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Symmetrical Acyclic Aryl Aldazines with Antibacterial and Antifungal Activity

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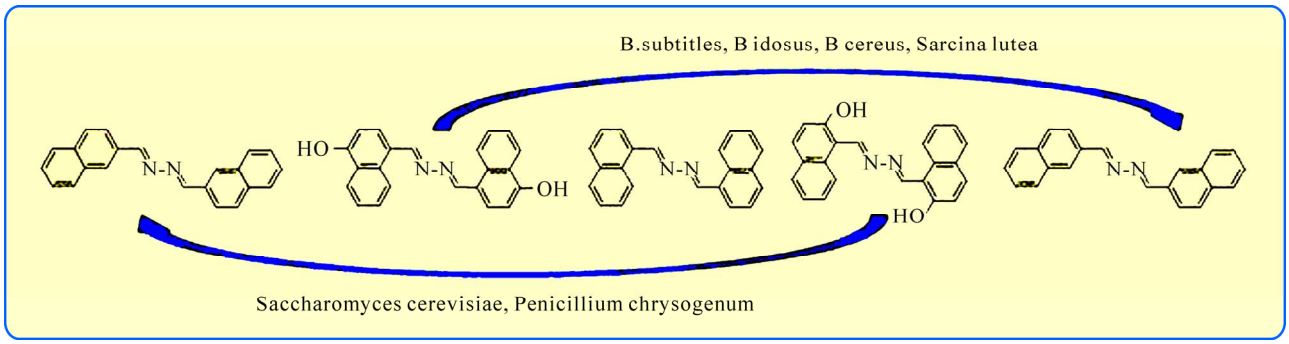
ABSTRACT

A series of 22 symmetrical acyclic aromatic aldazines were obtained and their qualitative antimicrobial activities were evaluated against 10 bacterial and 3 fungal species. The results demonstrated that the bi- and polycyclic aromatics studied are remarkably more active than benzaldazines. The latter possess antibacterial activities only, which were dramatically reduced by the introduction of substituents. The tests showed that the activities are strongly dependent on the type and position of the substituents and that the effects on antibacterial and antifungal activities are the opposite. 2-Naphtaldazine was significantly more active than its position isomer 1-naphthaldazine against Saccharomyces cerevisiae and Penicillium chrysogenum, whereas both compounds possess commensurable activities towards Candida tropicalis and the bacterial strains. From the other side, the presence of 4-hydroxy substituent in 1-naphthaldazine reduced the antibacterial and increased the antifungal activities, while the influence of 2-hydroxy group led to reversed results.



***Keywords*:** *Symmetrical Acyclic Aryl Aldazines, Synthesis, Antibacterial Activity, Antifungal Activity*

1. Introduction

Azines are a class of organic compounds containing $R_1R_2C = N\text{-}N = CR_3R_4$ fragment. Depending on the nature of the substituents R, they are divided in several sub-groups: 1) symmetrical ($R_1R_2 = R_3R_4$) and unsymmetrical ($R_1R_2 \neq R_3R_4$); 2) aldazines ($R_1 = R_3 = H$), ketazines ($R_1R_2R_3R_4 \neq H$) and mixed azines ($R_1 = H$, $R_2R_3R_4 \neq H$); 3) aromatic and aliphatic; 4) cyclic and acyclic. Numerous examples are well-known ever since 19th century but only a limited number of synthetic pathways are applied for their preparation. The classical scheme for the construction of acyclic aldazines is based on a reaction of aldehydes with hydrazine [1,2]. Despite the high toxicity of the latter, the protocol is very fast, simple and efficient and is still widely exploited. Semicarbazide has been also applied as a reagent in a two-step procedure involving thermolysis of the intermediately formed semicarbazones at high temperature [3,4]. Recently, the transformation has achieved as an environmentally benign solvent-free procedure under microwave irradiation [5,6].

Compounds possessing azine moiety are still the order of the day due to the broad spectrum of biological activeity profiles displayed. Ketazines, mixed azines, and cyclic compounds have exhibited antitumor [7-12], anti-

bacterial [13-20], anti-inflammatory [21], antimalarial dyes [22], anticonvulsant [23,24], insect growth regulators [25] and many other activities. Contrary, acyclic aldazines are much less studied. Unsymmetrical aldazines have shown antitumor [26], antibacterial [27,28], and antioxidant [29] activity. Symmetrical 4-bromo benzaldazine has evaluated as anticonvulsant agent but shown very low activity [30]. Similar monosubstituted benzaldazines have been tested as allosteric modulators [31] and has found that 2-fluoro and 3-fluoro compounds possessed positive activity, while 4-fluoro, 3-chloro, 3- and 4-methoxy, and 3-hydroxy analogues were not active. Recently, a series of unsymmetrical and two examples of symmetrical 3-indolyl aldazines have been studied and have found to exhibit antioxidant [29] and antibacterial [28] activity. The latter presents, to the best of our knowledge, the only record in the literature on the evaluation of antibacterial and antifungal activity of symmetrical aryl aldazines.

In this paper, we report on a synthesis, characterization and qualitative antibacterial and antifungal activity evaluation of a series of 22 symmetrical acyclic aryl aldazines.

2. Results and Discussion

2.1. Chemistry

The titled symmetrical aldazines were obtained by the classical protocol from aldehydes and hydrazine sulphate in ethanol, as shown on **Scheme 1**. Aromatic aldehydes with varied ring size and type and position of the substituents were chosen in an attempt to study the influence of different factors on the activity. The syntheses of aldazines 20-22 were carried out in ethanol/dimethylformamide instead of pure ethanol due to the limited solubility of the starting aldehydes. The compounds 1-16 and 18-22 were isolated in high to excellent yields (**Table 1**) after a very simple work-up. The *E*,*E*-configuration of the products was assumed on the bases of the previously confirmed by X-ray analysis stereochemistry of a similar symmetrical aryl aldazine sample [6].

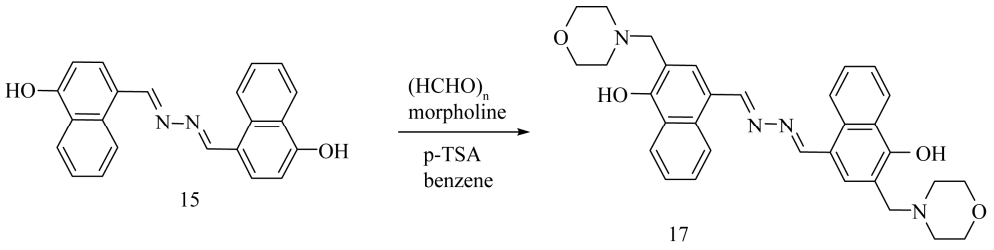
The naphthaldazine 17 possessing a non-conjugated side-chain was obtained in moderate yield from 15 by Mannich reaction (**Scheme 2**, **Table 1**). As it was found that 17 is less active than the corresponding unsubstituted compound 15, other examples were not synthesized.

All known aldazines, 1-11, 13-16, 18, 19, 21, and 22, were characterized by a comparison of the melting points with the literature data (**Table 1**) and by their NMR spectra, given in the experimental section. The structures of the new members, 12, 17 and 20, were additionally confirmed by electrospray ionization mass spectrometry.

2.2. Pharmacology

The *in vitro* antibacterial and antifungal activities of the synthesized compounds against a series of species were determined qualitatively by the agar cup test according to the European Pharmacopoeia [48]. Shortly, suspensions of the test microorganisms were inoculated into sterile melted nutrient agar media and poured into Petri dishes. The bacterial strains were grown in nutrient agar (Serva, Germany) for 24 h at 37˚C while the yeast and fungal strains were incubated in yeast peptone dextrose agar (YEPD) and in potato dextrose agar (PDA), respectively for 72 h at 28˚C. Six per dish wells, each 8 mm in diameter, were prepared. Fifty microliter of each sample in dimethylsulfoxide (25 mg/ml or 12.5 mg/ml) was added to the appropriate well. For pre-diffision the Petri dishes were placed at 4˚C for 2 h. The antimicrobial activity was estimated by the diameter of inhibitory zones (mm) in the agar layer. Control experiments were carried out with the pure solvent.

Scheme 1. Synthesis of symmetrical aryl aldazines 1-16 and 18-22.



Scheme 2. Synthesis of symmetrical aryl naphthaldazine 17.

Table 1. Synthesis and physical data of symmetrical aryl aldazines 1-22.

Azine	Ar group	Yield, %	m.p., ˚C (lit.)	R_f-value, (MP)[a]
1	Ph	90	91.5-92 (92 [32])	0.63 (A)
2	4-OH-C_6H_4	88	258-259 (268 [33])	0.36 (B)
3	3-OH-C_6H_4	94	205.5-206 (205 [34])	0.51 (B)
4	2-OH-C_6H_4	96	210-211 (213-214 [3])	0.85 (B)
5	3-OMe-2-OH-C_6H_3	98	192-193 (196 [35])	0.47 (A)
6	4-NMe_2-C_6H_4	87	254.5-255 (250-253 [33])	0.59 (A)
7	4-Cl-C_6H_4	93	210-211 (213 [36])	0.71 (A)
8	3-Cl-C_6H_4	93	142-143 (141 [37])	0.75 (A)
9	2-Cl-C_6H_4	89	143.5-144 (143.5 [38])	0.77 (A)
10	2,6-Cl_2-C_6H_3	87	152.5-153 (153 [39])	0.76 (A)
11	2,4-Cl_2-C_6H_3	95	218-219 (213 [40])	0.83 (A)
12	2-Cl-4-F-C_6H_3	97	193.5-194	0.80 (A)
13	3-F-C_6H_4	91	134-135 (132 [41])	0.72 (A)
14	1-naphthyl	96	156-156.5 (156 [42])	0.74 (A)
15	4-OH-1-naphthyl	84	235-236 (236 [43])	0.58 (B)
16	2-OH-1-naphthyl	89	290-293 (>290 [44])	0.86 (B)
17	4-OH-3-R-1-naphthyl[b]	35	232-232.5	0.28 (C)
18	2-naphthyl	93	232-232.5 (232 [45])	0.71 (A)
19	4-Ph-C_6H_4	64	243.5-244 (230-245 [46])	0.68 (A)
20	2-fluoryl	97	260-261	0.71 (A)
21	9-phenanthryl	82	232-232.5 (244 [47])	0.70 (A)
22	1-pyrenyl	94	299 (299 [39])	0.81 (A)

[a]Mobile phase (MP), A: CH_2Cl_2, B: CH_2Cl_2:MeOH 90:10, C: EtOAc:Et_3N 100:1; [b]Depicted on Scheme 2.

2.2.1. Antibacterial Activity

The antibacterial activities of aldazines 1-22 were evaluated against the Gram (+) strains *Bacillus subtilis* ATCC 6633, *Bacillus idosus* B241, *Bacillus megaterium* NRRL 1353895, *Bacillus mycoides* DSMZ 274, *Bacillus cereus* ATCC 11778, *Acinetobacter johnstonii* ATCC 17909, *Staphylococcus aureus* NRRL B 313, *Sarcina lutea* ATCC 9341, and *Micrococcus luteus* ATCC 9631, and the Gram (-) strain *Escherichia coli* ATCC 8739. *Streptomycin* and *Gentamycin* were used as standard drugs.

The antibacterial screening demonstrated that half of the tested products, listed on **Table 2**, are active against all strains. Inside the benzaldazine series 1-13, the unsubstituted compound 1 exhibited good activities, while the introduction of substituents in the phenyl ring led to loss of activity in general. The only exceptions were 4-hydroxy compound 2 and 2-chloro-4-fluoro derivative 12, both possessing lower activity than 1. The compareson with their non-active position analogues, 2 *vs* 3-5 and 12 *vs* 13, could be an indication that hydroxyl group and fluorine atom at *para*-position slightly reduce the activity of the unsubstituted azine 1, while their effect if *ortho*- or *meta*-positioned is significant. Contrary, the introduction of a hydroxyl group in 1-naphthaldazine 14 led to better inhibition against the most part of the Gram (+)-bacteria of the *ortho*-substituted compound, 14 *vs* 16, and commensurable or reduced activities of *para*-hydroxy product, 14 *vs* 15. The incorporation of a side-chain in 17,

Table 2. Aldazines with antibacterial activity; zone of inhibition[a] in mm.

Azine	*Bacillus subtilis*	*Bacillus idosus*	*Bacillus megat.*	*Bacillus mycoides*	*Bacillus cereus*	*Acinetob. johnst.*	*Staph. aureus*	*Sarcina lutea*	*Microc. luteus*	*E. coli*
1[b]	20	21	20	16	17	24	18	20	19	30
2[b]	10	18	17	15	26	17	17	17	16	20
12[b]	-	15	14	16	17	-	12	14	15	25
14[b]	19	18	20	11	22	18	21	23	21	24
15[b]	13	19	12	18	16	16	14	14	14	25
16[c]	17	26	24	19	25	27	15	25	22	25
17[c]	11	12	11	10	12	11	12	11	12	12
18[c]	20	23	21	16	20	25	22	25	23	30
19[c]	15	19	20	15	19	17	17	18	20	37
20[c]	22	25	25	14	22	26	23	20	25	23
22[c]	15	19	14	15	19	13	12	18	21	33
Ref 1[b,e]	35	30	30	35	30	30	32	27	30	35
Ref 2[d,f]	30	35	36	32	29	39	35	34	38	31

[a]DMSO solutions with different concentrations; indicated for each compound: [b]25 mg/ml; [c]12.5 mg/ml; [d]20 mg/ml; [e]*Streptomycin*; [f]*Gentamycin*.

where the hydroxyl proton is strongly hydrogen-bonded - with piperidine nitrogen, resulted in an additional reduction of the activity, 15 *vs* 17.

2.2.2. Antifungal Activity

The antifungal activity of compounds 1-22 were examined against the yeast strains *Candida tropicalis* ATCC 20336 and *Saccharomyces cerevisiae* ATCC 9763, and the fungal strain *Penicillium chrysogenum* CECT 2802. *Fluconazole* and *Itraconazole* were used as standard drugs.

The qualitative experiments showed that only four products, three naphthaldazines (14, 15 and 18) and a fluorenealdazine, listed on **Table 3**, exhibit significant antifungal activities. The rest of the aldazines gave commensurable zones of inhibition of maximum 10-12 mm. A comparison between the active compounds (**Table 3**) shows that inside the naphthaldazine series, 2-naphtal- dazine 18 is remarkably more active than its position isomer 1-naphthaldazine 14 against *Saccharomyces cer- evisiae* and *Penicillium chrysogenum*, while both com- pounds possess the same activity towards *Candida tropicalis*. From the other side, the position of the hydroxy substituent in 1-naphthaldazine displayed a reversed effect in respect to antibacterial tests. The pres ence of a 4-hydroxyl substituent, 14 *vs* 15, led to slight increase of the activity towards the yeast strains tested and reduced activity against the fungal strain, while 2-hydroxy derivative 16 was not active in general.

Table 3. Aldazines with antifungal activity; zone of inhibition[a] in mm.

Compound	*Candida tropicalis*	*Saccharomyces cerevisiae*	*Penicillium chrysogenum*
14[b]	20	18	18
15[b]	24	25	15
18[c]	20	30	35
20[c]	21	23	20
Fluconazol[b]	35	-	-
Itraconazole[c]	-	30	-

[a]DMSO solutions with different concentrations; indicated for each compound: [b]25 mg/ml; [c]12.5 mg/ml.

3. Conclusions

A series of 19 known and 3 new symmetrical acyclic aromatic aldazines were obtained. Their qualitative antimicrobial activities were evaluated against 10 bacterial and 3 fungal species. Eleven compounds exhibited good to moderate antibacterial activities, while only four bicyclic azines possessed significant antifungal activities. It was observed that the introduction of substituents in the phenyl ring led to loss of antibacterial activity in general, whereas none of the compounds showed significant antifungal activity. The position isomers 1-naphthaldazine and 2-naphthaldazine exhibited commensurable antibac-

terial activities, while 2-naphtaldazine was significantly more active against *Saccharomyces cerevisiae* and *Penicillium chrysogenum*. The introduction of a hydroxyl group in 1-naphthaldazine led to better inhibition against the most part of the Gram (+)-bacteria of the *ortho*-substituted compound and similar or reduced activities of *para*-hydroxy product. Contrary, the presence of a 4-hydroxy group led to slight increase of the activity towards the yeast strains tested and reduced activity against the fungal strain, whereas 2-hydroxy derivative was not active in general.

4. Experimental

4.1. General

All reagents were purchased from Aldrich, Merck and Fluka and were used without any further purification. Fluka silica gel/TLC-cards 60778 with fluorescent indicator 254 nm were used for TLC chromatography and R_f-values determination. The high performance flash chromatography (HPFC) purifications were carried out on a Biotage HorizonTM system (Charlottesville, Virginia, USA) on silica gel. The melting points were determined in capillary tubes on SRS MPA100 OptiMelt (Sunnyvale, CA, USA) automated melting point system. The NMR spectra were recorded on a Bruker Avance DRX 250 and Bruker Avance II+ 600 (where indicated) spectrometers (Rheinstetten, Germany); the chemical shifts were quoted in ppm in δ-values against tetramethylsilane (TMS) as an internal standard and the coupling constants were calculated in Hz. The chemical shifts are given with different decimals according to the accuracy (fid resolution) of the corresponding experiments. The assignment of the signals was achieved on the bases of the cross-peaks in the 2D experiments (COSY, NOESY, HSQC, HMBC). For simplicity, the carbon bearing the azine moiety is designated as C-1 in all products except 18, 20 and 21, where the nomenclature of the corresponding fused carbocycles is followed. The aldazines 11 and 19-22 are not enough soluble to record carbon spectra at room temperature in a reasonable time-scale. The ESI mass-spectra were recorded on a DFS High Resolution Magnetic Sector MS, Thermo Scientific (Waltham, MA, USA).

The reaction yields, melting points, and R_f-values of the products are listed on **Table 1**.

4.2. Preparation of Aldazines 1-16 and 18-22

To a solution of aldehyde (10 mmol) in EtOH (20 ml) and DMF (5 ml, only for the preparation of 20-22) hydrazine hydrate (5 mmol) and then a drop of conc. H_2SO_4 were added and the mixture was stirred at room temperature for 1 h. The residue formed was filtered off, washed with water and then with EtOH and was dried in air.

1,2-*Dibenzylidenehydrazine* (1). NMR ($CDCl_3$): ^{1}H 7.436 (m, 6H, C*H*-3, C*H*-4 and C*H*-5), 7.837 (dd, 4H, J 2.0, 7.8, C*H*-2 and C*H*-6), 8.661 (s, 2H, C*H* = N); ^{13}C 128.83 (C*H*-2 and C*H*-6), 129.39 (C*H*-3 and C*H*-5), 131.83 (*C*H-4), 134.27 (C_{quat}-1), 161.89 (*C*H = N).

1,2-*Bis*(4-*hydroxybenzylidene*)*hydrazine* (2). NMR ($CDCl_3$:DMSO-d_6 2:1): ^{1}H 6.79 (d, 4H, J 8.6, C*H*-3 and C*H*-5), 7.58 (d, 4H, J 8.6, C*H*-2 and C*H*-6), 8.45 (s, 2H, C*H* = N), 9.69 (bs, 2H, O*H*, exchangeable signal); ^{13}C 115.52 (*C*H-3 and *C*H-5), 125.09 (C_{quat}-1), 129.70 (*C*H-2 and *C*H-6), 159.85 (C_{quat}-4), 160.52 (*C*H = N).

1,2-*Bis*(3-*hydroxybenzylidene*)*hydrazine* (3). NMR ($CDCl_3$:DMSO-d_6 5:1): ^{1}H 6.86 (m, 2H, C*H*-5), 7.17 (m, 4H, C*H*-2 and C*H*-6), 7.24 (dd, 2H, J 1.2, 2.7, C*H*-2), 8.45 (s, 2H, C*H* = N), 9.16 (bs, 2H, O*H*, exchangeable signal); ^{13}C 114.20 (*C*H-2), 118.26 (*C*H-4), 119.49 (*C*H-6), 129.23 (*C*H-5), 134.70 (C_{quat}-1), 157.25 (C_{quat}-3), 161.15 (*C*H = N).

1,2-*Bis*(2-*hydroxybenzylidene*)*hydrazine* (4). NMR ($CDCl_3$:CF_3COOH 3:1): ^{1}H 7.18 (m, 4H, *C*H-3 and *C*H-5), 7.57 (dd, 2H, J 1.6, 8.0, C*H*-6), 7.69 (ddd, 2H, J 1.6, 7.3, 8.7, C*H*-4), 8.98 (s, 2H, C*H* = N), 11.69 (bs, O*H*, overlapped with COO*H* of CF_3COOH); ^{13}C 114.23 (C_{quat}-1), 118.03 (*C*H-3 or *C*H-5), 122.69 (*C*H-3 or *C*H-5), 136.06 (*C*H-4 or *C*H-6), 139.94 (*C*H-4 or *C*H-6), 160.49 (C_{quat}-2), 164.58 (*C*H = N); NMR (DMSO-d_6): ^{1}H 6.96 (m, 4H, *C*H-3 and *C*H-5), 7.40 (ddd, 2H, J 1.8, 7.2, 8.3, C*H*-4), 7.69 (dd, 2H, J 1.9, 8.3, C*H*-6), 9.00 (s, 2H, C*H* = N), 11.11 (bs, O*H*, exchangeable signal).

1,2-*Bis*(2-*hydroxy*-3-*methoxybenzylidene*)*hydrazine* (5). NMR ($CDCl_3$): ^{1}H 3.93 (s, 6H, OCH_3), 6.96 (m, 6H, C*H*), 8.70 (s, 2H, C*H*=N), 11.57 (bs, 2H, O*H*, exchangeable); ^{13}C 56.16 (OCH_3), 115.03 (*C*H-4), 117.29 (C_{quat}-1), 119.40 (*C*H-5), 124.01 (*C*H-6), 148.30 (C_{quat}), 149.63 (C_{quat}), 164.80 (*C*H = N); NMR (DMSO-d_6): ^{1}H 3.83 (s, 6H, OCH_3), 6.91 (t, 2H, J 7.9, C*H*-5), 7.13 (dd, 2H, J 1.4, 8.1, C*H*-4), 7.29 (dd, 2H, J 1.4, 7.9, C*H*-6), 8.98 (s, 2H, C*H* = N), 10.87 (s, 2H, O*H*); NMR (DMSO-d_6): ^{1}H 3.833 (s, 6H, OCH_3), 6.910 (t, 2H, C*H*-5), 7.127 (dd, 2H, J_{46} 1.4, J_{45} 8.1, C*H*-4), 7.288 (dd, 2H, J_{46} 1.4, J_{56} 7.9, C*H*-6), 8.985 (s, 2H, C*H* = N), 10.869 (s, 2H, O*H*).

1,2-*Bis*(4-*dimethylaminobenzylidene*)*hydrazine* (6). NMR ($CDCl_3$): ^{1}H 3.034 (s, 12H, NCH_3), 6.717 (d, 4H, J 8.9, C*H*-3 and C*H*-5), 7.699 (d, 4H, J 8.9, C*H*-2 and C*H*-6), 8.574 (s, 2H, C*H*=N); ^{13}C 40.16 (NCH_3), 111.67 (*C*H-3 and *C*H-5), 128.18 (C_{quat}-1), 129.85 (*C*H-2 and *C*H-6), 152.07 (C_{quat}-4), 160.77 (*C*H = N).

1,2-*Bis*(4-*chlorobenzylidene*)*hydrazine* (7). NMR ($CDCl_3$): ^{1}H 7.46 (ddd, 4H, J 1.8, 2.3, 8.4, C*H*-3 and C*H*-5), 7.81 (ddd, 4H, J 1.8, 2.3, 8.4, C*H*-2 and C*H*-6), 8.60 (s, 2H, C*H* = N); ^{13}C 129.15 (*C*H-2 and *C*H-6), 129.74 (*C*H-3

and *C*H-5 of Ar), 132.50 (C_{quat}-1), 137.34 (C_{quat}-4), 161.01 (*C*H = N).

1,2-*Bis*(3-*chlorobenzylidene*)*hydrazine* (8). NMR ($CDCl_3$): ^{1}H 7.46 (m, 4H, C*H*-4 and C*H*-5), 7.72 (dt, 2H, J 1.6, 7.2, C*H*-6), 7.88 (dd, 2H, J 1.6, 1.8, C*H*-2), 8.59 (s, 2H, C*H* = N); ^{13}C 126.99 (*C*H-2 or *C*H-6), 128.14 (*C*H-2 or *C*H-6), 130.06 (*C*H-4 or *C*H-5), 131.29 (*C*H-4 or *C*H-5), 135.00 (C_{quat}-1 or C_{quat}-3), 135.74 (C_{quat}-1 or C_{quat}-3), 161.06 (*C*H = N).

1,2-*Bis*(2-*chlorobenzylidene*)*hydrazine* (9). NMR ($CDCl_3$: DMSO-d_6 1:3): ^{1}H 7.43 (m, 2H, C*H*), 7.51 (m, 4H, C*H*), 8.16 (m, 2H, C*H*), 8.97 (s, 2H, C*H* = N); ^{13}C 127.21 (*C*H-5 or *C*H-6), 127.90 (*C*H-5 or *C*H-6), 129.82 (*C*H-3), 130.47 (C_{quat}-1), 132.59 (*C*H-4), 134.68 (C_{quat}-2), 160.52 (*C*H = N).

1,2-*Bis*(2,6-*dichlorobenzylidene*)*hydrazine* (10). NMR ($CDCl_3$): ^{1}H 7.28 (dd, 2H, J 7.0, 9.0, C*H*-4), 7.411 (d, 2H, J 7.0, C*H*-3 or C*H*-5, overlapped signals), 7.413 (d, 2H, J 9.0, C*H*-3 or C*H*-5, overlapped signals), 8.82 (s, 2H, C*H* = N); ^{13}C 128.94 (*C*H-3 and *C*H-5), 130.26 (C_{quat}-1), 130.96 (*C*H-4), 135.52 (C_{quat}-2 and C_{quat}-6), 157.47 (*C*H = N).

1,2-*Bis*(2,4-*dichlorobenzylidene*)*hydrazine* (11). NMR ($CDCl_3$:DMSO-d_6:CF_3COOH 3:1:0.05): ^{1}H 7.23 (dd, 2H, J 2.0, 8.6, C*H*-5), 7.36 (d, 2H, J 2.0, C*H*-3), 8.04 (d, 2H, J 8.6, C*H*-6), 8.84 (s, 2H, C*H* = N).

1,2-*Bis*(2-*chloro*-4-*fluorobenzylidene*)*hydrazine* (12). NMR ($CDCl_3$): ^{1}H 7.08 (dddd, 2H, $J_{5,CH=N}$ 0.6, $J_{3,5}$ 2.5, $J_{5,F}$ 7.8, $J_{5,6}$ 8.7, C*H*-5), 7.19 (dd, 2H, $J_{3,5}$ 2.5, $J_{5,F}$ 8.4, C*H*-3), 8.24 (dd, 2H, $J_{6,F}$ 6.3, $J_{5,6}$ 8.8, C*H*-6), 9.01 (d, 2H, $J_{5,CH=N}$ 0.6, C*H* = N); ^{13}C 114.92 (d, $J_{5,F}$ 21.7, *C*H-5), 117.34 (d, $J_{3,F}$ 24.9, *C*H-3), 127.89 (d, $J_{1,F}$ 3.6, C_{quat}-1), 129.94 (d, $J_{6,F}$ 9.2, *C*H-6), 136.79 (d, $J_{2,F}$ 10.5, C_{quat}-2), 158.10 (*C*H = N), 164.16 (d, $J_{4,F}$ 255.9, C_{quat}-4); MS (ESI^+) m/z 313 (M^+), $C_{14}H_8Cl_2F_2N_2$.

1,2-*Bis*(3-*fluorobenzylidene*)*hydrazine* (13). NMR ($CDCl_3$): ^{1}H 7.20 (dddd, 2H, $J_{4,6}$ 1.1, $J_{4,2}$ 2.6, $J_{4,5}$ 8.3, $J_{4,F}$ 9.3, C*H*-4), 7.46 (ddd, 2H, $J_{5,6}$ 6.8, $J_{4,5}$ 8.3, $J_{5,F}$ 13.7, C*H*-5), 7.57 (dt, 2H, $J_{4,6}$ 1.1, $J_{2,6}$ 1.4, $J_{5,6}$ 6.8, C*H*-6), 7.61 (dd, 2H, $J_{2,6}$ 1.4, $J_{2,4}$ 2.6, $J_{2,F}$ 9.2, C*H*-2), 8.61 (d, 2H, $J_{CH=N,F}$ 1.1, C*H* = N); ^{13}C 114.55 (d, $J_{2,F}$ 22.5, *C*H-2), 118.31 (d, $J_{4,F}$ 21.6, *C*H-4), 124.86 (d, $J_{6,F}$ 2.9, *C*H-6), 130.37 (d, $J_{5,F}$ 8.1, *C*H-5), 136.24 (d, $J_{1,F}$ 7.6, C_{quat}-1), 161.16 (d, $J_{CH=N,F}$ 3.1, *C*H = N), 163.02 (d, $J_{3,F}$ 246.9, C_{quat}-3).

1,2-*Bis*(*naphthalen*-1-*ylmethylene*)*hydrazine* (14). NMR (600 MHz, DMSO-d_6): ^{1}H 7.661 (ddd, 2H, J_{79} 1.1, J_{78} 6.8, J_{67} 8.0, C*H*-7), 7.691 (dd, 2H, J_{23} 7.3, J_{34} 8.1, C*H*-3), 7.725 (ddd, 2H, J_{68} 1.3, J_{78} 6.8, J_{89} 8.4, C*H*-8), 8.076 (d, 2H, J_{67} 8.0, C*H*-6), 8.147 (d, 2H, J_{34} 8.1, C*H*-4), 8.194 (dd, 2H, J_{24} 0.7, J_{23} 7.3, C*H*-2), 9.212 (d, 2H, J_{89} 8.4, C*H*-9), 9.459 (s, 2H, C*H*=N); ^{13}C 125.09 (*C*H-9), 125.56 (*C*H-3), 126.46 (*C*H-7), 127.62 (*C*H-8), 128.79 (*C*H-6), 129.17 (C_{quat}-5), 130.42 (*C*H-2), 130.63 (C_{quat}-10), 131.96 (*C*H-4), 133.55 (C_{quat}-1), 162.02 (*C*H=N).

1,2-*Bis*((4-*hydroxynaphthalen*-1-*yl*)*methylene*)*hydrazine* (15). NMR (DMSO-d_6): ^{1}H 7.03 (d, 2H, J 8.0, C*H*-3), 7.58 (ddd, 2H, J 1.1, 6.8, 8.2, C*H*-8), 7.70 (ddd, 2H, J 1.5, 6.8, 8.4, C*H*-7), 7. 97 (d, 2H, J 8.2, C*H*-2), 8.30 (dd, 2H, J 1.1, 8.2, C*H*-9), 9.25 (s, 2H, C*H* = N), 9.30 (d, 2H, J 8.4, C*H*-6), 10.96 (bs, O*H*); ^{13}C 108.54 (*C*H-3), 120.87 (C_{quat}-1), 123.11 (*C*H-9), 125.25 (C_{quat}-5), 125.64 (*C*H-6), 125.82 (*C*H-8), 128.33 (*C*H-7), 132.67 (C_{quat}-10), 133.38 (*C*H-2), 157.16 (C_{quat}-4), 162.00 (*C*H = N).

1,2-*Bis*((2-*hydroxynaphthalen*-1-*yl*)*methylene*)*hydrazine* (16). NMR ($CDCl_3$:CF_3COOH 3:1): ^{1}H 7.30 (d, 2H, J 9.0, C*H*-3), 7.50 (dd, 2H, J 7.1, 8.1, C*H*-7), 7.68 (ddd, 2H, J 1.2, 7.1, 8.5, C*H*-6), 7.81 (d, 2H, J 8.1, C*H*-8), 8.07 (d, 2H, J 9.0, C*H*-4), 8.23 (d, 2H, J 8.5, C*H*-5), 9.70 (s, 2H, C*H* = N), 11.08 (bs, O*H*, overlapped with COO*H* of CF_3COOH); ^{13}C 106.43 (C_{quat}-1), 118.08 (*C*H), 120.11 (*C*H), 126.13 (*C*H), 128.98 (C_{quat}), 130.27 (*C*H), 130.69 (*C*H), 132.79 (C_{quat}), 141.76 (*C*H), 157.90 (*C*H = N), 163.29 (C_{quat}-2).

1,2-*Bis*(*naphthalen*-2-*ylmethylene*)*hydrazine* (18). NMR (600 MHz, DMSO-d_6, 70˚C): ^{1}H 7.634 (m, 4H, C*H*-7 and C*H*-8), 8.012 (d, 2H, J_{67} 7.2, C*H*-6), 8.054 (m, 4H, C*H*-4 and C*H*-9), 8.162 (dd, 2H, J_{13} 1.3, J_{34} 8.5, C*H*-3), 8.395 (s, 2H, C*H*-1), 8.938 (s, 2H, C*H* = N); ^{13}C 123.99 (*C*H-3), 127.31 (*C*H-6), 128.10 (*C*H-7), 128.29 (*C*H-8), 129.00 (*C*H-9), 129.08 (*C*H-4), 131.04 (*C*H-1), 132.15 (C_{quat}-5), 133.33 (C_{quat}-10), 134.93 (C_{quat}-2), 161.48 (*C*H = N).

1,2-*Bis*(*biphenyl*-4-*ylmethylene*)*hydrazine* (19). NMR ($CDCl_3$:DMSO-d_6:CF_3COOH 1:1:0.1): ^{1}H 7.33 (m, 6H, C*H*), 7.54 (dt, 4H, J 1.5, 7.0, C*H*), 7.60 (dt, 4H, J 1.7, 8.4, C*H*), 7.82 (dt, 4H, J 1.7, 8.4, C*H*), 8.59 (s, 2H, C*H* = N).

1,2-*Bis*((9*H*-*fluoren*-2-*yl*)*methylene*)*hydrazine* (20). NMR (600 MHz, DMSO-d_6, 70˚C): ^{1}H 4.035 (s, 4H, CH_2), 7.391 (td, 2H, J 1.2, 7.3, C*H*-7), 7.440 (td, 2H, J 1.0, 7.3, C*H*-6), 7.647 (dt, 2H, J 0.9, 7.3, C*H*-8), 7.928 (dd, 2H, J 0.9, 7.9, C*H*-3), 7.974 (dd, 2H, J 1.0, 7.3, C*H*-5), 8.021 (d, 2H, J 7.9, C*H*-4), 8.126 (s, 2H, C*H*-1), 8.782 (s, 2H, C*H* = N); MS (ESI^+) m/z 385 (M^+), $C_{28}H_{20}N_2$.

1,2-*Bis*(*phenanthren*-9-*ylmethylene*)*hydrazine* (21). NMR (DMSO-d_6): ^{1}H 7.82 (m, 4H, C*H*), 8.17 (d, 2H, J 7.4, C*H*), 8.57 (s, 2H, C*H*-10), 8.93 (d, 2H, J 7.7, C*H*), 8.99 (m, 2H, C*H*), 9.38 (m, 2H, C*H*), 9.50 (s, 2H, C*H* = N).

1,2-*Bis*(*pyren*-1-*ylmethylene*)*hydrazine* (22). NMR (600 MHz, DMSO-d_6): ^{1}H 8.076 (t, 2H, J 7.6, C*H*-7), 8.161 (m, 4H, C*H*), 8.245 (m, 4H, C*H*), 8.291 (m, 4H, C*H*), 8.396 (d, 2H, J 8.1, C*H*), 8.708 (d, 2H, J 9.4, C*H*), 8.782 (s, 2H, C*H* = N).

4.3. Preparation of 1,2-bis((4-hydroxy-3-(morpholinomethyl) naphthalen-1-yl)methylene)hydrazine (17)

To a solution of 15 (1 mmol) in benzene (20 ml) mor-

pholine (2.1 mmol), paraformaldehyde (2.2 mmol), and *p*-toluenesulfonic acid (10 mg) were added and the mixture was refluxed with stirring for 4 h. The products were partitioned between aq. K_2CO_3 and CH_2Cl_2. The organic layer was washed with water, dried over Na_2SO_4, evaporated to dryness, and purified by HPFC on silica gel; mobile phase with a gradient of polarity from hexane:EtOAc:Et_3N 50:50:0.5 to EtOAc:Et_3N 100:1; NMR (DMSO-d_6:CF_3COOH 5:1): ^{1}H 3.264 (bm, 4H, C*H*$_2$-N morpholine), 3.387 (bm, 4H, C*H*$_2$-N morpholine), 3.706 (bm, 4H, C*H*$_2$-O morpholine), 3.922 (bm, 4H, C*H*$_2$-O morpholine), 4.583 (s, 4H, Ar- C*H*$_2$-N), 7.604 (ddd, 2H, J 1.1, 6.9, 8.4, C*H*-7 or C*H*-8), 7.703 (ddd, 2H, J 1.3, 6.9, 8.5, C*H*-7 or C*H*-8), 8.121 (s, 2H, C*H*-2), 8.467 (dd, 2H, J 1.1, 8.5, C*H*-6 or C*H*-9), 9.132 (dd, 2H, J 1.2, 8.4, C*H*-6 or C*H*-9), 9.273 (s, 2H, C*H* = N), 9.928 (bs, 2H, O*H*, exchangeable signal); ^{13}C 52.04 (*C*H$_2$-N morpholine), 55.76 (Ar-*C*H$_2$-N), 64.06 (*C*H$_2$-O morpholine), 110.83 (*C*$_{quat}$), 121.96 (*C*$_{quat}$), 124.25 (*C*H), 125.80 (*C*H), 126.20 (*C*$_{quat}$), 126.70 (*C*H), 129.51 (*C*H), 133.69 (*C*$_{quat}$), 135.59 (*C*H), 157.46 (*C*$_{quat}$-4), 161.50 (*C*H = N); MS (ESI$^+$) m/z 539 (M^+), $C_{32}H_{34}N_4O_4$.

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