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Synthesis and antifungal activity of 1*H*-indole-4,7-diones

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Abstract—1*H*-Indole-4,7-diones were synthesized and tested for in vitro antifungal activity against fungi. The synthesized 1*H*-indole-4,7-diones generally showed good antifungal activity against *Candida krusei*, *Cryptococcus neoformans*, and *Aspergillus niger*. The results suggest that 1*H*-indole-4,7-diones would be potent antifungal agents.

Heterocyclic quinone compounds represent an important class of biologically active molecules.[1] The quinones such as 5-*n*-undecyl-6-hydroxy-4,7-dioxobenzothiazole (UHDBT, **1**) blockade a mitochondrial electron transport in *Saccharomyces cerevisiae*.[2] The UHDBT (**1**) has been reported as inhibitors of mitochondrial cytochrome complex in yeast[3] and bacteria.[4] In our previous report, [5] 4,7-dioxobenzothiazoles **2** which could be analogues of UHDBT have demonstrated potent antifungal activity against pathogenic fungi (Fig. 1).

A variety of heterocyclic quinones with different substituents could exhibit the biological activities through different action and sometimes improve upon the activities. The presence of thio, amino, halo, and alkyl substituents of quinones was considerably important factor to affect their antifungal activity.[5] Based on this speculation, we further extended to synthesize 1*H*-indole-4,7-dione derivatives **3** and **4** which would be bioisosteres of quinones **2**, and evaluated their antifungal activity.

There have been many reports on 1*H*-indole-4,7-diones, exhibiting cytotoxic activities[6–10] against cancer cell lines, and antibacterial activity.[11] However, the inhibitory activity of compounds **3** and **4** on the antifungal properties has not been reported to the best of our knowledge. Therefore, the 1*H*-indole-4,7-diones **3** and **4** with various substituents were designed and synthesized to elucidate their contribution to the antifungal activity. The in vitro antifungal activity of compounds **3** and **4** against pathogenic fungi was determined by the 2-fold broth dilution method.

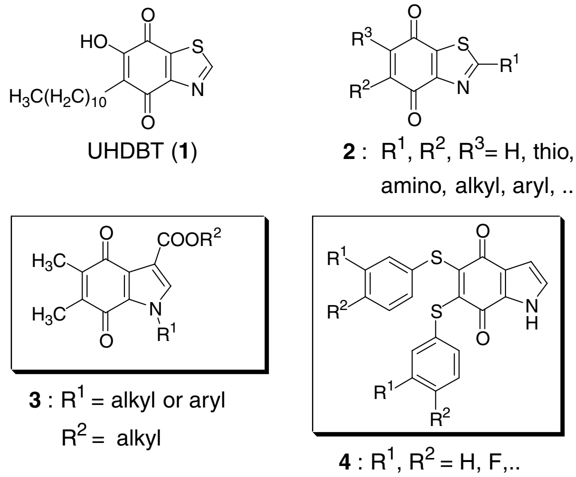

Figure 1. 1*H*-Indole-4,7-dione derivatives.

A method for the synthesis of 1*H*-indole-4,7-diones **3a**–**m** (Table 1) is shown in (Scheme 1). 2,3-Dichloro-5,6-dimethylcyclohexa-2,5-diene-1,4-dione (**5**) was prepared by oxidizing 2,3-dimethylbenzene-1,4-diol with HNO_3/HCl according to known method.[12] Methyl or ethyl 2-(2-chloro-4,5-dimethyl-3,6-dioxocyclohexa-1,4-dienyl)-2-cyanoacetate (**6a** or **6b**) was synthesized by nucleophilic substitution of compound **5** with equivalent of methyl or ethyl cyanoacetate in EtOH in the presence of NH_4OH. When equivalent amounts of compound **6a** and appropriate arylamines were mixed in EtOH and refluxed for 5 h, compounds **3c**–**m** were formed. In

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Keywords: 1*H*-Indole-4,7-dione; Antimicrobial compounds; Antifungal; Fungi; Substitution effects.

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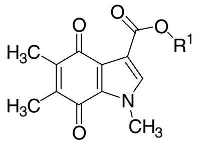
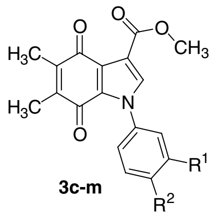
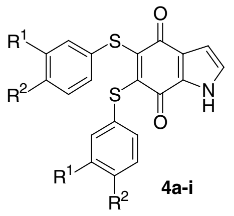
Table 1. Structures and in vitro antifungal activity for 1*H*-indole-4,7-diones



3a-b

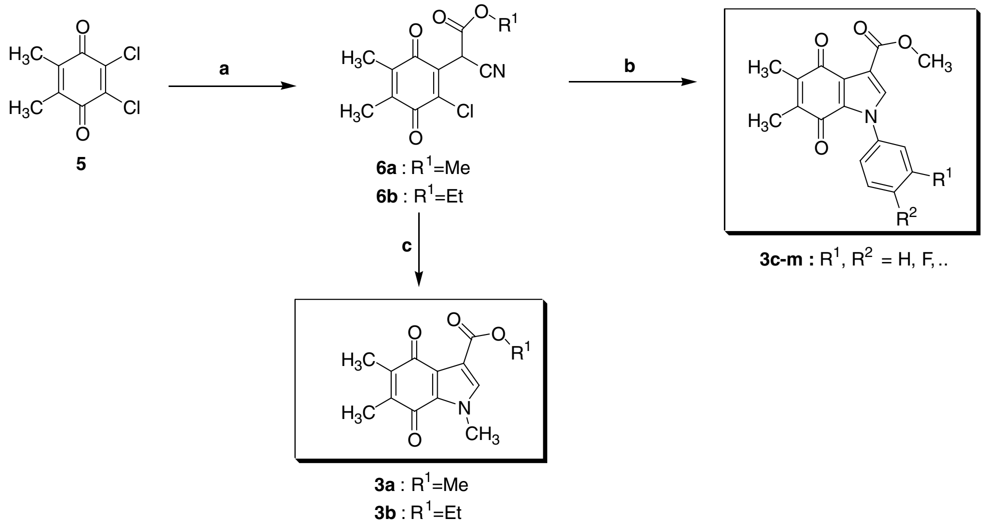




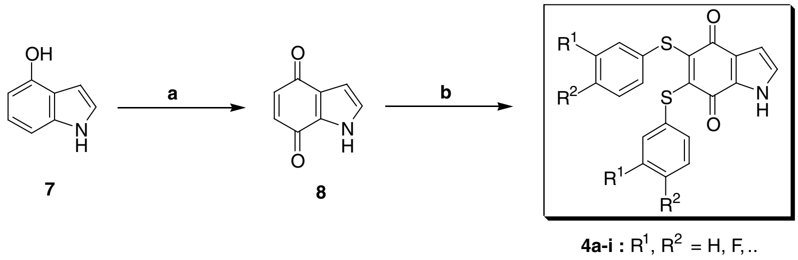
Compound	R^1	R^2	MIC[a] (μg/mL)				
			Candida albicans[b]	*Candida tropicalis*	*Candida krusei*	*Cryptococcus neoformans*	*Aspergillus niger*
3a	CH_3	—	>100	>100	3.2	1.6	>100
3b	CH_3CH_2	—	>100	25	50	100	>100
3c	H	H	3.2	12.5	1.6	6.3	25
3d	H	F	>100	>100	3.2	3.2	12.5
3e	H	Cl	12.5	12.5	0.8	12.5	25
3f	H	Br	50	6.3	50	50	3.2
3g	H	I	25	12.5	50	50	100
3h	H	CH_3	>100	>100	3.2	0.8	>100
3i	H	CH_3O	>100	50	3.2	100	>100
3j	CH_3	CH_3	12.5	>100	0.8	1.6	6.3
3k	H	CF_3O	>100	>100	6.3	1.6	3.2
3l	H	CH_3CH_2	25	50	50	50	3.2
3m	H	$(CH_3)_2CH$	12.5	12.5	100	100	3.2
4a	H	H	>100	>100	>100	12.5	50
4b	H	F	100	25	3.2	6.3	100
4c	H	Cl	>100	12.5	25	3.2	>100
4d	H	Br	>100	>100	>100	3.2	12.5
4e	CH_3	H	>100	12.5	>100	3.2	50
4f	CH_3	CH_3	>100	>100	>100	50	100
4g	F	F	>100	>100	12.5	50	>100
4h	Cl	H	6.3	1.6	25	3.2	25
4i	H	OH	50	50	>100	25	>100
6a	—	—	>100	>100	100	6.3	>100
6b	—	—	>100	>100	100	25	>100
5-Fluorocytosine			6.3	12.5	6.3	12.5	50

[a] The MIC value was defined as the lowest concentration of the antifungal agent. MIC values were read after 1 day for *Candida* species and *Cryptococcus neoformans*, and 2 days for *Aspergillus niger* in 37 °C. The inoculum sizes contained approximately 1×10^5 cells/mL. Culture media tested were the modified Sabouraud dextrose broth (Difco Lab.). The final concentration of antifungal agents was between 0.2 and 100 μg/mL.

[b] Fungi tested: *Candida albicans* Berkout KCCM 50235, *Candida tropicalis* Berkout KCCM 50662, *Candida krusei* Berkout KCCM 11655, *Cryptococcus neoformans* KCCM 50564 and *Aspergillus niger* KCTC 1231.



Scheme 1. Synthesis of 1*H*-indole-4,7-diones. Reagents and conditions: (a) methyl cyanoacetate or ethyl cyanoacetate/EtOH/NH_4OH/rt/10 min; (b) **6a**/arylamine/EtOH/reflux/5 h; (c) **6a** or **6b**/methylamine/EtOH/reflux/5 h.



Scheme 2. Synthesis of 5,6-bis(arylthio)-1*H*-indole-4,7-diones. Reagents and conditions: (a) Fremy's salt (2 equiv) in 0.3 M KH_2PO_4/EtOH/rt; (b) arylthiol (2 equiv)/EtOH/reflux/5 h.

similar manner, compounds **3a–b** were prepared by cyclization of compound **6a** or **6b** with methylamine in EtOH. Experimental details and data for this procedure are cited in the References and Notes.[13–17]

A convenient method for the synthesis of 5,6-bis(arylthio)-1*H*-indole-4,7-diones **4a–i** (Table 1) is shown in (Scheme 2). The preparation of 1*H*-indole-4,7-dione (**8**) by oxidation of 1*H*-indol-4-ol (**7**) was carried out with Fremy's salt (potassium nitrosodisulfonate) in 59% yield. The compounds **4a–i** were synthesized by nucleophilic substitution of the compound **8** with appropriate arylthiols. Most of these substitutions went as expected and had overall high yields of 72–91%.

The synthesized 1*H*-indole-4,7-diones **3a–m**, **4a–i**, and cyclohexa-2,5-diene-1,4-diones **6a–b** were tested in vitro for their growth inhibitory activity against pathogenic fungi by the standard method.[18] The MIC (minimum inhibitory concentration) values were determined by comparison with 5-fluorocytosine as a standard agent.[18] As indicated in Table 1, most of synthesized 1*H*-indole-4,7-diones **3a–m** generally showed potent antifungal activity against *Candida krusei*, *Cryptococcus neoformans*, and *Aspergillus niger*. The antifungal activity against *C. neoformans* was prominent. In contrast, compounds **3a–m** did not show significant antifungal activity against *C. albicans* and *C. tropicalis*, although compounds **3c**, **3e**, and **3m** exhibited good activity.

Many of 5,6-bis(arylthio)-1*H*-indole-4,7-diones **4a–i** also showed potent antifungal activity against *C. krusei*, *C. neoformans*, and *A. niger*. Actually, the activity of compounds **3c**, **3e**, and **4h** was superior or comparable to those of 5-fluorocytosine against all tested fungi. The compounds **3c**, **3e**, and **4h** completely inhibited the growth of all fungal species tested at the MIC level of 1.6–25 μg/mL.

In terms of structure–activity relationship, the 4,7-dihydro-5,6-dimethyl-4,7-dioxo-1*H*-indole-3-carboxylates **3** showed, in general, a more potent antifungal activity than the other 5,6-bis(arylthio)-1*H*-indole-4,7-diones **4**. The 1-aryl-compounds **3** exhibited good activity, indicating a correlation that may offer insight into the mode of action of these compounds. The halogen-moieties of substituents (R^1, R^2: H, F, Cl, ...) for the 1-aryl and 5,6-bis(arylthio) moieties of compounds **3c–m** and **4a–i** appear to contribute partially toward biological potency.

In addition, alkyl 2-(2-chloro-4,5-dimethyl-3,6-dioxocyclohexa-1,4-dienyl)-2-cyanoacetates (**6a** and **6b**) exhibited no or poor, if any, antifungal activity. The 1*H*-indole-4,7-diones **3a–m** and **4a–i** showed, in general, more potent antifungal activity than cyclohexa-2,5-diene-1,4-diones **6a–b**. Thus, 1*H*-indole-4,7-dione moiety appears to partially contribute to antifungal potency.

In conclusion, alkyl 2-(2-chloro-4,5-dimethyl-3,6-dioxocyclohexa-1,4-dienyl)-2-cyanoacetates **6a** and **6b** were synthesized by nucleophilic substitution of 2,3-dichloro-5,6-dimethylcyclohexa-2,5-diene-1,4-dione (**5**) with equivalent of alkyl cyanoacetates in the presence of NH_4OH. 1*H*-Indole-4,7-dione derivatives **3a–m** were synthesized by cyclization of compound **6a** or **6b** with appropriate amines. The 5,6-bis(arylthio)-1*H*-indole-4,7-diones **4a–i** were synthesized by nucleophilic substitution of 1*H*-indole-4,7-dione (**8**) with appropriate arylthiols in overall high yields. Among them tested, many of 1*H*-indole-4,7-dione derivatives **3a–m** and **4a–i** showed potent antifungal activity against *C. krusei*, *C. neoformans*, and *A. niger*. These 1*H*-indole-4,7-diones may thus be a promising lead for the development of antifungal agents. Moreover, the results should encourage the synthesis of 1*H*-indole-4,7-diones analogs for improving antifungal properties.

Acknowledgment

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13. *Experimental*: All melting points were measured with Büchi melting point B-545 and are uncorrected. ^1H NMR spectra were recorded on Varian Unity INOVA 400 MHz FT-NMR spectrometer using DMSO-d_6 or $CDCl_3$ with TMS. Mass spectra were taken with Jeol JMS AX505 WA. 2,3-Dimethylbenzene-1,4-diol and other reagents were purchased from Aldrich Chemical Co. The 2,3-dichloro-5,6-dimethylcyclohexa-2,5-diene-1,4-dione (**5**) was prepared by oxidizing 2,3-dimethylbenzene-1,4-diol with HNO_3/HCl variation according to known method.[12]
14. *Synthesis of alkyl 2-(2-chloro-4,5-dimethyl-3,6-dioxocyclohexa-1,4-dienyl)-2-cyanoacetates* (**6a** and **6b**): To a solution of compound **5** (1.295 g, 2.66 mmol) and methyl cyanoacetate or ethyl cyanoacetate (2.66 mmol) in 100 mL EtOH, NH_4OH solution (2 mL) was added dropwise. The mixture was stirred at rt for 10 min, d-HCl was then added. The mixture was then extracted several times with CH_2Cl_2, and the organic layer was washed with water, dried with anhydrous $MgSO_4$, and concentrated. The product **6a** or **6b** was separated by silica gel column chromatography with *n*-hexane/EtOAc. *Methyl 2-(2-chloro-4,5-dimethyl-3,6-dioxocyclohexa-1,4-dienyl)-2-cyanoacetate* (**6a**): brown oil (31%); ^1H NMR ($CDCl_3$) δ 2.01 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 5.25 (s, 1H, CH). MS (*m*/*z*) 267 (M^+).
15. *General procedure for synthesis of 4,7-dihydro-5,6-dimethyl-4,7-dioxo-1H-indole-3-carboxylates* (**3a** and **3b**): Equivalent weight of methylamine was added to the solution of compounds **6a** or **6b** 300 mg in 100 mL 95% EtOH and heated under reflux for 1 h. The products **3a** and **3b** were purified by silica gel column chromatography and crystallized from 95% EtOH (Table 1). Compound **3a**: dark violet powder (55%); mp 233–234 °C; ^1H NMR ($CDCl_3$) δ 2.01 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 3.82 (s, 3H, CH_3O), 3.91 (s, 3H, CH_3), 5.61 (s, 1H, pyrrole); MS (*m*/*z*) 263 (M^+); compound **3b**: dark violet powder (42%); mp 113–115 °C; ^1H NMR δ 1.26 (t, 3H, CH_3), 2.00 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 3.79 (s, 3H, CH_3), 4.36 (q, 2H, CH_2), 5.61 (s, 1H, pyrrole); MS (*m*/*z*) 276 (M^+).
16. *General procedure for synthesis of 4,7-dihydro-5,6-dimethyl-4,7-dioxo-1-aryl-1H-indole-3-carboxylates* (**3c**–**m**): Equivalent weight of arylamine was added to the solution of compound **6a** 300 mg in 100 mL 95% EtOH and heated under reflux for 1 h. The products **3c**–**m** were purified by silica gel column chromatography and crystallized from 95% EtOH. Compound **3c**: dark violet powder (55%); mp 253–254 °C; ^1H NMR($CDCl_3$) δ 2.07 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 3.89 (s, 3H, CH_3O), 7.00 (d, 1H, Ph), 7.18 (td, 1H, Ph), 7.35 (td, 1H, Ph), 7.59 (m, 2H, Ph), 7.66 (s, 1H, pyrrole); MS (*m*/*z*) 324 (M^+); compound **3d**: dark violet powder (60%); mp 227–228 °C; ^1H NMR δ 2.08 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 3.91 (s, 3H, CH_3O), 7.00 (q, 1H, Ph), 7.10 (m, 1H, Ph), 7.30 (m, 1H, Ph), 7.39 (q, 1H, Ph), 7.64 (s, 1H, pyrrole); MS (*m*/*z*) 342 (M^+); compound **3e**: dark purple powder (43%); mp 212 °C (dec); ^1H NMR δ 2.08 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 3.91 (s, 3H, CH_3O), 6.95 (q, 1H, Ph), 7.26 (m, 1H, Ph), 7.32 (m, 1H, Ph), 7.59 (s, 2H, Ph), 7.65 (s, 1H, pyrrole); MS (*m*/*z*) 358 (M^+); compound **3f**: purple powder (38%); mp 237–238 °C; ^1H NMR δ 2.08 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 3.91 (s, 3H, CH_3O), 6.89 (q, 1H, Ph), 7.26 (m, 1H, Ph), 7.46 (m, 2H, Ph), 7.59 (s, 1H, pyrrole), 7.79 (q, 1H, Ph); MS (*m*/*z*) 402 (M^+); compound **3g**: purple powder (58%); mp 229–230 °C; ^1H NMR δ 2.07 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 3.91 (s, 3H, CH_3O), 6.75 (q, 1H, Ph), 7.26 (m, 1H, Ph), 7.57 (s, 1H, pyrrole), 7.64 (m, 2H, Ph), 7.96 (m, 1H, Ph); MS (*m*/*z*) 450 (M^+); compound **3h**: dark violet powder (65%); mp 220–221 °C; ^1H NMR δ 2.05 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.90 (s, 3H, CH_3O), 6.90 (d, 1H, Ph), 7.12 (m, 2H, Ph), 7.43 (t, 1H, Ph), 7.65 (s, 1H, pyrrole); MS (*m*/*z*) 323 (M^+); compound **3i**: dark violet powder (83%); mp 214 °C (dec); ^1H NMR δ 2.06 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 3.82 (s, 3H, CH_3O), 3.89 (s, 3H, CH_3O), 6.91 (dd, 1H, Ph), 6.96 (d, 1H, Ph), 7.14 (d, 1H, Ph), 7.59 (s, 1H, pyrrole); MS (*m*/*z*) 354 (M^+); compound **3j:** dark violet powder (91%); mp 232–233 °C; ^1H NMR δ 2.03 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.24 (s, 6H, CH_3), 3.87 (s, 3H, CH_3O), 6.78 (s, 1H Ph), 7.37 (s, 2H, Ph), 7.52 (s, 1H, pyrrole); MS (*m*/*z*) 352 (M^+); compound **3k**: dark violet powder (55%); mp 183–184 °C; ^1H NMR δ 2.10(s, 3H, CH_3), 2.12 (s, 3H, CH_3), 3.91 (s, 3H, CH_3O), 7.04 (d, 1H, Ph), 7.2 5 (m, 2H, Ph), 7.54 (d, 1H, Ph), 7.65 (s, 1H, pyrrole); MS (*m*/*z*) 408 (M^+); compound **3l**: dark violet powder (70%); mp 209–210 °C; ^1H NMR δ 1.22 (t, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.64 (q, 2H, CH_2), 3.88 (s, 3H, CH_3O), 6.92 (q, 1H, Ph), 7.14 (m, 1H, Ph), 7.26 (m, 1H, Ph), 7.46 (m, 2H, Ph), 7.56 (s, 1H, pyrrole); MS (*m*/*z*) 352 (M^+); compound **3m**: dark violet powder (73%); mp 203–204 °C; ^1H NMR δ 1.23 (d, 6H, CH_3), 2.07 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.32 (sept, 1H, CH), 3.86 (s, 3H, CH_3O), 6.93 (m, 1H, Ph), 7.22 (m, 1H, Ph), 7.26 (m, 1H, Ph), 7.48 (m, 2H, Ph), 7.56 (s, 1H, pyrrole): MS (*m*/*z*) 366 (M^+).
17. *General procedure for synthesis of 5,6-bis(arylthio)-1H-indole-4,7-diones* **4a**–**i**: To a solution of 1*H*-indol-4-ol (**7**) (0.2 g, 1.5 mmol) in 15 EtOH/KH_2PO_4 was added a solution of potassium nitrosodisulfonate (1.5 g, 5.60 mmol) in the KH_2PO_4 buffer (0.3 M, 200 mL). The mixture was stirred at rt for 5 h and was extracted twice with $CHCl_3$. The extract was evaporated and purified by column chromatography with $CHCl_3$. *1H-Indole-4,7-dione* (**8**) was obtained: dark orange powder (23%); mp 174–175 °C; ^1H NMR (DMSO-d_6), δ 5.75 (s, 1H, NH), 6.53 (d, 1H, $J = 7.1$, pyrrole), 6.63 (s, 2H, quinone), 7.25 (s, 1H, $J = 7.1$, pyrrole); MS (*m*/*z*) 147 (M^+). A solution of compound **8** (0.147 g, 1 mmol) in 20 mL of 95% EtOH was added to a solution of the arylthiol (2.1 mmol) in 10 mL of 95% EtOH and then refluxed for 5 h. After the reaction mixture was kept overnight, the precipitate was collected by the filtration. The crude product was purified by silica gel column chromatography with $CHCl_3$ or crystallized from 95% EtOH. Crystallization from aq. EtOH afforded 5,6-bis(arylthio)-1*H*-indole-4,7-diones **4a**–**i**. Compound **4a**: red needle (71%); mp 235–236 °C; ^1H NMR (DMSO-d_6), δ 6.52 (d, 1H, pyrrole), 7.22 (s, 1H, pyrrole), 7.24–7.36 (m, 10H, Ph), 12.70 (s, 1H, NH); MS (*m*/*z*) 363 (M^+); compound **4b**: red needle (45%); mp 217–218 °C; ^1H NMR δ 6.51 (d, 1H, pyrrole), 7.23 (d, 1H, pyrrole), 7.17 (q, 4H, Ph), 7.45 (m, 4H, Ph), 12.64 (s, 1H, NH); MS (*m*/*z*)

399 (M^+); compound **4c**: black powder (60%); mp 215–216 °C; ^1H NMR δ 6.53 (d, 1H, pyrrole), 7.26 (s, 1H, pyrrole), 7.35–7.48 (m, 8H, Ph), 12.82 (s, 1H, NH); MS (*m*/*z*) 431 (M^+); compound **4d**: dark brown powder (61%); mp 215–217 °C; ^1H NMR δ 6.53 (d, 1H, pyrrole), 7.26 (s, 1H, pyrrole), 7.35 (q, 4H, Ph), 7.49 (d, 4H, Ph), 12.61 (s, 1H, NH); MS (*m*/*z*) 519 (M^+); compound **4e**: red powder (58%); mp 195–197 °C; ^1H NMR δ 2.26 (s, 3H, CH_3) 6.51 (d, 1H, pyrrole), 7.25 (d, 1H, pyrrole), 7.05 (m, 2H, Ph), 7.17 (m, 6H, Ph); MS (*m*/*z*) 392 (M^+); compound **4f**: red powder (66%); mp 211–212 °C; ^1H NMR δ 2.21 (s, 12H, CH_3), 6.48 (d, 1H, pyrrole), 7.07 (d, 4H, Ph), 7.15 (d, 2H, Ph), 7.21 (d, 1H, pyrrole), 12.71 (s, 1H, NH); MS (*m*/*z*) 419 (M^+); compound **4g**: dark red crystal (71%); mp 195–196 °C; ^1H NMR δ 6.55 (d, 1H, pyrrole), 7.26 (d, 1H, pyrrole), 7.35 (m, 4H, Ph), 7.65 (m, 2H, Ph), 12.64 (s, 1H, NH); MS (*m*/*z*) 435 (M^+); compound **4h**: red powder (42%); mp 188–189 °C; ^1H NMR δ 6.56 (d, 1H, pyrrole), 7.27 (d, 1H, pyrrole), 7.33 (m, 6H, Ph), 7.52 (d, 2H, Ph), 12.62(s, 1H, NH); MS (*m*/*z*) 431 (M^+); compound **4i:** dark brown powder (50%); mp 241.0–241.5 °C; ^1H NMR δ 6.45 (d, 1H, pyrrole), 6.71 (m, 4H, Ph), 7.21 (m, 4H, Ph), 7.22 (d, 1H, pyrrole), 9.66 (s, 2H, OH), 12.69 (s, 1H, NH); MS (*m*/*z*) 395 (M^+).

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