Microwave-Assisted Synthesis of *N*-Substituted Maleimide Derivatives as Exogenous Antioxidant Agents

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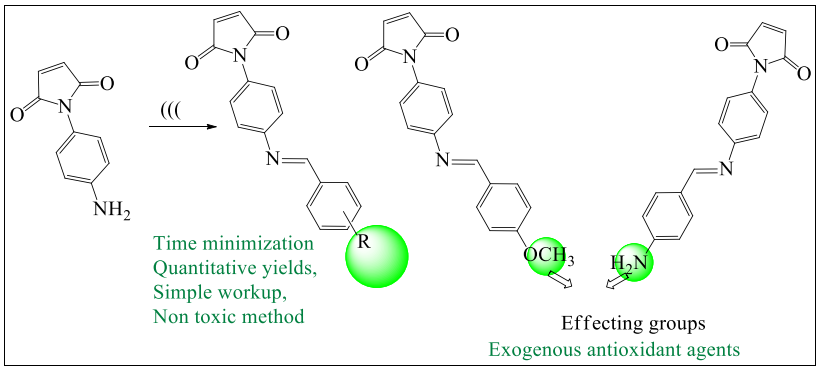
Received July 3, 2018
DOI 10.1002/jhet.3421
Published online 00 Month 2018 in Wiley Online Library (wileyonlinelibrary.com).



A series of *N*-substituted maleimide derivatives have been developed *via* acetic acid-mediated microwave reaction pathway, which was identified as the incomparable method for this maleimide compounds. All the synthesized compounds were tested for antioxidant activity by DPPH and H_2O_2 methods. Compounds **5h** and **5m** were displayed with higher antioxidant activity in two methods. The structure–activity relationship demonstrated that the compounds having electron releasing substitutions **5h** and **5m** generally show beneficial activity than electron capture substitution cores. Thus, compounds **5h** and **5m** may be useful as an exogenous antioxidant.

INTRODUCTION

Development of an exogenous antioxidant agent is always fresh and unremitting research in the medicinal chemistry field. Still, medicinal research needs to identify the best antioxidant agent. Time-saving, quantitative yields, eco-friendly solvents, inexpensive, and non-tedious workup actions are interesting tackles to develop biological active compounds. Utmost in the world, researchers are applying any of the previous key points in their scientific developments. A microwave grounded synthetic track may likely to possess all those circumstances [1,2]. In the synthesis of heterocycles particularly, pyrrole substituted derivatives preparation was always a fascinated route because their analogs are considered as a source of biologically potent and found in countless natural products [3,4], vitamin B12, hemoglobin, L-tryptophan, and chlorophyll [5–7]. Numerous compounds have pyrrole motif exposed biological properties, for example, antibacterial [8], antifungal [9], anticonvulsant [10], anti-inflammatory, analgesic [11], anticancer [12], and anti-HIV [13]. Moreover, merging of peculiar pharmacophores in a pyrrole moiety has led to the development of novel active compounds. Additionally, this nitrogenated heterocyclic structure is existing in several compounds of synthetic origin known for their antimycobacterial activity and DNA cross-linking properties [14,15]. Meanwhile, pyrrole with tri substitution pattern exhibits notable biological properties as illustrated by the anti-inflammatory agents amtolmetin and tolmetin [16,17]. Because of their therapeutic meaning, several methods have been industrialized for the synthesis of substituted pyrroles, which includes the Hantzsch [18], Knorr [19], and Paal Knorr reaction [20]. Some researchers used heavy catalysts to develop pyrrole moieties such as PS-PTSA [21], $NiCl_2$-$6H_2O$ [22], graphite [23], and the reaction of enamino esters and nitroolefins [24]. Most of the approaches are supportive for synthesis of pyrroles. But they have

thoughtful downsides such as unsatisfactory yields, multistep synthetic operations, and accessibility of starting materials, regiospecificity, functional group compatibility, and drastic reaction conditions.

In continuation of our research work, the present work was aimed to synthesize a series of *N*-substituted maleimide derivatives under microwave conditions [25–27]. Also, the titled compounds were studied to testify their free radical scavenging activity. All the products formed with quantitative yields.

RESULTS AND DISCUSSION

Chemistry. Initially, the present synthetic work performed under conventional method. Treatment of compound maleic anhydride (**1**) with 4-aminoaniline (**2**) in the presence of ethanol under microwave irradiation condition gave the product (4-aminophenyl)-1*H*-pyrrole-2,5-dione (**3**). Further, a condensation reaction was performed between compound **3** and different aryl aldehydes (**4a**–**o**) in the presence of ethanol under reflux condition (Method A in Scheme 1). The targets *N*-substituted maleimide derivatives (**5a**–**o**) formed with yields between 25% and 63% (Table 1). Further, all these reactions were performed in two different solvents under microwave irradiation. The ethanol-mediated microwave reaction product yields improved than conventional method and was in the range of 40–76% (Method B in Scheme 1). Encouraged by this result and seeking for quantitative yields of all the products, the same reaction path was performed by using acetic acid solvent under same irradiation (Method C in Scheme 1). The products formed with the highest yield range between 71–93% and these results quite impressible. Thus, for this synthetic path, microwave irradiation under acetic acid solvent media was a prominent route to develop *N*-substituted maleimide derivatives. All the compounds were characterized by the proton NMR, carbon NMR, and HRMS analysis.

Table 1

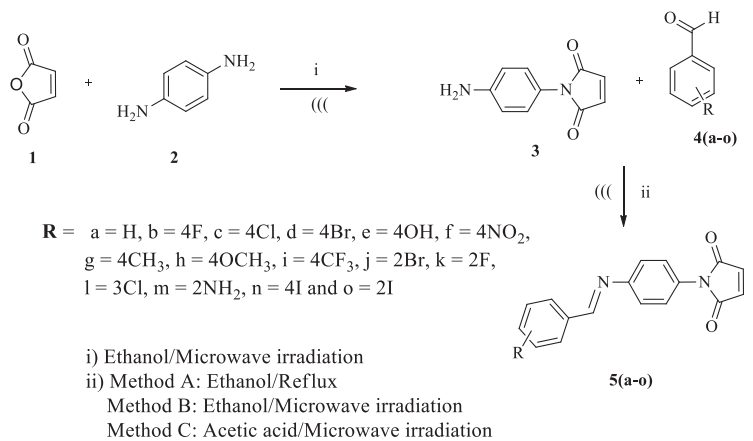
Yields of synthesized compounds **5a**–**o**.

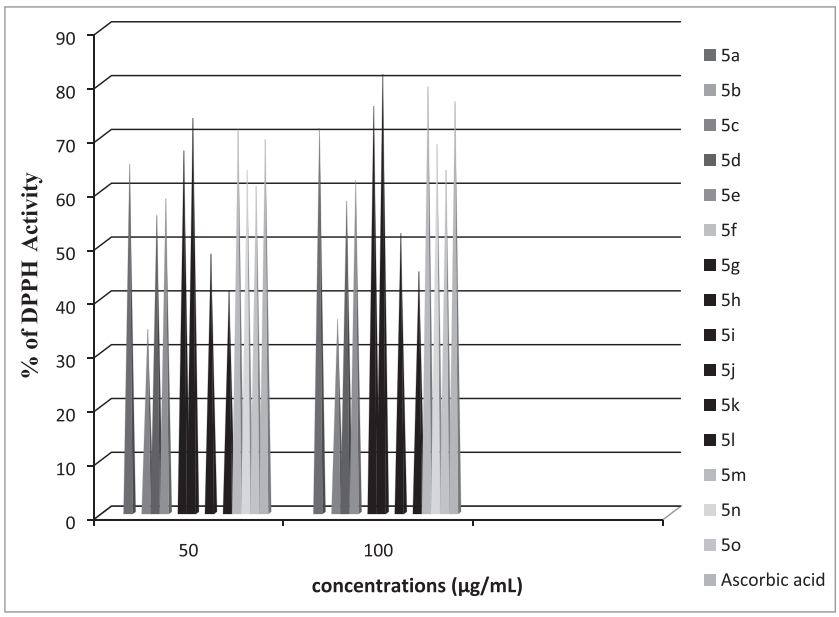
Compound	Method A Conventional 7 h	Method B MW in ethanol (10 min)	Method C MW in acetic acid (10 min)
5a	54	62	78
5b	52	58	82
5c	63	70	86
5d	43	40	93
5e	32	59	80
5f	45	42	71
5g	55	76	88
5h	59	63	75
5i	54	55	86
5j	60	58	92
5k	45	51	81
5l	39	46	89
5m	63	64	76
5n	40	52	86
5o	25	57	77

Biological assay. ***Antioxidant activity.*** The antioxidant assay of reported moieties **5a**–**o** was examined by DPPH (2,2′-diphenyl-1-picrylhydrazyl) [28–30] and H_2O_2 (hydrogen peroxide) [30] methods.

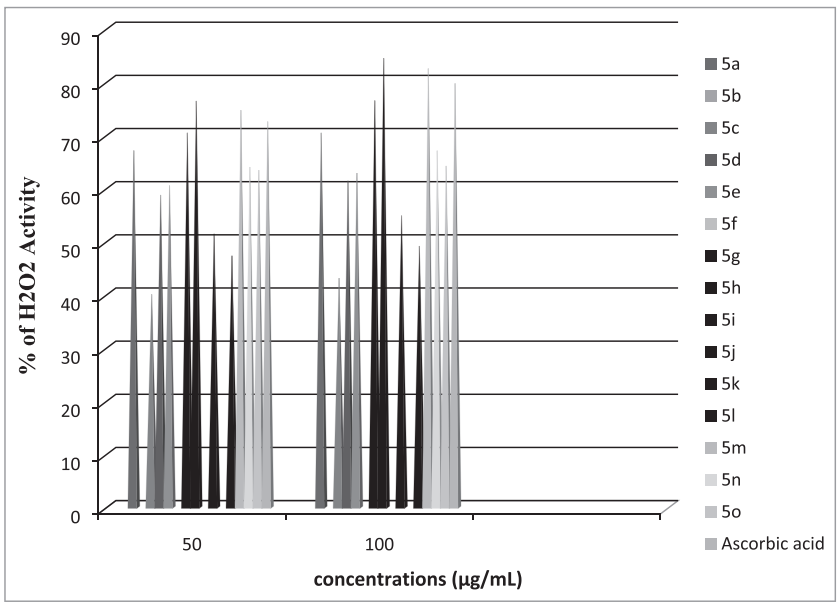
In this effort, the free radical scavenging activity of 15 molecules against DPPH and H_2O_2 methods were evaluated (Graphs 1 and 2). All the tested results that were formulated in Tables 2 and 3 revealed that most of the compounds possessed higher to moderate activity and except four compounds were inactive. The title compounds displayed higher antioxidant activity in the H_2O_2 method. Here, an interesting point was the antioxidant activity of compounds was raised with

Scheme 1. Synthetic route of *N*-substituted maleimide derivatives **5a**–**o**.





Graph 1. The *in vitro* antioxidant activity of compounds **5a–o** in DPPH method.



Graph 2. The *in vitro* antioxidant activity of compounds **5a–o** in H_2O_2 method.

increasing concentrations in two methods. The maximum antioxidant activity has been displayed by compounds **5h**, **5m**, and **5g** followed closely by **5a**. In those, the motifs **5h** and **5m** exhibited higher therapeutic activity than the reference drug ascorbic acid in all the two methods. The activity values of compounds 5h and 5m in DPPH method were 73.38 & 81.54 and 71.25 & 79.21 µg/mL. Similarly, the antioxidant activity results of the compounds 5h and 5m in H_2O_2 were 76.45 & 84.47 and 74.71 & 82.54 µg/mL. In fact, the maleimide derivative **5a** showed admirable antioxidant activity in two methods, whereas other active compounds **5c**, **5d**, **5e**, **5l**, **5j**, **5n**, and **5o** were given well to moderate antioxidant assay. The other *N*-substituted maleimide derivatives were inactive. This may be due to the presence of most electron capture substitution on core moiety. The clear evidence from the activity results indicated that the free radical scavenging activity of the reported motifs was

Table 2

The *in vitro* antioxidant activity of compounds **5a–o** in DPPH method.

	Concentration (μg/mL)	
Compound	50	100
5a	64.85 ± 0.11	71.52 ± 0.23
5b	—	—
5c	34.17 ± 0.20	36.05 ± 0.84
5d	55.28 ± 0.85	57.96 ± 0.58
5e	58.41 ± 0.12	61.85 ± 0.52
5f	—	—
5g	67.32 ± 0.15	75.58 ± 0.85
5h	73.38 ± 0.75	81.54 ± 0.12
5i	—	—
5j	48.16 ± 0.86	51.96 ± 0.51
5k	—	—
5l	41.26 ± 0.15	44.86 ± 0.45
5m	71.25 ± 0.07	79.21 ± 0.36
5n	63.66 ± 0.19	68.50 ± 0.09
50	60.74 ± 0.29	63.71 ± 0.11
Ascorbic acid	69.40 ± 0.11	76.43 ± 0.58
Blank	—	—

(—) Showed no scavenging activity. Values were the means of three replicates ±SD.

Table 3

The *in vitro* antioxidant activity of compounds **5a–o** in H_2O_2 method.

	Concentration (μg/mL)	
Compound	50	100
5a	67.12 ± 0.71	70.45 ± 0.21
5b	—	—
5c	40.05 ± 0.59	43.11 ± 0.56
5d	58.76 ± 0.06	61.43 ± 0.22
5e	60.51 ± 0.64	62.89 ± 0.50
5f	—	—
5g	70.45 ± 0.87	76.52 ± 0.12
5h	76.45 ± 0.14	84.47 ± 0.89
5i	—	—
5j	51.45 ± 0.03	54.86 ± 0.11
5k	—	—
5l	47.33 ± 0.56	49.16 ± 0.40
5m	74.71 ± 0.85	82.54 ± 0.08
5n	64.02 ± 0.86	67.09 ± 0.15
50	63.44 ± 0.40	64.22 ± 0.76
Ascorbic acid	72.56 ± 0.45	79.75 ± 0.20
Blank	—	—

(—) Showed no scavenging activity. Values were the means of three replicates ±SD.

associated with substitution on the core moiety. On the other hand, outstanding antioxidant active compounds have electron releasing substitutions on their phenyl ring lead to enhance the activity.

Structure activity relationship and mechanism of action. From the analysis of the structure activity relationship, in reported composites, the radical resonance is probable over aromatic OCH_3 and NH_2 cleavage. The single electron species formed **5h**, and **5m** cleavage of OCH_3 and NH_2 bond has capability for resonance and stabilization *via* two unsaturated rings linked with *N*-methyleneethenamine core (Fig 1). Besides, in compound **5e** situation, the substitution moiety –OH gave phenoxyl radical formed resonance and had stability. But these compounds possessed low antioxidant activity than above two. Thus, the previous results demonstrated that the compounds having electron releasing substitutions generally beneficial activity compare with electron capture substitution cores. These compounds may be used as an exogenous antioxidant.

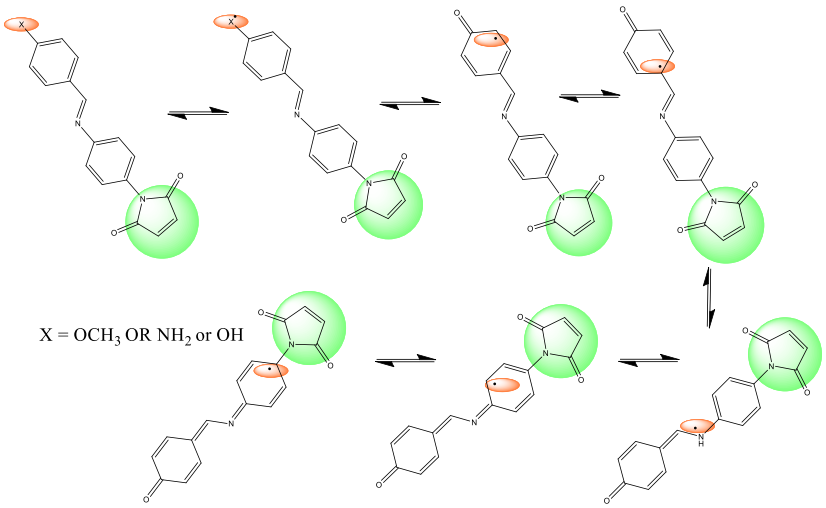


Figure 1. Mechanism of stabilization radical by resonance in most active compounds. [Color figure can be viewed at wileyonlinelibrary.com]

CONCLUSIONS

The present work demonstrated that acetic acid-mediated microwave reaction condition was the prominent method for the synthesis of *N*-substituted maleimide derivatives. Quantitative yielding, modesty, time-saving, environmentally benign, easy workup, and without chromatographic purification were the adventitious tools of this method. All the synthesized compounds were evaluated for their antioxidant activity; most of the compounds exhibited good to moderate antioxidant activities, except few. Among all the active compounds, motifs 5h and 5m were showed higher antioxidant activity in DPPH and H_2O_2 methods.

EXPERIMENTAL DATA

General chemistry. Melting points were determined using a kofler hot stage apparatus and are uncorrected. NMR spectra were recorded on 300 MHz spectrophotometer operating at 300 MHz (^{1}H) and 75 MHz (^{13}C) using tetramethylsilane (TMS) as an internal standard. By using ESI ionization, HRMS data and low-resolution MS were found. For synthesis of reactions, Catalyst-4R microwave oven was used.

Protocol for the synthesis of intermediate (3). Maleic anhydride (**1**) reacted with 4-aminoaniline (**2**) in ethanol under MW irradiation at 130°C (250 W) for 10 min. After completion of the reaction confirmed by thin-layer chromatography, the crude mixture was poured into ice, neutralized with dilute hydrogen chloride, extracted with dichloromethane, dried and recrystallization yield (4-aminophenyl)-1*H*-pyrrole-2,5-dione (**3**).

(4-Aminophenyl)-1H-pyrrole-2,5-dione (3). Light yellow solid. mp 174–176°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.12–7.56 (m, 6H, Ar-H), 4.61 (b, 2H, NH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.0, 145.5, 125.1, 123.9, 120.8, 120.6 ppm.

Protocol for the synthesis of N-substituted maleimide 5a–o: Method A. Compound **3** (1 mmol) with benzaldehyde **4a** (1 mmol) was heated under reflux for 7 h. After the product formation, the reaction mixture was poured into crushed ice, extracted with dichloromethane, dried and recrystallized by using methanol solvent got the desired product **5a**. Like this, all the remaining products were prepared by using their respective substituted anilines.

Methods B and C. The reaction between compound **3** (1 mmol) and benzaldehyde **4a** (1 mmol) in ethanol (Method B)/acetic acid (Method C) under microwave irradiation at 130 0C (250 W) for 10 min. After the product formation, the reaction mixture was poured into crushed ice and extracted with dichloromethane. The organic layer was dried followed by the recrystallization yielded compound **5a**. The other products were also synthesized under the same methods with the help of their respective substituted benzaldehydes.

(E)-1-(4-(Benzylideneamino)phenyl)-1H-pyrrole-2,5-dione (5a). Light yellow solid. mp 153–155°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.82 (m, 11H, Ar-H), 9.35 (s, 1H, HC=N) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0, 160.8, 142.2, 131.8, 131.6, 128.9, 127.1, 124.5, 120.9, 120.6, 114.9 ppm. HRMS: *m/z* Calcd for $C_{17}H_{12}N_2O_2$ $(M + H)^+$ 277.0977; Found 277.0974.

(E)-1-(4-((4-Fluorobenzylidene)amino)phenyl)-1H-pyrrole-2,5-dione (5b). Light yellow solid. mp 138–140°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22–7.97 (m, 10H, Ar-H),

9.28 (s, 1H, HC=N) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.0, 160.8, 142.9, 132.7, 130.0, 129.8, 128.9, 128.2, 127.4, 127.1, 120.3 ppm. HRMS: *m/z* Calcd for $C_{17}H_{11}FN_2O_2$ $(M + H)^+$ 295.0883; Found 295.0881.

(E)-1-(4-((4-Chlorobenzylidene)amino)phenyl)-1H-pyrrole-2,5-dione (5c). Light yellow solid. mp 187–189°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.00–7.57 (m, 10H, Ar-H), 9.30 (s, 1H, HC=N) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.3, 160.7, 141.7, 137.5, 131.6, 129.9, 128.3, 127.4, 125.1, 123.6, 120.8 ppm. HRMS: *m/z* Calcd for $C_{17}H_{11}ClN_2O_2$ $(M + H)^+$ 311.0587; Found 311.0584.

(E)-1-(4-((4-Bromobenzylidene)amino)phenyl)-1H-pyrrole-2,5-dione (5d). Light yellow solid. mp 164–166°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.97–7.50 (m, 10H, Ar-H), 9.09 (s, 1H, HC=N) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.6, 161.6, 141.7, 136.0, 131.1, 127.8, 126.2, 119.8, 118.7, 118.1, 117.9 ppm. HRMS: *m/z* Calcd for $C_{17}H_{11}BlN_2O_2$ $(M + H)^+$ 355.0082; Found 355.0079.

(E)-1-(4-((4-Hydroxybenzylidene)amino)phenyl)-1H-pyrrole-2,5-dione (5e). Light yellow solid. mp 142–145°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.08–7.59 (m, 10H, Ar-H), 9.07 (s, 1H, HC=N) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.7, 160.7, 140.9, 135.2, 130.6, 130.5, 128.6, 120.1, 115.4, 115.3, 105.5 ppm. HRMS: *m/z* Calcd for $C_{17}H_{12}N_2O_3$ $(M + H)^+$ 293.0926; Found 293.0921.

(E)-1-(4-((4-Nitrobenzylidene)amino)phenyl)-1H-pyrrole-2,5-dione (5f). Light yellow solid. mp 127–129°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.06–8.05 (m, 10H, Ar-H), 9.28 (s, 1H, HC=N) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.8, 162.8, 140.6, 136.8, 130.8, 128.9, 128.4, 127.4, 127.2, 125.6, 125.3 ppm. HRMS: *m/z* Calcd for $C_{17}H_{11}N_3O_4$ $(M + H)^+$ 322.0828; Found 322.0827.

(E)-1-(4-((4-Methylbenzylidene)amino)phenyl)-1H-pyrrole-2,5-dione (5g). Light yellow solid. mp 130–132°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.49 (S, 3H, CH_3), 6.95–7.50 (m, 10H, Ar-H), 9.16 (s, 1H, HC=N) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.8, 160.9, 141.7, 136.5, 132.0, 129.2, 127.3, 124.8, 123.0, 120.2, 117.1, 38.4 ppm. HRMS: *m/z* Calcd for $C_{18}H_{14}N_2O_2$ $(M + H)^+$ 291.1134; Found 291.1131.

(E)-1-(4-((4-Methoxybenzylidene)amino)phenyl)-1H-pyrrole-2,5-dione (5h). Light yellow solid. mp 159–161°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.87 (S, 3H, OCH_3), 6.88–7.30 (m, 10H, Ar-H), 9.11 (s, 1H, HC=N) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4, 153.7, 141.5, 134.3, 130.9, 129.1, 128.6, 124.8, 120.9, 120.7, 117.4, 62.1 ppm. HRMS: *m/z* Calcd for $C_{18}H_{14}N_2O_3$ $(M + H)^+$ 307.1083; Found 307.1080.

(E)-1-(4-((4-Trifluorobenzylidene)amino)phenyl)-1H-pyrrole-2,5-dione (5i). Light yellow solid. mp 195–197°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–8.38 (m, 10H, Ar-H), 9.36 (s, 1H, HC=N) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.7, 162.2, 141.2, 140.0, 137.3, 135.2, 132.7, 132.0, 129.6, 123.5, 123.3, 120.1 ppm. HRMS: *m/z* Calcd for $C_{18}H_{11}F_3N_2O_2$ $(M + H)^+$ 345.0851; Found 345.0847.

(E)-1-(4-((2-Bromobenzylidene)amino)phenyl)-1H-pyrrole-2,5-dione (5j). Light yellow solid. mp 177–179°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.03–7.59 (m, 10H, Ar-H), 9.13 (s, 1H, HC=N) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.7, 156.9, 148.0, 145.7, 142.6, 134.8, 130.6, 129.9, 128.3, 120.2, 117.4, 105.9, 102.7 ppm. HRMS: *m/z* Calcd for $C_{17}H_{11}BrN_2O_2$ $(M + H)^+$ 355.0082; Found 355.0081.

(E)-1-(4-((2-Fluorobenzylidene)amino)phenyl)-1H-pyrrole-2,5-dione (5k). Light yellow solid. mp 148–150°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19–7.88 (m, 10H, Ar-H), 9.29 (s, 1H, HC=N) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.5, 161.5, 143.5, 137.6, 136.4, 131.0, 127.6, 126.3, 120.5, 120.2, 119.4, 118.0, 117.7 ppm. HRMS: *m/z* Calcd for $C_{17}H_{11}FN_2O_2$ $(M + H)^+$ 295.0883; Found 295.0878.

(E)-1-(4-((3-Chlorobenzylidene)amino)phenyl)-1H-pyrrole-2,5-dione (5l). Light yellow solid. mp 121–123°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15–7.62 (m, 10H, Ar-H), 9.10 (s, 1H, HC=N) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.7, 158.2, 142.8, 137.6, 136.4, 133.8, 133.2, 132.2, 129.5, 128.6, 125.1, 123.2, 119.9 ppm. HRMS: *m/z* Calcd for $C_{17}H_{11}ClN_2O_2$ $(M + H)^+$ 311.0587; Found 295.0585.

(E)-1-(4-((2-Aminobenzylidene)amino)phenyl)-1H-pyrrole-2,5-dione (5m). Light yellow solid. mp 183–185°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.93–7.49 (m, 10H, Ar-H), 9.05 (s, 1H, HC=N) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 163.6, 144.8, 135.1, 130.5, 130.2, 129.9, 128.8, 127.2, 127.0, 124.2, 122.5, 120.6 ppm. HRMS: *m/z* Calcd for $C_{17}H_{13}N_3O_2$ $(M + H)^+$ 292.1086; Found 292.1085.

(E)-1-(4-((4-Iodobenzylidene)amino)phenyl)-1H-pyrrole-2,5-dione (5n). Light yellow solid. mp 171–173°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20–7.98 (m, 10H, Ar-H), 9.14 (s, 1H, HC=N) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.4, 160.8, 143.9, 142.4, 131.9, 128.7, 127.0, 124.5, 121.4, 120.0, 115.0 ppm. HRMS: *m/z* Calcd for $C_{17}H_{11}IN_2O_2$ $(M + H)^+$ 402.9943; Found 402.9941.

(E)-1-(4-((2-Iodobenzylidene)amino)phenyl)-1H-pyrrole-2,5-dione (5o). Light yellow solid. mp 211–213°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25–7.87 (m, 10H, Ar-H), 9.10 (s, 1H, HC=N) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.4, 160.9, 141.3, 140.3, 136.9, 133.4, 131.5, 130.2, 128.6, 128.5, 120.0, 115.7, 155.5 ppm. HRMS: *m/z* Calcd for $C_{17}H_{11}IN_2O_2$ $(M + H)^+$ 402.9943; Found 402.9940.

Acknowledgments. A. R. is thankful to Sri Venkateswara University for lab facilities, and G. M. R is grateful to Brazilian Higher Education Personnel Training Coordination (CAPES: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior) under PNPD program and Ural Federal University, Russia.

REFERENCES AND NOTES

[1] Rocchi, D.; Gonza´ lez, J. F.; Mene´ ndez, J. C. Green Chem 2013, 15, 511.

[2] Anvar, S.; Mohammadpoor Baltork, I.; Tangestaninejad, S.; Moghadam, M.; Mirkhani, V.; Khosropoura, A.; Reza, K. RSC Adv 2012, 2, 8713.
[3] Clive, D. L. J.; Cheng, P. Tetrahedron 2013, 69, 5067.
[4] Fan, H.; Peng, J.; Hamann, M. T.; Hu, J. F. Chem Rev 2008, 108, 264.
[5] Walsh, C. T.; Garneau, T. S.; Howard Jones, A. R. Nat Prod Rep 2006, 23, 517.
[6] Young, I. S.; Thornton, P. D.; Thompson, A. Nat Prod Rep 2010, 27, 1801.
[7] Fucuda, F.; Ishibashi, T.; Iwao, M. Heterocycles 2010, 83, 491.
[8] Daidone, G.; Maggio, B.; Schillari, D. Pharmazie 1990, 45, 441.
[9] Meshram, H. M.; Prasad, B. R. V.; Kumar, D. A. Tetrahedron Lett 2010, 51, 3477.
[10] Patil, V.; Sinha, R.; Masand, N.; Jain, J. J Nanomater Biostruct 2009, 4, 471.
[11] Battilocchio, C.; Poce, G.; Alfonso, S.; Porretta, G. C.; Consalvi, S.; Sautebin, L.; Pace, S.; Rossi, A.; Ghelardini, C.; Mannelli, L. D. C.; Schenone, S.; Giordani, A.; Francesco, L. D.; Patrignani, P.; Biava, M. Bioorg Med Chem 2013, 21, 3695.
[12] Yanga, F.; Nickolsa, N. G.; Lia, B. C.; Marinovc, G. K.; Saidd, J. W.; Dervana, P. B. Proc Natl Acad Sci 2013, 110, 1863.
[13] Jiang, S.; Lu, H.; Liu, S.; Zhao, Q.; He, Y.; Debnath, A. K. Antimicrob Agents Chemother 2004, 48, 4349.
[14] Biava, M.; Porretta, G. C.; Poce, G.; Battilocchio, C.; Alfonso, S.; Logu, A.; Manetti, F.; Botta, M. Med Chem 2011, 6, 593.
[15] Su, T. L.; Lee, T. C.; Kakadiya, R. Eur J Med Chem 2013, 69, 609.
[16] Bertaccini, G.; Coruzzi, G. Gastroenterology 1998, 114, 72.
[17] Sheu, M. T.; Wu, J.; Chen, C. J.; Chao, S. H.; Wua, A. B. Tetrahedron Lett 2004, 45, 8107.
[18] Hantzsch, A. Ber Dtsch Chem Ges 1890, 23, 1474.
[19] Knorr, L. Ber Dtsch Chem Ges 1884, 17, 1635.
[20] Pall, C. Ber Dtsch Chem Ges 1885, 18, 367.
[21] Shinde, V. V.; Lee, S. D.; Jeong, Y. S.; Jeong, Y. T. Tetrahedron Lett 2015, 56, 859.
[22] Khan, A. T.; Lal, M.; Bagdi, P. R.; Basha, R. S.; Saravanan, P.; Patra, S. Tetrahedron Lett 2012, 53, 4145.
[23] Nandeesh, K. N.; Raghavendra, G. M.; Revanna, C. N.; Vijay, T. A. J.; Rangappa, K. S.; Mantelingu, K. Syn Comm 2014, 44, 1103.
[24] Guan, Z.; Li, L.; Ren, Z.; Li, J.; Zhao, M. Green Chem 2011, 13, 1664.
[25] Reddy, V. H.; Reddy, G. M.; Reddy, M. T.; Reddy, Y. V. R. Res Chem Intermed 2015, 41, 9805.
[26] Reddy, G. M.; Garcia, J. R.; Reddy, V. H.; De Andrade, A. M.; Camilo, A.; Ribeiro, R. A.; De Lazaro, S. R. Eur J Med Chem 2016, 123, 508.
[27] Reddy, G. M.; Garcia, J. R. J Heterocyclic Chem 2017, 54, 89.
[28] Burits, M.; Bucar, F. Phytother Res 2000, 14, 323.
[29] Cuendet, M.; Hostettmann, K.; Potterat, O.; Dyatmiko, W. Helv Chim Acta 1997, 80, 1144.
[30] Ruch, R. J.; Cheng, S. J.; Klaunig, J. E. Carcinogenesis 1989, 10, 1003.

SUPPORTING INFORMATION

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