxidation process to give the intermediate **12** (Scheme 3). Upon heating, N_2 and CO would then be eliminated, as shown in Scheme 3, to produce **11** (Scheme 3).

2.3. Reaction of Compounds 11a−11e and 12a−12e with Diethyl Acetylenedicarboxylate (8b) and Preparation of 1,3,4-Oxazole Derivative 17. Further investigation was done toward compounds **11a−11e** and **12a−12e** through their reactions with diethyl acetylenedicarboxylate (**8b**). The corresponding oxothiazoles **14a−14e** and **15a−15e** were obtained and were identified by IR and NMR spectra in addition to HRMS. For example, the structure of compound **14b** was elucidated by ^{1}H NMR spectrum *via* the appearance of the aromatic protons as two multiplets at δ_H = 7.58−7.27 (for 5H) and at δ_H = 6.66−6.22 ppm (6H), whereas the vinyl-proton of the exocyclic double bond resonated as a singlet δ_H = 6.78 ppm. A quartet at δ_H = 5.22 (J = 8.2 Hz, for CH_2) and as a triplet (3H) at δ_H = 1.20 (J = 6.9 Hz, CH_3) appeared to indicate the ethyl ester protons. The benzyl protons are clearly resonated as a double-doublet at δ_H = 4.17 ppm (J = 14.3, 6.8 Hz). The ^{13}C NMR spectrum supported the structure of compound of **14b** *via* the appearance of the carbonyl carbon signals at δ_C = 150.3 and at 147.5 ppm. The ester carbons and the benzyl carbon signals appeared at δ_C = 61.4 (ester-CH_2), 13.90 (ester-CH_3), and 45.9 ppm (CH_2-benzyl).

The structure of compound **14b** was totally confirmed by X-ray analysis as shown in Figure 5. X-ray structure analysis also

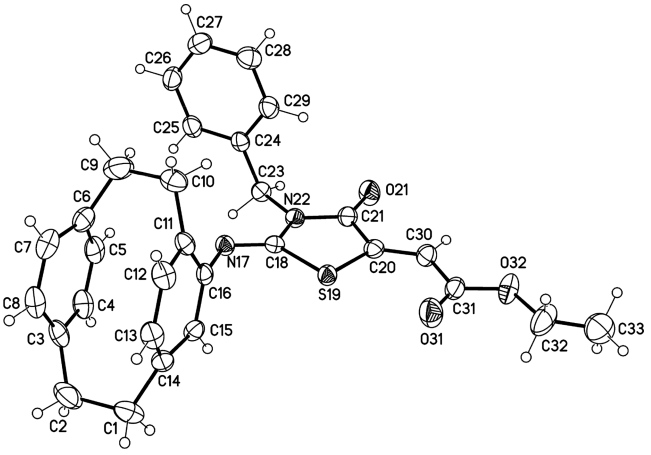
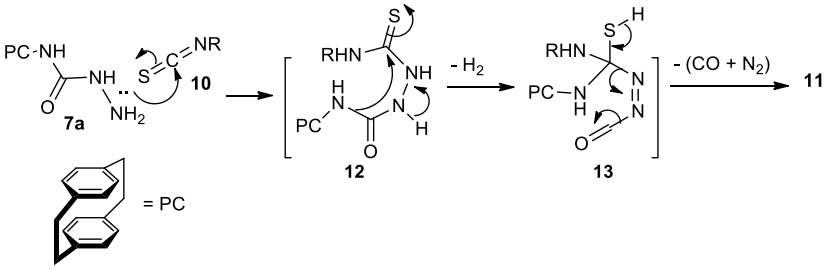


Figure 5. Molecular structure of compound **14b** (minor disordered parts omitted for clarity, displacement parameters are drawn at 50% probability level).

proved the structure of the other thiazole named (*rac*)-ethyl-(*E*)-2-((*E*)-2-(4′-[2.2]paracyclophanylimino)-3-cyclopropyl-4-oxothiazolidin-5-ylidene)acetate (Figure 6).

Scheme 3. Mechanism Describing the Formation of Compounds 11a−11e and 12a−12e



https://doi.org/10.1021/acsomega.2c00141
ACS Omega 2022, 7, 12879−12890

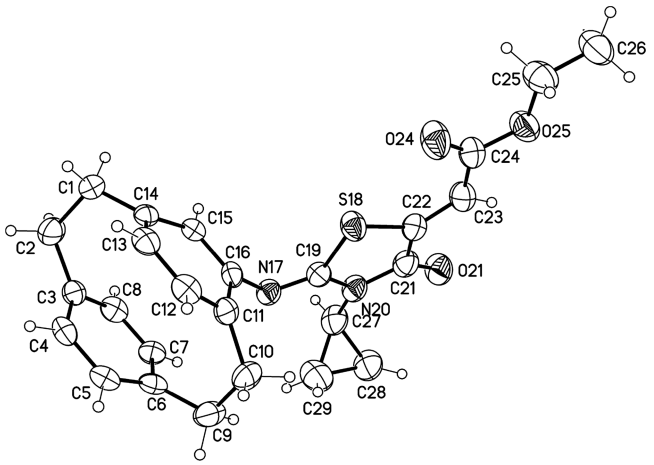


Figure 6. Molecular structure of compound **14e** (displacement parameters are drawn at 50% probability level).

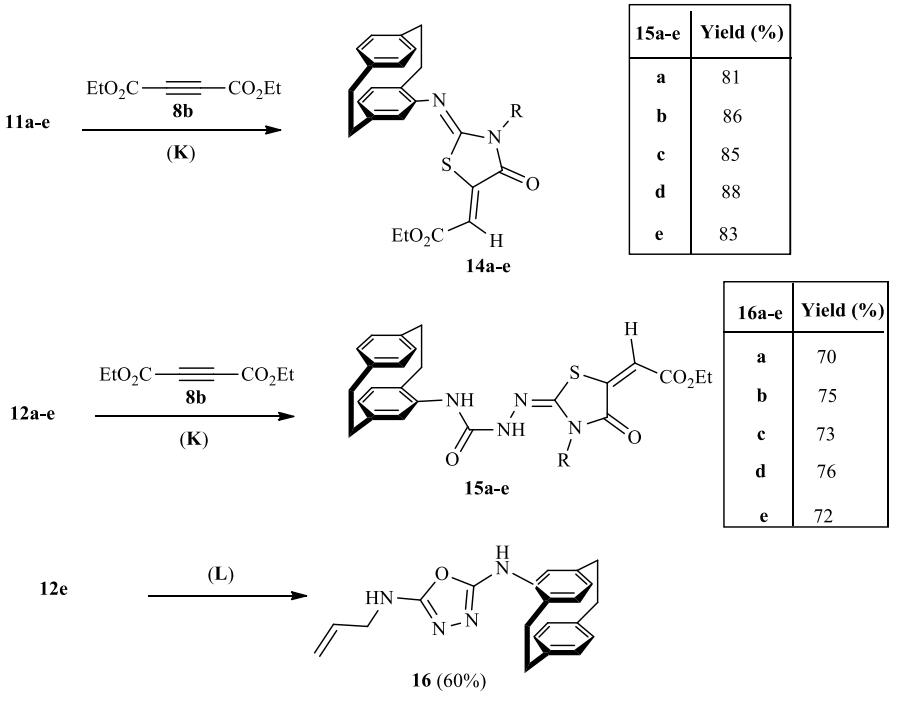
On the other side, compound **15c** was obtained in 75% yield and it was identified as (*rac*)-ethyl-(*E*)-2-((*E*)-2-(2-(4′-[2.2]-paracyclophanylcarbamoyl)-hydrazineylidene)-3-allyl-4-oxo-thiazolidin-5-ylidene)acetate. The ^{1}H NMR spectrum indicated the NH protons as two singlets at δ_H = 9.25 (NH-2) and 8.53 ppm (NH-1). The vinyl proton resonated as a singlet at δ_H = 6.80. The allyl protons appeared at δ_H = 6.08 as ddd (CH-allyl, J = 22.4, 10.3, 5.2 Hz), at δ_H = 5.12−4.93 as a multiplet for CH_2-allyl, and at δ_H = 4.29 ppm as a doublet (J = 5.3 Hz). Finally the ethyl protons appeared, as expected, as a quartet at δ_H = 4.18 (CH_2, J = 7.1 Hz), and triplet at δ_H = 1.14 ppm (CH_3, J = 7.1 Hz). Three distinguished carbonyl carbon signals in the ^{13}C NMR spectrum were present at δ_C = 165.3 (CO), 165.1 (CO), and 162.9 ppm. Besides that, the allyl carbons are shown at δ_C = 132.8 (=CH), 117.6 (=CH_2), and at 44.5 ppm (CH_2−).

In the way to synthesize 1,3,4-oxazole derivative **16**, one example, such as **12e**, was chosen (Scheme 4). The disappearance of the carbonyl and C=S carbons in the IR and ^{13}C NMR indicated that cyclization occurred (Scheme 4). The ^{1}H NMR spectrum of **16** showed the two NH protons as two singlets at δ_H = 9.41 and 8.44 ppm (see the Experimental Section). The allyl protons appeared as a doublet at δ_H = 6.76 (J = 1.4 Hz), besides two multiplets at δ_H = 5.98−5.90 and at δ_H = 5.35 and 5.25. According to the ^{13}C NMR spectrum of compound **16**, three carbons were distinguished for the allyl carbons at δ_C = 46.3 (CH_2), 115.8 (=CH_2), and 132.3 ppm (=CH−), respectively.

3. EXPERIMENTAL SECTION

Uncorrected melting points were taken in a Gallenkamp melting point apparatus (Weiss-Gallenkamp, Loughborough, U.K.). The infrared spectra were determined with a Bruker Alpha ATR instrument. The NMR spectra of the title compounds described herein were recorded on a Bruker Avance 400 NMR instrument at 400 MHz for ^{1}H NMR and 101 MHz for ^{13}C NMR; the references used were the ^{1}H and ^{13}C peaks of the solvents, d_6-dimethyl sulfoxide ($(CD_3)_2SO$-d_6): 2.50 ppm for ^{1}H NMR and 39.4 ppm for ^{13}C NMR. For the characterization of centrosymmetric signals, the signal's median point was chosen; for multiplets, the signal range was given. The following abbreviations were used to describe the proton splitting pattern: d = doublet, t = triplet, m = multiplet, dd = doublet of a doublet. The following abbreviations were used to distinguish between signals: H^{Ar} = aromatic-CH, H^{Pc} = [2.2]paracyclophane-CH_2. Signals of the ^{13}C NMR spectra were assigned with the help of DEPT90 and DEPT135 and were specified in the following way: + = primary or tertiary

Scheme 4. Synthesis of Thiazoles 14a−14e and 15a−15e in Addition to 1,3,4-Oxadiazole Derivative 16[a]



15a-e	Yield (%)
a	81
b	86
c	85
d	88
e	83

16a-e	Yield (%)
a	70
b	75
c	73
d	76
e	72

[a]Reagents and conditions: (K) EtOH, reflux; (L) NaOH (2 N), EtOH, reflux 3 h.

https://doi.org/10.1021/acsomega.2c00141
ACS Omega 2022, 7, 12879−12890

carbon atoms (positive DEPT signal), − = secondary carbon atoms (negative DEPT signal), C_q = quaternary carbon atoms (no DEPT signal). Mass spectra observed by fast atom bombardment (FAB) experiments were recorded using a Finnigan, MAT 90 (70 eV) instrument. TLC silica plates coated with fluorescence indicator from Merck (silica gel 60 F254, thickness 0.2 mm) were used to purify the crude products; flash chromatography with silica gel 60 (0.040 mm × 0.063 mm, Merck) was used.

3.1. General Procedures. Compounds **2**−**5** were prepared according to the literature.[23]

3.2. Synthesis of Compound 6. Isocyanato[2.2]-paracyclophane (**5**)[23] (1.00 g, 4.1 mmol, 1.00 equiv) was fused with benzylamine (5 mL) at 100 °C for 10 h. The reaction mixture was then cooled to room temperature until a precipitate was formed (24 h). The precipitate of **6** was filtered and washed with 150 mL of hexane (three times) and then was dried.

*(rac)-1-(4′-[2.2]Paracyclophanyl))-3-benzylurea (**6**).* R_f = 0.30 (cyclohexane/ethyl acetate, 4:1). Colorless crystals (EtOH), 310 mg (87%). Mp: 150−152 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 7.73 (s, 1H, NH^1), 7.44−7.17 (m, 5H, H^{Ar}), 6.75 (s, 1H, NH^2), 6.55−6.22 (m, 7H, H^{Ar}), 4.24 (d, J = 6.0 Hz, 2H, CH_2^{benzyl}), 3.09−2.81 (m, 7H, H^{Pc}), 2.67−2.62 ppm (m, 1H, H^{Pc}). ^{13}C NMR (101 MHz, DMSO-d_6): δ_C = 158.1 (C_q, CO), 155.1 (C_q, C^{Ar}), 140.9 (C_q, C^{Ar}), 140.4 (C_q, C^{Ar}), 139.9 (C_q, C^{Ar}), 138.8 (C_q, C^{Ar}), 138.5 (+, CH^{Ar}), 134.6 (+, CH^{Ar}), 132.9 (+, CH^{Ar}), 131.8 (+, CH^{Ar}), 128.6 (+, CH^{Ar}), 128.3 (+, CH^{Ar}), 128.2 (+, CH^{Ar}), 127.7 (C_q, C^{Ar}), 127.1 (+, CH^{Ar}), 126.7 (+, CH^{Ar}), 126.5 (+, CH^{Ar}), 126.0 (+, CH^{Ar}), 125.2 (+, CH^{Ar}), 42.9 (−, CH_2^{benzyl}), 34.7 (−, CH_2), 34.6 (−, CH_2), 33.1 (−, CH_2), 32.6 ppm (−, CH_2). IR (ATR): $\tilde{\nu}$ = 3340−3210 (br), 3186 (w), 2910 (s), 2856 (m), 1630 cm^{-1} (s). MS (FAB, 3-NBA): m/z (%) = 357 (60) $[M + H]^+$, 356 (30) $[M]^+$. HRMS (FAB, 3-NBA, $C_{24}H_{25}N_2O$, $[M + H]^+$) calcd, 357.1967; found, 357.1960.

3.3. Synthesis of Compound 7a. Under an argon atmosphere, a mixture of isocyanato[2.2]paracyclophane (**5**)[23] (5.00 g, 20.1 mmol, 1.00 equiv) was dissolved in 25 mL of hydrazine monohydrate and heated under reflux for 20 h. The reaction mixture was then cooled to room temperature until a precipitate was formed (24 h). Product **7a** was then filtered and washed with 150 mL of hexane (three times) and then dried.

*(rac)-N-(4′-[2.2]Paracyclophanyl)hydrazinecarboxamide (**7a**).* R_f = 0.27 (cyclohexane/ethyl acetate, 4:1). Colorless crystals (EtOH), 5 g (89%). Mp: 170−172 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 7.59 (s, 1H, NH^2), 6.88 (s, 1H, NH^1), 6.82 (dd, J = 7.7, 1.7 Hz, 1H, H^{Ar}), 6.62−6.50 (m, 1H, H^{Ar}), 6.47−6.29 (m, 3H, H^{Ar}), 6.74 (d, J = 1.4 Hz, 1H, H^{Ar}), 6.15−5.93 (m, 1H, H^{Ar}), 4.72 (s, 2H, NH^2) 3.29−2.80 (m, 7H, H^{Pc}), 2.80−2.66 ppm (m, 1H, H^{Pc}). ^{13}C NMR (101 MHz, DMSO-d_6): δ_C = 157.3 (C_q, CO), 140.3 (C_q, C^{Ar}), 139.3 (C_q, C^{Ar}), 139.1 (C_q, C^{Ar}), 138.6 (C_q, C^{Ar}), 135.3 (+, CH^{Ar}), 133.6 (+, CH^{Ar}), 133.3 (+, CH^{Ar}), 132.4 (+, CH^{Ar}), 131.8 (+, CH^{Ar}), 126.9 (+, CH^{Ar}), 121.9 (+, CH^{Ar}), 120.7 (C_q, C^{Ar}), 35.4 (−, CH_2), 35.1 (−, CH_2), 32.9 (−, CH_2), 32.3 (−, CH_2), 21.0 ppm (+, CH_3). IR (ATR): $\tilde{\nu}$ = 3352−3214 (br), 3196 (w), 2927 (s), 2848 (m), 1632 cm^{-1} (s). MS (FAB, 3-NBA): m/z (%) = 282 (50) $[M + H]^+$, 281 (30) $[M]^+$. HRMS (FAB, 3-NBA, $C_{17}H_{20}N_3O$, $[M + H]^+$) calcd, 282.1606; found, 282.1603.

3.4. Synthesis of Compound 7b. Under an argon atmosphere, a mixture of isocyanato[2.2]paracyclophane (**5**)[23] (0.249 g, 1.00 equiv) was added to phenylhydrazine (0.108 g, 1.00 equiv) in 100 mL of toluene and was refluxed for 20 h. The reaction mixture was then cooled to room temperature until a precipitate was formed (24 h). Product **7b** was then filtered and washed with 50 mL of hexane (three times) and then dried.

*(rac)-N-(4′-[2.2]Paracyclophanyl)-2-phenylhydrazine-1-carboxamide (**7b**).* R_f = 0.20 (cyclohexane/ethyl acetate, 4:1). Colorless crystals (EtOH), 321 mg (94%). Mp: 147−149 °C. − ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 8.36 (s, 1H, NH^2), 7.97 (br, 1H, NH^1), 7.89 (s, 1H, H^{Ar}), 7.26 (t, J = 7.6 Hz, 3H, H^{Ar}), 6.73 (s, 2H, H^{Ar}), 6.60 (s, 1H, NH^3), 6.48 (dd, J = 7.8, 1.7 Hz, 2H, H^{Ar}), 6.33 (ddd, J = 28.8, 7.6, 2.1 Hz, 4H, H^{Ar}), 3.20−2.78 (m, 6H, H^{Pc}), 2.63 ppm (ddd, J = 17.0, 10.6, 6.4 Hz, 2H, H^{Pc}). ^{13}C NMR (101 MHz, DMSO-d_6): δ_C = 155.8 (C_q, CO), 149.1 (C_q, C^{Ar}), 140.7 (C_q, C^{Ar}), 139.3 (C_q, C^{Ar}), 139.2 (C_q, C^{Ar}), 138.6 (C_q, C^{Ar}), 132.4 (+, 2 × CH^{Ar}), 131.4 (+, 2 × CH^{Ar}), 129.4 (+, 2 × CH^{Ar}), 128.1 (+, CH^{Ar}), 127.8 (C_q, C^{Ar}), 127.3 (+, CH^{Ar}), 124.0 (+, CH^{Ar}), 120.3 (+, CH^{Ar}), 116.1 (+, 2 × CH^{Ar}), 36.4 (−, CH_2), 36.1 (−, CH_2), 35.7 (−, CH_2), 32.2 ppm (−, CH_2). IR (ATR): $\tilde{\nu}$ = 3372−3314 (br), 3200 (w), 2927 (s), 2868 (m), 1642 cm^{-1} (s). MS (FAB, 3-NBA): m/z (%) = 358 (55) $[M + H]^+$, 357 (20) $[M]^+$. HRMS (FAB, 3-NBA, $C_{23}H_{24}N_3O$, $[M + H]^+$) calcd, 358.1919; found, 358.1920.

3.5. Synthesis of Compound 9. A mixture of [2.2]-paracyclophanyl hydrazinecarboxamide (**7a**, 0.281 g, 1.00 mmol, 1.00 equiv) and dimethyl acytelenedicarboxylate (**8a**, 0.142 g, 1.00 mmol, 1.00 equiv) in absolute ethanol (40 mL) was refluxed for 4 h (the reaction was monitored by thin-layer chromatography). After removal of the solvent under reduced pressure, the crude product was purified by column chromatography using cyclohexane/EtOAc 10:1 to afford *racemic*-**9**.

*(rac)-Dimethyl (Z)-2-(2-(4′-[2.2]paracyclophanyl-carbamoyl)hydrazineylidene)succinate (**9**).* R_f = 0.25 (dichloromethane/methanol, 10:1). Pale yellow crystals (EtOH), 338 mg (80%). Mp: 208−210 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 11.01 (s, 1H, NH^2), 8.45 (s, 1H, NH^1), 6.82 (s, 1H, H^{Ar}), 6.72−6.60 (m, 1H, H^{Ar}), 6.55−6.40 (m, 5H, H^{Ar}), 3.90 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 3.35−3.20 (m, 5H, H^{Pc}), 3.05 (s, 2H, CH_2^{vinyl}), 2.95−2.64 ppm (m, 3H, H^{Pc}). ^{13}C NMR (101 MHz, DMSO-d_6): δ_C = 168.3 (C_q, CO), 164.1 (C_q, CO), 151.5 (C_q, CO), 140.6 (C_q, C═N), 138.7 (C_q, C^{Ar}), 138.4 (C_q, C^{Ar}), 136.9 (C_q, C^{Ar}), 134.8 (C_q, C^{Ar}), 133.3 (+, CH^{Ar}), 132.9 (+, CH^{Ar}), 132.2 (+, CH^{Ar}), 131.5 (+, CH^{Ar}), 129.0 (+, CH^{Ar}), 127.3 (+, CH^{Ar}), 127.2 (+, CH^{Ar}), 125.2 (C_q, C^{Ar}), 52.5 (+, CH_3), 52.1 (+, CH_3), 34.6 (−, CH_2), 34.4 (−, CH_2), 32.6 (−, CH_2), 32.1 (−, CH_2), 31.9 ppm (−, CH_2^{vinyl}). IR (ATR): $\tilde{\nu}$ = 3300 (w), 3206 (w), 3070 (w), 2920 (w), 2808 (vw), 1640 (w), 1601 (m), 1547 cm^{-1} (s). MS (FAB, 3-NBA): m/z (%) = 424 (45) $[M + H]^+$, 423 (35) $[M]^+$. HRMS (FAB, 3-NBA, $C_{23}H_{26}O_5N_3$, $[M + H]^+$) calcd, 424.1872; found, 424.1870.

3.6. Synthesis of Compounds 11a−11e and 12a−12e. A mixture of [2.2]paracyclophanehydrazinecarboxamide (**7a**, 1.00 equiv) and the substituted isothiocyanates (**10**, 1.00 equiv) in 60 mL of ethanol was refluxed 80 °C for 4−8 h (the reaction was monitored by thin-layer chromatography). After removal of the solvent under reduced pressure, the crude residue was purified by column chromatography using ethyl acetate/hexane 5:1 to give compounds **11a−11e** and **12a−12e**.

https://doi.org/10.1021/acsomega.2c00141
ACS Omega 2022, 7, 12879−12890

*(rac)-2′(4′-[2.2]Paracyclophanyl)-16-yridinedin-3-yl)-hydrazine-1-carbothioamide (**11a**).* R_f = 0.42 (dichloromethane/methanol, 10:1). Buff crystals (EtOH), 223 mg (60%). Mp: 155−157 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 9.64 (s, 1H, NH^1), 9.05 (s, 1H, NH^3), 7.51−7.30 (m, 2H, H^{Ar}), 7.21−7.08 (m, 2H, H^{Ar}), 6.63−6.27 (m, 6H, H^{Ar}), 6.20−6.06 (m, 1H, H^{Ar}), 3.12−2.93 (m, 6H, H^{Pc}), 2.91−2.85 (m, 1H, H^{Pc}), 2.81−2.64 (m, 1H, H^{Pc}), 2.35−2.19 ppm (m, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 179.98 (C_q, CS), 140.50 (C_q, C^{Ar}), 139.79 (C_q, C^{Ar}), 139.22 (C_q, C^{Ar}), 137.98 (C_q, C^{Ar}), 137.56 (C_q, C^{Ar}), 136.11 (C_q, C^{Ar}), 135.3 (+, CH^{Ar}), 134.05 (+, CH^{Ar}), 134.02 (+, CH^{Ar}), 133.56 (+, CH^{Ar}), 133.21 (+, CH^{Ar}), 132.69 (+, CH^{Ar}), 130.9 (+, CH^{Ar}), 130.2 (C_q, C^{Ar}), 129.24 (+, 2 × CH^{Ar}), 124.24 (+, 2 × CH^{Ar}), 35.2 (−, CH_2), 34.8 (−, CH_2), 34.5 (−, CH_2), 33.7 (−, CH_2), 21.0 ppm (+, CH_3). IR (ATR): $\tilde{\nu}$ = 3296 (w), 3206 (w), 3091 (w), 2925 (w), 1659 (vs), 1594 (m), 1577 (m), 1538 (vs), 1516 (vs), 1494 (vs), 1455 (m), 1436 cm^{-1} (w). MS (FAB, 3-NBA): m/z (%) = 373 (100) [M + H]$^+$, 372 (50) [M]$^+$. HRMS (FAB, 3-NBA, $C_{24}H_{25}N_2{}^{32}S_1$, [M + H]$^+$) calcd, 373.1738; found, 373.1740.

*(rac)-1-(4′-[2.2]Paracyclophanyl)-3-benzylthiourea (**11b**).* R_f = 0.40 (dichloromethane/methanol, 10:1). Buff crystals (EtOH), 185 mg (50%). Mp: 165−167 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 9.06 (s, 1H, NH^1), 7.99 (s, 1H, NH^3), 7.34 (d, J = 4.4 Hz, 4H, H^{Ar}), 7.25 (dt, J = 5.1, 4.2 Hz, 1H, H^{Ar}), 6.86 (d, J = 5.3 Hz, 1H, H^{Ar}), 6.53 (dd, J = 7.8, 1.7 Hz, 1H, H^{Ar}), 6.49−6.39 (m, 4H, H^{Ar}), 6.16 (d, J = 1.1 Hz, 1H, H^{Ar}), 4.72 (ddd, J = 19.8, 14.7, 5.7 Hz, 2H, $CH_2{}^{benzyl}$), 3.16−3.07 (m, 1H, H^{Pc}), 3.02−2.86 (m, 6H, H^{Pc}), 2.65 (ddd, J = 13.5, 10.1, 5.9 Hz, 1H, H^{Pc}) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 181.2 (C_q, CS), 140.8 (C_q, C^{Ar}), 139.7 (C_q, C^{Ar}), 139.7 (C_q, C^{Ar}), 139.2 (C_q, C^{Ar}), 137.5 (C_q, C^{Ar}), 136.0 (+, CH^{Ar}), 133.5 (+, CH^{Ar}), 133.3 (+, CH^{Ar}), 133.1 (+, CH^{Ar}), 132.9 (+, CH^{Ar}), 130.1 (+, CH^{Ar}), 130.3 (+, CH^{Ar}), 129.2 (+, CH^{Ar}), 128.7 (+, 2 × CH^{Ar}), 128.1 (C_q, C^{Ar}), 127.8 (+, CH^{Ar}), 127.4 (+, CH^{Ar}), 48.0 (−, $CH_2{}^{benzyl}$), 35.2 (−, CH_2), 34.8 (−, CH_2), 34.4 (−, CH_2), 33.5 ppm (−, CH_2). IR (ATR) $\tilde{\nu}$ = 3296 (w), 3206 (w), 3091 (w), 2925 (w), 2839 (vw), 1645 (w), 1604 (m), 1557 (s), 1456 (s), 1279 (m), 1129 (vs), 795 (w), 725 (m), 613 (vs), 514 cm^{-1} (w). MS (FAB, 3-NBA): m/z (%) = 373 (100) [M + H]$^+$, 372 (50) [M]$^+$. HRMS (FAB, 3-NBA, $C_{24}H_{25}N_2{}^{32}S_1$, [M + H]$^+$) calcd, 373.1738; found, 373.1737.

*(rac)-1-(4′-[2.2]Paracyclophanyl)-3-allylthiourea (**11c**).* R_f = 0.39 (dichloromethane/methanol, 10:1). Buff crystals (EtOH), 167 mg (52%). Mp: 160−162 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 9.04 (s, 1H, NH^1), 7.67 (s, 1H, NH^3), 6.87 (dd, J = 7.7, 1.2 Hz, 1H, H^{Ar}), 6.60−6.40 (m, 5H, H^{Ar}), 6.15 (d, J = 1.4 Hz, 1H, H^{Ar}), 5.96−5.84 (m, 1H, CH^{allyl}), 5.26−5.06 (m, 2H, $CH_2{}^{allyl}$), 4.28−4.00 (m, 2H, $CH_2{}^{allyl}$), 3.19−3.06 (m, 1H, H^{Pc}), 3.01−2.87 (m, 6H, H^{Pc}), 2.70 ppm (ddd, J = 13.5, 10.1, 5.9 Hz, 1H, H^{Pc}). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 180.9 (C_q, CS), 140.8 (C_q, C^{Ar}), 139.7 (C_q, C^{Ar}), 139.2 (C_q, C^{Ar}), 137.5 (C_q, C^{Ar}), 136.0 (+, CH^{Ar}), 135.5 (+, 2 × CH^{Ar}), 133.4 (+, CH^{Ar}), 133.1 (+, CH^{allyl}), 132.8 (+, CH^{Ar}), 130.9 (+, CH^{Ar}), 130.2 (+, CH^{Ar}), 129.2 (C_q, C^{Ar}), 116.2 (−, $CH_2{}^{allyl}$), 46.9 (−, $CH_2{}^{allyl}$), 35.2 (−, CH_2), 34.8 (−, CH_2), 34.5 (−, CH_2), 33.5 ppm (−, CH_2). IR (ATR): $\tilde{\nu}$ = 3296 (w), 3206 (w), 3091 (w), 2925 (w), 2839 (vw), 1645 (w), 1604 (m), 1557 (s), 1456 cm^{-1} (s). MS (FAB, 3-NBA): m/z (%) = 323 (100) [M + H]$^+$, 322 (55) [M]$^+$. HRMS (FAB, 3-NBA, $C_{20}H_{23}N_2{}^{32}S_1$, [M + H]$^+$) calcd, 323.1582; found, 323.1583.

*(rac)-1-(4′-[2.2]Paracyclophanyl)-3-ethylthiourea (**11d**).* R_f = 0.35 (dichloromethane/methanol, 10:1). Buff crystals (MeOH), 179 mg (58%). Mp: 168−170 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 8.99 (s, 1H, NH^1), 7.50 (s, 1H, NH^3), 6.86 (dd, J = 7.7, 1.7 Hz, 1H, H^{Ar}), 6.55 (dd, J = 7.8, 1.8 Hz, 1H, H^{Ar}), 6.51−6.40 (m, 4H, H^{Ar}), 6.12 (d, J = 1.5 Hz, 1H, H^{Ar}), 3.61 (q, 2H, J = 7.2 Hz, $CH_2{}^{ethyl}$), 3.12−3.02 (m, 1H, H^{Pc}), 3.01−2.88 (m, 6H, H^{Pc}), 2.70 (ddd, J = 13.4, 10.0, 5.9 Hz, 1H, H^{Pc}), 1.08 ppm (dt, J = 13.2, 7.1 Hz, 3H, $CH_3{}^{ethyl}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 180.2 (C_q, CS), 140.9 (C_q, C^{Ar}), 139.7 (C_q, C^{Ar}), 139.1 (C_q, C^{Ar}), 137.4 (C_q, C^{Ar}), 136.2 (+, CH^{Ar}), 135.6 (+, CH^{Ar}), 133.4 (+, CH^{Ar}), 133.0 (+, CH^{Ar}), 132.9 (+, CH^{Ar}), 130.8 (+, CH^{Ar}), 129.9 (+, CH^{Ar}), 129.2 (C_q, C^{Ar}), 56.5 (−, $CH_2{}^{ethyl}$), 35.2 (−, CH_2), 34.8 (−, CH_2), 34.5 (−, CH_2), 33.5 (−, CH_2), 14.9 ppm (+, $CH_3{}^{ethyl}$). IR (ATR): $\tilde{\nu}$ = 3296 (w), 3206 (w), 3091 (w), 2925 (w), 2839 (vw), 1645 (w), 1604 (m), 1557 (s), 1456 cm^{-1} (s). MS (FAB, 3-NBA): m/z (%) = 311 (65) [M + H]$^+$, 310 (30) [M]$^+$. HRMS (FAB, 3-NBA, $C_{19}H_{23}N_2{}^{32}S_1$, [M + H]$^+$) calcd, 311.1582; found, 311.1584.

*(rac)-1-(4′-[2.2]Paracyclophanyl)-3-cyclopropylthiourea (**11e**).* R_f = 0.35 (dichloromethane/methanol, 10:1). Buff crystals (MeOH), 173 mg (54%). Mp: 168−170 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 9.36 (s, 1H, NH^1), 8.32 (s, 1H, NH^3), 6.85 (dd, J = 7.8, 1.7 Hz, 2H, H^{Ar}), 6.57−6.06 (m, 5H, H^{Ar}), 3.12 (dd, J = 20.4, 9.9 Hz, 1H, H^{Pc}), 3.07−2.81 (m, 7H, H^{Pc}), 2.75−2.62 (m, 1H, CH^{cyclo}), 0.75−0.69 (m, 2H, $CH_2{}^{cyclo}$), 0.65−0.47 ppm (m, 2H, $CH_2{}^{cyclo}$). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 182.2 (C_q, CS), 140.6 (C_q, C^{Ar}), 139.7 (C_q, C^{Ar}), 139.2 (C_q, C^{Ar}), 135.8 (C_q, C^{Ar}), 135.2 (+, CH^{Ar}), 133.5 (+, CH^{Ar}), 133.3 (+, CH^{Ar}), 133.1 (+, CH^{Ar}), 132.7 (+, CH^{Ar}), 130.6 (+, CH^{Ar}), 130.1 (+, CH^{Ar}), 128.8 (C_q, C^{Ar}), 35.2 (−, CH_2), 34.8 (−, CH_2), 34.3 (−, CH_2), 33.7 (−, CH_2), 26.8 (+, $CH^{cyclo.}$), 7.1 ppm (−, 2 × $CH_2{}^{cyclo}$). IR (ATR): $\tilde{\nu}$ = 3296 (w), 3206 (w), 3091 (w), 2925 (w), 2839 (vw), 1645 (w), 1604 (m), 1557 (s), 1456 cm^{-1} (s). MS (FAB, 3-NBA): m/z (%) = 323 (55) [M + H]$^+$, 322 (20) [M]$^+$. HRMS (FAB, 3-NBA, $C_{20}H_{23}N_2{}^{32}S_1$, [M + H]$^+$) calcd, 323.1582; found, 323.1583.

*(rac)-N-(4′-[2.2]Paracyclophanyl)-2-(p-tolylcarbamothioyl)hydrazine-1-carboxamide (**12a**).* R_f = 0.17 (cyclohexane/ethyl acetate, 4:1). Colorless crystals (MeOH), 129 mg (30%). Mp: 190−192 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 9.87 (s, 1H, NH^3), 9.58 (s, 1H, NH^2), 8.52 (s, 1H, NH^4), 7.81 (s, 1H, NH^1), 7.48−7.32 (m, 2H, H^{Ar}), 7.15 (d, J = 8.2 Hz, 3H, H^{Ar}), 6.90 (dd, J = 7.7, 1.5 Hz, 1H, H^{Ar}), 6.74 (d, J = 1.4 Hz, 1H, H^{Ar}), 6.62−6.25 (m, 4H, H^{Ar}), 3.15−2.79 (m, 7H, H^{Pc}), 2.69 (dt, J = 13.8, 9.4 Hz, 1H, H^{Pc}), 2.29 ppm (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6): δ_C = 180.0 (C_q, CS), 155.0 (C_q, CO), 140.6 (C_q, C^{Ar}), 139.3 (C_q, C^{Ar}), 139.2 (C_q, C^{Ar}), 139.0 (C_q, C^{Ar}), 138.2 (C_q, C^{Ar}), 137.0 (+, CH^{Ar}), 135.2 (+, 2 × CH^{Ar}), 133.5 (+, CH^{Ar}), 133.2 (+, CH^{Ar}), 132.4 (+, CH^{Ar}), 129.6 (+, CH^{Ar}), 129.2 (C_q, C^{Ar}), 129.1 (C_q, C^{Ar}), 128.8 (+, CH^{Ar}), 127.3 (+, CH^{Ar}), 125.8 (+, CH^{Ar}), 124.2 (+, CH^{Ar}), 35.2 (−, CH_2), 35.1 (−, CH_2), 33.4 (−, CH_2), 33.0 (−, CH_2), 21.0 ppm (+, CH_3). IR (ATR): $\tilde{\nu}$ = 3980 (vw), 3954 (vw), 3922 (vw), 3903 (vw), 3870 (vw), 3852 (vw), 3412 (vw), 3352 (vw), 2978 (w), 2925 (w), 2884 (w), 1720 (s), 1696 (m), 1616 (m), 1592 cm^{-1} (vs). MS (FAB, 3-NBA): m/z (%) = 431 (85) [M + H]$^+$, 430 (20)

https://doi.org/10.1021/acsomega.2c00141
ACS Omega 2022, 7, 12879−12890

$[M]^+$. HRMS (FAB, 3-NBA, $C_{25}H_{27}O_1N_4{}^{32}S_1$, $[M + H]^+$) calcd, 431.1906; found, 431.1905.

*(rac)-N-(4′-[2.2]Paracyclophanyl)-2-(benzylcarbamothioyl)hydrazine-1-carboxamide (**12b**).* R_f = 0.16 (cyclohexane/ethyl acetate, 4:1). Colorless crystals (EtOH), 163 mg (38%). Mp: 186−188 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 9.43 (s, 1H, NH^3), 8.76 (s, 1H, NH^2), 8.44 (s, 1H, NH^4), 7.68 (s, 1H, NH^1), 7.32 (dt, J = 19.4, 7.6 Hz, 4H, H^{Ar}), 7.23 (t, J = 7.2 Hz, 1H, H^{Ar}), 6.85 (dd, J = 7.7, 1.2 Hz, 1H, H^{Ar}), 6.71 (d, J = 1.5 Hz, 1H, H^{Ar}), 6.51−6.31 (m, 5H, H^{Ar}), 4.80 (ddd, J = 40.4, 15.1, 5.8 Hz, 2H, $CH_2{}^{benzyl}$), 3.26−3.18 (m, 1H, H^{Pc}), 3.02−2.83 (m, 6H, H^{Pc}), 2.67 ppm (dt, J = 13.7, 8.3 Hz, 1H, H^{Pc}). ^{13}C NMR (101 MHz, DMSO-d_6): δ_C = 183.6 (C_q, CS), 155.0 (C_q, CO), 140.6 (C_q, C^{Ar}), 139.7 (C_q, C^{Ar}), 139.3 (C_q, C^{Ar}), 139.0 (C_q, C^{Ar}), 138.1 (C_q, C^{Ar}), 135.2 (+, CH^{Ar}), 133.5 (+, CH^{Ar}), 133.2 (+, CH^{Ar}), 132.3 (+, CH^{Ar}), 129.6 (+, CH^{Ar}), 128.8 (+, CH^{Ar}), 128.5 (C_q, C^{Ar}), 128.4 (C_q, C^{Ar}), 127.7 (+, CH^{Ar}), 127.6 (+, CH^{Ar}), 127.4 (+, CH^{Ar}), 127.1 (+, CH^{Ar}), 125.8 (+, CH^{Ar}), 47.2 (−, $CH_2{}^{benzyl}$), 35.2 (−, CH_2), 35.1 (−, CH_2), 33.3 (−, CH_2), 32.9 ppm (−, CH_2). IR (ATR): $\tilde{\nu}$ = 3060 (w), 2983 (w), 2975 (w), 2925 (w), 1715 (s), 1697 (s), 1687 (m), 1628 (m), 1596 cm^{-1} (vs). MS (FAB, 3-NBA): m/z (%) = 431 (90) $[M + H]^+$, 430 (30) $[M]^+$. HRMS (FAB, 3-NBA, $C_{25}H_{27}O_1N_4{}^{32}S_1$, $[M + H]^+$) calcd, 431.1906; found, 431.1904.

*(rac)-N-(4′-[2.2]Paracyclophanyl)-2-(allylcarbamothioyl)-hydrazine-1-carboxamide (**12c**).* R_f = 0.18 (cyclohexane/ethyl acetate, 4:1). Colorless crystals (EtOH), 148 mg (39%). Mp: 180−182 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 9.35 (s, 1H, NH^3), 8.40 (s, 1H, NH^2), 8.09 (s, 1H, NH^4), 7.66 (s, 1H, NH^1), 6.85 (d, J = 7.7 Hz, 1H, H^{Ar}), 6.71 (d, J = 1.2 Hz, 1H, H^{Ar}), 6.50 (dd, J = 7.8, 1.6 Hz, 1H, H^{Ar}), 6.42−6.35 (m, 3H, H^{Ar}), 6.31 (dd, J = 7.7, 1.6 Hz, 1H, H^{Ar}), 5.86 (dddt, J = 27.4, 17.1, 10.3, 5.1 Hz, 1H, CH^{allyl}), 5.21−5.02 (m, 2H, $CH_2{}^{allyl}$), 4.16 (dd, J = 20.8, 15.8 Hz, 2H, $CH2^{allyl}$), 3.23 (dd, J = 10.8, 6.2 Hz, 1H, H^{Pc}), 3.03−2.86 (m, 6H, H^{Pc}), 2.72−2.64 ppm (m, 1H, H^{Pc}). ^{13}C NMR (101 MHz, DMSO-d_6): δ_C = 182.8 (C_q, CS), 154.9 (C_q, CO), 140.6 (C_q, C^{Ar}), 139.3 (C_q, C^{Ar}), 139.0 (C_q, C^{Ar}), 138.1 (C_q, C^{Ar}), 135.4 (+, CH^{Ar}), 135.2 (+, CH^{Ar}), 133.5 (+, CH^{Ar}), 133.2 (+, CH^{allyl}), 132.3 (+, CH^{Ar}), 129.5 (+, CH^{Ar}), 128.8 (+, CH^{Ar}), 127.3 (C_q, C^{Ar}), 125.8 (+, CH^{Ar}), 115.0 (−, $CH_2{}^{allyl}$), 46.4 (−, $CH_2{}^{allyl}$), 35.2 (−, CH_2), 35.1 (−, CH_2), 33.4 (−, CH_2), 32.9 ppm (−, CH_2). IR (ATR): $\tilde{\nu}$ = 3241 (m), 3233 (m), 3109 (m), 2925 (m), 2846 (w), 1646 (w), 1608 (m), 1591 (m), 1560 (vs), 1487 (vs), 1436 (vs) cm^{-1}. MS (FAB, 3-NBA): m/z (%) = 381 (100) $[M + H]^+$, 380 (20) $[M]^+$. HRMS (FAB, 3-NBA, $C_{21}H_{25}O_1N_4{}^{32}S_1$, $[M + H]^+$) calcd, 381.1749; found, 381.1750.

*(rac)-N-(4′-[2.2]Paracyclophanyl)-2-(ethylcarbamothioyl)-hydrazine-1-carboxamide (**12d**).* R_f = 0.15 (cyclohexane/ethyl acetate, 4:1). Colorless crystals (MeOH), 117 mg (32%). Mp: 176−178 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 9.29 (s, 1H, NH^3), 8.37 (s, 1H, NH^2), 8.29 (s, 1H, NH^4), 7.59 (s, 1H, NH^1), 6.85 (dd, J = 7.7, 1.3 Hz, 1H, H^{Ar}), 6.71 (d, J = 1.2 Hz, 1H, H^{Ar}), 6.50 (dd, J = 7.8, 1.6 Hz, 1H, H^{Ar}), 6.42−6.28 (m, 4H, H^{Ar}), 3.61 (q, 2H, J = 7.2 Hz, CH_2-ethyl), 3.27−3.17 (m, 1H, H^{Pc}), 3.05−2.83 (m, 6H, H^{Pc}), 2.68 (ddd, J = 13.8, 10.0, 7.5 Hz, 1H, H^{Pc}), 1.12 ppm (t, J = 7.1 Hz, 3H, $CH_3{}^{ethyl}$). ^{13}C NMR (101 MHz, DMSO-d_6): δ_C = 182.6 (C_q, CS), 155.0 (C_q, CO), 140.6 (C_q, C^{Ar}), 139.2 (C_q, C^{Ar}), 139.0 (C_q, C^{Ar}), 138.0 (C_q, C^{Ar}), 135.2 (+, CH^{Ar}), 133.5 (+, CH^{Ar}), 133.2 (+, CH^{Ar}), 132.3 (+, CH^{Ar}), 129.4 (+, CH^{Ar}), 128.7 (+, CH^{Ar}), 127.3 (C_q, C^{Ar}), 125.7 (+, CH^{Ar}), 39.0 (−, $CH_2{}^{ethyl}$), 35.2 (−, CH_2), 35.0 (−, CH_2), 33.3 (−, CH_2), 32.9 (−, CH_2), 14.9 ppm (+, $CH_3{}^{ethyl}$). IR (ATR): $\tilde{\nu}$ = 3241 (m), 3233 (m), 3109 (m), 2925 (m), 2846 (w), 1646 (w), 1608 (m), 1591 (m), 1560 (vs), 1487 cm^{-1} (vs). MS (FAB, 3-NBA): m/z (%) = 369 (50) $[M + H]^+$, 368 (20) $[M]^+$. HRMS (FAB, 3-NBA, $C_{20}H_{25}O_1N_3{}^{32}S_1$, $[M + H]^+$) calcd, 369.1749; found, 369.1750.

*(rac)-N-(4′-[2.2]Paracyclophanyl)-2-(cyclopropylcarbamothioyl)hydrazine-1-carboxamide (**12e**).* R_f = 0.18 (cyclohexane/ethyl acetate, 4:1). Colorless crystals (DMF/EtOH), 140 mg (37%). Mp: 191−193 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 9.36 (s, 1H, NH^3), 8.31 (s, 1H, NH^2), 8.25 (s, 1H, NH^4), 7.63 (s, 1H, NH^1), 6.97−6.78 (m, 1H, H^{Ar}), 6.78−6.65 (m, 1H, H^{Ar}), 6.49 (dt, J = 31.4, 15.7 Hz, 1H, H^{Ar}), 6.42−6.23 (m, 4H, H^{Ar}), 3.30−3.18 (m, 1H, H^{Pc}), 3.05−2.83 (m, 6H, H^{Pc}), 2.70−2.58 (m, 1H, H^{Pc}), 1.26−1.14 (m, 1H, CH^{cyclo}), 0.76−0.68 (m, 2H, $CH_2{}^{cyclo}$), 0.67−0.60 ppm (m, 2H, $CH_2{}^{cyclo}$). ^{13}C NMR (101 MHz, DMSO-d_6): δ_C = 184.7 (C_q, CS), 156.2 (C_q, CO), 140.6 (C_q, C^{Ar}), 139.3 (C_q, C^{Ar}), 139.0 (C_q, C^{Ar}), 138.2 (C_q, C^{Ar}), 135.2 (+, CH^{Ar}), 133.5 (+, CH^{Ar}), 133.2 (+, CH^{Ar}), 132.3 (+, CH^{Ar}), 129.4 (+, CH^{Ar}), 128.8 (+, CH^{Ar}), 127.2 (C_q, C^{Ar}), 125.6 (+, CH^{Ar}), 35.2 (−, CH_2), 35.1 (−, CH_2), 33.3 (−, CH_2), 32.9 (−, CH_2), 26.8 (+, CH^{cyclo}), 6.8 ppm (−, 2 × $CH_2{}^{cyclo}$). IR (ATR): $\tilde{\nu}$ = 3271 (w), 2927 (w), 1751 (m), 1718 (w), 1694 (m), 1656 (vs), 1618 (m), 1601 (m), 1578 (s), 1553 cm^{-1} (s). MS (FAB, 3-NBA): m/z (%) = 381 (45) $[M + H]^+$,380 (20) $[M]^+$. HRMS (FAB, 3-NBA, $C_{21}H_{25}O_1N_3{}^{32}S_1$, $[M + H]^+$) calcd, 381.1749; found, 381.1750.

3.7. Synthesis of Thiazoles 14a−14e. A mixture of *N*-substituted [2.2]paracyclophanylthioureas (**11a−11e**, 1.00 mmol, 1.00 equiv) and **8b** (0.170 g, 1.00 mmol, 1.00 equiv) in absolute ethanol (40 mL) was refluxed for 3−4 h (the reaction was monitored by thin-layer chromatography). After removal of the solvent under reduced pressure, the crude product was purified by column chromatography using EtOAc/hexane, 5:1 to give compounds **14a−14e**.

*(rac)-(E)-2-((E)-2-(4′-[2.2]Paracyclophanylimino)-4-oxo-3-(p-tolyl)thiazolidin-5-ylidene)acetate (**14a**).* R_f = 0.25 (dichloromethane/methanol, 10:1). Yellow crystals (DMF/EtOH), 401 mg (81%). Mp: 238−240 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 8.82 (s, 1H, H^{Ar}), 8.16 (s, 1H, H^{Ar}), 7.77 (s, 1H, H^{vinyl}), 7.30 (d, J = 8.4 Hz, 1H, H^{Ar}), 7.02 (d, J = 8.3 Hz, 1H, H^{Ar}), 6.84 (dd, J = 7.7, 1.5 Hz, 1H, H^{Ar}), 6.75−6.62 (m, 2H, H^{Ar}), 6.50−6.20 (m, 4H, H^{Ar}), 3.37 (dd, J = 12.4, 10.4 Hz, 2H, CH_2), 3.11−2.76 (m, 6H, H^{Pc}), 2.75−2.54 (m, 2H, H^{Pc}), 2.17 (s, 3H, $CH_3{}^{phenyl}$), 0.98 ppm (t, J = 7.0 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6): δ_C = 152.3 (C_q, CO), 151.9 (C_q, CO), 140.0 (C_q, C═N), 138.8 (C_q, C═C), 138.7 (C_q, C^{Ar}), 138.6 (C_q, C^{Ar}), 138.1 (C_q, C^{Ar}), 138.0 (C_q, C^{Ar}), 137.4 (C_q, C^{Ar}), 134.8 (C_q, C^{Ar}), 134.6 (+, CH^{Ar}), 133.0 (+, CH^{Ar}), 132.8 (+, CH^{Ar}), 132.7 (+, CH^{Ar}), 131.8 (+, CH^{Ar}), 130.3 (+, CH^{Ar}), 129.9 (+, CH^{Ar}), 129.2 (+, CH^{Ar}), 128.0 (+, CH^{Ar}), 126.8 (+, CH^{Ar}), 126.6 (+, CH^{Ar}), 125.7 (C_q, C^{Ar}), 118.0 (+, CH^{vinyl}), 61.2 (+, CH_2), 34.7 (−, CH_2), 34.5 (−, CH_2), 33.3 (−, CH_2), 33.1 (−, CH_2), 32.6 (+, $CH_3{}^{phenyl}$), 20.3 ppm (+, CH_3). IR (ATR): $\tilde{\nu}$ = 3296 (w), 3206 (w), 3091 (w), 2925 (w), 2839 (vw), 1645 (w), 1604 (m), 1557 cm^{-1} (s). MS (FAB, 3-NBA): m/z (%) = 497 (45) $[M + H]^+$, 496 (30) $[M]^+$. HRMS (FAB, 3-NBA, $C_{30}H_{29}O_3N_2{}^{32}S_1$, $[M + H]^+$) calcd, 497.1899; found, 497.1891.

*(rac)-(E)-2-((E)-2-(4′-[2.2]Paracyclophanylimino)-3-benzyl-4-oxothiazolidin-5-ylidene)acetate (**14b**).* R_f = 0.20 (cyclohexane/ethyl acetate, 4:1). Yellow crystals (EtOH),

https://doi.org/10.1021/acsomega.2c00141
ACS Omega 2022, 7, 12879−12890

226 mg (86%). Mp: 230−232 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 7.58−7.27 (m, 5H, H^{Ar}), 6.78 (s, 1H, H^{vinyl}), 6.66−6.22 (m, 6H, H^{Ar}), 5.82 (s, 1H, H^{Ar}), 5.22 (q, J = 8.2 Hz, 2H, CH_2), 4.17 (dd, J = 14.3, 6.8 Hz, 2H, CH_2^{benzyl}), 3.12−2.59 (m, 8H, H^{Pc}), 1.20 ppm (t, J = 8.0 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6): δ_C = 150.3 (C_q, CO), 147.5 (C_q, CO), 141.4 (C_q, C═N), 139.0 (C_q, C═C), 138.6 (C_q, C^{Ar}), 136.0 (C_q, C^{Ar}), 134.8 (C_q, C^{Ar}), 133.7 (C_q, C^{Ar}), 133.1 (C_q, C^{Ar}), 132.5 (+, CH^{Ar}), 132.0 (+, CH^{Ar}), 131.7 (+, CH^{Ar}), 130.5 (+, CH^{Ar}), 129.7 (+, CH^{Ar}), 129.2 (+, CH^{Ar}), 128.8 (+, CH^{Ar}), 128.6 (+, CH^{Ar}), 127.6 (+, CH^{Ar}), 127.1 (+, CH^{Ar}), 126.6 (+, CH^{Ar}), 122.4 (+, CH^{Ar}), 121.2 (C_q, C^{Ar}), 115.5 (+, CH^{vinyl}), 61.4 (−, CH_2), 45.9 (−, CH_2^{benzyl}), 34.6 (−, CH_2), 34.4 (−, CH_2), 33.3 (−, CH_2), 31.8 (−, CH_2), 13.9 ppm (+, CH_3). IR (ATR): $\tilde{\nu}$ = 3296 (w), 3206 (w), 3091 (w), 2925 (w), 2839 (vw), 1645 (w), 1604 (m), 1557 cm^{-1} (s). MS (FAB, 3-NBA): m/z (%) = 497 (65) $[M + H]^+$, 496 (35) $[M]^+$. HRMS (FAB, 3-NBA, $C_{30}H_{29}O_3N_2{}^{32}S_1$, $[M + H]^+$) calcd, 497.1899; found, 497.1896.

*(rac)-Ethyl-(E)-2-((E)-2-(4′-[2.2]paracyclophanylimino)-3-allyl-4-oxothiazolidin-5-ylidene)acetate (**14c**).* R_f = 0.17 (cyclohexane/ethyl acetate, 4:1). Yellow crystals (EtOH), 379 mg (85%). Mp: 241−243 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 6.92 (dd, J = 7.7, 1.6 Hz, 1H, H^{Ar}), 6.74 (s, 1H, H^{vinyl}), 6.61−6.32 (m, 5H, H^{Ar}), 6.08 (ddd, J = 22.4, 10.3, 5.2 Hz, 1H, CH^{Allyl}), 5.84 (d, J = 1.0 Hz, 1H, H^{Ar}), 5.42−5.27 (m, 2H, CH_2^{Allyl}), 4.64 (d, J = 5.1 Hz, 2H, CH_2^{Allyl}), 4.17 (q, J = 7.1 Hz, 2H, CH_2), 3.24−3.12 (m, 1H, H^{Pc}), 3.08−2.88 (m, 6H, H^{Pc}), 2.68−2.55 (m, 1H, H^{Pc}), 1.20 ppm (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6): δ_C = 165.2 (C_q, CO), 163.7 (C_q, CO), 147.1 (C_q, C═N), 144.8 (C_q, C═C), 141.5 (C_q, C^{Ar}), 140.8 (C_q, C^{Ar}), 139.1 (C_q, C^{Ar}), 138.6 (C_q, C^{Ar}), 134.8 (+, CH^{Ar}), 133.2 (+, CH^{Ar}), 132.7 (+, CH^{Ar}), 132.5 (+, CH^{Allyl}), 131.7 (+, CH^{Ar}), 131.5 (+, CH^{Ar}), 129.6 (+, CH^{Ar}), 129.3 (+, CH^{Ar}), 126.7 (C_q, C^{Ar}), 117.1 (−, CH_2^{Allyl}), 115.2 (+, CH^{vinyl}), 61.4 (−, CH_2), 44.8 (−, CH_2^{Allyl}), 34.7 (−, CH_2), 34.3 (−, CH_2), 33.4 (−, CH_2), 32.1 (−, CH_2), 13.9 ppm (+, CH_3). IR (ATR): $\tilde{\nu}$ = 3421 (vw), 3303 (w), 3063 (w), 2945 (w), 2925 (w), 2851 (w), 1697 (s), 1655 (s), 1602 (vs), 1538 cm^{-1} (m). MS (FAB, 3-NBA): m/z (%) = 447 (100) $[M + H]^+$, 446 (40) $[M]^+$. HRMS (FAB, 3-NBA, $C_{26}H_{27}O_3N_2{}^{32}S_1$, $[M + H]^+$) calcd, 447.1747; found, 447.1737.

*(rac)-Ethyl-(E)-2-((E)-2-(4′-[2.2]paracyclophanylimino)-3-ethyl-4-oxothiazolidin-5-ylidene)acetate (**14d**).* R_f = 0.14 (cyclohexane/ethyl acetate, 4:1). Yellow crystals (EtOH), 381 mg (88%). Mp: 220−222 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 6.94 (d, J = 6.6 Hz, 1H, H^{Ar}), 6.71 (s, 1H, H^{vinyl}), 6.60−6.32 (m, 5H, H^{Ar}), 5.85 (s, 1H, H^{Ar}), 4.16 (q, J = 7.1 Hz, 2H, CH_2), 4.06 (q, J = 7.1 Hz, 2H, CH_2^{ethyl}), 3.25−3.21 (m, 1H, H^{Pc}), 3.04−2.90 (m, 6H, H^{Pc}), 2.69−2.61 (m, 1H, H^{Pc}), 1.40 (t, J = 6.7 Hz, 3H, CH_3^{ethyl}), 1.19 ppm (t, J = 7.0 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6): δ_C = 165.2 (C_q, CO), 163.8 (C_q, CO), 147.4 (C_q, C═N), 145.0 (C_q, C═C), 141.7 (C_q, C^{Ar}), 140.8 (C_q, C^{Ar}), 139.1 (C_q, C^{Ar}), 138.7 (C_q, C^{Ar}), 134.8 (+, CH^{Ar}), 133.2 (+, CH^{Ar}), 132.6 (+, 2 × CH^{Ar}), 131.7 (C_q, C^{Ar}), 129.6 (+, CH^{Ar}), 129.2 (+, CH^{Ar}), 126.8 (+, CH^{Ar}), 114.9 (+, CH^{vinyl}), 61.3 (−, CH_2), 38.0 (−, CH_2^{ethyl}), 34.6 (−, CH_2), 34.3 (−, CH_2), 33.5 (−, CH_2), 32.2 (−, CH_2), 13.9 (+, CH_3), 12.5 ppm (+, CH_3^{ethyl}). IR (ATR): $\tilde{\nu}$ = 3163 (vw), 3030 (vw), 2929 (w), 2815 (w), 2628 (vw), 1694 (s), 1649 (m), 1606 (vs), 1545 cm^{-1} (s). MS (FAB, 3-NBA): m/z (%) = 435 (100) $[M + H]^+$, 434 (90) $[M]^+$. HRMS (FAB, 3-NBA, $C_{25}H_{27}O_3N_2{}^{32}S_1$, $[M + H]^+$) calcd, 435.1742; found, 435.1743.

*(rac)-Ethyl-(E)-2-((E)-2-(4′-[2.2]paracyclophanylimino)-3-cyclopropyl-4-oxothiazolidin-5-ylidene)acetate (**14e**).* R_f = 0.55 (cyclohexane/ethyl acetate, 1:1). Yellow crystals (EtOH), 370 mg (83%). Mp: 180−182 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 7.01 (d, J = 7.3 Hz, 1H, H^{Ar}), 6.65 (s, 1H, H^{vinyl}), 6.60−6.34 (m, 5H, H^{Ar}), 5.82 (s, 1H, H^{Ar}), 4.14 (q, J = 7.1 Hz, 2H, CH_2), 3.29−3.18 (m, 1H, H^{Pc}), 3.12−2.91 (m, 7H, H^{Pc}), 2.70−2.58 (m, 1H, CH^{cyclo}), 1.17−1.14 (m, 4H, 2 × CH_2^{cyclo}), 1.06 ppm (t, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6): δ_C = 165.3 (C_q, CO), 164.4 (C_q, CO), 148.2 (C_q, C═N), 145.5 (C_q, C═C), 142.0 (C_q, C^{Ar}), 140.8 (C_q, C^{Ar}), 139.2 (C_q, C^{Ar}), 138.6 (C_q, C^{Ar}), 134.7 (+, CH^{Ar}), 133.2 (+, CH^{Ar}), 132.5 (+, CH^{Ar}), 132.4 (+, CH^{Ar}), 131.8 (+, CH^{Ar}), 129.3 (C_q, C^{Ar}), 129.2 (+, CH^{Ar}), 126.8 (+, CH^{Ar}), 114.4 (+, CH^{vinyl}), 61.2 (−, CH_2), 34.7 (−, CH_2), 34.3 (−, CH_2), 33.4 (−, CH_2), 32.2 (−, CH_2), 25.6 (+, CH^{cyclo}), 13.9 (+, CH_3^{ethyl}), 6.4 (−, CH_2^{cyclo}), 6.3 ppm (−, CH_2^{cyclo}). IR (ATR): $\tilde{\nu}$ = 3315 (vw), 3187 (vw), 3013 (w), 2927 (m), 2851 (w), 1714 (s), 1697 (s), 1653 (s), 1606 (vs), 1545 cm^{-1} (s). MS (FAB, 3-NBA): m/z (%) = 447 (70) $[M + H]^+$, 446 (35) $[M]^+$. HRMS (FAB, 3-NBA, $C_{26}H_{27}O_3N_2{}^{32}S_1$, $[M + H]^+$) calcd, 447.1742; found, 447.1739.

3.8. Synthesis of Thiazoles 15a−15e. A mixture of *N*-substituted [2.2]paracyclophanylhydrazinecarbothioamides (**12a−12e**, 1.00 mmol, 1.00 equiv) and diethyl acetylenedicarboxylate (DEAD) (**8b**, 0.170 g, 1.00 mmol, 1.00 equiv) in absolute ethanol (40 mL) was refluxed for 3−6 h (the reaction was monitored by thin-layer chromatography). After removal of the solvent under reduced pressure, the crude product was purified by column chromatography using EtOAc/hexane, 5:1 to afford **15a−15e**.

*(rac)-Ethyl-(E)-2-((E)-2-(2-(4′-[2.2]-paracyclophanylcarbamoyl)hydrazineylidene)-4-oxo-3-(p-tolyl)thiazolidin-5-ylidene)acetate (**15a**).* R_f = 0.30 (dichloromethane/methanol, 10:1). Yellow crystals (EtOH), 387 mg (70%). Mp: 268−270 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ_H = 11.32 (s, 1H, NH^2), 10.75 (s, 1H, NH^1), 7.65−7.40 (m, 4H, H^{Ar}), 7.30−7.22 (m, 1H, H^{Ar}), 7.07−6.90 (m, 1H, H^{Ar}), 6.80 (s, 1H, H^{vinyl}), 6.75−6.62 (m, 1H, H^{Ar}), 6.59−6.40 (m, 3H, H^{Ar}), 3.37 (dd, J = 12.4, 10.4 Hz, 2H, CH_2), 3.25−2.70 (m, 8H, H^{Pc}), 2.18 (s, 3H, CH_3^{phenyl}), 1.40 ppm (t, J = 7.0 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ_C = 165.4 (C_q, CO), 160.4 (C_q, CO), 152.0 (C_q, CO), 141.0 (C_q, C═N), 140.2 (C_q, C═C), 139.6 (C_q, C^{Ar}), 139.4 (C_q, C^{Ar}), 139.3 (C_q, C^{Ar}), 138.9 (C_q, C^{Ar}), 137.7 (C_q, C^{Ar}), 135.0 (C_q, C^{Ar}), 134.0 (+, CH^{Ar}), 132.6 (+, CH^{Ar}), 132.4 (+, CH^{Ar}), 132.2 (+, CH^{Ar}), 132.1 (+, CH^{Ar}), 131.2 (+, CH^{Ar}), 129.6 (+, CH^{Ar}), 129.5 (+, CH^{Ar}), 129.0 (+, CH^{Ar}), 128.1 (+, CH^{Ar}), 125.2 (+, CH^{Ar}), 120.5 (C_q, C^{Ar}), 118.0 (+, CH^{vinyl}), 52.6 (+, CH_2), 34.7 (−, CH_2), 34.5 (−, CH_2), 34.3 (−, CH_2), 34.2 (−, CH_2), 32.5 (+, CH_3^{phenyl}), 20.9 ppm (+, CH_3). IR (ATR) $\tilde{\nu}$ = 3296 (w), 3206 (w), 3091 (w), 2925 (w), 2839 (vw), 1645 (w), 1604 (m), 1557 (s), 1456 cm^{-1} (s). MS (FAB, 3-NBA): m/z (%) = 555 (65) $[M + H]^+$, 554 (30) $[M]^+$. HRMS (FAB, 3-NBA, $C_{31}H_{31}O_4N_4{}^{32}S_1$, $[M + H]^+$) calcd, 555.2066; found, 555.2063.

*(rac)-Ethyl-(E)-2-((E)-2-(2-(4′-[2.2]-Paracyclophanylcarbamoyl)hydrazineylidene)-3-benzyl-4-oxothiazolidin-5-ylidene)acetate (**15b**).* R_f = 0.34 (cyclohexane/ethyl acetate, 4:1). Yellow crystals (ethanol), 415 mg (75%). Mp: 280−282 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ_H = 10.88 (s, 1H, NH^2), 8.40 (s, 1H, NH^1), 7.58−7.20 (m, 5H, H^{Ar}), 6.78 (s, 1H, H^{vinyl}), 6.86−6.20 (m, 7H, H^{Ar}), 5.19 (q, J = 15.2 Hz, 2H, CH_2), 4.18 (dd, J = 14.3, 6.8 Hz, 2H, CH_2^{benzyl}),

https://doi.org/10.1021/acsomega.2c00141
ACS Omega 2022, 7, 12879−12890

3.12−2.50 (m, 8H, H^{Pc}), 1.21 ppm (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6): δ_C = 165.9 (C_q, CO), 161.5 (C_q, CO), 154.4 (C_q, CO), 140.5 (C_q, C═N), 139.1 (C_q, C═C), 138.6 (C_q, C^{Ar}), 137.8 (C_q, C^{Ar}), 135.2 (C_q, C^{Ar}), 132.5 (C_q, C^{Ar}), 132.4 (C_q, C^{Ar}), 132.3 (+, CH^{Ar}), 132.2 (+, CH^{Ar}), 131.6 (+, CH^{Ar}), 131.3 (+, CH^{Ar}), 131.2 (+, CH^{Ar}), 128.5 (+, 2 × CH^{Ar}), 128.2 (+, CH^{Ar}), 127.8 (+, CH^{Ar}), 127.3 (+, CH^{Ar}), 127.2 (+, 2 × CH^{Ar}), 127.0 (C_q, C^{Ar}), 116.6 (+, CH^{vinyl}), 60.4 (−, CH_2), 45.8 (−, CH_2^{benzyl}), 34.8 (−, CH_2), 34.6 (−, CH_2), 34.5 (−, CH_2), 34.2 (−, CH_2), 13.8 ppm (+, CH_3). IR (ATR): $\tilde{\nu}$ = 3296 (w), 3206 (w), 3091 (w), 2925 (w), 2839 (vw), 1645 (w), 1604 (m), 1557 (s), 1456 cm^{-1} (s). MS (FAB, 3-NBA): m/z (%) = 555 (75) $[M + H]^+$, 554 (20) $[M]^+$. HRMS (FAB, 3-NBA, $C_{31}H_{31}O_4N_4{}^{32}S_1$, $[M + H]^+$) calcd, 555.2066; found, 555.2063.

*(rac)-Ethyl-(E)-2-((E)-2-(2-(4′-[2.2]paracyclophanylcarbamoyl)hydrazineylidene)-3-allyl-4-oxothiazolidin-5-ylidene)acetate (**15c**).* R_f = 0.37 (cyclohexane/ethyl acetate, 4:1). Yellow crystals (EtOH), 368 mg (73%). Mp: 291−293 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 9.25 (s, 1H, NH^2), 8.53 (s, 1H, NH^1), 6.80 (s, 1H, H^{vinyl}), 6.76−6.55 (m, 2H, H^{Ar}), 6.36−5.89 (m, 4H, H^{Ar}), 6.08 (ddd, J = 22.4, 10.3, 5.2 Hz, 1H, CH^{allyl}), 5.84 (d, J = 1.0 Hz, 1H, H^{Ar}), 5.12−4.93 (m, 2H, CH_2^{allyl}), 4.29 (d, J = 5.3 Hz, 2H, CH_2^{allyl}), 4.18 (q, J = 7.1 Hz, 2H, CH_2), 3.05−2.70 (m, 7H, H^{Pc}), 2.56 (dd, J = 17.6, 8.3 Hz, 1H, H^{Pc}), 1.14 ppm (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6): δ_C = 165.3 (C_q, CO), 165.1 (C_q, CO), 162.9 (C_q, CO), 161.8 (C_q, C═N), 154.5 (C_q, C═C), 153.0 (C_q, C^{Ar}), 147.0 (C_q, C^{Ar}), 140.6 (C_q, C^{Ar}), 140.0 (C_q, C^{Ar}), 139.0 (+, CH^{Ar}), 138.4 (+, CH^{Ar}), 134.9 (+, CH^{Ar}), 132.8 (+, CH^{Allyl}), 132.0 (+, CH^{Ar}), 130.8 (+, CH^{Ar}), 128.6 (+, CH^{Ar}), 127.7 (+, CH^{Ar}), 126.0 (C_q, C^{Ar}), 117.6 (−, CH_2^{Allyl}), 116.1 (+, CH^{vinyl}), 61.5 (−, CH_2), 44.5 (−, CH_2^{Allyl}), 34.7 (−, CH_2), 34.5 (−, CH_2), 33.0 (−, CH_2), 32.9 (−, CH_2), 14.0 ppm (+, CH_3). IR (ATR): $\tilde{\nu}$ = 3291 (w), 3285 (w), 3271 (w), 2980 (w), 2966 (w), 2927 (w), 2851 (w), 1742 (m), 1707 (s), 1693 (s), 1660 (vs), 1613 cm^{-1} (s). MS (FAB, 3-NBA): m/z (%) = 505 (55) $[M + H]^+$, 504 (25) $[M]^+$. HRMS (FAB, 3-NBA, $C_{27}H_{29}O_4N_4{}^{32}S_1$, $[M + H]^+$) calcd, 505.1910; found, 505.1906.

*(rac)-Ethyl-(E)-2-((E)-2-(2-(4′-[2.2]paracyclophanylcarbamoyl)hydrazineylidene)-3-ethyl-4-oxothiazolidin-5-ylidene)acetate (**15d**).* R_f = 0.34 (cyclohexane/ethyl acetate, 4:1). Yellow crystals (EtOH), 374 mg (76%). Mp: 285−287 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 9.46 (s, 1H, NH^2), 8.45 (s, 1H, NH^1), 6.90 (d, J = 6.6 Hz, 1H, H^{Ar}), 6.74 (s, 1H, H^{vinyl}), 6.45−6.20 (m, 6H, H^{Ar}), 4.18 (q, J = 7.1 Hz, 2H, CH_2), 4.02 (q, J = 7.1 Hz, 2H, CH_2^{ethyl}), 3.04−2.80 (m, 6H, H^{Pc}), 2.68−2.65 (m, 1H, H^{Pc}), 1.25 (t, J = 6.7 Hz, 3H, CH_3^{ethyl}), 1.15 ppm (t, J = 7.0 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6): δ_C = 164.8 (C_q, CO), 161.3 (C_q, CO), 153.9 (C_q, CO), 146.5 (C_q, C═N), 140.1 (C_q, C═C), 139.5 (C_q, C^{Ar}), 138.5 (C_q, C^{Ar}), 137.9 (C_q, C^{Ar}), 136.6 (C_q, C^{Ar}), 134.3 (+, CH^{Ar}), 132.3 (+, CH^{Ar}), 131.5 (+, 2 × CH^{Ar}), 130.2 (C_q, C^{Ar}), 128.1 (+, CH^{Ar}), 127.1 (+, CH^{Ar}), 125.4 (+, CH^{Ar}), 115.6 (+, CH^{vinyl}), 61.0 (−, CH_2), 40.7 (−, CH_2^{ethyl}), 34.2 (−, CH_2), 34.0 (−, CH_2), 32.5 (−, CH_2), 32.4 (−, CH_2), 14.0 (+, CH_3), 13.4 ppm (+, CH_3^{ethyl}). IR (ATR) ν = 3163 (vw), 3030 (vw), 2929 (w), 2815 (w), 2628 (vw), 1694 (s), 1649 (m), 1606 (vs), 1545 cm^{-1} (s). MS (FAB, 3-NBA): m/z (%) = 493 (100) $[M + H]^+$, 492 (30) $[M]^+$. HRMS (FAB, 3-NBA, $C_{26}H_{29}O_4N_4{}^{32}S_1$, $[M + H]^+$) calcd, 493.1910; found, 493.1905.

*(rac)-Ethyl-(E)-2-((E)-2-(4′-[2.2]paracyclophanylcarbamoyl)hydrazineylidene)-3-cyclopropyl-4-oxothiazolidin-5-ylidene)acetate (**15e**).* R_f = 0.37 (cyclohexane/ethyl acetate, 1:1). Yellow crystals (EtOH), 363 mg (72%). Mp: 260−262 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 9.36 (s, 1H, NH^2), 8.43 (s, 1H, NH^1), 6.87 (s, 1H, H^{vinyl}), 6.80−6.70 (m, 1H, H^{Ar}), 6.49 (d, J = 7.8 Hz, 2H, H^{Ar}), 6.45−6.27 (m, 4H, H^{Ar}), 4.29 (q, J = 6.9 Hz, 2H, CH_2), 3.31−3.20 (m, 1H, H^{Pc}), 3.09−2.80 (m, 7H, H^{Pc}), 2.72−2.55 (m, 1H, CH^{cyclo}), 1.29 (t, J = 7.0 Hz, 3H, CH_3), 1.03−0.86 (m, 2H, CH_2^{cyclo}), 0.79−0.66 ppm (m, 2H, CH_2^{cyclo}). ^{13}C NMR (101 MHz, DMSO-d_6): δ_C = 165.2 (C_q, CO), 161.5 (C_q, CO), 152.8 (C_q, CO), 145.8 (C_q, C═N), 140.0 (C_q, C═C), 138.9 (C_q, C^{Ar}), 138.7 (C_q, C^{Ar}), 138.5 (+, CH^{Ar}), 137.5 (C_q, C^{Ar}), 136.9 (C_q, C^{Ar}), 134.9 (+, CH^{Ar}), 132.7 (+, CH^{Ar}), 132.1 (+, CH^{Ar}), 131.6 (+, CH^{Ar}), 128.7 (C_q, C^{Ar}), 127.9 (+, CH^{Ar}), 126.2 (+, CH^{Ar}), 115.7 (+, CH^{vinyl}), 61.5 (−, CH_2), 34.7 (−, CH_2), 34.5 (−, CH_2), 34.4 (−, CH_2), 34.1 (−, CH_2), 33.1 (+, CH^{cyclo}), 14.0 (+, CH_3^{ethyl}), 8.1 ppm (−, 2 × CH_2^{cyclo}). IR (ATR): $\tilde{\nu}$ = 3315 (vw), 3187 (vw), 3013 (w), 2927 (m), 2851 (w), 1714 (s), 1697 (s), 1653 (s), 1606 (vs), 1545 (s), 1436 cm^{-1} (m). MS (FAB, 3-NBA): m/z (%) = 505 (90) $[M + H]^+$, 504 (25) $[M]^+$. HRMS (FAB, 3-NBA, $C_{27}H_{29}O_4N_4{}^{32}S_1$, $[M + H]^+$) calcd, 505.1910; found, 505.1905.

3.9. Synthesis of Compound 16. A stirring mixture of *N*-allyl [2.2]paracyclophanylhydrazinecarbothioamides (**12e**, 0.380 g, 1.00 mmol, 1.00 equiv) and 10 mL of sodium hydroxide (1.00 mmol, as a 2 N solution) dissolved in 40 mL of ethanol was refluxed for 3 h. After cooling, the solution was acidified with 10 mL of hydrochloric acid (6 M) and the formed precipitate was filtered.

*N^2-(4′-[2.2]Paracyclophanyl)-N^5-allyl-1,3,4-oxadiazole-2,5-diamine (**16**).* R_f = 0.46 (dichloromethane/methanol, 10:1), colorless crystals ($CHCl_3$/EtOH), 207 mg (60%). Mp: 206−208 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 9.41 (s, 1H, NH), 8.44 (s, 1H, NH), 7.72 (s, 1H, H^{Ar}), 6.91 (dd, J = 7.7, 1.3 Hz, 1H, H^{Ar}), 6.91 (dd, J = 7.7, 1.3 Hz, 1H, H^{Ar}), 6.76 (d, J = 1.4 Hz, 1H, CH^{allyl}), 6.56−6.35 (m, 4H, H^{Ar}), 5.98−5.90 (m, 2H, CH_2^{allyl}), 5.75−5.25 (m, 2H, CH_2^{allyl}), 3.10−2.89 ppm (m, 8H, H^{Pc}). ^{13}C NMR (101 MHz, DMSO-d_6): δ_C = 155.0 (C_q, C^{Ar}), 140.6 (C_q, C^{Ar}), 139.7 (C_q, C^{Ar}), 139.3 (C_q, C^{Ar}), 139.0 (C_q, C^{Ar}), 138.1 (C_q, C^{Ar}), 135.4 (+, CH^{Ar}), 135.2 (+, CH^{Ar}), 133.5 (+, CH^{Ar}), 133.2 (+, CH^{Ar}), 132.3 (+, CH^{allyl}), 129.5 (+, CH^{Ar}), 128.8 (+, CH^{Ar}), 127.3 (+, CH^{Ar}), 125.8 (C_q, C^{Ar}), 115.8 (−, CH_2^{allyl}), 46.3 (−, CH_2^{allyl}), 35.5 (−, CH_2), 35.2 (−, CH_2), 33.4 (−, CH_2), 32.9 ppm (−, CH_2). IR (ATR) $\tilde{\nu}$ = 3214 (w), 3156 (w), 3013 (w), 2946 (m), 2925 (m), 2888 (m), 2856 (w), 1717 (w), 1653 (vs), 1623 (vs), 1595 cm^{-1} (s). MS (FAB, 3-NBA): m/z (%) = 347 (100) $[M + H]^+$, 346 (50) $[M]^+$. HRMS (FAB, 3-NBA, $C_{21}H_{23}O_1N_4$, $[M + H]^+$) calcd, 347.1872; found, 347.1870.

3.10. Crystal Structure Determinations. The single-crystal X-ray diffraction study were carried out on a Bruker D8 Venture diffractometer with a PhotonII detector at 123(2) K or 173(2) K using Cu−Kα radiation (λ = 1.54178 Å). Dual space/intrinsic methods[25] were used for structure solution, and refinement was carried out using SHELXL-2014 (full-matrix least-squares on F^2).[26] Hydrogen atoms were localized by difference electron density determination and refined using a riding model (H(N) free). Semiempirical absorption corrections were applied. For **14b**, an extinction correction was applied. In **14b**, the ethyl moiety is disordered (see the cif files for details). **14e** was refined as a twin with two domains.

https://doi.org/10.1021/acsomega.2c00141
ACS Omega 2022, 7, 12879−12890

9: Yellow crystals, $C_{23}H_{25}N_3O_5$, M_r = 423.46, crystal size 0.16 × 0.12 × 0.04 mm^3, monoclinic, space group $P2_1/n$ (no. 14), a = 13.3388(5) Å, b = 8.1948(3) Å, c = 19.9695(8) Å, β = 106.989(2)°, V = 2087.58(14) Å^3, Z = 4, ρ = 1.347 Mg/m^{-3}, μ(Cu−K$_\alpha$) = 0.79 mm^{-1}, F(000) = 896, T = 123 K, $2\theta_{max}$ = 144.6°, 32299 reflections, of which 4117 were independent (R_{int} = 0.035), 288 parameters, 2 restraints, R_1 = 0.071 (for 3572$I > 2\sigma(I)$), wR_2 = 0.213 (all data), S = 1.05, largest diff. peak/hole = 1.00/−0.20 e Å^{-3}.

11d: Colorless crystals, $C_{19}H_{22}N_2S$, M_r = 310.44, crystal size 0.16 × 0.06 × 0.04 mm^3, triclinic, space group P-1 (no. 2), a = 11.3925(3) Å, b = 12.0321(3) Å, c = 13.4654(4) Å, α = 88.526(1)°, β = 65.296(1)°, γ = 76.086(1)°, V = 1621.79(8) Å^3, Z = 4, ρ = 1.271 Mg/m^{-3}, μ(Cu−K$_\alpha$) = 1.74 mm^{-1}, F(000) = 664, T = 123 K, $2\theta_{max}$ = 144.8°, 30263 reflections, of which 6380 were independent (R_{int} = 0.029), 409 parameters, 4 restraints, R_1 = 0.038 (for 5802$I > 2\sigma(I)$), wR_2 = 0.107 (all data), S = 1.05, largest diff. peak/hole = 0.41/−0.27 e Å^{-3}.

14b: Yellow crystals, $C_{30}H_{28}N_2O_3S$, M_r = 496.60, crystal size 0.16 × 0.04 × 0.02 mm^3, monoclinic, space group $P2_1/c$ (no. 14), a = 10.0473(4) Å, b = 34.0461(14) Å, c = 7.5093(3) Å, β = 100.286(2)°, V = 2527.43(18) Å^3, Z = 4, ρ = 1.305 Mg/m^{-3}, μ(Cu−K$_\alpha$) = 1.42 mm^{-1}, F(000) = 1048, T = 173 K, $2\theta_{max}$ = 144.6°, 18990 reflections, of which 4720 were independent (R_{int} = 0.053), 325 parameters, 2 restraints, R_1 = 0.045 (for 4229$I > 2\sigma(I)$), wR_2 = 0.122 (all data), S = 1.04, largest diff. peak/hole = 0.51/−0.51 e Å^{-3}.

14e: Yellow crystals, $C_{26}H_{26}N_2O_3S$, M_r = 446.55, crystal size 0.21 × 0.15 × 0.03 mm^3, monoclinic, space group $P2_1/c$ (no. 14), a = 24.6864(10) Å, b = 7.8388(3) Å, c = 11.4055(5) Å, β = 91.995(1)°, V = 2205.76(16) Å^3, Z = 4, ρ = 1.345 Mg/m^{-3}, μ(Cu−K$_\alpha$) = 1.56 mm^{-1}, F(000) = 944, T = 173 K, $2\theta_{max}$ = 144.6°, 16496 reflections, of which 4306 were independent (R_{int} = 0.043), 290 parameters, R_1 = 0.096 (for 3868$I > 2\sigma(I)$), wR_2 = 0.278 (all data), S = 1.04, largest diff. peak/hole = 1.48/−0.52 e Å^{-3}.

CCDC-2128196 (**9**), CCDC-2128197 (**11d**), CCDC-2128199 (**14b**), and CCDC-2128199 (**14e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

4. CONCLUSION

In the current study, a novel series assembly of thio(ureas), semicarbazides, thiosemicarbazides, thiazoles, and oxadiazole derived from [2.2]paracyclophane were effectively synthesized. Therefore, it would be potentially applied to the symmetrical disubstituted PC. We are encouraging to synthesize numerous new heterocycles derived from [2.2]paracyclophanes aiming to increase attention on that important asymmetric molecule toward biological activity. Previous reports have dealt with effective biological activities resulting from conjugation between paracyclophane and heterocycle molecules. That might led to the discovery of promising novel hybrids of interesting heterocyclic/paracyclophanes as a starting point in medicinal chemistry art that warrants further research and development as potential biological active candidates.

AUTHOR INFORMATION

Corresponding Authors

Ashraf A. Aly − *Chemistry Department, Faculty of Science, Minia University, 61519 El-Minia, Egypt;* orcid.org/0000-0002-0314-3408; Phone: +201006268742; Email: ashrafaly63@yahoo.com, ashraf.shehata@mu.edu.eg

Stefan Bräse − *Institute of Organic Chemistry, Karlsruhe Institute of Technology, 76131 Karlsruhe, Germany; Institute of Biological and Chemical Systems (IBCS-FMS), Karlsruhe Institute of Technology, 76344 Eggenstein-Leopoldshafen, Germany;* orcid.org/0000-0003-4845-3191; Phone: +49 721 608-42902; Email: braese@kit.edu

Authors

Mohammed B. Alshammari − *Chemistry Department, College of Sciences and Humanities, Prince Sattam bin Abdulaziz University, Al-Kharij 11942, Saudi Arabia*

Martin Nieger − *Department of Chemistry, University of Helsinki, 00014 Helsinki, Finland*

Lamiaa E. Abd El-Haleem − *Chemistry Department, Faculty of Science, Minia University, 61519 El-Minia, Egypt*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.2c00141

Author Contributions

M.B.A. (writing, editing, and revision), A.A.A. (concept, experiments, writing, editing, revision, and submitting); S.B. (writing, editing, and revision); M.N. (X-ray analysis and editing); and L.E.A.E.-H. (experiments, writing, and revision).

Notes

The authors declare no competing financial interest.

CCDC-2128196 (**9**), CCDC-2128197 (**11d**), CCDC-2128199 (**14b**), and CCDC-2128199 (**14e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

ACKNOWLEDGMENTS

The authors thank the DFG for providing Professor Ashraf A. Aly with a 1-month fellowship, enabling him to carry out the compound analysis at the Karlsruhe Institute of Technology, Karlsruhe, Germany, in July−August 2019. We also acknowledge support by the KIT-Publication Fund of the Karlsruhe Institute of Technology.

REFERENCES

(1) Hassan, Z.; Spuling, E.; Knoll, D. M.; Lahann, J.; Brase, S. Planar chiral [2.2]paracyclophanes: from synthetic curiosity to applications in asymmetric synthesis and materials. *Chem. Soc. Rev.* **2018**, *47*, 6947−6963.

(2) Hopf, H.; Narayanan, S. V.; Jones, P. G. The preparation of new functionalized [2.2]paracyclophane derivatives with *N*-containing functional groups. *Beilstein J. Org. Chem.* **2015**, *11*, 437−445.

(3) Braun, C.; Bräse, S.; Schafer, L. L. Planar-Chiral [2.2]-Paracyclophane-Based Amides as Proligands for Titanium- and Zirconium-Catalyzed Hydroamination. *Eur. J. Org. Chem.* **2017**, *2017*, 1760−1764.

(4) Gibson, S. E.; Knight, J. D. [2.2]Paracyclophane derivatives in asymmetric catalysis. *Organic & Biomol. Chem.* **2003**, *1* (8), 1256−1269.

(5) Meyer, E. A.; Castellano, R. K.; Diederich, F. Interactions with Aromatic Rings in Chemical and Biological Recognition. *Angew. Chem. (Int. Ed.)* **2003**, *42* (11), 1210−1250.

(6) Aly, A. A.; Brase, S.; Hassan, A. A.; Mohamed, N. K.; El-Haleem, L. E. A.; Nieger, M.; Morsy, N. M.; Alshammari, M. B.; Ibrahim, M. A. A.; Abdelhafez, E. M. N. Design, Synthesis and Molecular Docking of

Paracyclophanyl-Thiazole Hybrids as Novel CDK1 Inhibitors; Apoptosis-Inducing Anti-Melanoma Agents. *Molecules* **2020**, *25* (23), 5569.
(7) Aly, A. A.; Brown, A. B. Asymmetric and fused heterocycles based on [2.2] paracyclophane. *Tetrahedron* **2009**, *65* (39), 8055.
(8) Aly, A. A.; Hopf, H.; Ernst, L.; Dix, I.; Jones, P. G. New Cycloadditions of (E)-N, α-Dimethyl-α-(4-[2.2] paracylophanyl)-nitrone. *Eur. J. Org. Chem.* **2006**, *2006* (13), 3001−3006.
(9) Aly, A. A. Cycloaddition of (*E*)-*N*-[2-([2.2] paracyclophan-4-yl)ethylidene] methylamine-*N*-oxide with 2,3-diphenylcyclopropenones and dibenzoyl acetylene; synthesis of new paracyclophanylpyrroles. *J. Chem. Res.* **2007**, *2007* (8), 451−454.
(10) Aly, A. A.; Brase, S.; Hassan, A. A.; Mohamed, N. K.; El-Haleem, L. E. A.; Nieger, M. Synthesis of New Planar-Chiral Linked [2.2]Paracyclophanes-*N*-([2.2]-Paracyclophanylcarbamoyl)-4-([2.2]-Paracyclophanylcarboxamide, [2.2]Paracyclophanyl-Substituted Triazolethiones and Substituted Oxadiazoles. *Molecules* **2020**, *25* (15), 3315.
(11) Aly, A. A.; Hopf, H.; Jones, P. G.; Dix, I. Cycloadditions of α-(4-[2.2] paracyclophanyl)-*N*-methyl nitrone. *Tetrahedron* **2006**, *62* (18), 4498−4505.
(12) Hopf, H.; Aly, A. A.; Swaminathan, V. N.; Ernst, L.; Dix, I.; Jones, P. G. A simple route to a pyridinyl [2.2] paracyclophane. *Eur. J. Org. Chem.* **2005**, *2005* (1), 68−71.
(13) Dyniewicz, J.; Lipiński, P. F. J.; Kosson, P.; Bochyńska-Czyż, M.; Matalińska, J.; Misicka, A. Antinociceptive and Cytotoxic Activity of Opioid Peptides with Hydrazone and Hydrazide Moieties at the C-Terminus. *Molecules* **2020**, *25* (15), 3429.
(14) Kotali, A.; Nasiopoulou, D.; Tsoleridis, C.; Harris, P.; Kontogiorgis, C.; Hadjipavlou-Litina, D. Antioxidant Activity of 3-[*N*-(Acylhydrazono)ethyl]-4-hydroxy-coumarins. *Molecules* **2016**, *21* (2), 138.
(15) Dutta, M. M.; Goswami, B. N.; Kataky, J. C. S. Studies on biologically active heterocycles. Part I. Synthesis and antifungal activity of some new aroyl hydrazones and 2,5-disubstituted-1,3,4-oxadiazoles. *J. Heterocycl. Chem.* **1986**, *23*, 793−795.
(16) Bernardino, A. M. R.; Gomes, A. O.; Charret, K. S.; Freitas, A. C. C.; Machado, G. M. C.; Canto-Cavalheiro, M. M.; Leon, L. L.; Amaral, V. F. Synthesis and leishmanicidal activities of 1-(4-X-phenyl)-*N*′-[(4-Y-phenyl)methylene]-1*H*-pyrazole-4-carbohydrazides. *Eur. J. Med. Chem.* **2006**, *41*, 80−87.
(17) Terzioglu, N.; Gürsoy, A. Synthesis and anticancer evaluation of some new hydrazone derivatives of 2,6-dimethylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbohydrazide. *Eur. J. Med. Chem.* **2003**, *38*, 781−786.
(18) Xia, Y.; Fan, C.-D.; Zhao, B.-X.; Zhao, J.; Shin, D.-S.; Miao, J.-Y. Synthesis of novel substituted pyrazole-5-carbohydrazide hydrazone derivatives and discovery of a potent apoptosis inducer in A549 lung cancer cells. *Eur. J. Med. Chem.* **2008**, *43*, 2347−2353.
(19) Zheng, L.-W.; Wu, L.-L.; Zhao, B.-X.; Dong, W.-L.; Miao, J.-Y. Synthesis of novel substituted pyrazole-5-carbohydrazide hydrazone derivatives and discovery of a potent apoptosis inducer in A549 lung cancer cells. *Bioorg. Med. Chem.* **2009**, *17*, 1957−1962.
(20) Markham, P.; Klyachko, E.; Crich, D.; Jaber, M.; Johnson, M.; Mulhearn, D.; Neyfakh, A. (2001). PCT Int. Appl. WO 01 70:213.
(21) Saeed, S.; Rashid, N.; Jones, P. G.; Ali, M.; Hussain, R. Synthesis, characterization and biological evaluation of some thiourea derivatives bearing benzothiazole moiety as potential antimicrobial and anticancer agents. *Eur. J. Med. Chem.* **2010**, *45*, 1323−1231.
(22) Ghorab, M. M.; Alsaid, M. S.; El-Gaby, M. S. A.; Elaasser, M. M.; Nissan, Y. M. Antimicrobial and anticancer activity of some novel fluorinated thiourea derivatives carrying sulfonamide moieties: synthesis, biological evaluation and molecular docking. *Chem. Cental J.* **2017**, *11*, 32.
(23) Salahuddin; Mazumder, A.; Yar, M. S.; Mazumder, R.; Chakraborthy, G. S.; Ahsan, M. J.; Rahman, M. U. Updates on synthesis and biological activities of 1,3,4-oxadiazole: a review. *Synth. Commun.* **2017**, *47* (20), 1805−1847.
(24) Hopf, H.; Narayanan, S. V.; Jones, P. G. The preparation of new functionalized [2.2]paracyclophane derivatives with *N*-containing functional groups. *Beilstein J. Org. Chem.* **2015**, *11*, 437−445.
(25) Sheldrick, G. M. *SHELXT* - Integrated space-group and crystal-structure determination. *Acta Crystallogr.* **2015**, *A71*, 3−8.
(26) Sheldrick, G. M. Crystal structure refinement with *SHELXL*. *Acta Crystallogr.* **2015**, *C71*, 3−8.

https://doi.org/10.1021/acsomega.2c00141
ACS Omega 2022, 7, 12879−12890