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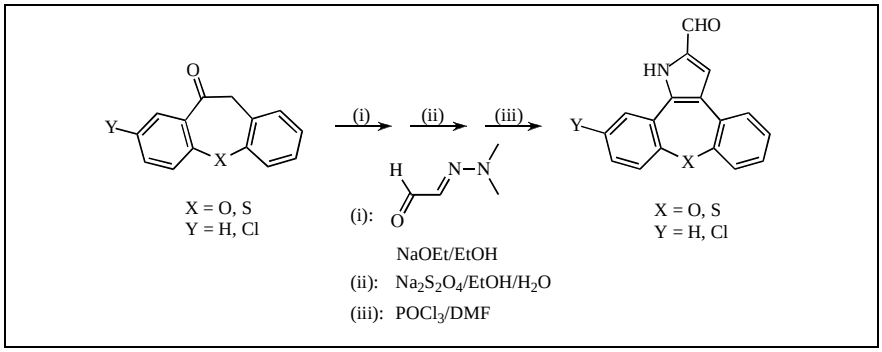

Synthesis of a novel heterocyclic class of compounds, 1-aza-dibenzo[*e,h*]azulenes [1] (**6a-c** and **7a-c**), derived from dibenzo[*b,f*]oxepin, its 8-chloro analogue and dibenzo[*b,f*]thiepin, respectively, is described. Aldol condensation of the starting ketones **4a-c** with (dimethyl-hydrazono)-acetaldehyde affords hydrazonoethylidene derivatives **5a-c**, which on reduction with sodium dithionite and subsequent cyclization provide the target tetracyclic 1-aza-dibenzo[*e,h*]azulenes **6a-c**. Regiospecific formylation of **6a-c** with Vilsmeier reagent leads to 2-formyl derivatives **7a-c**. A series of derivatives **6a-c** and **7a-c** was tested for antiinflammatory activity as potential inhibitors of tumor necrosis factor alpha (TNF-α) production *in vitro*.

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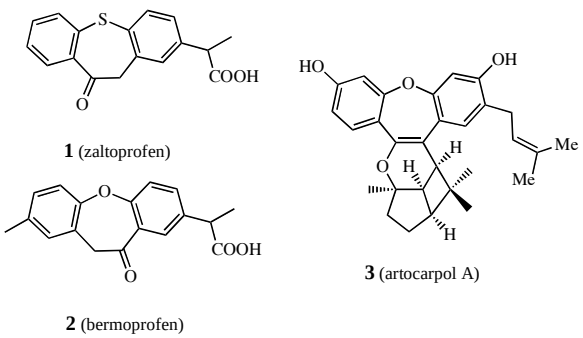
INTRODUCTION

An important and accepted therapeutic approach for potential drug intervention in a various inflammatory disorders is the inhibition of the overproduction of cytokines involved in mechanism of inflammation. Proinflammatory cytokines tumor necrosis factor alpha (TNF-α) and interleukin-1β (IL-1β), along with several other related proteins like p38 MAP kinase (p38) and COX-2 enzyme, are among the most relevant and the most studied mediators of inflammatory response. Extensive research efforts have been committed to finding new potent inhibitors of these biological targets.

Our search for novel antiinflammatory agents, particularly inhibitors of TNF-α production, is directed towards tetracyclic compounds which embody dibenzo-[*b,f*]oxepin or dibenzo[*b,f*]thiepin moiety, since similar structural features are found within a variety of medicinally important compounds, particularly those with antiinflammatory activity. For example, zaltoprofen (**1**) and bermoprofen (**2**), containing dibenzo[*b,f*]thiepin and dibenzo-[*b,f*]oxepin framework, respectively, are well known nonsteroidal antiinflammatory agents (Figure 1) [2,3].

On the other hand, some of diaryl-substituted heterocycles are also known to possess significant antiinflammatory activity [5]. Vicinal aryl/pyridine-4-yls with a central five-membered ring nitrogen heterocycle,

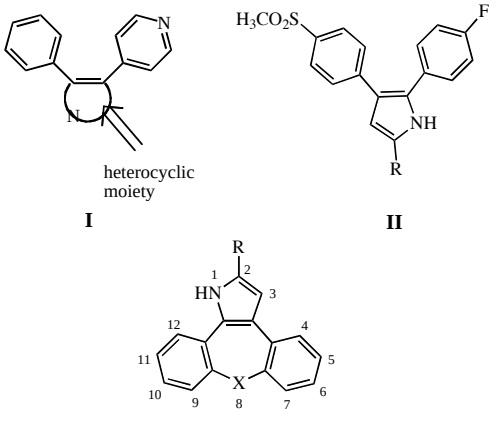


1 (zaltoprofen)

3 (artocarpol A)

2 (bermoprofen)

Figure 1



I **II**

III (X = O, S)

Figure 2

represented by structure **I**, are strong inhibitors of p38 MAP kinase (Figure 2) [5,6]. Specifically, some 2-substituted 4,5-diarylpyrroles (**II**) were found to have potent oral antiinflammatory activity *in vivo* [7].

Taking into account the aforementioned important role of dibenzo[*b*,*f*]thiepin and dibenzo[*b*,*f*]oxepin structural motifs in "profens" (**1**, **2**) and artocarpol A (**3**), as well as pyrrole ring as a pharmacophoric element in **II**, we envisioned a new class of compounds, 1-aza-dibenzo[*e*,*h*]azulenes (**III**), Figure 2. The prototype structure **III** represents a novel heterocyclic class characterized by non-planar, conjugated polycyclic skeleton with pyrrole ring fused to central boat-shaped seven-membered ring of dibenzo[*b*,*f*]oxepin or dibenzo[*b*,*f*]thiepin unit. Derivatives of the new polycyclic structure **III** (R = H, CHO) reported here are expected to show interesting biological and pharmacological behavior.

RESULTS AND DISCUSSION

Synthesis of the target 1-aza-dibenzo[*e*,*h*]azulene scaffold was achieved by the general route shown in Scheme 1. Firstly, activated α-methylene group of starting tricyclic ketones **4a-c** [8,9], was reacted with (dimethylhydrazono)-acetaldehyde, prepared by reaction of glyoxal with *N*,*N*-dimethylhydrazine [10], providing hydrazonoethylidene derivatives **5a-c**. Compounds **5a-c** were obtained as mixtures of double-bond isomers. This assumption was confirmed by NMR experiments for **5a** and its thia-analogue **5c** (Figure 3). As a result, the one- and two-dimensional NMR spectra of isomeric mixtures **5a** and **5c** consisted of two sets of resonance lines. For example, in **5a** proton H(12) is found as a doublet at 7.64 ppm (J = 10.1 Hz) and 6.89 ppm (J = 9.8 Hz), while H(13) is found as a doublet at 7.05 ppm (J = 10.1 Hz) and 8.24 ppm (J = 9.8 Hz). Likewise, in **5c** H(12) is found as a doublet at 7.75 ppm (J = 10.1 Hz) and 6.78 ppm (J = 9.8 Hz), while H(13) is found as a doublet at 6.76 ppm (J = 10.1 Hz) and 8.26 ppm (J = 9.8 Hz). Both sets of resonance lines displayed chemical shifts and correlation peaks characteristic of the structures shown in Figure 3, indicating that both, oxa- as well as thia-analogue, are a mixture of *E* and *Z* isomer.

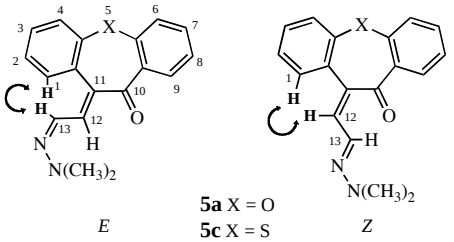


Figure 3. *E* and *Z* isomer of hydrazonoethylidene derivatives **5a** and **5c**.

In order to determine which set of resonance lines corresponds to which isomer the analysis of nuclear Overhauser effect (NOE) contacts was performed. The NOE contact between protons H(1) (7.50 ppm for **5a** or 7.46 ppm for **5c**) and H(13) (7.05 ppm for **5a** or 6.76 ppm for **5c**) confirmed that isomer with higher intensity of ^{1}H signals is *E* isomer. Accordingly, the NOE contact between protons H(1) (7.41 ppm for both **5a** and **5c**) and H(12) (6.89 ppm for **5a** or 6.78 ppm for **5c**) confirmed that isomer with lower intensity of ^{1}H signals is *Z* isomer. Calculation of the integrated proton peak intensities involving H(12) and H(13) was used to determine the ratios between isomers. *E vs*. *Z* isomer ratio is estimated to be 80%:20% for oxa- (**5a**) and 85%:15% for thia-analogue (**5c**).

The reduction of hydrazonoethylidene derivatives **5a-c** was performed with sodium dithionite in aqueous ethanol and afforded the target tetracyclic structures, 1-aza-dibenzo[*e*,*h*]azulenes **6a-c**. We assume that reductive cleavage of hydrazones **5a-c** leads to intermediary γ-amino ketones **8a-c**, which by cyclization form pyrrole ring fused to the tricyclic moiety (Scheme 2).

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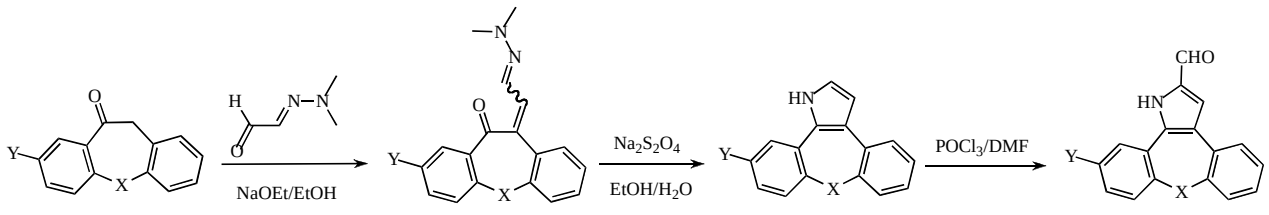
Scheme 1



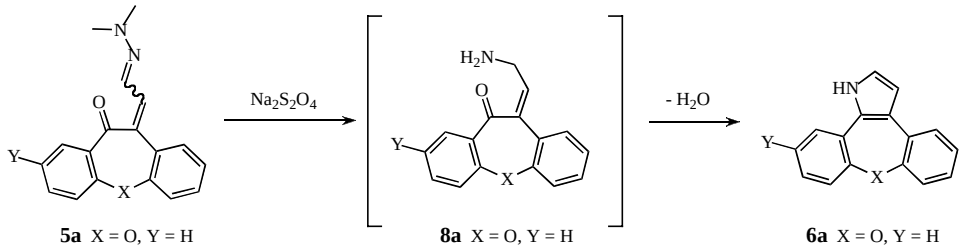
4a X = O, Y = H
4b X = O, Y = Cl
4c X = S, Y = H

5a X = O, Y = H
5b X = O, Y = Cl
5c X = S, Y = H

6a X = O, Y = H
6b X = O, Y = Cl
6c X = S, Y = H

7a X = O, Y = H
7b X = O, Y = Cl
7c X = S, Y = H

Scheme 2



5a X = O, Y = H
5b X = O, Y = Cl
5c X = S, Y = H

8a X = O, Y = H
8b X = O, Y = Cl
8c X = S, Y = H

6a X = O, Y = H
6b X = O, Y = Cl
6c X = S, Y = H

The reaction provides the expected products **6a-c** in 50-57% yield after column chromatography, while reported similar preparations are characterized with slightly lower yields (21-48%), sometimes requiring indirect methods such as catalytic dehydrogenation for formation of pyrrole ring from hydrazones [10]. NMR spectra of compounds **6a-c** are characterized by multiplets at around 6.5 ppm and 7.1 ppm for the pyrrole ring protons and with broad singlet at 11.6 ppm corresponding to the proton attached to nitrogen atom.

Finally, formylation of **6a-c** was performed with Vilsmeier reagent [11] giving **7a-c** on regiospecific substitution at C(2) position of the pyrrole ring, with 30-55% yield after purification by column chromatography.

The structure of **7a-c** is proved by combined spectroscopic data. MS spectra showed the presence of the expected molecular ion, while IR and NMR analyses confirmed the existence of aldehyde carbonyl group. It is well known that pyrrole ring undergoes electrophilic substitution preferably at the α-position [12]. However, we were concerned about possibility of substitution at β-position, since there are reported examples of β-attack, although in the presence of a large pyrrole-*N*-substituent [13,14] and/or bulky electrophilic species [15]. Hence, to confirm regiospecificity of substitution at α-position, we performed additional NMR analyses yet again for oxa- (**7a**) and thia-analogue (**7c**). According to data found in the literature for somewhat similar ring systems [16,17], chemical shifts of quaternary C(2) at 133.6 ppm and 132.8 ppm for **7a** and **7c**, respectively, and chemical shifts of unsubstituted C(3) at 118.1 ppm and 119.3 ppm for **7a** and **7c**, respectively, suggest that the aldehyde group is positioned at carbon C(2) adjacent to nitrogen N(1). Additional support for α-substitution is the existence of NOE cross-peak between atoms H(3) (7.48 ppm for **7a** or 7.43 ppm for **7c**) and H(4) (7.61 ppm for **7a** or 7.62 ppm for **7c**).

Compounds **6a-c** and **7a-c** were tested for antiinflammatory activity *in vitro* on lipopolysaccharide (LPS) induced TNF-α production in human peripheral blood mononuclear cells (hPBMCs). None of the compounds showed significant inhibition when tested in concentrations of 10 μmol dm^{-3} and 3 μmol dm^{-3}, which are the inhibitory concentrations (IC) considered as minimal criterion to recognize compounds as biologically active. In order to attain anticipated antiinflammatory properties we will consider additional modifications of the scaffolds **6** and **7**.

CONCLUSION

Synthesis of 1-aza-dibenzo[*e,h*]azulenes, a new class of heterocyclic compounds, is described. Synthetic route starts with aldol condensation of 11*H*-dibenzo[*b,f*]oxepin-10-one (**4a**), its 8-chloro analogue (**4b**) and 11*H*-dibenzo-[*b,f*]thiepin-10-one (**4c**), respectively, with (dimethylhydrazono)-acetaldehyde to obtain corresponding hydrazonoethylidene derivatives **5a-c** as mixtures of double-bond isomers. Reductive cleavage of **5a-c** after subsequent cyclization provides the target tetracyclic compounds, 1-aza-dibenzo[*e,h*]azulenes **6a-c**, which are transformed by Vilsmeier reagent to 2-formyl derivatives **7a-c**. The regiospecificity of this substitution at α–position of the pyrrole ring was confirmed by NMR. *In vitro* results indicate that compounds **6a-c** and **7a-c** do not inhibit TNF-α production (IC_{50} > 10 μmol dm^{-3}). According to these preliminary results further work will be focused on the synthesis of new variously substituted 1-aza-dibenzo[*e,h*]azulenes in order to obtain compounds with drug-like properties.

EXPERIMENTAL

a) Chemistry. Commercial reagents were used as received without additional purification. All used chemicals and solvents were of p.a. purity. Melting points were determined using Büchi Melting Point B-545 apparatus and are uncorrected. IR spectra of samples in form of potassium bromide pastilles were recorded on Nicolet Magna IR 760 FT IR-spectrophotometer. One- and two-dimensional NMR spectra were recorded at 25 °C on Bruker Avance DRX 500 (500 MHz) and Bruker Avance DPX 300 (300 MHz) spectrometer. Deuterated dimethyl sulfoxide (DMSO-d_6) was used as solvent and tetramethylsilane (TMS) as internal standard. For NOE contact analysis NOESY spectra were recorded with mixing time set to 400 ms. Purity of the compounds was determined on HPLC-MS system Waters 2690 + Micromass Quattro Micro and on HPLC-UV system Waters 2690 + Waters 996 Photodiode Array Detector. HRMS data

were acquired using Q-TOF 2 Waters system. Microanalyses were performed using Perkin-Elmer 2400 C H N S analyzer. Thin layer chromatography (TLC) was performed on aluminum plates Merck Silica gel 60 F_{254} with UV light detection at 254 nm and/or 365 nm. Proportions of solvents used for TLC are by volume. Column chromatography was performed on silica gel 60 (Merck, 0.063-0.200 nm). Compounds **4a-c** and (dimethyl-hydrazono)-acetaldehyde were synthesized as described before [8-10].

General Procedure for the Reaction of Ketones 4a-c with (Dimethyl-hydrazono)-acetaldehyde. Freshly prepared solution of sodium ethoxide in ethanol (0.203 g, 0.85 mmol of sodium in 25 mL of ethanol) was carefully dropwise added to the solution of ketone **4** (8.85 mmol) and (dimethyl-hydrazono)-acetaldehyde (0.886 g, 8.85 mmol) in 25 mL of ethanol. Reaction mixture was stirred at reflux temperature for 3 hours (TLC control, ethyl acetate/*n*-hexane 1:1). After cooling of reaction mixture to room temperature, water was added and organic product was extracted with dichloromethane. Organic extracts were dried over anhydrous sodium sulfate and filtered, then solvent was evaporated and crude product purified by column chromatography (ethyl acetate/*n*-hexane 1:1) to give compound **5** as a mixture of *cis-trans* double-bond isomers.

11-[2-(Dimethyl-hydrazono)-ethylidene]-11*H*-dibenzo[*b,f*]-oxepin-10-one (5a). The mixture of *cis-trans* isomers was obtained starting from **4a** as yellow solid (37%); E isomer: ^{1}H NMR (DMSO-d_6): δ 3.09 (s, 6H, 2xCH_3), 7.05 (d, J = 10.1 Hz, 1H, CH=CH), 7.23-7.45 (m, 5H, arom.), 7.50 (dd, J = 7.6, 1.7 Hz, 1H, arom.), 7.58-7.62 (m, 1H, arom.), 7.64 (d, J = 10.1 Hz, 1H, CH=CH), 7.85 ppm (dd, J = 7.8, 2.0 Hz, 1H, arom.); ^{13}C NMR (DMSO-d_6): δ 42.4 (CH_3); 125.24 (HC=N); 121.04, 121.11, 125.21, 125.63, 129.25, 131.09, 131.55, 134.60 (CH arom.); 130.00 (*C*=CH); 140.21 (H*C*=C); 128.22, 129.84, 156.62, 160.0 (C, arom.), 186.46 ppm (C=O); MS: m/z 293 (MH^+). *Anal.* Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.68; H, 5.43; N, 9.47.

8-Chloro-11-[2-(dimethyl-hydrazono)-ethylidene]-11*H*-dibenzo[*b,f*]oxepin-10-one (5b). The mixture of *cis-trans* isomers was obtained starting from **4b** as yellow solid (37%); ^{1}H NMR (DMSO-d_6): δ 3.11 (s, 6H, 2xCH_3), 7.05 (d, J = 10.2 Hz, 1H, CH=CH), 7.25-7.31 (m, 2H, 1H, arom.), 7.32-7.37 (m, 1H, arom.), 7.45 (d, 1H, J = 10.2 Hz, CH=CH), 7.51 (dd, J = 7.5, 1.7 Hz, 1H, arom.), 7.62-7.69 (m, 2H, arom.), 7.78 ppm (d, J = 2.7 Hz, 1H, arom.); ^{13}C NMR (DMSO-d_6): δ 42.54 (CH_3); 121.16, 123.30, 125.02, 125.91, 129.39, 130.25, 131.73, 134.06, 141.06 (*C*H=*C*H + CH arom.); 127.93, 129.07, 129.44, 131.37, 156.40, 158.54 (*C*=CH + C arom.); 185.19 ppm (C=O); MS: m/z 326, 328 (MH^+, 100%, 37%). *Anal.* Calcd. for $C_{18}H_{15}ClN_2O_2$: C, 66.16; H, 4.63; N, 8.57. Found: C, 66.25; H, 4.57; N, 8.21.

11-[2-(Dimethyl-hydrazono)-ethylidene]-11*H*-dibenzo[*b,f*]-thiepin-10-one (5c). The mixture of *cis-trans* isomers was obtained starting from **4c** as yellow solid (45%); *E* isomer: ^{1}H NMR (DMSO-d_6): δ 3.04 (s, 6H, 2xCH_3), 6.76 (d, 1H, J = 10.1 Hz, CH=CH), 7.29 (dd, J = 7.5, 1.6 Hz, 1H, arom.), 7.36-7.45 (m, 3H, arom.), 7.46 (dd, J = 7.7, 1.6 Hz 1H, arom.), 7.52-7.57 (m, 1H, arom), 7.67-7.70 (m, 2H, arom), 7.75 ppm (d, J = 10.1 Hz, 1H, CH=CH); ^{13}C NMR (DMSO-d_6): δ 42.31 (CH_3); 125.58 (HC=N); 128.20, 128.82, 128.96, 131.39, 131.74, 131.89, 132.03, 132.91 (CH arom.); 140.07 (H*C*=C); 133.63 (*C*=CH); 135.46, 137.16, 138.95, 141.27 (C arom.); 189.46 ppm (C=O); MS: m/z 308 (MH^+). *Anal.* Calcd. for $C_{18}H_{16}N_2OS$: C, 70.10; H, 5.23; N, 9.08; S, 10.40. Found: C, 69.86; H, 5.16; N, 9.08; S, 10.57.

General Procedure for the Reaction of Hydrazonoethylidene Derivatives 5a-c with Sodium Dithionite. To a solution of hydrazonoethylidene derivative **5** (1.4 mmol) in 50 mL of ethanol, sodium dithionite (6.3 g, 0.036 mol) and 23 mL of water were added. The reaction mixture was stirred at reflux temperature for 4 hours (TLC control, ethyl acetate/*n*-hexane 1:1). Hot reaction mixture was then poured into the mixture of ice and water and organic product was extracted with dichloromethane. Organic extracts were dried over anhydrous sodium sulfate and filtered, solvent was evaporated and crude product purified by column chromatography (ethyl acetate/*n*-hexane 1:1) yielding **6**.

1*H*-8-Oxa-1-aza-dibenzo[*e,h*]azulene (6a). This compound was obtained starting from **5a** as light yellow solid (50%), mp 157-158.5 °C; ^{1}H NMR (DMSO-d_6): δ 6.54 (m, 1H, pyrrole), 7.05 (m, 1H, pyrrole), 7.15-7.18 (m, 1H, arom.), 7.20-7.21 (m, 1H, arom.), 7.23 (d, J = 1.8 Hz, 1H, arom.), 7.25 (d, J = 2.1 Hz, 1H, arom.), 7.28-7.29 (m, 1H, arom.), 7.30-7.32 (m, 1H, arom.), 7.49 (dd, J = 7.2, 2.1 Hz, 1H, arom.), 7.53 (dd, J = 7.2, 1.8 Hz, 1H, arom.), 11.59 ppm (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 106.97, 120.79, 121.48, 121.75, 125.31, 125.45, 125.49, 127.06, 127.43, 128.29 (CH, arom.); 119.78, 126.10, 126.53, 129.06, 154.57, 154.62 ppm (C, arom.); MS: m/z 234 (MH^+), 232 (M-H); HRMS: m/z calcd. for $C_{16}H_{12}NO$: 234.0919 (MH^+), found 234.0913. *Anal.* Calcd. for $C_{16}H_{11}NO$: C, 82.38; H, 4.75; N, 6.00. Found: C, 82.04; H, 4.58; N, 5.94.

11-Chloro-1*H*-8-oxa-1-aza-dibenzo[*e,h*]azulene (6b). This compound was obtained starting from **5b** as yellow solid (53%), mp 130-131 °C; ^{1}H NMR (DMSO-d_6): δ 6.57 (m, 1H, pyrrole), 7.10 (m, 1H, pyrrole), 7.18-7.38 (m, 5H, arom.), 7.50 (dd, J = 7.1, 2.0 Hz, 1H, arom.), 7.58 (d, J = 2.3 Hz, 1H, arom.), 11.69 ppm (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 107.25, 121.48, 121.63, 123.52, 124.79, 125.71, 127.21, 127.63, 127.77 (CH, arom.); 120.66, 125.11, 128.62, 129.37, 153.06, 154.28 ppm (C, arom.); MS: m/z 268.27 (MH^+, 100 %, 37 %), 266, 268 (M-H; 100%, 37%); HRMS: m/z calcd. for $C_{16}H_{11}ClNO$: 268.0529 (MH^+), found 268.0519. *Anal.* Calcd. for $C_{16}H_{10}ClNO$: C, 71.78; H, 3.77; N, 5.23. Found: C, 71.65; H, 3.73; N, 5.02.

1*H*-8-Thia-1-aza-dibenzo[*e,h*]azulene (6c). This compound was obtained starting from **5c** as yellow solid (57%), mp 91-93 °C; ^{1}H NMR (DMSO-d_6): δ 6.52 (m, 1H, pyrrole), 7.07 (m, 1H, pyrrole), 7.22-7.59 (m, 8H, arom.), 11.60 ppm (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 108.89, 120.17, 127.23, 127.37, 128.10, 128.44, 128.84, 128.98, 132.54, 132.69 (CH, arom.); 124.39, 129.83, 131.71, 132.39, 136.02, 139.38 (C, arom.); MS: m/z 250 (MH^+), 248 (M-H); HRMS: m/z calcd. $C_{16}H_{12}NS$: 250.0690 (MH^+), found 250.0676. *Anal.* Calcd. for $C_{16}H_{11}NS$: C, 77.07; H, 4.45; N, 5.62; S, 12.86. Found: C, 76.91; H, 4.41; N, 5.78; S, 12.54.

General Procedure for the Reaction of 1-Azadibenzo-[*e,h*]azulene Analogues 6a-c with Vilsmeier Reagent. To *N,N*-dimethylformamide (1.9 mL, 22.5 mmol) previously cooled to 0 °C, phosphorus(III) oxychloride (1.4 mL, 15 mmol) was added dropwise, while maintaining the reaction temperature below 10 °C. The reaction mixture was then stirred at room temperature for 15 minutes and afterwards again cooled to 0 °C before the solution of **6** (1.5 mmol) in 5 mL of DMF was added dropwise. Reaction mixture was stirred at reflux temperature for 2 hours, cooled to room temperature, pH adjusted to pH 8-9 by addition of 50% aqueous sodium hydroxide and stirred at 70 °C for additional 60 minutes. Hot reaction mixture was poured into the mixture of ice and water followed by extraction of organic product with ethyl acetate. Organic extracts were dried over

anhydrous sodium sulfate, filtered, solvent was evaporated and crude product purified by column chromatography (ethyl acetate/*n*-hexane 1:1) yielding **7**.

1*H*-8-Oxa-1-aza-dibenzo[*e,h*]azulene-2-carbaldehyde (7a). This compound was obtained starting from **6a** as yellow solid (52%), mp 218.5-220 °C (decomp.); IR (potassium bromide): 3256, 2811 (C-H), 1646 (C=O), 1605, 1569, 1525, 1506, 1475, 1449, 1417 (arom.) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.25 (dd, J = 7.5, 1.3 Hz, 1H, arom.), 7.28-7.39 (m, 3H, arom.), 7.39-7.47 (m, 2H, arom.), 7.48 (d, J = 2.2 Hz, 1H, arom.), 7.61 (dd, J = 7.7, 1.3 Hz, 1H, arom.), 7.79 (d, J = 7.7 Hz, 1H, arom.), 9.65 (s, 1H, CHO), 12.76 ppm (1H, NH); ^{13}C NMR (DMSO-d_6): δ 118.13; 121.44, 121.16, 125.42, 125.69, 127.37, 127.45, 128.50, 130.55 (CH, arom.); 121.85, 124.23, 127.26, 133.53, 134.16, 155.11, 156.08 (C, arom.); 179.67 ppm (CHO); MS: m/z 262 (MH^+). *Anal*. Calcd. for $C_{17}H_{11}NO_2$: C, 78.15; H, 4.24; N, 5.36. Found: C, 77.95; H, 3.90; N, 5.25.

11-Chloro-1*H*-8-oxa-1-aza-dibenzo[*e,h*]azulene-2-carbaldehyde (7b). This compound was obtained starting from **6b** as yellow solid (30%), mp 290-292 °C (decomp.); ^1H NMR (DMSO-d_6): δ 7.24-7.29 (m, 1H, arom.), 7.31-7.35 (m, 1H, arom.), 7.37 (m, 1H, arom.), 7.39-7.45 (m, 1H, arom.), 7.47 (d, J = 2.7 Hz, 1H, arom.), 7.49 (s, 1H, arom.), 7.60-7.63 (m, 1H, arom.), 7.89 (d, J = 2.2 Hz, 1H, arom.), 9.67 (s, 1H, CHO), 12.82 ppm (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 117.89, 121.45, 123.61, 125.94, 126.82, 127.48, 128.74, 129.93 (CH, arom.); 122.37, 125.89, 126.95, 129.48, 132.40, 134.09, 154.59, 154.79 (C, arom.); 179.95 ppm (CHO); MS: m/z 296, 298 (MH^+, 100%, 37%). *Anal*. Calcd. for $C_{17}H_{10}ClNO_2$: C, 69.05; H, 3.41; N, 4.74. Found: C, 69.40; H, 3.03; N, 4.89.

1*H*-8-Thia-1-aza-dibenzo[*e,h*]azulene-2-carbaldehyde (7c). This compound was obtained starting from **6c** as yellow solid (33%), mp 253-255 °C (decomp.); IR (potassium bromide): 3250, 3091, 3022, 2842, 2708 (C-H), 1647 (C=O), 1585, 1561, 1550, 1512, 1499, 1414 (arom.) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.33 (dd, J = 7.5, 1.6 Hz, 1H, arom.), 7.40-7.50 (m, 4H, arom.), 7.59-7.62 (m, 2H, arom.), 7.65 (dd, J = 7.5, 1.8 Hz, 1H, arom.), 7.69 (dd, J = 7.5, 1.7 Hz, 1H, arom.), 9.69 (s, 1H, CHO), 12.76 ppm (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 119.56, 128.16, 128.79, 129.03, 129.31, 129.38, 129.97, 132.69, 132.96 (CH, arom.); 126.32, 132.74, 134.17, 134.42, 137.23, 137.88 (C, arom.); 180.19 ppm (CHO); MS: m/z 278 (MH^+); HRMS: m/z calcd. for $C_{17}H_{12}NOS$: 278.0640 (MH^+), found 278.0618. *Anal*. Calcd. for $C_{17}H_{11}NOS$: C, 73.62; H, 4.00; N, 5.05; S, 11.56. Found: C, 73.51; H, 3.97; N, 5.31; S, 11.73.

b) Biology. One of the most used *in vitro* tests for selection of compounds with potential antiinflammatory activity is one in which peripheral blood mononuclear cells were induced on TNF-α overproduction using lipopolysaccharide (LPS) [18,19]. For that purpose blood was taken from healthy volunteer donor and was separated by centrifugation on FicollPaque™Plus (Amersham) on 400 g for 30 min. Collected PBMC were washed in RPMI and cultured $3.5x10^4$ in 96 well tissue culture plate (Falcon) in RPMI with addition of 10% inactivated fetal bovine serum (Gibco). Cells were stimulated on TNF-α production by addition of LPS (serotype 0111:B4, Sigma) at final concentration of 1 ng/mL. Stock solutions of tested compounds were prepared as 10 mmol dm^{-3} in DMSO. Final concentrations of 10 μmol dm^{-3} and 3 μmol dm^{-3}, made in medium, were tested when they had been added together with LPS. Negative and positive control samples were prepared in sextaplicates while samples containing compounds were prepared in triplicates. After overnight incubation in humidified atmosphere containing 5% CO_2, supernatants were collected and quantified for a TNF-α content using set of specific antibodies (R&D Systems) by enzyme linked immunosorbent assay (ELISA).

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REFERENCES AND NOTES

[1a] The substitutive nomenclature is used here for this class of compounds, but the correct IUPAC defined nomenclature is as follows: **6a**, 1*H*-dibenzo[2,3:6,7]oxepino[4,5-*b*]pyrrole; **6b**, 11-chloro-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*b*]pyrrole; **6c**, 1*H*-dibenzo[2,3:6,7]thiepino-[4,5-*b*]pyrrole; **7a**, 1*H*-dibenzo[2,3:6,7]oxepino[4,5-*b*]pyrrole-2-carbaldehyde; **7b**, 11-chloro-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*b*]pyrrole-2-carbaldehyde; **7c**, 1*H*-dibenzo[2,3:6,7]thiepino[4,5-*b*]pyrrole-2-carbaldehyde; [1b] Olivera, R.; SanMartin, R.; Churruca, F.; Domínguez, E. *J. Org. Chem.* **2002**, *67*, 7215.

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