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Synthesis and antifungal evaluation of 6-hydroxy-1*H*-carbazole-1,4(9*H*)-diones

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ABSTRACT

6-Hydroxy-1*H*-carbazole-1,4(9*H*)-diones were synthesized and tested for in vitro antifungal activity against two pathogenic strains of fungi. Among them tested, many compounds showed good antifungal activity. The results suggest that 6-hydroxy-1*H*-carbazole-1,4(9*H*)-diones would be potent antifungal agents.

Heterocyclic quinone compounds represent an important class of biologically active molecules.[1] 4,7-Dioxobenzothiazole derivative, a heterocyclic quinone, inhibits cytochrome B-complex by the blockade of mitochondrial electron transport in *Saccaromyces cerevisiae*, which is different from commonly used antifungal drugs.[2] UHDBT as a 4,7-dioxobenzothiazole has been reported as an inhibitor of mitochondrial cytochrome complex in yeast[3] and bacteria.[4] In our previous Letters[5–8], heterocyclic quinone compounds such as arylamino- or arylthio-4,7-dioxobenzothiazoles,[5] benzo[*d*]oxazole-4,7-diones,[6] 4,7-benzimidazolediones,[7] 7-dioxobenzo[*b*]thiophenes[8] **1**, and bis(arylthio)-benzo[*d*]oxazole-4,7-diones[6] **2** have demonstrated potent antifungal activity against pathogenic fungi (Fig. 1).

Structure–activity relationship studies from quinonoid compounds indicated that the ring number and the position of nitrogen atoms substituted in the heterocyclic ring were considerably important factors to affect the biological activities.[9–11]

We speculated that incorporation of a nitrogen atom into the ring of the quinone skeleton would change the physicochemical properties and lead to a new pharmacophore with a different biological profile from quinone compounds **1** and **2**. The presence of arylamino, arylthio, or alkyl moiety to the quinones was considerably an important factor to affect their antifungal activity.[10,11]

Based on this speculation, 3-arylamino-6-hydroxy-1*H*-carbazole-1,4(9*H*)-diones **3**, 3-arylthio-6-hydroxy-1*H*-carbazole-1,4-(9*H*)-diones **4**, and 3,4-bis(arylthio)-6-hydroxy-1*H*-carbazole-1,4(9*H*)-diones **5** which would be analogs of quinones **1** and **2**, were synthesized and evaluated for their antifungal activity (Fig. 1). There have been a few Letters[12] on 1*H*-carbazole-1,4(9*H*)-diones that exhibit inhibitors of *Toxoplasma gondii* purine nucleoside

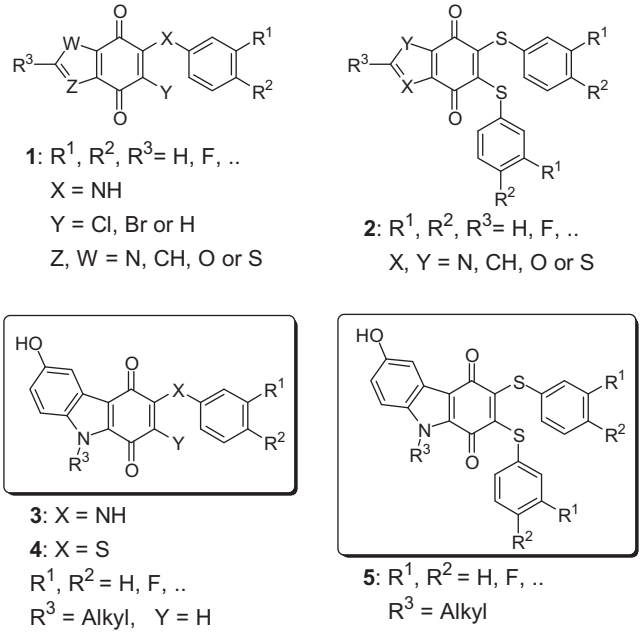

Figure 1. Antifungal heterocyclic quinone compounds and 6-hydroxy-1*H*-carbazole-1,4(9*H*)-dione derivatives.

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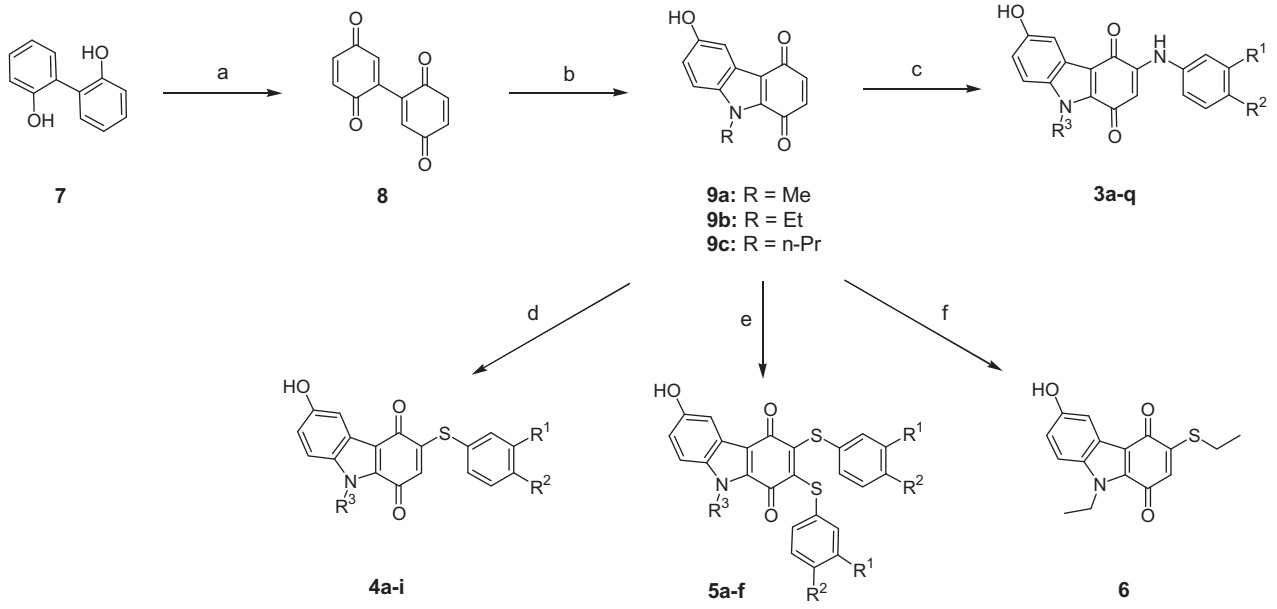


Scheme 1. Synthesis of 1*H*-carbazole-1,4(9*H*)-dione derivatives. Reagents and conditions: (a) PbO_2/70% $HClO_4$/AcCN/0.5 h/0 °C/56%; (b) R-NH_2/$CHCl_3$/2 h/rt/59–82%; (c) **9a**, **9b**, or **9c**/arylamine (1 equiv)/$CeCl_3$ (0.1 equiv)/EtOH/3 h/rt/42–95%; (d) **9a** or **9b**/arylthiol (1 equiv)/$CeCl_3$ (0.1 equiv)/EtOH/3 h/rt/63–86%; (e) **9a** or **9b**/arylthiol (2 equiv)/EtOH/18 h/reflux/45–81%; (f) **9b**/ethylthiol (1 equiv)/$CeCl_3$ (0.1 equiv)/EtOH/48 h/60 °C/25%.

phosphorylase. The antifungal activity of 1*H*-carbazole-1,4(9*H*)-diones **3–6** and **9** on fungi has not been reported to the best of our knowledge. Therefore, 1*H*-carbazole-1,4(9*H*)-diones **3–6** and **9** with various substituents were designed and synthesized to elucidate their contribution to the antifungal activity (Scheme 1). We describe herein our results on the synthesis of 1*H*-carbazole-1,4(9*H*)-diones **3–6** and **9** with their antifungal activity on the pathogenic fungal strains.

A convenient method for synthesis of 1*H*-carbazole-1,4(9*H*)-diones **3a–m**, **4a–i**, **5a–f**, and **6** is shown in Scheme 1 and Table 1.

9-Alkyl-6-hydroxy-1*H*-carbazole-1,4(9*H*)-diones **9a**, **9b**, and **9c** were prepared in two steps from commercially available [1,1′-biphenyl]-2,2′-diol (**7**) through its oxidation to [1,1′-bi(cyclohexane)]-3,3′,6,6′-tetraene-2,2′,5,5′-tetraone (**8**)[13] followed by the reaction of compound **8** with methyl-, ethyl-, or *n*-propylamine according to the reported method[12] with minor modification. The compound **8** was synthesized through the oxidation of compound **7** with PbO_2 in the presence of $HClO_4$ in 56% yield. To prepare 1*H*-carbazole-1,4(9*H*)-diones **9a**, **9b**, and **9c** by nucleophilic addition of alkylamine and to avoid a further nucleophilic addition of alkylamine to **9**, an equivalent amount of each metyl-, ethyl-, or *n*-propylamine was treated with compound **8**. 9-Alkyl-3-arylamino-6-hydroxy-1*H*-carbazole-1,4(9*H*)-diones **3a–q** were synthesized by regioselective nucleophilic addition of compound **9a**, **9b**, or **9c** with appropriate arylamines and subsequent oxidation. When compound **9a**, **9b**, or **9c** with 1 equiv amount of appropriate arylamines in EtOH were refluxed for 3 h in the presence of $CeCl_3$[14], compounds **3a–q** were formed. Most of these additions went as expected and had overall high yields of 42–95%.

In similar manner, 9-alkyl-3-arylthio-6-hydroxy-1*H*-carbazole-1,4(9*H*)-diones **4a–i** were synthesized by nucleophilic addition of compound **9a** or **9b** with arylthiols and subsequent oxidation. When compound **9a** or **9b** with 1 equiv of appropriate arylthiols in EtOH were refluxed for 3 h, compounds **4a–i** were formed in overall high yields of 63–86%.

9-Alkyl-3,4-bis(arylthio)-6-hydroxy-1*H*-carbazole-1,4(9*H*)-diones 5a–**f** were synthesized by nucleophilic addition on compound **9a** or **9b** with 2 equiv of appropriate arylthiols in EtOH by reflux for 18 h and had overall yields of 45–81%.

The compound **6** was synthesized through the addition of compound **9b** with 1 equiv of ethylthiol in the presence of $CeCl_3$.

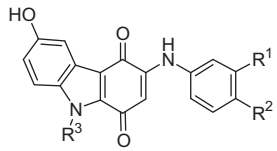
The compounds **3–6** were identified by ^{1}H NMR, ^{13}C NMR, or mass spectra. The mechanism of formation of compounds **3–6** was cited in Ref. 15. The experimental data of representative compounds **3a**, **4a**, **5a**, and **6** was provided in Ref. 16.

The synthesized 1*H*-carbazole-1,4(9*H*)-diones **3a–q**, **4a–i**, **5a–f**, **6**, and **9a–c** were tested in vitro for their growth inhibitory activity against pathogenic fungi using the standard twofold broth dilution method.[17] The MIC (minimum inhibitory concentration) values were determined by a comparison with fluconazole and 5-fluorocytosine as standard agents.[17] As indicated in Table 1, most of 9-alkyl-3-arylthio-6-hydroxy-1*H*-carbazole-1,4(9*H*)-diones **4a–i**, 9-alkyl-3,4-bis(arylthio)-6-hydroxy-1*H*-carbazole-1,4(9*H*)-diones **5a–f**, and quinones **9a–c** generally showed potent antifungal activity against all pathogenic fungal strain tested. In contrast, 9-alkyl-3-arylamino-6-hydroxy-1*H*-carbazole-1,4(9*H*)-diones **3a–q** did not show significant antifungal activity against all pathogenic fungal strain tested, although many of the compounds **3a–q** also showed potent antifungal activity against *Candida krusei* and *Cryptococcus neoformans*.

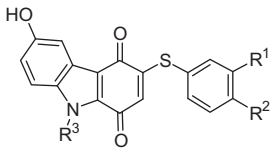
Actually, the activity of compounds **4c**, **4h**, and **9b** was superior or comparable to those of 5-fluorocytosine against all tested fungi. The compounds **4c**, **4h**, and **9b** completely inhibited the growth of all fungal species tested at the MIC level of 1.6–25 μg/mL. The activity of many tested compounds were superior to those of 5-fluorocytosine against all fungi.

In terms of structure–activity relationship, the 3-arylthio-6-hydroxy-1*H*-carbazole-1,4(9*H*)-diones **4**, 3,4-bis(arylthio)-6-hydroxy-1*H*-carbazole-1,4(9*H*)-diones **5**, and 6-hydroxy-1*H*-carbazole-1,4(9*H*)-diones **9** showed, in general, more potent antifungal activity than the other 3-arylamino-6-hydroxy-1*H*-carbazole-1,4(9*H*)-diones **3**. The 3-arylthio-compounds **4** and 3,4-bis(arylthio)-compounds **5** exhibited good activity, indicating a correlation that may offer insight into the mode of action of these compounds. The substituents (R^1, R^2, R^3: H, F, Me, Et, ...) for the 3-arylthio, 3-arylamino, and 9-alkyl moieties of compounds **3**, **4**, and **5** may not contribute partially toward biological potency. Thus, the substituents (R^1, R^2, R^3: H, F, Me, Et, ...) for the 3-arylamino and 9-alkyl

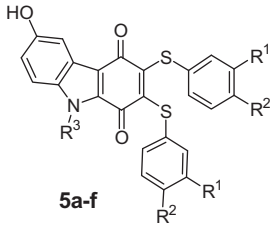
Table 1
Structures and in vitro antifungal activity for 1*H*-carbazole-1,4(9*H*)-dione derivatives



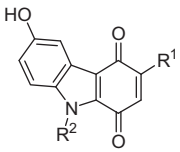
3a-q



4a-i



5a-f



6, 9a-c

Compound	R^1	R^2	R^3	MIC[a] (μg/mL)					
				C. albicans [b]	*C. tropicalis*	*C. krusei*	*C. neoformans*	*A. niger*	*A. flavus*
3a	H	CH_3O	CH_3CH_2	>50.0	25.0	25.0	25.0	>100.0	50.0
3b	H	H	CH_3CH_2	50.0	12.5	25.0	12.5	25.0	25.0
3c	H	CH_3	CH_3CH_2	>100.0	12.5	50.0	12.5	50.0	50.0
3d	H	Br	CH_3CH_2	25.0	>100.0	12.5	25.0	25.0	>100.0
3e	H	Cl	CH_3CH_2	25.0	>100.0	3.2	50.0	6.3	50.0
3f	H	CF_3O	CH_3CH_2	50.0	50.0	6.3	12.5	50.0	12.5
3g	H	I	CH_3CH_2	25.0	>100.0	50.0	25.0	50.0	50.0
3h	H	F	CH_3CH_2	50.0	50.0	25.0	25.0	50.0	>100.0
3i	H	OH	CH_3CH_2	6.3	25.0	6.3	12.5	25.0	50.0
3j	OH	H	CH_3CH_2	25.0	25.0	6.3	12.5	12.5	25.0
3k	F	H	CH_3	12.5	25.0	12.5	25.0	12.5	25.0
3l	H	F	CH_3	12.5	12.5	6.3	25.0	6.3	25.0
3m	H	Cl	CH_3	6.3	25.0	12.5	25.0	6.3	12.5
3n	H	CH_3	*n*-Pr	25.0	>100.0	25.0	>100.0	50.0	50.0
3o	H	CH_3O	*n*-Pr	1.6	25.0	25.0	25.0	50.0	25.0
3p	H	Cl	*n*-Pr	3.2	25.0	6.3	12.5	50.0	12.5
3q	H	F	*n*-Pr	6.3	>100.0	12.5	>100.0	12.5	25.0
4a	H	CH_3O	CH_3CH_2	1.6	25.0	12.5	6.3	3.2	25.0
4b	H	OH	CH_3CH_2	6.3	50.0	25.0	25.0	3.2	12.5
4c	H	H	CH_3CH_2	1.6	3.2	3.2	3.2	6.3	25.0
4d	CH_3	H	CH_3CH_2	0.8	6.3	1.6	12.5	12.5	25.0
4e	H	CH_3	CH_3CH_2	0.8	50.0	3.2	25.0	3.2	6.3
4f	CH_3	CH_3	CH_3CH_2	12.5	50.0	6.3	50.0	6.3	25.0
4g	H	H	CH_3	3.2	25.0	6.3	12.5	6.3	12.5
4h	F	H	CH_3	3.2	6.3	3.2	6.3	3.2	6.3
4i	H	H	CH_3	12.5	12.5	6.3	25.0	6.3	12.5
5a	H	CH_3O	CH_3CH_2	12.5	50.0	25.0	25.0	12.5	25.0
5b	H	OH	CH_3CH_2	3.2	50.0	25.0	6.3	0.8	50.0
5c	F	H	CH_3	3.2	6.3	3.2	12.5	12.5	12.5
5d	Cl	H	CH_3	6.3	12.5	6.3	25	12.5	12.5
5e	F	F	CH_3	12.5	25.0	3.2	12.5	12.5	25.0
5f	H	Cl	CH_3	6.3	12.5	6.3	25.0	6.3	12.5
6	CH_3CH_2S	CH_3CH_2	—	6.3	25.0	25.0	50.0	6.3	25.0
7	—	—	—	>100.0	>100.0	100.0	25.0	>100.0	100.0
9a	H	CH_3	—	0.8	50.0	6.3	12.5	1.6	25.0
9b	H	CH_3CH_2	—	3.2	6.3	3.2	3.2	3.2	12.5
9c	H	*n*-Pr	—	3.2	25.0	3.2	6.3	3.2	12.5
Fluconazole	—	—	—	12.5	6.3	12.5	12.5	12.5	100.0
5-FC[c]	—	—	—	3.2	3.2	6.3	6.3	3.2	25.0

[a] The MIC value is defined as lowest concentration of the antifungal agent exhibiting no fungal growth. MIC values were read after 1 day for *Candida* species and *C. neoformans*, and 2 days for *A. niger*, *A. flavus* 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, *C. tropicalis* Berkout KCCM 50662, *C. krusei* Berkout KCCM 11655, *Cryptococcus neoformans* KCCM 50564, *Aspergillus niger* KCTC 1231, and *A. flavus* KCCM 11899.

[c] 5-FC: 5-fluorocytosine.

moieties appear to be not an important factor to affect their antifungal activity. The activity of compounds **9** was comparable to those of compounds **3–6**. Therefore, the 3-arylthio-, 3,4-bis(arylthio)-, and 3-arylamino-substituents could not be essential for the antifungal activity of compounds **3**, **4**, and **5**.

In addition, [1,1′-biphenyl]-2,2′-diol (**7**) and exhibited no or poor, if any, antifungal activity. In contrast, most of 1*H*-carbazole-1,4(9*H*)-diones **3–6** and **9** showed more potent antifungal activity than compound **7**. Thus, the quinone moiety in 1*H*-carbazole-1,4(9*H*)-diones **3–6** and **9** should be essential for the activity, for example, as nonquinonoid compound **7** lost the activity.

In conclusion, 3-arylamino-6-hydroxy-1*H*-carbazole-1,4(9*H*)-diones **3** were synthesized by nucleophilic addition of 1*H*-carbazole-1,4(9*H*)-diones **9** with 1 equiv of appropriate arylamines. 3-Arylthio-6-hydroxy-1*H*-carbazole-1,4(9*H*)-diones **4** were synthesized by nucleophilic addition on 1*H*-carbazole-1,4(9*H*)-diones **9** with 1 equiv of appropriate arylthiols. 3,4-bis(Arylthio)-6-hydroxy-1*H*-carbazole-1,4(9*H*)-diones **5** were synthesized by nucleophilic addition on 1*H*-carbazole-1,4(9*H*)-diones **9** with 2 equiv of arylthiols.

Among them tested, many of compounds **3–6** and **9** showed potent antifungal activity against pathogenic fungal strain. These 1*H*-carbazole-1,4(9*H*)-diones may thus be a promising lead for the

development of antifungal agents. Moreover, the results should encourage the synthesis of 1*H*-carbazole-1,4(9*H*)-dione analogs for improving antifungal properties.

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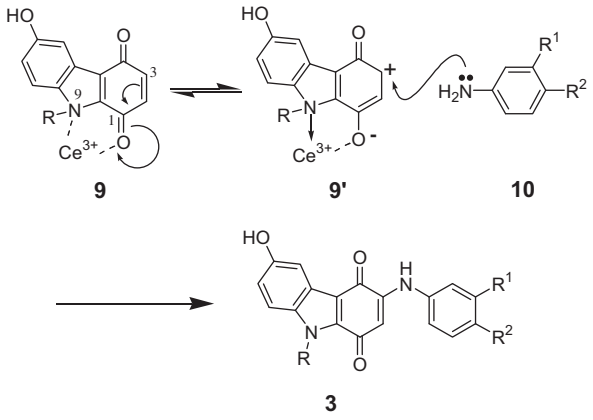
15. 3-Substituted-1*H*-carbazole-1,4(9*H*)-diones **3**, **4**, and **6** were formed by regioselective nucleophilic addition of compounds **9** with 1 equiv of appropriate arylamines **10** or thiols in the presence of $CeCl_3$. As results of catalytic action of Ce^{3+} ions, the addition in compounds **9** gave mainly 3-substituted products **3**, **4**, and **6**. The regioselectivity should be originated from the selective increment of the electrophilicity of 3-position in compounds **9** by the formation of Ce(III) chelate between carbonyl oxygen at 1-position and nitrogen at 9-position. The catalysis by Ce^{3+} ions is understood from the intermediate **9′**. The 3-arylamino products **3** were formed by a Michael-type addition of arylamines **10** to **9′**. These additions were similar to the regioselective reaction of arylamines **10** on 5,8-quinolinedione or 5,8-quinazolinedione the presence of Ce(III).[14]



In similar manner, the 3-arylthio products **4** and **6** were formed by an addition of arylthiols to **9′**. Most of these reactions went as expected. Actually, the additions in compounds **9** gave mainly 3-substituted products **3**, **4**, and **6** along with traces of 2-substituted compounds as by-product. The products **3**, **4**, and **6** were separated by silica gel column chromatography. Purity of products **3**, **4**, and **6** was determined both by to TLC and GC. The results showed that a single compound was contained in each product. TLC was performed on precoated silica gel (60G 254, Merck) using $CHCl_3$ for solvent. The compounds were detected under UV light (254 nm). The purity of products was also verified by GC (Hewlett Packard 5890A, HP-5 capillary column at 260 °C, N_2, 17 mL/mim as carrier gas, FID).

16. *Experimental*: All melting points were measured with Büchi melting point B-545 and were uncorrected. ^{1}H NMR spectra or ^{13}C NMR spectra were recorded on Varian Unity INOVA 400 MHz FT-NMR spectrometer with TMS. Mass spectra were taken with Jeol JMS AX505 WA. *9-Ethyl-6-hydroxy-3-(4-methoxy-phenylamino)-9H-carbazole-1,4-dione* (**3a**): mp 176–178 °C; ^{1}H NMR (DMSO-d_6) δ 1.32 (t, J = 7.2, 3H, CH_2CH_3), 3.78 (s, 3H, OCH_3), 4.63 (q, J = 7.2, 2H, CH_2CH_3), 6.99 (m, 1H), 7.02 (d, J = 9.2, 2H), 7.33 (d, J = 9.2, 2H), 7.45 (d, 1H), 7.62 (d, 1H), 9.13 (s, 1H), 9.58 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 178.6, 173.1, 157.3, 154.1, 151.6, 140.5, 138.5, 135.7, 132.2, 124.8, 118.5, 114.2, 113.1, 110.3, 107.9, 103.3, 56.9, 43.9, 15.4; MS (m/z) 362 (M^+). *9-Ethyl-6-hydroxy-3-(4-methoxy-phenylthio)-9H-carbazole-1,4-dione* (**4a**): mp 273–274 °C; ^{1}H NMR ($CDCl_3$) δ 1.42 (t, J = 7.2, 3H, CH_2CH_3), 3.87 (s, 3H, OCH_3), 4.57 (q, J = 7.2, 2H, CH_2CH_3), 5.54 (s, 1H), 5.65 (s, 1H), 7.01 (m, 2H), 7.04 (m, 1H), 7.33 (m, 1H), 7.45 (d, 2H), 7.72 (d, 1H); ^{13}C NMR ($CDCl_3$) δ 176.5, 173.1, 157.6, 157.1, 152.9, 139.8, 137.7, 134.4, 131.7, 127.9, 124.2, 123.3, 116.2, 114.9, 109.2, 104.1, 56.1, 43.8, 16.0; MS (m/z) 379 (M^+). *9-Ethyl-6-hydroxy-2,3-bis-(4-methoxy-phenylthio)-9H-carbazole-1,4-dione* (**5a**): mp 166–168 °C; ^{1}H NMR ($CDCl_3$) δ 1.45 (t, J = 7.2, 3H, CH_2CH_3), 3.71 (s, 6H, OCH_3), 4.72 (q, J = 7.2, 2H, CH_2CH_3), 6.65 (m, 4H), 6.98 (m, 4H), 7.09 (m, 1H), 7.25 (d, J = 8.0, 1H), 7.33 (d, J = 8.0, 1H), 7.82 (s, 1H); MS (m/z) 517 (M^+). *9-Ethyl-3-ethythio-6-hydroxy-9H-carbazole-1,4-dione* (**6**): mp 275–277 °C; ^{1}H NMR (DMSO-d_6) δ 1.43 (t, J = 7.4, 3H, CH_2CH_3), 1.42 (t, J = 7.1, 3H, CH_2CH_3), 2.88 (q, J = 7.4, 2H, CH_2CH_3), 4.61 (q, J = 7.1, 2H, CH_2CH_3), 6.22 (s, 1H), 6.98 (t, 1H), 7.41 (d, 1H), 7.53 (d, 1H), 9.42 (s, 1H); MS (m/z) 301 (M^+).
17. Mcginnis, M. R.; Rindali, M. G. In *Antibiotics in Laboratory Medicine*; Lorian, V., Ed., 4th ed.; Williams and Wilkins: Baltimore, 1996; pp 176–211.