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FACILE SYNTHESIS OF (2-BENZIMIDAZOLYL)-1-AZAAZULENES, (2-BENZOTHIAZOLYL)-1-AZAAZULENES, AND RELATED COMPOUNDS AND EVALUATION OF THEIR ANTICANCER IN VITRO ACTIVITY†

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Abstract – Facile syntheses of 2-, 3,- and 8-(2-benzimidazolyl)-1-azaazulenes (**2a-c**, **5**, **7**, **9**) and 2-, 3-, and 8-(2-benzothiazolyl)-1-azaazulenes (**13b-c**, **16**, **17**, **18**) were achieved by the condensation of corresponding 1-azaaazulene-carbaldehydes with *o*-phenylenediamine and 2-aminothiophenol in alcoholic solvents at rt or under reflux under airobic conditions. Reaction of 1-azaazulenecarbaldehyds with 2-aminophenol gave Schiff's bases (**10a-c**, **11**, **12**). Reaction of 2-chloro-1-azaazulene-3-carbaldehyde (**1a**) with 2-amino-thiophenol in refluxing 1-BuOH gave benzothiazapine-fused 1-azaazulene (**20**). Reaction of 4-amino-3-mercapto-4*H*-1,2,4-triazoles (**21a-d**) with in refluxing 1-BuOH gave triazolothiadizapine-fused 1-azaazulene (**22a-d**). The structure of trifluolomethyl derivative (**22c**) was determined by X-ray structure analysis. 3-(2-Benz- imidazolyl)-2-chloro-1-azaazulene (**2a**) showed anticancer activity against HeLa S3 cells (IC_{50}: 5.3 μM).

† Dedicated to Professor Dr. Ryoji Noyori on occasion of his 70th birthday.

INTRODUCTION

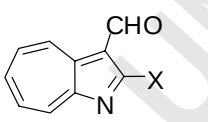
Benzazoles such as benzimidazoles, benzothiazoles, and benzoxazoles, are important subunits for the development of functional molecules of pharmaceutical and biological interest. Substituted benzothiazoles and benzimidazoles have found application in a wide range of therapeutic areas such as antiulcers, anticancers, antihistamics, antifungals, and antivirals to name a few.[1-10]

The chemistry of azaazulenes[11] is of interest for their physiological properties[12,13] as well as physical and chemical properties. Therefore, it is expected that benzazolyl-1-azaazulenes have potential bioactivities. Numerical methods for the synthesis of benzazols are reported. We previously reported that 2-chloro-1-azaazulene-3-carboaldehyde reacted with *o*-phenylenediamine to give 3-(benzimidazol-2-yl)-2-chloro-1-azaazulene.[14] Therefore, we expand the investigation about the syntheses of benzazolyl-1-azaazulenes by condensation reaction of formyl-1-azaazulenes with *o*-phenylenediamine, 2-aminophenol, and 2-aminothiophenol.

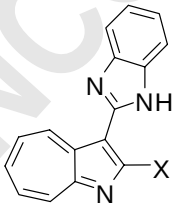
RESULTS AND DISCUSSION

Synthesis of (benzimidazol-2-yl)- and (benzothiazol-2-yl) -1-azaazulenes

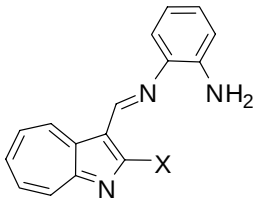
Under open air conditions, the reaction of 2-chloro-1-azaazulene-3-carbaldehyde (**1a**) with *o*-phenylenediamine in EtOH for 48 h at rt underwent to give **2a** in 78% yield along with recovered (**1a** : 15%). In the reaction, the intermediate imine (**3a**) was not observed. Reactivity of **1b** was slightly low than that of **1a**, and heating under reflux of **1b** with *o*-phenylenediamine in EtOH for 37 h gave **2b** in 59% yield along with a trace amount of **1b**, and **3b** was not obtained. Reactivity of **1c** was moreover low, and when **1c** was treated with *o*-phenylenediamine in EtOH for 44 h at rt to give the imine derivative (**3c**) in 62% yield along with **1c** (15%). Heating under reflux of **1c** with *o*-phenylenediamine in 1-BuOH for 37 h achieved **2c** in 88% yield. Extent of electron-donation of the sunstituent at C-2, which



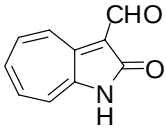
1a : X = Cl
1b : X = OEt
1c : X = NH_2



2a : X = Cl
2b : X = OEt
2c : X = NH_2



3a : X = Cl
3b : X = OEt
3c : X = NH_2



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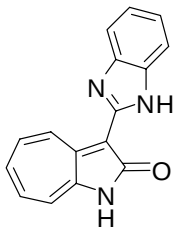

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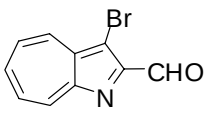

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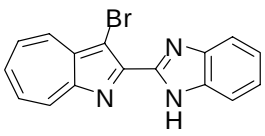

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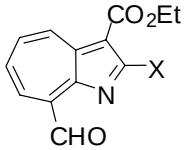
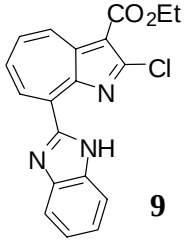


8a : X = Cl
8b : X = OEt



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conjugated with carbonyl at C3, would affect the reactivity.

Similar treatment of 3-bromo-1-azaazulene-2-carbaldehyde (**6**) and 1-azaazulene-8-carbaldehyde (**8a**) with *o*-phenylenediamine in EtOH at rt gave **7** and **9** in 40% and 38% yields, respectively. In these reactions, **6** and **8** were not recovered because of their lability.

The structures of obtained compounds were determined by spectroscopic data as well as elemental analyses as shown in EXPERIMENTAL. The imine (**3c**) was decided by X-Ray structure analysis and its ORTEP drawing[15] is shown in Figure 1.

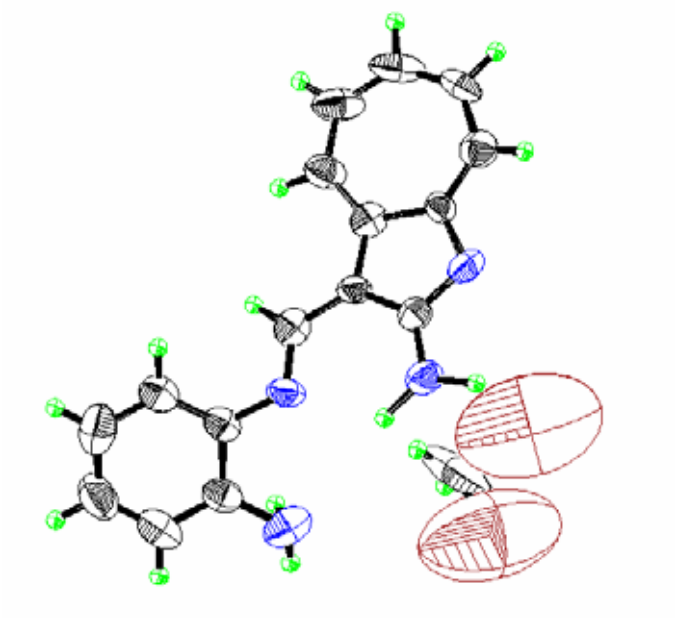
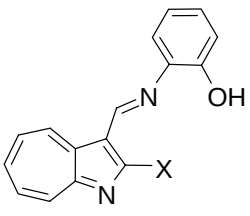
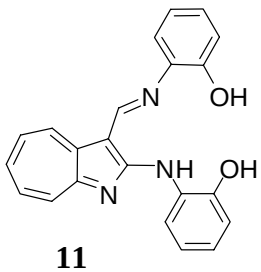


Figure 1. ORTEP drawing with thermal ellipsoids (50% probability) of **3c**.

Next, we examined the reaction of 1-azaazulene-3-carbaldehydes (**1a**-**1c**) with 2-aminophenol. When **1a** was treated with 2-aminophenol in refluxing EtOH for 15 min, **10a** precipitated as orange crystals in 60% yield. When the heating was continued, the precipitates were dissolved and after heating of the mixture for 15 h, compound (**11**) was obtained in 37% yield. When the reaction was carried out at 50 °C for 40 min, **10a** was obtained in 80% yield. Similarly, treatment of **1b** with 2-aminophenol in



10a : X = Cl
10b : X = OEt
10c : X = NH_2



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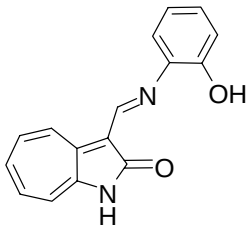

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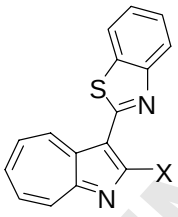
refluxing EtOH for 24 h and treatment of **1c** with 2-aminophenol in refluxing 1-BuOH for 22 h gave **10b** (48%) and **1c** (91%), respectively. Similar treatment of **4** with 2-aminophenol in refluxing EtOH gave **12** in 54% yield.

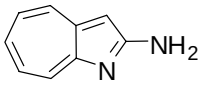
It is known that the reaction under presence of oxidizing reagents facilitates the cyclization to benzimidazoles and benzoxazoles.[16-18] Therefore, we performed the reaction of **1b** with 2-aminophenol in the presence of DDQ in EtOH under reflux for 24h. In the reaction, a new spot was seen on the TLC, but after work-up, **1b** (69 %) was recovered with a trace amount of **2b**, and benzoxazole derivative was not obtained. It seems that **1b** formed CT-complex with DDQ, and the reaction underwent scarcely. Then, we treated **1c** with 2-aminophenol under reflux for 48 h in the presence of I_2, but a complex mixture was produced and the benzoxazole derivative was not obtained again.

Next, we examined the synthesis of benzothiazole derivatives. It expected that high nucleophilicity of S-atom would facilitate the attack to imine moiety. Indeed, the reaction of **1b** with 2-aminothiophenol in EtOH under reflux for 4.5 h underwent and **13b** was obtained in 66% yield. Similar treatment of **4**, **6**, and **8b** with 2-aminothiophenol gave **16** (53%), **17** (32%), and **18b** (54%), respectively.

Interestingly, when **1c** was treated with 2-aminothiophenol in EtOH under reflux, the reaction was not proceeded. But when of **1c** was treated with 2-aminothiophenol in 1-BuOH under reflux for 190 h, **13c** (36%) and 2-amino-1-azaazulene (**14**: 59%) were obtained. In the reaction, benzothiazole was detected. Plausible reaction mechanism is shown in Scheme 1. At first, the imine (**A**) would be produced, and a successive cyclization affords **B**. Auto oxidation of **B** furnishes **13c** (path a), and elimination of benzothiazole from **B** gave **14** (path b).



13b : X = OEt
13c : X = NH_2



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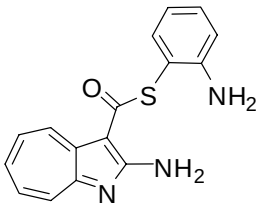

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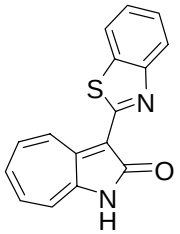

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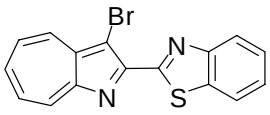

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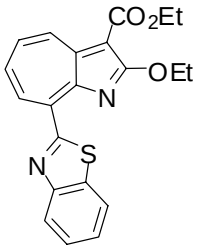

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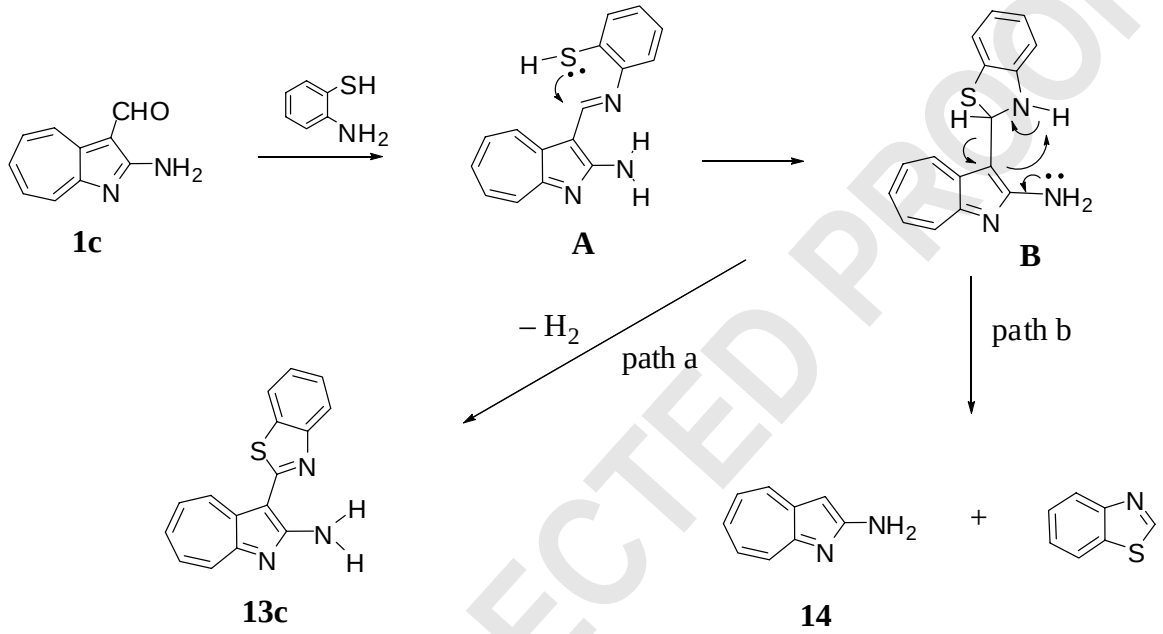
Above consideration suggested that the use of oxidation reagent would improve the reaction. Therefore,

we carried out the reaction of **1c** with 2-aminothiophenol in the presence of I_2 in 1-BuOH under reflux for 48 h, and **13c** (24%) and **15** (52%) were obtained together with **1c** (7%). Attack of S-atom to aldehyde group of **1c** and successive oxidation by I_2 would produce **15**. When the reaction was carried out in DMF at 100 °C for 24 h, **13c** was obtained only in 25% yield along with **1c** (51%). In this case, the compound (**15**) was not obtained. Reaction of **1c** with 2-aminothiophenol in the presence of $FeCl_3$ in 1-BuOH under reflux for 48 h gave **13c** in 31% along with **1c** (11%).



Scheme 1

The structure of **13c** was confirmed by X-ray structure analysis (Figure 2). The bond length of C(2)-N(amino) is rather short (1.331 Å), and hydrogen bonding N-H---N (2.08 Å) is observed. The results suggest that contribution of resonance form (**13c-A**) is large. The electronic spectra of **13b**, **13c**,

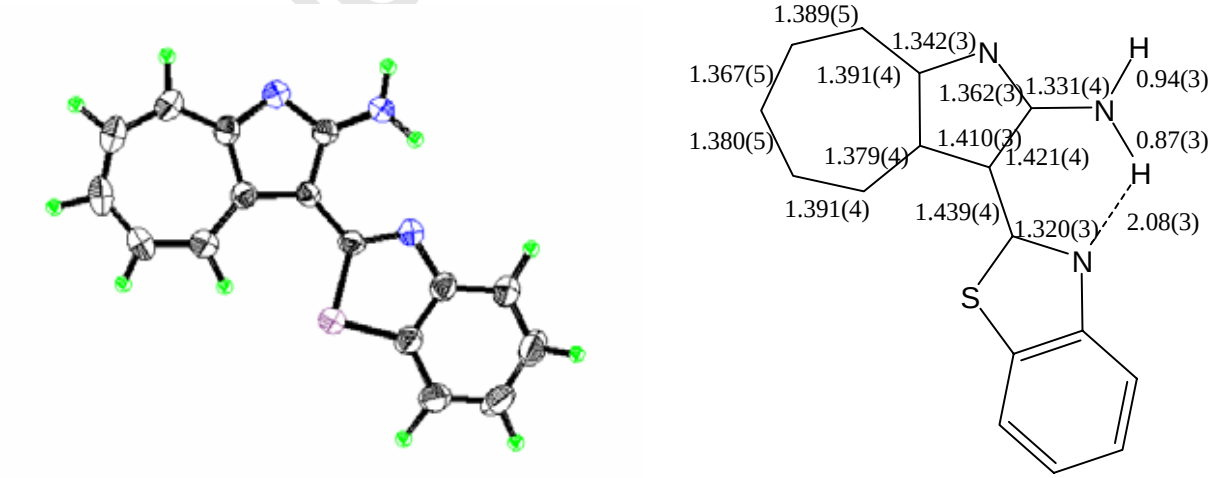


Figure 2. ORTEP drawing with thermal ellipsoids (50% probability) and selective bond lengths of **13c**.

and **16** in EtOH are shown in Figure3. Interestingly, the spectral features of **13c** and **16** resemble, and those of **13c** and **13b** are rather different. The results suggest that tautomerisation between **13c** and **19** exists in the solution.

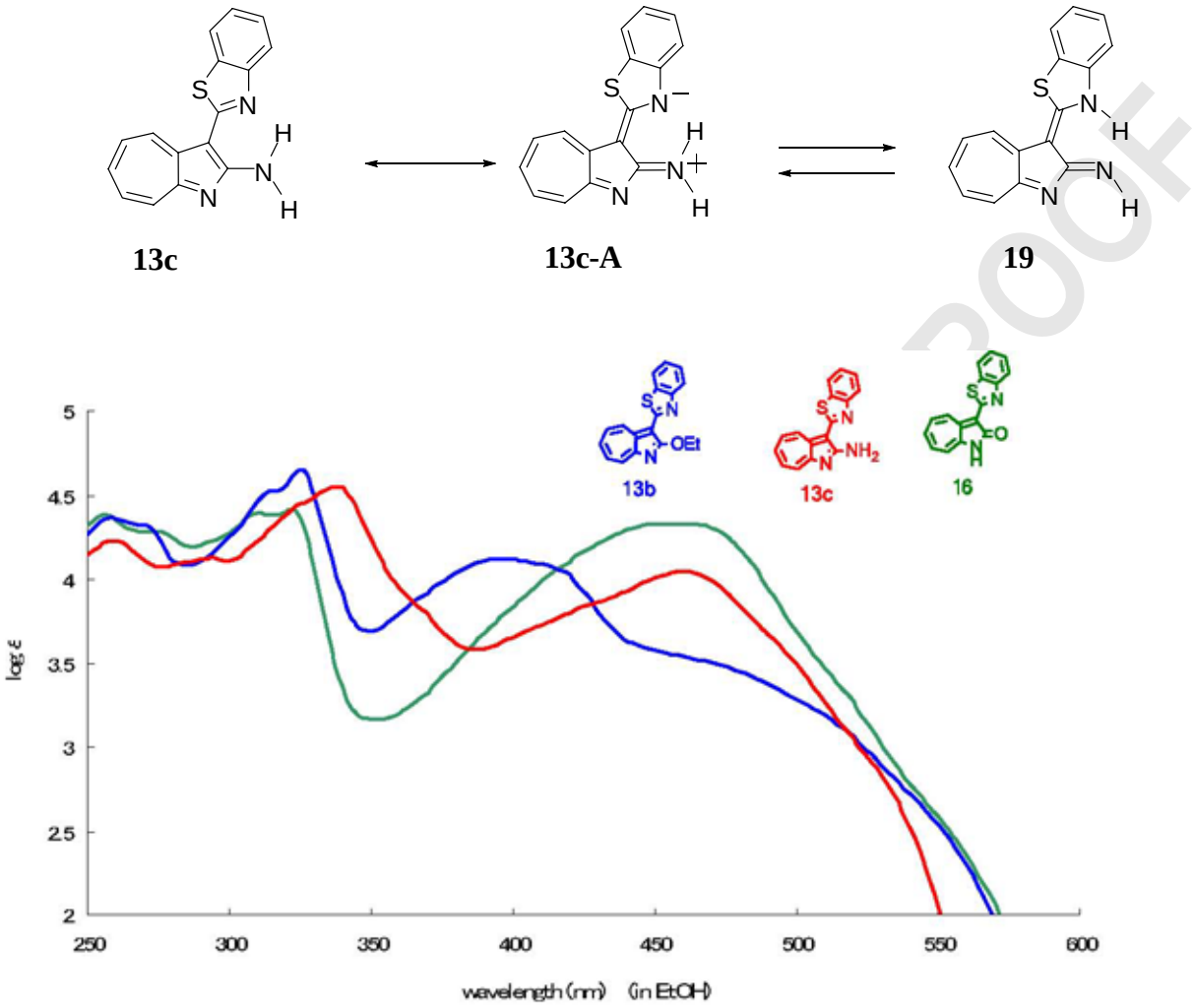


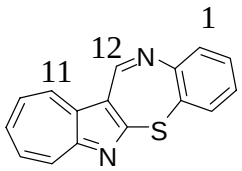
Figure 3. UV and Visible spectra of **13b**, **13c**, and **16**.

Syntheses of benzothiaazepine-fused and triazolothiadiazepine fused 1-azaazulenes

Interestingly, the reaction of 2-chloro-1-azaazulene-3-carboaldehyde (**1a**) with 2-aminothiophenol showed a different aspect. Treatment of **1a** with 2-aminothiophenol in EtOH under reflux gave a complex mixture and distinct product was not obtained. When the reaction performed in 1-BuOH under reflux for 45 h, cyclized compound (**20**) was obtained in a 41% yield. The structure of **20** was determined by spectroscopic data as well as elemental analysis. In its ^{1}H NMR spectrum, low field resonated 1H singlet assigned to H-12 was observed at δ 10.61, owing to the anisotropic effect of seven-menbered ring.

We expand the examination for synthesis of fused 1-azaazulenes containing thiadiazepine ring. Thus,

1a was treated with 4-amino-3-mercapto-1,2,4-triazoles (**21a-d**) in refluxing 1-BuOH for a few min, and **22a-d** were obtained in 49%, 67%, 33%, and 43% yields, respectively. The structure of **22c** was confirmed by X-ray structure analysis (Figure 4).



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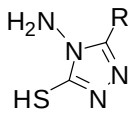
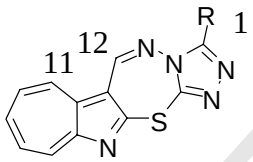


21a : R = H
21b : R = Me
21c : R = CF_3
21d : R = 4-Py



22a : R = H
22b : R = Me
22c : R = CF_3
22d : R = 4-Py

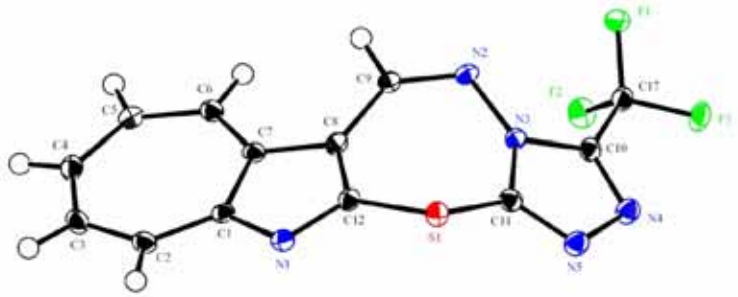


Figure 4. ORTEP drawing with thermal ellipsoids (50% probability) of **22c.**

Biological evaluation

Some new synthesized products (**2a**, **2b**, **2c**, **5**, **13b**, **16**) were evaluated for their anticancer activity (cytotoxic activity) against HeLa S3 cells. The IC_{50} values [μM] are summarized in Table 1. In several cases (denoted >), the minimum inhibitory concentration could not be determined due to limited solubility of the compounds in the testing medium. The data revealed that compounds (**2a**) showed moderate activity against HeLa S3 cells, and others would be inactive (IC_{50} > 30 μM).

Table 1. Cytotoxic evaluation of compounds (**2a**, **2b**, **2c**, **5**, **13b**, **16**) expressed in μM.

	2a	**2b**	**2c**	**5**	**13b**	**16**
IC_{50}	5.3±0.4	62±3	>9.6	>38	>8.1	>4.4

CONCLUSION

Benzimidzolyl- and benzthiazolyl-1-azaazulenes are easily synthesized by the treatment of

formyl-1-azaazulenes with *o*-phenylenediamine and 2-aminothiophenol in alcoholic solvent under airobic conditions. Reaction of formyl-1-azaazulenes with 2-aminophenol gave only Schiff's bases and benzoxazolyl-1-azaazulenes were not obtained. Reactions of 2-chloro-1-azaazulene-3-carbaldehyde with 2-aminothiophenol and 4-amino-3-mercapto-1,2,4-triazoles gave 5-thia-6,13-diazacyclohepta-[*a*]benz[*f*]azulene and 4-thia-2,3,5,12,12a-pentaazaazuleno[5,6-*b*]azulenes. Benzimidzolyl- and benzthiazolyl-1-azaazulenes showed anticancer activity (cytotoxic activity) against HeLa S3 cells.

EXPERIMENTAL

Mps are measured using a Yanagimoto micro-melting apparatus and uncorrected. ^{1}H NMR spectra (including HH-COSY and CH-COSY NMR)) were recorded on a Bruker AVANCE 400S (400 MHz) and ^{13}C NMR spectra were recorded on a Bruker AVANCE 400S (100.6 MHz) using DMSO-d_6 as a solvent with TMS as an internal standard unless otherwise stated; *J* values are recorded in Hz. IR spectra were recorded for KBr pellets on a Nicolet FT-IR Avatar 370DTGS. Electronic spectra were recorded with Shimadzu UV-1600PC spectrophotometer using EtOH as a solvent. Elemental analyses were taken with a Perkin Elmer 2400II. Kieselgel 60 was used for column chromatography and Kieselgel 60G was used for thin-layer chromatography.

Reactions of 2-chloro-1-azaazulene-3-carbaldehyde (1a) with *o*-phenylenediamine

A mixture of **1a** (0.071 g, 0.37 mmol) and *o*-phenylenediamine (0.042 g, 0.39 mmol) in EtOH (20 mL) was stirred for 48 h at rt. The solvent was evaporated, and the chromatography of the residue with hexane-AcOEt gave **2a** (0.081 g, 78%) and recovered (**1a**) (0.011 g, 15%).

2a: Red plates (from CH_2Cl_2-hexane), mp 221-223 °C; ^{1}H NMR δ 12.59 (1H, s), 9.68 (1H, d, *J* 10.0), 8.79 (1H, d, *J* 9.6), 8.27 (1H, dd, *J* 10.0, 9.6), 8.13 (1H, dd, *J* 10.0, 9.6), 8.11 (1H, dd, *J* 10.0, 9.6), 7.76-7.67 (2H, m), 7.31-7.23 (2H, m); ^{13}C NMR δ 155.4, 153.4, 144.9, 143.9, 141.0, 138.7 (br), 137.5, 137.2, 132.5, 132.4, 122.1, 115.1 (br), 112.1; ν_{max} / cm^{-1} 3368 (NH); λ_{max} nm (log ε) 228 (4.45), 262 (4.49), 306 (4.53), 366 (3.91), 478 (3.09). *Anal*. Calcd for $C_{16}H_{10}N_3Cl$: C, 68.70; H, 3.60; N, 15.02. Found: C, 68.57; H, 3.78; N, 14.78.

Reactions of 2-ethoxy-1-azaazulene-3-carbaldehyde (1b) with *o*-phenylenediamine

A mixture of **1b** (0.061 g, 0.31 mmol) and *o*-phenylenediamine (0.034 g, 0.32 mmol) in EtOH (20 mL) was heated under reflux for 37 h. The solvent was evaporated, and the chromatography of the residue with hexane-AcOEt gave **2b** (0.052 g, 59%).

2b: Orange needles (from CH_2Cl_2-hexane), mp 173-175 °C; ^{1}H NMR δ 11.96 (1H, br s), 9.80 (1H, d, *J* 9.6), 8.44-8.36 (1H, m), 7.98-7.82 (3H, m), 7.72-7.64 (2H, m), 7.25-7.19 (2H, m), 4.89 (2H, q, *J* 7.0), 1.59 (3H, t, *J* 7.0); ^{13}C NMR δ 171.6, 155.6, 146.4, 143.8, 138.5 (br), 135.6, 133.1, 132.1, 131.9, 131.8,

121.7, 114.7 (br), 99.4, 65.5, 14.7; ν_{max} / cm^{-1} 3271 (NH), 1604 and 1563 (C=N); λ_{max} nm (log ε) 234 (4.41), 262 (4.55), 320 (4.70), 392 (4.07). *Anal*. Calcd for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.44; H, 5.27; N, 14.11.

Reactions of 2-amino-1-azaazulene-3-carbaldehyde (1c) with *o*-phenylenediamine

a) A mixture of **1c** (0.053 g, 0.30 mmol) and *o*-phenylenediamine (0.099 g, 0.91 mmol) in 1-BuOH (10 mL) was heated at 70 °C for 44 h. The solvent was evaporated, and the chromatography of the residue with AcOEt gave 2-amino-3-[(2-aminophenyl)iminomethyl]-1-azaazulene (**3c**) (0.050 g, 62%) and recovered (**1c**) (0.012 g, 22%).

b) A mixture of **1c** (0.051 g, 0.30 mmol) and *o*-phenylenediamine (0.098 g, 0.90 mmol) in 1-BuOH (10 mL) was heated under reflux for 48 h. The solvent was evaporated, and the chromatography of the residue with AcOEt gave 2-amino-3-(2-benzimidazoyl)-1-azaazulene (**2c**) (0.068 g, 88%).

2c: Orange needles (from EtOH), mp 289-291 °C; ^{1}H NMR δ 12.50 (1H, s), 8.54 (1H, d, *J* 10.4), 8.20 (2H, br s), 7.92 (1H, d, *J* 9.6), 7.70-7.55 (4H, m), 7.47 (1H, dd, *J* 10.0, 9.6), 7.22 (1H, dd, *J* 10.0, 9.6), 7.22 (1H, dd, *J* 8.8, 0.8); ^{13}C NMR δ 168.7, 160.3, 148.2, 142.7 (br), 142.4, 134.3 (br), 132.0, 130.8, 130.3, 126.3, 125.4, 121.7, 117.7 (br), 111.1 (br), 98.5; ν_{max} / cm^{-1} 3432 , 3288, 3222 (NH); λ_{max} nm (log ε) 244 (4.37), 270 (4.52), 328 (4.69), 448 (3.99). *Anal*. Calcd for $C_{16}H_{12}N_4$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.83; H, 4.79; N, 21.08.

3c: Red plates (from CH_2Cl_2-hexane), mp 210-212 °C; ^{1}H NMR δ 9.14 (1H, s), 8.56 (1H, d, *J* 9.9), 8.03 (2H, s), 7.90 (1H, d, *J* 9.8), 7.65 (1H, dd, *J* 9.9, 9.8), 7.58 (1H, dd, *J* 9.9, 9.7), 7.47 (1H, dd, *J* 9.9, 9.7), 7.15 (1H, dd, *J* 7.8, 1.1), 6.94 (1H, ddd, *J* 7.9, 7.2, 1.1), 6.74 (1H, dd, *J* 7.9, 1.1), 6.62 (1H, ddd, *J* 7.8, 7.2, 1.1), 5.06 (2H, br); ^{13}C NMR ($CDCl_3$) δ 168.7, 161.1, 152.1, 147.5, 141.2, 139.6, 133.4, 132.0, 131.7, 128.6, 127.1, 125.2, 119.3, 118.3, 115.6, 107.0; ν_{max} / cm^{-1} 3486, 3465, 3370, 3342 (NH); λ_{max} nm (log ε) 226(4.39), 271 (4.30, sh), 300 (4.43), 352 (4.29), 463 (4.10). *Anal*. Calcd for $C_{16}H_{14}N_4$: C, 73.26; H, 5.38; N, 21.36. Found: C, 73.56; H, 5.48; N, 20.96.

Reactions of 2-oxo-1,2-dihydro-1-azaazulene-3-carbaldehyde (4) with *o*-phenylenediamine

A mixture of **4** (0.0526 g, 0.30 mmol) and *o*-phenylenediamine (0.0339 g, 0.31 mmol) in EtOH (10 mL) was heated under reflux for 20 h. The solvent was evaporated, and the chromatography of the residue with hexane-AcOEt gave 3-(2-benzimidazoyl)-1-azaazulen-2(1*H*)-one (**5**) (0.0345 g, 43%).

5: Red powders (from CH_2Cl_2-hexane), mp 277-279 °C; ^{1}H NMR δ 12.28 (1H, s), 12.19 (1H, s), 9.38 (1H, d, *J* 11.2), 7.76-7.66 (2H, m), 7.63 (1H, dd, *J* 11.2, 9.6), 7.53 (1H, dd, *J* 10.0, 9.2), 7.43 (1H, d, *J* 9.2), 7.31 (1H, dd, *J* 10.0, 9.6), 7.22-7.13 (2H, m); ^{13}C NMR δ 168.1, 147.3, 145.6, 143.3 (br), 141.1, 134.5, 134.1, 133.3 (br), 131.2, 129.8, 121.5, 117.8 (br), 116.8, 112.0 (br), 101.2; ν_{max} / cm^{-1} 3428, 3346 (NH), 1660 (C=O); λ_{max} nm (log ε) 226 (4.25), 242 (4.26), 262 (4.32), 308 (4.34), 318 (4.36), 448 (4.22). *Anal*. Calcd for $C_{16}H_{11}N_3O$: C, 73.55; H, 4.24; N, 16.08. Found: C, 72.95; H, 4.28; N, 15.88.

Reactions of 3-bromo-1-azaazulene-2-carbaldehyde (6) with *o*-phenylenediamine

A mixture of **6** (0.0425 g, 0.18 mmol) and *o*-phenylenediamine (0.0233 g, 0.22 mmol) in EtOH (10 mL) was stirred for 15 h at rt. The solvent was evaporated, and the chromatography of the residue with hexane-AcOEt gave 2-(benzimidazol-2-yl)-3-bromo-1-azaazulene (**7**) (0.0233 g, 40%).

7 : Red needles (from CH_2Cl_2-hexane), mp 150-152 °C; ^{1}H NMR δ 13.42 (1H, br s), 8.81 (1H, d, *J* 10.0), 8.73 (1H, d, *J* 9.6), 8.20 (1H, dd, *J* 10.0, 9.6), 8.06 (1H, dd, *J* 10.0, 9.6), 8.03 (1H, dd, *J* 10.0, 9.6), 7.90-7.75 (1H, m), 7.70-7.55 (1H, m), 7.40-7.20 (2H, m); ^{13}C NMR δ 155.9, 151.8, 146.7, 144.2, 140.6, 137.8, 136.3, 131.4, 130.7, 123.9, 122.1, 119.7, 117.3, 114.5, 112.1, 99.0; ν_{max} / cm^{-1} 3423 (NH); λ_{max} nm (log ε) 220 (4.52), 274 (4.65), 336 (4.43), 400 (4.29), 524 (3.45). *Anal*. Calcd for $C_{16}H_{10}N_3Br\cdot 3/4H_2O$: C, 56.91; H, 3.43; N, 12.44. Found: C, 57.24; H, 3.55; N, 12.31.

Reaction of ethyl 2-chloro-8-formyl-1-azaazulene-3-carboxylate (8a) with *o*-phenylenediamine

A mixture of **8a** (0.0526 g, 0.30 mmol) and *o*-phenylenediamine (0.0231 g, 0.21 mmol) in EtOH (10 mL) was stirred for 4 h at rt. The solvent was evaporated, and the chromatography of the residue with hexane-AcOEt gave ethyl 8-(benzimidazol-2-yl)-1-azaazulene-3-carboxylate (**9**) (0.0190 g, 38%).

9: Orange needles (from CH_2Cl_2-hexane), mp 187-189 °C; ^{1}H NMR δ 13.51 (1H, br s), 9.59 (1H, d, *J* 10.4), 9.52 (1H, d, *J* 10.0), 8.42 (1H, dd, *J* 10.4, 10.0), 8.24 (1H, dd, *J* 10.0, 10.0), 7.94-7.82 (2H, m), 7.43-7.31 (2H, m), 4.44 (2H, q, *J* 7.2), 1.43 (3H, t, *J* 7.2); ^{13}C NMR ($CDCl_3$) δ 163.3, 157.0, 151.9, 150.1, 148.3, 138.8, 137.1, 134.6, 134.2, 133.9, 125.2, 123.5, 120.4, 112.4, 112.2, 60.9, 14.4; ν_{max} / cm^{-1} 3224 (NH), 1692 (C=O), 1651 (C=N); λ_{max} nm (log ε) 225 (4.17), 281 (4.10), 293 (4.13), 330 (3.95), 409 (4.03), 451 (3.55, sh). *Anal*. Calcd for $C_{19}H_{14}N_3ClO_2$: C, 64.87; H, 4.01; N, 11.94. Found: C, 64.73; H, 4.22; N, 12.12.

Reactions of 2-chloro-1-azaazulene-3-carbaldehyde (1a) with 2-aminophenol

a) A mixture of **1a** (0.0579 g, 0.30 mmol) and 2-aminophenol (0.0331 g, 0.30 mmol) in EtOH (10 mL) was heated under reflux for 10 min. The solvent was evaporated, and the chromatography of the residue with hexane-AcOEt gave 2-chloro-3-[(2-hydroxyphenyl)iminomethyl]-1-azaazulene (**10a**) (0.0512 g, 60%) and 2-[(2-hydroxyphenyl)amino]-3-[(2-hydroxyphenyl)iminomethyl]-1-azaazulene (**11**) (trace).

b) A mixture of **1a** (0.0589 g, 0.31 mmol) and *o*-aminophenol (0.0356 g, 0.33 mmol) in EtOH (10 mL) was heated at 50 °C for 40 min. The solvent was evaporated, and the chromatography of the residue with hexane-AcOEt gave **10a** (0.0692 g, 80%) and **11** (trace).

c) A mixture of **1a** (0.0728 g, 0.38 mmol) and 2-aminophenol (0.0582 g, 0.53 mmol) in EtOH (15 mL) was heated under reflux for 15 h. The solvent was evaporated, and the chromatography of the residue with hexane-AcOEt gave **10a** (trace) and **11** (0.0505 g, 37%).

10a: Orange needles (from CH_2Cl_2-hexane), mp 179-181 °C; ^{1}H NMR δ 10.04 (1H, d, *J* 10.0), 9.11 (1H, s), 8.95 (1H, s), 8.78 (1H, d, *J* 9.6), 8.30 (1H, dd, *J* 10.0, 9.6), 8.18 (1H, dd, *J* 10.0, 9.6), 8.16 (1H, dd, *J*

10.0, 9.6), 7.21 (1H, dd, *J* 7.6, 1.6), 7.10 (1H, ddd, *J* 8.0, 7.6, 1.6), 6.94 (1H, dd, *J* 8.0, 1.2), 6.88 (1H, td, *J* 7.6, 1.2); ^{13}C NMR δ 158.2, 156.7, 152.7, 150.5, 142.8, 141.5, 139.5, 138.3, 137.9, 134.2, 133.6, 126.9, 119.7, 119.4, 116.1, 114.3; ν_{max} / cm^{-1} 3375 (OH), 1616 (C=N); λ_{max} nm (log ε) 254 (4.33), 259 (4.33), 291 (4.45, sh), 298 (4.46), 324 (4.15, sh), 394 (3.97), 482 (3.25, sh). *Anal*. Calcd for $C_{16}H_{11}N_2ClO$: C, 67.97; H, 3.92; N, 9.91. Found: C, 67.87; H, 3.68; N, 9.64.

11: Orange powders (from CH_2Cl_2-hexane), mp 235-237 °C: ^{1}H NMR δ 11.43 (1H, s), 10.77 (1H, br s), 9.57 (1H, s), 8.88 (1H, dd, *J* 7.2), 8.71 (1H, d, *J* 10.0), 8.49 (1H, br s), 8.21 (1H, d, *J* 9.6), 7.78 (1H, dd, *J* 10.0, 9.6), 7.72 (1H, dd, *J* 10.0, 9.2), 7.64 (1H, dd, *J* 10.0, 9.2), 7.59 (1H, d, *J* 7.6), 7.12 (1H, dd, *J* 7.6, 7.2), 7.03-6.89 (5H, m); ^{13}C NMR δ 162.7, 159.9, 152.3, 150.5, 145.8, 145.7, 137.3, 133.3,132.8, 131.9, 129.4, 128.2, 126.8, 122.6, 119.8, 119.54, 119.47, 118.9, 115.7, 114.5, 107.6; ν_{max} / cm^{-1} 3415 (OH), 3259 (NH); λ_{max} nm (log ε) 234 (4.22), 294 (4.41), 329 (4.40), 345 (4.40), 374 (4.39), 484 (4.14). *Anal*. Calcd for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82. Found: C, 74.70; H, 5.05; N, 11.57.

Reactions of 2-ethoxy-1-azaazulene-3-carbaldehyde (1b) with 2-aminophenol

a) A mixture of **1b** (0.0582 g, 0.29 mmol) and 2-aminophenol (0.0425 g, 0.39 mmol) in EtOH (10 mL) was heated under reflux for 24 h. The solvent was evaporated, and the chromatography of the residue with hexane-AcOEt gave 2-ethoxy-3-[(2-hydroxyphenyl)iminomethyl]-1-azaazulene (**10b**) (0.0761 g, 90%).

b) A mixture of **1b** (0.0632 g, 0.31 mmol), 2-aminophenol (0.0368 g, 0.34 mmol) and DDQ (0.0692, 0.31 mmol) in EtOH (10 mL) was heated under reflux for 24 h. The solvent was evaporated, and the residue was chromatographed with hexane-AcOEt to give a trace amount of **10b** and recovered **1b** (0.0440 g, 69%).

10b: Orange needles (from CH_2Cl_2-hexane), mp 205-207 °C; ^{1}H NMR δ 9.66 (1H, dd, *J* 10.0, 1.6), 8.88 (1H, s), 8.82 (1H, s), 8.41 (1H, dd, *J* 9.6, 1.6), 7.94-7.87 (3H, m), 7.12 (1H, dd, *J* 7.6, 1.6), 7.05 (1H, ddd, *J* 8.0, 7.6, 1.6), 6.91 (1H, dd, *J* 8.0, 1.6), 6.85 (1H, td, *J* 7.6, 1.6), 4.72 (2H, q, *J* 7.0), 1.48 (3H, t, *J* 7.0); ^{13}C NMR δ 174.4, 157.0, 152.1, 150.4, 143.8, 140.1, 136.1, 134.1, 133.4, 132.9, 132.6, 126.2, 119.6, 119.1, 115.8, 106.1, 65.1, 14.6; ν_{max} / cm^{-1} 3206 (OH); λ_{max} nm (log ε) 256 (4.11), 305 (4.29), 413 (3.93). *Anal*. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.96; H, 5.52; N, 9.58. Found: C, 73.77; H, 5.64; N, 9.36.

Reactions of 2-amino-1-azaazulene-3-carbaldehyde (1c) with 2-aminophenol

a) A mixture of **1c** (0.0594 g, 0.35 mmol) and 2-aminophenol (0.0762 g, 0.70 mmol) in 1-BuOH (10 mL) was heated under reflux for 22 h. The solvent was evaporated, and the chromatography of the residue with hexane-AcOEt gave 2-amino-3-[(2-hydroxyphenyl)iminomethyl]-1-azaazulene (**10c**) (0.0827 g, 91%).

b) A mixture of **1c** (0.0498 g, 0.29 mmol), *o*-aminophenol (0.0590 g, 0.54 mmol) and I_2 (0.0386, 0.15 mmol) in 1-BuOH (10 mL) was heated under reflux for 48 h. The solvent was evaporated, and the

residue was chromatographed with hexane-AcOEt to give **10c** (0.0273g, 36%) and recovered **1b** (trace).

10c: Dark red prisms (from CH_2Cl_2-hexane), mp 207.5-209 °C; ^{1}H NMR δ 9.21 (1H, s), 9.01 (1H, br s), 8.50 (1H, d, *J* 9.9), 8.21 (2H, br s), 7.88 (1H, d, *J* 9.8), 7.64 (1H, dd, *J* 9.9, 9.8), 7.57 (1H, dd, *J* 9.9, 9.8), 7.45 (1H, dd, *J* 9.9, 9.8), 7.32 (1H, dd, *J* 7.9, 1.4), 7.04 (1H, ddd, *J* 8.0, 7.9, 1.4), 6.92-6.82 (2H, m); ^{13}C NMR ($CDCl_3$) δ 168.3, 161.2, 153.1, 150.7, 148.0, 139.2, 133.9, 132.6, 132.2, 129.2, 127.7, 125.4, 121.0, 117.6, 115.3, 106.6; ν_{max} / cm^{-1} 3387 (OH), 3284, 3235 (NH); λ_{max} nm (log ε) 241 (4.69), 286 (4.54), 349 (4.44), 362 (4.38, sh), 461 (4.13). *Anal*. Calcd for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96. Found: C, 73.07; H, 5.03; N, 15.87.

Reactions of 2-oxo-1,2-dihydro-1-azaazulene-3-carbaldehyde (4) with 2-aminophenol

A mixture of **4** (0.0650 g, 0.38 mmol) and 2-aminophenol (0.0615 g, 0.56 mmol) in EtOH (10 mL) was heated under reflux for 12 h. The solvent was evaporated, and the chromatography of the residue with hexane-AcOEt gave 3-[(2-hydroxyphenyl)iminomethyl]-1-azaazulen-2(1*H*)-one (**12**) (0.0531 g, 54%).

12: Orange powders (from CH_2Cl_2-hexane), mp 247-250 °C (decomp); ^{1}H NMR δ 9.19 (1H, d, *J* 10.8), 8.67 (1H, s), 7.59 (1H, t, *J* 10.0), 7.57 (1H, dd, *J* 10.8, 10.0), 7.46 (1H, d, *J* 9.6), 7.31 (1H, dd, *J* 10.0, 9.6), 7.07 (1H, d, *J* 7.6), 7.03 (1H, ddd, *J* 8.0, 7.6, 1.2), 6.89 (1H, dd, *J* 8.0, 1.2), 6.83 (1H, td, *J* 7.6, 1.2), (NH and OH protons were not observed); ^{13}C NMR δ 170.1, 152.9, 150.4, 148.1, 142.5, 139.9, 136.0, 135.3, 131.5, 130.0, 126.2, 119.6, 118.8, 117.8, 115.8, 107.6; ν_{max} / cm^{-1} 3407 (NH, OH), 1654 (C=O); λ_{max} nm (log ε) 258 (4.16), 287 (4.14), 363 (3.41), 422 (3.76, sh), 444 (3.92), 475 (3.63, sh), 510 (3.40, sh). *Anal*. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.64. Found: C, 72.83; H, 4.82; N, 9.89.

Reactions of 2-ethoxy-1-azaazulene-3-carbaldehyde (1b) with 2-aminothiophenol

A mixture of **1b** (0.0816 g, 0.41 mmol) and 2-aminothiophenol (0.0538 g, 0.43 mmol) in EtOH (10 mL) was heated under reflux for 4.5 h. The mixture was evaporated, and the chromatography of the residue with hexane-AcOEt gave 3-(benzothiazol-2-yl)-2-ethoxy-1-azaazulene (**13b**) (0.0823 g, 66%).

13b: Orange needles (from CH_2Cl_2-hexane), mp 177-179 °C; ^{1}H NMR δ 9.94 (1H, d, *J* 10.0), 8.53-8.44 (1H, m), 8.14 (1H, d, *J* 7.6), 8.09 (1H, d, *J* 8.0), 8.08-8.01 (1H, m), 8.01-7.93 (2H, m), 7.54 (1H, dd, *J* 8.0, 7.6), 7.42 (1H, t, *J* 7.6), 4.85 (2H, q, *J* 7.0), 1.59 (3H, t, *J* = 7.0); ^{13}C NMR δ 171.9, 159.8, 156.1, 152.8, 143.4, 136.5, 133.5, 133.3, 133.3, 133.1, 133.0, 126.2, 124.3, 121.7, 121.6, 102.6, 66.0, 14.8; ν_{max} / cm^{-1} 1600 (C=N); λ_{max} nm (log ε) 222 (4.52), 258 (4.37), 270 (4.32, sh), 315 (4.52, sh), 326 (4.66), 396 (4.12), 464 (3.53, sh). *Anal*. Calcd for $C_{18}H_{14}N_2OS$: C, 70.56; H, 4.61; N, 9.14. Found: C, 70.89; H, 4.70; N, 9.05.

Reactions of 2-amino-1-azaazulene-3-carbaldehyde (1c) with 2-aminothiophenol

a) A mixture of 2-amino-1-azaazulene-3-carbaldehyde (**1c**) (0.0427 g, 0.25 mmol) and 2-aminothiophenol (0.103 g, 0.82 mmol) in 1-BuOH (30 mL) was heated at 125 ℃ for 190 h. The solvent was evaporated, and the chromatography of the residue with hexane-AcOEt to give

2-amino-3-(2-benzothiazoyl)-1-azaazulene (**13c**) (0.0246 g, 36%), 2-amino-1-azaazulene (**14**) (0.0212 g, 59%), and a trace amount of benzothiazole.

b) A mixture of **1c** (0.0357 g, 0.21 mmol), 2-aminothiophenol (0.0332 g, 0.27 mmol), and I_2 (0.0262 g, 0.10 mmol) in 1-BuOH (25 mL) was refluxed for 24 h. To the mixture 10% $Na_2S_2O_3$ solution (18 mL) was added, and the precipitate was filtered off. The filtrate was evaporated, and the chromatography of the residue with hexane-AcOEt gave **13c** (0.0209 g, 36%), 2-amino-3-(2-aminophenyl-mercaptocalbonyl)-1-azaazulene (**15**) (0.0102 g, 17%), and **1c** (0.0026 g, 7%).

c) A mixture of **1c** (0.0348 g, 0.20 mmol), 2-aminothiophenol (0.0374 g, 0.30 mmol), and sat. $FeCl_3$ solution (2.0 mL) in 1-BuOH (10 mL) was refluxed for 24 h. To the mixture water (30 ml) was added, and the mixture was extracted with $CHCl_3$. The extract was dried over Na_2SO_4, and the solvent was evaporated. Chromatography of the residue with hexane-AcOEt gave **13c** (0.0176 g, 31%) and **1c** (0.0028 g, 11%).

13c: Orange prisms (from EtOAc), mp 247-250 °C; ^{1}H NMR δ 8.49 (1H, d, *J* 10.1) 8.48 (2H, s), 8.15 (1H, d, *J* 8.1), 8.07 (1H, d, *J* 8.2), 8.02 (1H, d, *J* 9.9), 7.81 (1H, dd, *J* 10.1, 9.8), 7.79 (1H, dd, *J* 10.0, 9.9), 7.59 (1H, dd, *J* 10.0, 9.8), 7.56 (1H, ddd, *J* 8.1, 7.9, 1.2), 7.43 (1H, ddd, *J* 8.2, 7.9, 1.2); ^{13}C NMR δ 161.17, 158.94, 151.67, 133.62, 132.18, 131.99, 131.13, 127.51, 126.56, 125.04, 124.34, 122.52, 121.69, 121.45, 120.37, 109.04; ν_{max} / cm^{-1} 3342, 3276 (NH); λ_{max} nm (log ε) 222 (4.39), 260 (4.23), 294 (4.13), 338 (4.55), 460 (4.04). *Anal*. Calcd. for $C_{16}H_{11}N_3S$: C, 69.29; H, 4.00; N, 15.15. Found: C, 69.69; H, 4.14; N, 14.88.

15: Red plates (from $CHCl_3$-hexane), mp 190-191 °C; ^{1}H NMR ($CDCl_3$) δ 8.21 (1H, d, *J* 10.2), 7.98 (1H, d, *J* 9.7), 7.57 (1H, dd, *J* 10.0, 9.7), 7.51 (1H, dd, *J* 10.2, 9.5), 7.42 (1H, dd, *J* 10.0, 9.5), 7.01 (1H, ddd, *J* 7.9, 7.4, 1.1), 6.92 (1H, dd, *J* 7.8, 1.4), 6.71 (1H, dd, *J* 7.9, 1.1), 6.59 (1H, ddd, *J* 7.8, 7.4, 1.4), 5.69 (2H, br s), 4.22 (2H, br s); ^{13}C NMR ($CDCl_3$) δ 196.61, 168.67, 159.16, 149.60, 145.34, 131.63, 131.45, 130.79, 130.79, 128.11, 127.31, 127.25, 119.64, 119.58, 115.83, 97.07; ν_{max} / cm^{-1} 3430, 3343, 3277, 3214 (NH), 1639 (C=O); λ_{max} nm (log ε) 239 (4.29, sh), 280 (4.47), 320 (4.27, sh), 434 (3.61). *Anal*. Calcd for $C_{16}H_{13}N_3OS$: C, 65.06; H, 4.44; N, 14.23. Found: C, 65.28; H, 4.79; N, 14.10.

Reactions of 2-oxo-1,2-dihydro-1-azaazulene-3-carbaldehyde (4) with 2-aminothiophenol

A mixture of **4** (0.0538 g, 0.31 mmol) and 2-aminothiophenol (0.0404 g, 0.32 mmol) in EtOH (10 mL) was heated under reflux for 15 h. The solvent was evaporated, and the chromatography of the residue with hexane-AcOEt gave 3-(2-benzothiazolyl)-1-azaazulen-2(*1H*)-one (**16**) (0.0460 g, 53%).

16: Red plates (from EtOH), mp >300 °C; ^{1}H NMR δ 12.38 (1H, s), 9.51 (1H, d, *J* 11.2), 8.10 (1H, d, *J* 7.6), 8.04 (1H, d, *J* 8.0), 7.77 (1H, dd, *J* 11.2, 10.8), 7.67 (1H, dd, *J* 10.0, 9.6), 7.58 (1H, d, *J* 9.6), 7.52 (1H, dd, *J* 10.8, 10.0), 7.39 (1H,dd, *J* 7.6, 7.2); ^{13}C NMR δ 167.5, 160.2, 152.4, 146.2, 141.0, 136.1, 135.4, 133.4, 132.1, 129.7, 125.9, 124.1, 121.6, 121.4, 118.2, 104.3; ν_{max} / cm^{-1} 3436 (NH), 1684 (C=O);

λ_{max} nm (log ε) 231 (4.46), 256 (4.39), 274 (4.28), 310 (4.39), 322 (4.41), 456 (4.33). *Anal*. Calcd for $C_{16}H_{10}N_2OS$: C, 69.05; H, 3.62; N, 10.06. Found: C, 69.26; H, 3.55; N, 9.84.

Reactions of 3-bromo-1-azaazulene-2-carbaldehyde (6) with 2-aminothiophenol

A mixture of **6** (0.0434 g, 0.18 mmol) and 2-aminothiophenol (0.0262 g, 0.21 mmol) in EtOH (10 mL) was heated under reflux for 1 h. The solvent was evaporated, and the chromatography of the residue with hexane-AcOEt gave 2-(benzothiazol-2-yl)-3-bromo-1-azaazulene (**17**) (0.0198 g, 32%).

17: Reddish violet needles (from CH_2Cl_2-hexane); mp 119-121 °C. ^{1}H NMR δ 8.88 (1H, d, *J* 9.6), 8.79 (1H, d, *J* 9.6), 8.27 (1H, dd, *J* 10.0, 9.6), 8.25 (1H, dd, *J* 8.0, 0.8), 8.21 (1H, d, *J* 8.0), 8.08 (1H, dd, *J* 10.0, 9.6), 8.07 (1H, t, *J* 9.6), 7.63 (1H, ddd, *J* 8.0, 7.2, 1.2), 7.57 (1H, ddd, *J* 8.0, 7.2, 0.8); ^{13}C NMR δ 163.0, 155.8, 154.3, 152.9, 144.5, 141.8, 139.2, 137.7, 135.4, 131.8, 131.1, 126.8, 126.4, 123.7, 122.4, 98.4; ν_{max} / cm^{-1} 1611 (C=N); λ_{max} nm (log ε) 223 (4.22), 242 (3.91), 276 (4.12), 302 (4.04), 331 (4.19), 379 (3.98), 397 (3.97), 533 (3.11). *Anal*. Calcd for $C_{16}H_9N_2BrS$: C, 56.32; H, 2.66; N, 8.21. Found: C, 56.67; H, 2.89; N, 8.10.

Reaction of ethyl 2-ethoxy-8-formyl-1-azaazulene-3-carboxylate (8b) with 2-aminothiophenol

A mixture of **8b** (0.0329 g, 0.12 mmol) and 2-aminothiophenol (0.0229 g, 0.18 mmol) in EtOH (10 mL) was stirred for 15 min at rt. The solvent was evaporated, and the chromatography of the residue with hexane-AcOEt gave ethyl 8-(2-benzothiazolyl)-1-azaazulene-3-carboxylate (**18**) (0.0244 g, 54%).

18: Yellow needles (from CH_2Cl_2-hexane), mp 176-178 °C; ^{1}H NMR ($CDCl_3$) δ 9.21 (1H, dd, *J* 9.6, 1.6), 8.34 (1H, dd, *J* 9.6, 1.2), 7.70 (1H, td, *J* 9.6, 1.2), 7.63 (1H, ddd, *J* 9.6, 9.6, 1.6), 7.02 (1H, dd, *J* 8.0, 1.2), 6.98 (1H, ddd, *J* 8.0, 7.6, 1.2), 6.80 (1H, dd, *J* 8.0, 1.2), 6.76 (1H, ddd, *J* 8.0, 7.6, 1.2), 4.83 (2H, q, *J* 7.0), 4.43 (2H, q, *J* 7.2), 1.56 (3H, t, *J* 7.2), 1.44 (3H, t, *J* 7.0); ^{13}C NMR ($CDCl_3$) δ 173.6, 165.1, 164.2, 152.5, 151.6, 149.9, 139.2, 134.0, 133.5, 133.4, 132.8, 126.2, 125.7, 123.7, 121.4, 100.7, 67.3, 60.1, 14.7, 14.5; ν_{max} / cm^{-1} 1687 (C=O);λ_{max} nm (log ε) 226 (4.62), 246 (4.35, sh), 299 (4.47), 343 (4.34, sh), 351 (4.36), 351 (4.36), 375 (4.38), 397 (4.33), 465 (3.50). *Anal*. Calcd for $C_{21}H_{18}N_2O_3S$: C, 66.65; H, 4.79; N, 12.68. Found: C, 66.88; H, 4.79; N, 12.52.

Reactions of 2-chloro-1-azaazulene-3-carbaldehyde (1a) with 2-aminothiophenol

A mixture of **1a** (0.0632 g, 0.33 mmol) and 2-aminothiophenol (0.0469 g, 0.38 mmol) in 1-BuOH (5 mL) was heated under reflux for 45 h. The solvent was evaporated, and the chromatography of the residue with hexane-AcOEt gave 5-thia-6,13-diazacyclohepta[*a*]benz[*f*]azulene (**20**) (0.0357 g, 41%).

20: Redddish violet powders (from CH_2Cl_2-hexane), mp 251-253 °C; ^{1}H NMR δ 10.61 (1H, s), 7.41 (1H, d, *J* 8.8), 7.21-7.02 (4H, m), 7.06 (1H, dd, *J* 7.6, 1.2), 7.04 (1H, ddd, *J* 8.0, 7.6, 1.2), 6.89 (1H, dd, *J* 8.0,1.2), 6.84 (1H,, *J* 7.6, 1.2); ^{13}C NMR δ 158.6, 136.5, 130.8, 130.2, 128.7, 127.2, 126.7, 125.2, 123.0, 117.5, 115.5, 97.8; ν_{max} / cm^{-1} 1630 (C=N); λ_{max} nm (log ε) 251 (4.18), 274 (4.32), 312 (3.93), 342 (4.15), 363 (4.06, sh), 454 (3.43, sh), 479 (3.55), 509 (3.46, sh), 543 (3.40, sh), 602 (3.11, sh), 653 (2.65, sh).

Anal. Calcd for $C_{16}H_{10}N_2S$: C, 73.26; H, 3.84; N, 10.68. Found: C, 73.83; H, 4.22; N, 10.61.

Reactions of 2-chloro-1-azaazulene-3-carbaldehyde (1a) with 4-amino-3-mercapto-4*H*-1,2,4-triazol

A mixture of **1a** (0.0597 g, 0.31 mmol) and 4-amino-3-mercapto-1,2,4-triazol (**21a**) (0.0415 g, 0.36 mmol) in 1-BuOH (10 mL) was heated under reflux for 3 min. The solvent was evaporated, and the chromatography of the residue with hexane-AcOEt gave 4-thia-2,3,5,12,12a-pentaazaazuleno[5,6-*b*]-azulene (**22a**) (0.0391 g, 49%).

22a: Orange powders (from $CHCl_3$-EtOH), mp 202-203 °C; ^{1}H NMR (TFA-*d*) δ 9.82 (1H, s), 9.52 (1H, d, *J* 9.6), 9.40 (1H, d, *J* 9.6), 9.33 (1H, s), 9.02 (1H, t, *J* 9.6), 8.87 (2H, t, *J* 9.6); ^{13}C NMR (TFA-*d*) δ 156.3, 152.3, 151.0, 148.8, 147.8, 146.2, 144.8, 144.1, 143.9, 143.6, 139.5, 119.5; ν_{max} / cm^{-1} 1614 (C=N); λ_{max} nm (log ε) 233 (3.68), 290 (4.31, sh), 315 (4.47), 365 (3.78, sh), 462 (3.40). *Anal*. Calcd for $C_{12}H_7N_5S$: C, 56.90; H, 2.79; N, 27.65. Found: C, 57.02; H, 3.14; N, 26.93.

In a similar manner, reactions of **1a** with **21b**, **21c**, and **21d** gave **22b**, **22c** and **22d** in 67%, 33%, and 43%, respectively.

22b: Orange powders (from EtOH-$CHCl_3$), mp 270-272 °C; ^{1}H NMR (TFA-*d*) δ 9.50 (1H, d, *J* 9.6), 9.36 (1H, d, *J* 10.0), 9.32 (1H, s), 9.01 (1H, dd, *J* 10.0, 9.6), 8.86 (1H, dd, *J* 10.0, 9.6), 8.84 (1H, dd, *J* 10.0, 9.6), 2.99 (3H, s); ^{13}C NMR (TFA-*d*) δ 159.2, 155.4, 152.3, 151.0, 148.9, 146.0, 144.9, 144.1, 143.8, 143.7, 139.4, 119.4, 11.0; ν_{max} / cm^{-1} 1615 (C=N); λ_{max} nm (log ε) 239 (4.20), 275 (4.42), 318 (4.59), 364 (3.90, sh), 465 (3.27). *Anal*. Calcd for $C_{13}H_9N_5S$: C, 58.41; H, 3.39; N, 26.20. Found: C, 58.43; H, 3.40; N, 26.17.

22c: Yellow prisms (from EtOH-$CHCl_3$), mp 224-226 °C; ^{1}H NMR (TFA-*d*) δ 9.47 (1H, d, *J* 10.0), 9.32 (1H, d, *J* 10.0), 9.24 (1H, s), 9.00 (1H, t, *J* 10.0), 8.84 (2H, t, *J* 10.0); ^{13}C NMR (TFA-*d*) δ 154.0, 152.0, 151.0, 149.4, 149.0 (q, J_{CCF} 45.0), 146.9, 144.7, 143.9, 143.6, 143.5, 139.1, 119.9, 118.5 (q, J_{CF} 271.7); ν_{max} / cm^{-1} 1617 (C=N); λ_{max} nm (log ε) 253 (3.86), 270 (4.01), 275 (4.00), 314 (4.29), 364 (3.53, sh), 456 (2.99); *Anal*. Calcd for $C_{16}H_{12}N_4$: C, 48.60; H, 1.88; N, 21.80. Found: C, 49.10; H, 1.95; N, 21.55.

22d: Yellow prisms (from EtOH-$CHCl_3$), mp 249-250 °C; ^{1}H NMR (TFA-*d*) δ 9.57-9.50 (1H, m), 9.40-9.35 (2H, m), 9.24-9.16 (2H, m), 9.05-8.96 (3H, m), 8.89-8.81 (2H, m); ^{13}C NMR (TFA-*d*) δ 154.7, 152.7, 152.1, 151.1, 149.6, 146.9, 144.7, 144.6, 143.9, 143.8, 143.6, 139.2, 129.4, 119.3; ν_{max} / cm^{-1} 1633 (C=N); λ_{max} nm (log ε) 240 (3.74), 272 (3.99, sh), 288 (4.27), 322 (4.45), 370 (3.72, sh), 458 (3.14). *Anal*. Calcd for $C_{17}H_{10}N_6S$: C, 61.80; H, 3.05; N, 25.44. Found: C, 61.54; H, 3.01; N, 25.78.

X-Ray structure determination

Crystal data of 3c: brown prismatic, $C_{17}H_{16}N_4Cl$, *M* = 347.25, monoclinic, space group $P2_{1/n}$, *a* =

12.699(3) Å, b = 7.502(3) Å, c = 18.935(4) Å, β = 108.74(2)°, V = 1708.3(8) Å^3, Z = 4, D_{cale} = 1.350 g/cm^3, crystal dimensions 0.06×0.62×0.80 mm. Data were measured on a Rigaku AFC5S radiation diffractometer with graphite monochromated MoKα radiation. Total 4010 reflections (3827 unique) were collected using ω-2θ scan technique with in a 2θ range of 55.0°. The structure was solved by direct methods (SIR92),[19] and refined a full-matrix least squares methods with 208 variables and 1213 ovserved reflections [I>2.00σ (I)]. The final refinement converged to R = 0.126 and Rw = 0.148. All calculations were performed using the CrystalStracture crystallographic software package.[20,21]

Crystal data of 13c: brown plate, $C_{16}H_{11}N_3S$, M = 277.34, monoclinic, space group $P2_{1/c}$, a = 6.125(6) Å, b = 8.883(8) Å, c = 23.697(5) Å, β = 94.82(5)°, V = 1284.8(17) Å^3, Z = 4, D_{cale} = 1.434 g/cm^3, crystal dimensions 1.00×0.48×0.04 mm. Data were measured on a Rigaku AFC5S radiation diffractometer with graphite monochromated MoKα radiation. Total 3215 reflections (2940 unique) were collected using ω-2θ scan technique with in a 2θ range of 55.0°. The structure was solved by direct methods (SIR92),[19] and refined a full-matrix least squares methods with 225 variables and 1879 observed reflections [I > 2σ(I)]. The final refinement converged to R = 0.0496 and Rw = 0.0358. All calculations were performed using the CrystalStracture crystallographic software package.[20,21]

Crystal data of 22c: yellow block, $C_{13}H_6F_3N_5S$, M = 321.28, orthorhombic, space group Pbca, a = 13.32671(13) Å, b = 7.37808(13) Å, c = 24.4650(7) Å, V = 2405.53(8) Å^3, Z = 8, D_{cale} = 1.774 g/cm^3, crystal dimensions 0.12×0.10×0.08 mm. Data were measured on a Rigaku RAXIS-RAPID radiation diffractometer with graphite monochromated CuKα radiation. Total 15184 reflections (2194 unique) were collected using ω-2θ scan technique with in a 2θ range of 136.4°. The structure was solved by direct methods (SHELX97)[22] and expanded using Fourier techniques[23], and refined a full-matrix least squares methods with 200 variables and 2194 observed reflections [I>2.00σ (I)]. The final refinement converged to R = 0.0304 and Rw = 0.0844. All calculations were performed using the CrystalStructure crystallographic software package.[20,21]

Biological assay

HeLa S3 cells were obtained from AIST and used after cultivation. The cultivated HeLa S3 cells were cell counted and the culture fluid was prepared to the cell consistency of 2 × 10^4 clles/mL. The compounds added to the medium in DMSO solutions. To the aliquot of the culture fluid, which was incubated for 3 h at 37 °C, the test sample was added and then the culture fluid was incubated for 72 h. To the culture fluid, MTT (3-[4,5-dimethylthiazol]-2-yl-2,5-diphenyltetrazolium bromide) solution was added, and incubated for 4 h. Then the sample was centrifuged at 3000 rpm for 10 min at 4 °C, and the solvent was evaporated. Then DMSO was added to the obtained mixture. The MTT-foemazan was

dissolved by plate-mixing and OD540 was measured. The rate of outlive determined to refer with un-dosed control. Dose-response curve was drawn up and IC_{50} was pursued. Every experiment in the cycotoxic assay was replicated twice in order to define the IC values.

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