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Article *in* Monatshefte fuer Chemie/Chemical Monthly · April 2016

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ORIGINAL PAPER

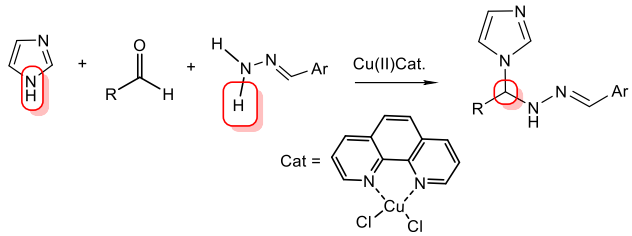
Synthesis of novel three compound imidazole derivatives via Cu(II) catalysis and their larvicidal and antimicrobial activities

Abdullah Alaklab[1] · Radhakrishnan Surendra Kumar[2] · Anis Ahamed[3] · Ibrahim A. Arif[3] · Aseer Manilal[4] · Akbar Idhayadhulla[2,5]

Received: 4 December 2015 / Accepted: 21 March 2016

Abstract One-pot three-component reactions of 1-[[2-(furan-2-ylmethylene)hydrazinyl](phenyl)methyl]-1*H*-imidazole and other imidazole derivatives were synthesized by Mannich base method in the presence of Cu(II) catalysis. Cu(Phen)Cl_2 catalysis was performed well compared with other Cu(II) catalysis. Synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectra, and elemental analysis. Synthesized compounds were evaluated by antimicrobial and larvicidal activities. 4-[[2-(Furan-2-ylmethylene)hydrazinyl](1*H*-imidazol-1-yl)methyl]-*N*,*N*-dimethylaniline was highly active (MIC: 0.5 μg/cm^3) against *Staphylococcus aureus* compared with standard ciprofloxacin in antibacterial screening. 1-[(4-Chlorophenyl)[2-(furan-2-ylmethylene)hydrazinyl]methyl]-1*H*-imidazole was highly active (MIC: 0.25 μg/cm^3) against *Candida albicans* compared with standard clotrimazole (MIC: 0.5 μg/cm^3) in antifungal screening. Larvicidal activity was assessed to the urban mosquito, *Culex quinquefasciatus*, using a standard bioassay protocol. 1-[1-[2-(Furan-2-ylmethylene)hydrazinyl]-4,8-dimethylnona-3,7-dienyl]-1*H*-imidazole showed high toxicity levels of larvicidal activity based their half maximal lethal dose (LD_{50}) values. Therefore, some compounds are lead molecules for the growth of new classes of antimicrobial and larvicidal agents.

Graphical abstract



Keywords Imidazole · Catalysis · Mannich bases · Bioorganic chemistry · Antimicrobial activity · Larvicidal activity

Electronic supplementary material The online version of this article (doi:10.1007/s00706-016-1746-2) contains supplementary material, which is available to authorized users.

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Introduction

Culex is a main genus of mosquito as a vector for several serious diseases, such as filariasis, west nile virus, dengue fever, yellow fever, chikungunya, and other encephalitides. About 3.3 billion people of the world's population are at risk of malaria [1]. More than 1.3 billion people in 72 countries worldwide are threatened by lymphatic filariasis,

Published online: 20 April 2016

commonly known as elephantiasis. Over 120 million people are currently infected, with about 40 million disfigured and incapacitated by the disease [2]. Various control agents were reported against mosquito larvae such as organophosphates, natural products, and heterocycles type's molecules [3–5], however which have high toxic and high production cost. It is an urgent need to develop new insecticides which are more environmentally safe and also biodegradable and target specific against mosquitoes. Azoles (imidazole and triazole) are available in many effective of medicinal properties such as antimicrobial [6, 7], anticancer [8], antioxidant [9], antiviral [10], antitubercular [11] activities.

Imidazole derivatives are extensively used in topical antifungal chemotherapy because of their broad spectrum and high accessibility [12], it has been documented that imidazole act with at least two distinct antifungal mechanisms. One is the inhibition of ergosterol biosynthesis at low concentration, which is accountable for fungistatic action. The other is direct physicochemical cell membrane damage exerted at higher concentration (i.e., 5–10 mg/cm^3), which causes the fungicidal effect [13].

Since a high concentration is essential for the latter effect, conventional imidazole moieties not act as fungicidal but fungistatic agents under therapeutic conditions. Although fungistatic drugs are efficient for improving the condition of patients, recurrence of the condition is often observed after suspension of the application. Enhancement of the fungicidal activity of imidazole antifungal agents is expected to overcome such problem.

For example, Fig. 1 shows that tioconazole (used to treat women's vaginal yeast infections) [14], ketoconazole (used to treat candidal paronychia and pityriasis versicolor) [15], oxiconazol (used to treat infections, such as athlete's foot, jock itch, and ringworm), sertaconazole (used to treat skin infections such as athlete's foot), and sulconazole (used to treat skin infections such as athlete's foot, ringworm, jock itch, and sun fungus) [16].

Optically active α,β-diamino acids are key structural components in a variety of peptide antibiotics, antifungal dipeptides, and other biologically active compounds [17]. Jorgensen and co-workers reported the first example of this reaction using a phosphino-oxazoline-copper(I) complex as the catalyst, for which excellent enantioselectivity was obtained [18].

Deju Shang et al. [19] reported that Mannich-type reaction (Scheme 1) of glycine Schiff base using the *N*,*N*′-dioxide ligand—$Cu(OAc)_2{\cdot}H_2O$ complex as catalyst in good yields 97 %.

Okamura et al. [20] reported that a copper-catalyzed Mannich reaction of terminal alkynes and secondary amines with aqueous formaldehyde is accelerated by the use of a catalytic amount of an imidazole ligand carrying a long alkyl chain. Similarly, Meyet et al. [21] reported that copper(II) triflate catalyst with various alkynes and aldehydes without the addition of ligand or base of three-component alkynylation. Likewise, present investigation (Scheme 2), we are try to synthesis three compounds Mannich base reaction with catalysis of $Cu(OAc)_2{\cdot}H_2O$, CuI, copper(II) triflate, and other copper-catalyzed.

Basically, Mannich base products are considerable importance for biologically active compounds [22] such as anticancer [23–25], anticonvulsant [26], antimycobacterial [27], remarkable anti-HIV, antitubercular activities [28], antimalarial [29] activities and other pharmacological studies [30, 31]. In this paper, we express to design and synthesis of novel imidazole Mannich base derivatives via $Cu(Phen)Cl_2$ catalysis, which are expected to enhance antimicrobial and larvicidal activities.

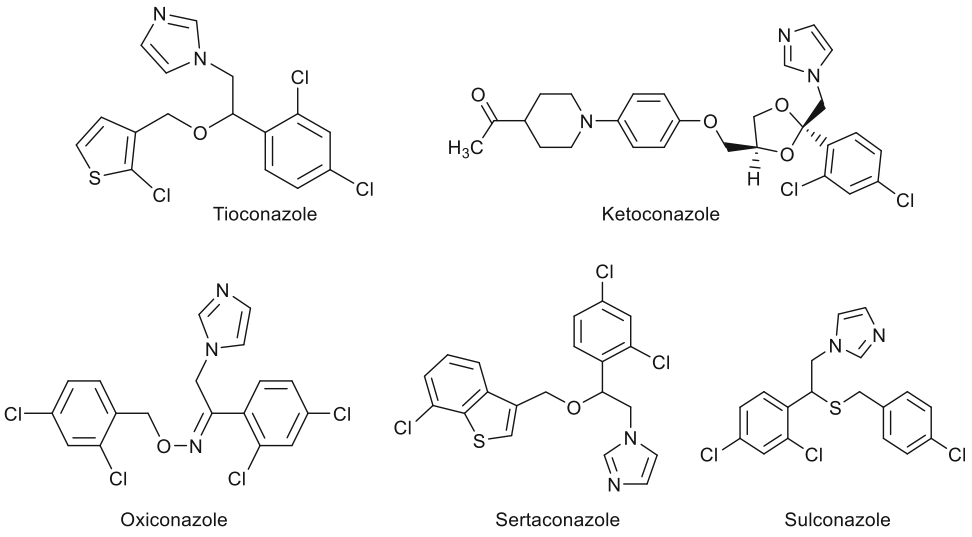


Fig. 1 Imidazole bioactive molecules

Results and discussion

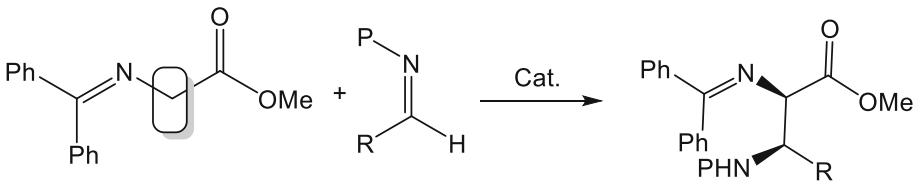
Chemistry

Compounds **1**–**24** were synthesized by Mannich base method, reaction sequences of synthesis outline in Schemes 1, 2, and 3. In our initial endeavor, we have investigated a three component reaction of imidazole, (furan-2-ylmethylidene)hydrazine and 4-substituted benzaldehyde in different solvent systems like toluene, CH_2Cl_2, MeCN, H_2O, EtOH, benzene, THF, and DMF (Table 1) and in presence of various Cu(II) catalysis under reflex condition to afford 1-[[2-(furan-2-ylmethylene)hydrazinyl](phenyl)methyl]-1*H*-imidazole (**1**, Scheme 3). Among the Cu(II) catalysis, $Cu(Phen)Cl_2$ complex catalyzed (Table 2, entry 7) has the reaction in shorter reaction time with high yield 96 % compared other Cu complex. The best results were obtained by refluxing the reaction mixture in ethanol in presence of 10 mol % of Cu complex.

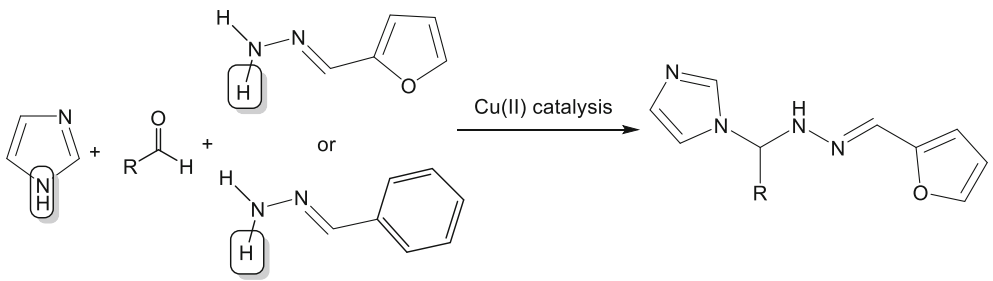
Under optimized conditions with $Cu(phen)Cl_2$ catalysis, imidazole, (furan-2-ylmethylidene)hydrazine, and 4-substituted benzaldehyde or different aldehyde to provide imidazole derivatives **1**–**24** in good yields (54–96 %, Schemes 4, 5). Based on the above results, a plausible mechanism is proposed (Scheme 6).

Reactions of imidazole with benzaldehyde and (furan-2-ylmethylidene)hydrazine in the presence of different Cu(II) catalysts (10 mol %) and different solvents at room temperature were first attempted (Tables 1, 2). Using 10 mol % of $Cu(Phen)Cl_2$ at room temperature for 3 h in ethanol, the desired product **1** was obtained in 90 % yield (entry 7,

Scheme 1



Scheme 2



Scheme 3

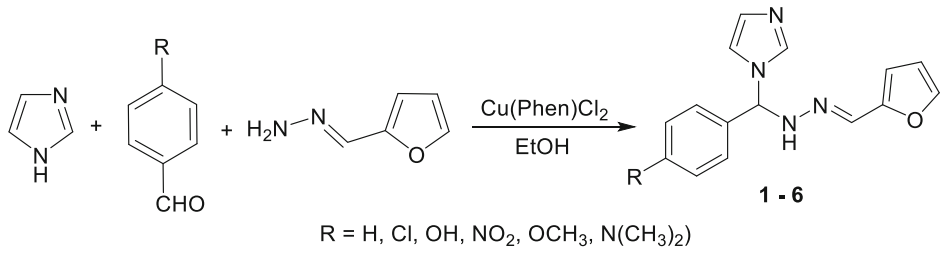


Table 1 The compound **1** from different solvent with Cu(phen)Cl_2 catalysis

Entry	Solvent	Yield/%
1	Toluene	No reaction
2	CH_2Cl_2	46
3	MeCN	74
4	H_2O	35
5	EtOH	96
6	Benzene	No reaction
7	THF	No reaction
8	DMF	No reaction

All reactions were carried out at r.t. for 3 h

Table 2). Meyet et al. [21] reported that three component coupling more rapidly and with a yield of 79 % from imine 10 mol % of Cu(OTf)$_2$ in toluene at 100 °C, and other product one step to products with multiple functional groups with yield 73 %, at same time we are using same catalysis Cu(OTf)$_2$ in our system, which have low yield 77 % in EtOH medium at r.t. The compound **1** was prepared from with 10 mol % of copper(II) acetate, copper(II) acetylacetonate, copper(II) hydroxide, $Cu_2(OH)PO_4$, copper(II) trifluoromethanesulfonate, tetrakis(pyridine)copper(II) triflate, $CuCl_2$, and CuI as catalysts in ethanol to give yield of 63, 67, 56, 60, 77, 71, 54, and 57 %, respectively (Table 2, entries 1–9). For example, reactions using 10 % Cu(Phen)Cl_2 as catalyst in ethanol gave **13** in 92 % yield (Table 3). When other solvents, such as toluene, dichloromethane, tetrahydrofuran, acetonitrile, dimethylformamide, dimethylsulfoxide, or water were used, the yield of compound **13** somewhat decreased compared to ethanol, the compounds **13–24** are summarized in Table 3.

The structure of compound **1** was determined by analyzing spectral data and by comparison with literature values. The ^{1}H NMR spectrum of **1** showed the characteristic CH group as a doublet at $\delta = 6.23$–6.18 ppm and a NH signal on at $\delta = 7.41$–7.38 ppm as a doublet ($J = 8.10$ Hz). In the ^{13}C NMR spectrum, one characteristic carbon signal corresponding to the CH bond appeared at $\delta = 71.8$ ppm. In addition, the mass spectrum of compound **1** showed the molecular ion signal at $m/z = 266.34$ which matched exactly the expected mass (266.34). To explore the generality and scope of this methodology, further reactions between different substituted imiazole, arylaldehydes, and (furan-2-ylmethylidene)hydrazine or benzylidenehydrazine were carried out under our optimized conditions.

Antibacterial activity

Antibacterial activity of compounds **1–24** were evaluated for their antibacterial activity in vitro against Gram-positive and Gram-negative bacterial species using disc diffusion method. Inhibition zones were measured at mm. The compounds **6** (MIC: 0.5 μg/cm^3), **7** (MIC: 1 μg/cm^3), and **23** (MIC: 0.5 μg/cm^3) are highly active against *Staphylococcus aureus* compared with standard. The compound **7** highly active against *Escherichia coli* and compound **23** highly active against *Pseudomonas aeruginosa* compared with standard. The bacterial zones of inhibition values are given in Table 4.

Antifungal activity

Compounds **1–24** were evaluated for their antifungal activity against in vitro *Aspergillus niger*, *C. albicans*, *Microsporum audouinii*, and *Cryptococcus neoformans* (recultured) using disc diffusion method. The compounds **2** and **23** (MIC: 0.25 and 0.5 μg/cm^3) are highly active against *C. albicans* compared with standard (MIC: 0.5 μg/cm^3). The compound **6** (MIC: 0.5 μg/cm^3) is highly active against *C. neoformans* and compound **19** also highly active against *A. niger* compared with standard clotrimazole. The values are summarized in Table 5. The MIC values were determined as the lowest concentration that completely inhibited visible growth of the microorganisms Table 6.

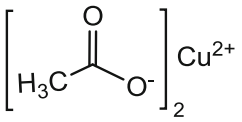
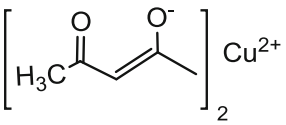
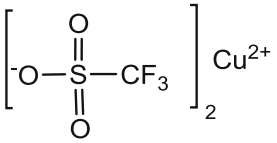
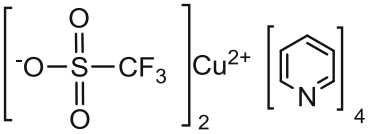
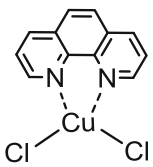
Larvicidal activity

Larvicidal activity was screened for compounds **1–24** at 24 h suggested that second instar larvae and test was carried out by room temperature. The compounds **2**, **3**, **4**, **5**, **6**, and **16** are produced 100 % mortality at 30 μg/cm^3 and the compounds **1**, **8**, **9**, **17**, **21**, **23**, and **24** were produced 100 % mortality at concentration 40 μg/cm^3. Compounds **13** and **20** have lethal effect and killed 50 % of second instars larvicidal when their LD_{50} value was 0.7 and 6.4 μg/cm^3, respectively. The compound **13** is highly toxic LD_{50} value when compared other compounds. The values are summarized in Table 7.

Structure activity relationship

Structural activity relationship were investigated by synthesized compounds **1–24**, among the compounds **2**,**6**, **13**, **19**, and **23** are highly active compared with other compounds (Fig. 2). Imidazole and 4-substituted phenyl ring acts as a biological importance of this domain, in particularly the compound **6** containing –N(CH$_3$)$_2$ group in phenyl ring shows that highly active against *S. aureus* compared with ciprofloxacin and highly active against *C. neoformans* in antifungal screening. The compound **2** containing Cl group in phenyl ring shows that highly active against *C. albicans* whereas the compound **19** containing benzo[*d*] [1,

Table 2 The compound **1** synthesized from ethanol solvent with different Cu(II) catalysis

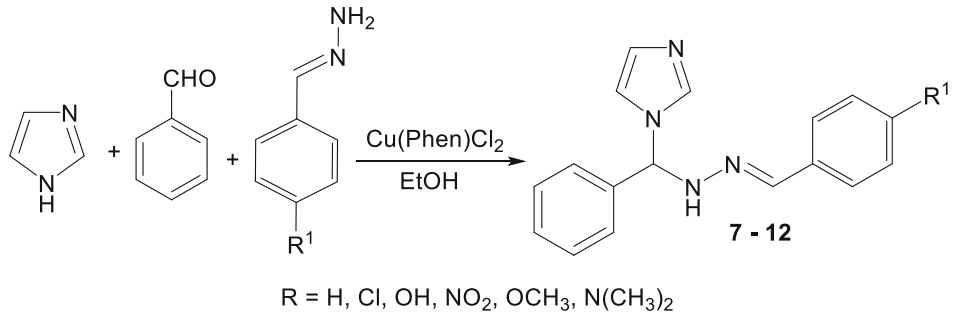
Entry	Catalyst	Yield/%
1		63
2		67
3	$Cu(OH)_2$	56
4	$Cu_2(OH)PO_4$	60
5		77
6		71
7		96
8	$CuCl_2$	54
9	CuI	57

All reactions were carried out with 10 mol % of catalyst for 3 h in EtOH at r.t

3] dioxole group highly active against *A. niger* compared with clotrimazole in antifungal screening.

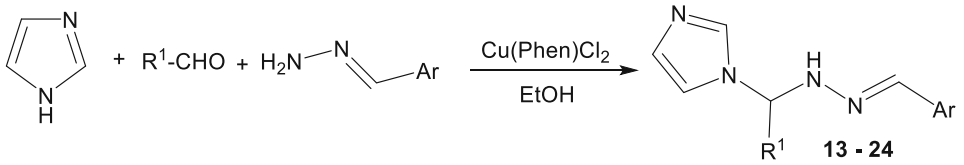
The compound **13** containing 2,6-dimethylocta-2,6-diene group is high active against *E. coli and S. aureus* compound with ciprofloxacin in antibacterial screening and also high toxic (LD_{50}: 0.75 μg/cm^3) in larvicidal screening compared with other compounds. The compound **19** containing thiazole group is highly active against *S. aureus* and *C. albicans* in antimicrobial screening and their comparable for standard ciprofloxacin and clotrimazole.

Scheme 4



R = H, Cl, OH, NO_2, OCH_3, $N(CH_3)_2$

Scheme 5



Scheme 6

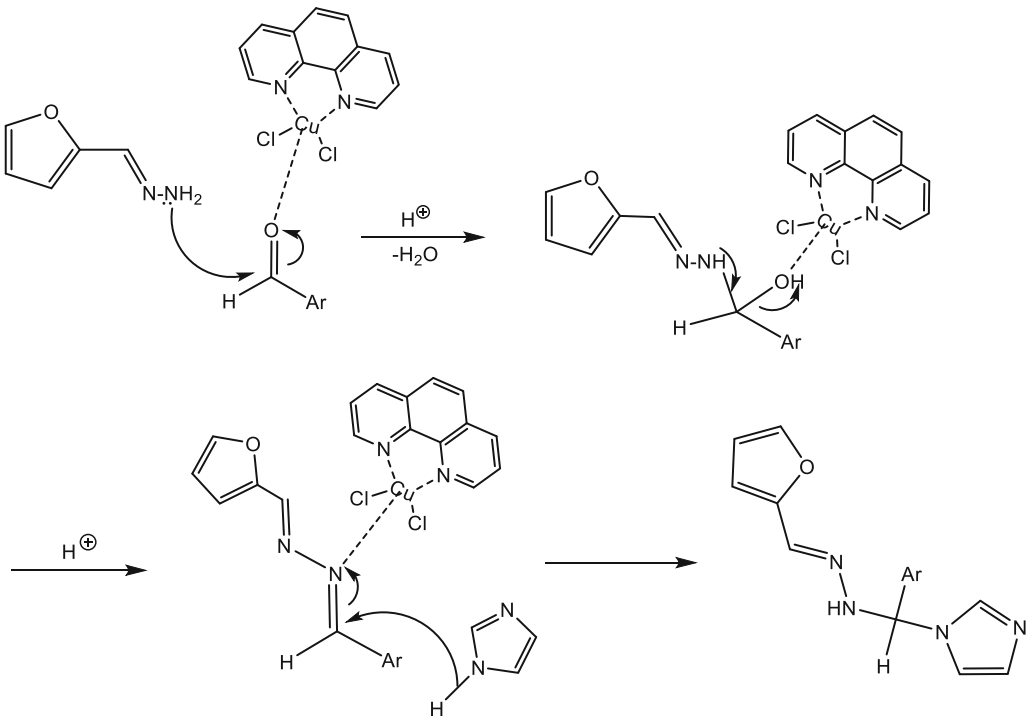
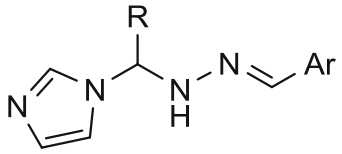


Table 3 Compounds **1–24** synthesized with $Cu(phen)Cl_2$



Comp	R	Ar	Yield/%
1	C_6H_5	2-Furanyl	78
2	4-Cl-C_6H_4	2-Furanyl	82
3	4-OH-C_6H_4	2-Furanyl	87
4	4-NO_2-C_6H_4	2-Furanyl	80
5	4-CH_3O-C_6H_4	2-Furanyl	72
6	4-$(CH_3)_2N$-C_6H_4	2-Furanyl	89
7	C_6H_5	C_6H_5	83
8	C_6H_5	4-Cl-C_6H_4	82
9	C_6H_5	4-OH-C_6H_4	84
10	C_6H_5	4-NO_2-C_6H_4	80
11	C_6H_5	4-CH_3O-C_6H_4	78
12	C_6H_5	4-$(CH_3)_2N$-C_6H_4	76
13	2,6-Dimethyl-1,5-heptadienyl	2-Furanyl	92
14	2,6-Dimethyl-1,5-heptadienyl	C_6H_5	93
15	1*H*-Indol-3-yl	2-Furanyl	84
16	1*H*-Indol-3-yl	C_6H_5	87
17	2-Furanyl	2-Furanyl	86
18	2-Furanyl	C_6H_5	88
19	Benzo[*d*] [1,3] dioxol-5-yl	2-Furanyl	88
20	Benzo[*d*] [1,3] dioxol-5-yl	C_6H_5	84
21	2-Pyridinyl	2-Furanyl	84
22	2-Pyridinyl	C_6H_5	88
23	Thiazol-5-yl	2-Furanyl	87
24	Thiazol-5-yl	C_6H_5	85

All reactions were carried out at r.t. For 3 h

Conclusion

New series of imidazole Mannich base derivatives **1–24** were synthesized, Cu(II) as a catalysis of this reaction and screened for antimicrobial and larvicidal activity. Among these compounds **6** and **23** are high active against *S. aureus* compared with standard in antibacterial screening and compound **2** has highly active against *C. albicans* compared with standard in antifungal screening. Compound **13** shows that highly active compared with other compounds in larvicidal screening. Though, the mechanism of the antimicrobial and larvicidal activity needs further investigations, which are in progress.

Experimental

Melting points were recorded in open capillary tubes. The IR spectra were recorded in KBr on a Shimadzu 8201pc (4000–400 cm^{-1}). The ^1H NMR spectra were recorded on a Bruker DRX-300 MHz. The elemental analysis (C, H, and N) were recorded using an Elemental analyzer model (Varian EL III). The purity of the compounds was checked by thin layer chromatography (TLC) with silica gel plates.

*General procedure for synthesis of compounds **1–24***

To a mixture of imidazole (0.1 mol), (furan-2-ylmethylidene)hydrazine (0.1 mol), and 4-subsituted benzaldehyde

Table 4 Anti-bacterial activity of compounds **1**–**24**, zone of inhibition/mm

Compounds	Gram positive		Gram negative	
	Escherichia coli	*Staphylococcus aureus*	*Klebsiella pneumoniae*	*Pseudomononas aeruginosa*
1	–	–	8	10
2	16	12	10	13
3	10	–	13	12
4	–	12	10	–
5	10	19	13	–
6	20	24	12	18
7	14	10	12	10
8	17	14	10	15
9	15	16	14	10
10	10	10	10	14
11	10	12	10	15
12	14	12	14	16
13	28	24	20	19
14	19	14	17	16
15	18	17	10	10
16	10	18	12	14
17	14	10	12	16
18	17	15	12	10
19	16	14	12	12
20	20	10	14	24
21	18	15	10	10
22	21	14	14	18
23	20	24	23	25
24	19	11	14	19
Ciprofloxacin	27	22	19	32

(0.1 mol) in 30 cm^3 of EtOH was added $Cu(Phen)Cl_2$ (10 mol %) at room temperature. The reaction mixture was refluxed for 5 h. The reaction was checked by TLC, and then the solvent was removed under reduced pressure. The final product was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc.

1-[[2-(Furan-2-ylmethylene)hydrazinyl](phenyl)methyl]-1H-imidazole (**1**, $C_{15}H_{14}N_4O$)
Yield: 78 %; yellow solid; m.p.: 121 °C; IR (KBr): $\overline{V}$ = 3034 (aromatic C–H str), 2974 (NH), 1653 (C=N), 1062 (N–CH–N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 8.10 (s, 1H, HC=N), 7.71–7.64 (d, J = 6.08 Hz, 1H, furyl), 7.67 (s, 1H, imadzole), 7.41–7.38 (d, J = 8.10, Hz, 1H, NH), 7.33–7.22 (m, 5H, Ph-H), 7.20–7.17 (d, J = 11.02 Hz, 1H, HC=CH in imidazole), 6.90–6.94 (d, J = 6.14 Hz, 1H, furyl), 6.72–6.70 (d, J = 11.12 Hz, 1H, HC=CH in imidazole), 6.55–6.41 (d, J = 6.44 Hz, 1H, furyl), 6.23–6.18 (d, J = 8.19 Hz, 1H, CH) ppm; ^{13}C NMR (DMSO-d_6): δ = 148.2, 144.9, 117.9, 113.9 (furyl ring), 138.1, 128.0, 126.0, 126.9, 126.7 (phenyl), 137.0 (CH in imidazole), 134.9 (HC=N), 128.7 (CH in imidazole), 120.9 (CH in imidazole), 71.8 (CH) ppm; EI-MS: m/z (%) = 266.34 (56).

1-[(4-Chlorophenyl)[2-(furan-2-ylmethylene)hydrazinyl]methyl]-1H-imidazole (**2**, $C_{15}H_{13}ClN_4O$)
Yield: 82 %; light brown solid; m.p.: 148 °C; IR (KBr): $\overline{V}$ = 3012 (aromatic C–H str), 2970 (NH), 1659 (C=N), 1060 (N–CH–N), 830 (C–Cl) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 8.14 (s, 1H, HC=N), 7.66–7.64 (d, J = 6.10 Hz, 1H, furyl ring), 7.60 (s, 1H, imidazole), 7.49–7.45 (d, J = 8.12 Hz, 1H, NH), 7.32 (d, J = 11.22 Hz, 1H, HC=CH in imidazole), 7.15–7.11 (dd, J = 6.34–6.89 Hz, 4H, Ph), 6.87–6.84 (d, J = 6.17 Hz, 1H, furyl ring), 6.76–6.72 (d, 1H, J = 11.32 Hz, HC=CH in imidazole), 6.50–6.46 (dd, J = 6.22 Hz, 1H, furyl ring), 6.06–6.02 (d, J = 8.09 Hz, 1H, CH) ppm; ^{13}C NMR (DMSO-d_6): δ = 149.6, 144.0, 116.1, 112.4 (furyl ring), 137.8, 127.0, 127.8, 126.0, 125.9 (phenyl), 136.8 (CH in imidazole),

Table 5 Antifungal activity of compounds **1**–**24**, zone of inhibition/mm

Compound	*Aspergillus niger*	*Candida albicans*	*Microsporum audouinii*	*Cryptococcus neoformans*
1	10	12	8	12
2	16	26	–	10
3	12	15	–	11
4	–	–	–	10
5	8	12	–	11
6	8	12	8	26
7	13	10	–	–
8	8	20	13	16
9	10	14	–	10
10	12	10	–	08
11	16	12	16	–
12	–	10	08	10
13	19	15	10	12
14	12	10	8	7
15	10	8	–	–
16	15	–	–	10
17	10	–	10	12
18	19	6	14	10
19	25	14	10	12
20	20	–	–	10
21	13	–	–	8
22	–	–	–	5
23	10	25	16	–
24	8	10	12	10
Clotrimazole	22	24	26	24

133.1 (HC=N), 129.9 (CH in imidazole), 121.0 (CH in imidazole), 71.6 (CH) ppm; EI-MS: *m/z* (%) = 300.70 (12).

4-[[2-(Furan-2-ylmethylene)hydrazinyl](1H-imidazol-1-yl)methyl]phenol (**3**, $C_{15}H_{14}N_4O_2$)
Yield: 87 %; brown solid; m.p.: 128 °C; IR (KBr): $\overline{V}$ = 3398 (OH), 3037 (aromatic C–H str), 2966 (NH), 1650 (C=N), 1061 (N–CH–N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 9.29 (s, 1H, –OH), 8.09 (s, 1H, HC=N), 7.77–7.73 (d, J = 6.39 Hz, 1H, furyl ring), 7.60 (s, 1H, imidazole), 7.34–7.30 (d, J = 8.18 Hz, 1H, NH), 7.15–7.11 (d, J = 11.12 Hz, 1H, HC=CH in imidazole), 7.10–6.98 (dd, 4H, Ph), 6.91–6.88 (d, J = 6.34 Hz, 1H, furyl ring), 6.80–6.75 (dd, J = 11.12 Hz, 1H, HC=CH in imidazole), 6.50–6.44 (dd, J = 6.41 Hz, 1H, furyl ring), 6.10–6.06 (d, J = 8.22 Hz, 1H, CH) ppm; ^{13}C NMR (DMSO-d_6): δ = 148.0, 144.3, 117.1, 113.0 (furyl ring), 137.1 (CH in imidazole), 134.6 (HC=N), 128.0 (CH in imidazole), 126.1, 126.8, 128.3, 126.0, 138.1 (phenyl), 120.1 (CH in imidazole), 71.5 (CH) ppm; EI-MS: *m/z* (%) = 350.10 (26).

1-[[2-(Furan-2-ylmethylene)hydrazinyl](4-nitrophenyl)methyl]-1H-imidazole (**4**, $C_{15}H_{13}N_5O_3$)
Yield: 80 %; yellow solid; m.p.: 146 °C; IR (KBr): $\overline{V}$ = 3030 (aromatic C–H str), 2979 (NH), 1650 (C=N), 1609 (NO_2), 1061 (N–CH–N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 8.07 (s, 1H, HC=N), 7.70–7.64 (d, J = 6.34 Hz, 1H, furyl), 7.61 (s, 1H, imidazole), 7.47–7.40 (dd, 4H, Ph), 7.39–7.36 (d, J = 8.12 Hz, 1H, NH), 7.21–7.08 (d, J = 8.12 Hz, 1H, HC=CH in imidazole), 6.92–6.87 (d, J = 6.48 Hz, 1H, furyl), 6.86–6.84 (d, J = 8.12 Hz, 1H, HC=CH in imidazole), 6.57–6.53 (dd, J = 6.44 Hz, 1H, furyl), 6.08–6.04 (d, J = 8.12 Hz, 1H, CH) ppm; ^{13}C NMR (DMSO-d_6): δ = 148.3, 144.7, 117.0, 113.6 (furyl ring), 137.2 (CH in imidazole), 138.0, 128.4, 126.8, 126.2, 126.0 (phenyl), 134.0 (HC=N), 128.2 (CH in imidazole), 120.2 (CH in imidazole), 71.1 (CH) ppm; EI-MS: *m/z* = 311.56.

1-[[2-(Furan-2-ylmethylene)hydrazinyl](4-methoxyphenyl)methyl]-1H-imidazole (**5**, $C_{16}H_{16}N_4O_2$)
Yield: 72 %; light yellow solid; m.p.: 128 °C; IR (KBr): $\overline{V}$ = 3036 (aromatic C–H str), 2970 (NH), 1651 (C=N),

Table 6 The minimum inhibitory concentrations of compounds **1**–**24**

Comp. No.	Minimum inhibitory concentration (MIC)/μg/cm^3							
	Antibacterial activity				Antifungal activity			
	E. c.	*S. a.*	*K. p.*	*P. a.*	*A. n.*	*C. a.*	*M. a.*	*Cr. n.*
1	–	>100	–	>100	>100	12	>100	>100
2	>100	>100	16	64	32	0.25	–	>100
3	–	>100	>100	>100	>100	15	–	>100
4	>100	>100	–	–	–	–	–	>100
5	8	>100	>100	–	>100	12	–	>100
6	64	0.5	64	32	>100	12	>100	0.5
7	64	>100	>100	>100	64	>100	–	–
8	16	64	>100	32	>100	2	64	32
9	64	32	64	>100	>100	64	–	>100
10	>100	>100	>100	64	>100	>100	–	>100
11	>100	>100	>100	32	32	64	32	–
12	64	>100	>100	32	–	>100	>100	>100
13	2	1	0.5	16	16	15	>100	>100
14	16	8	16	16	>100	>100	>100	>100
15	16	>100	16	>100	>100	>100	–	–
16	8	>100	>100	32	64	–	–	>100
17	>100	>100	8	32	>100	–	>100	>100
18	32	>100	16	>100	19	>100	64	>100
19	64	>100	16	8	0.5	14	>100	>100
20	>100	32	8	4	20	–	–	>100
21	32	>100	16	>100	>100	–	–	>100
22	64	64	4	8	–	–	–	>100
23	8	0.5	8	2	>100	0.5	16	–
24	>100	64	16	4	>100	>100	>100	>100
Ciprofloxacin	4	2	1	0.5	–	–	–	
Clotrimazole	–	–	–	–	1	0.5	0.25	1

1060 (N–CH–N) cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta = 8.11$ (s, 1H, HC=N), 7.72–7.68 (d, $J = 6.76$ Hz, 1H, furyl), 7.66 (s, 1H, imadzole), 7.40–7.36 (d, $J = 8.11$ Hz, 1H, NH), 7.24–7.20 (d, $J = 11.12$ Hz, 1H, HC=CH in imidazole), 6.94–6.90 (d, $J = 6.61$, 1H, furyl), 6.81–6.78 (d, $J = 11.16$ Hz, 1H, HC=CH in imidazole), 6.72–6.31 (dd, $J = 5.65$, 5.89 Hz, 4H, Ph), 6.54–6.51 (dd, $J = 6.42$ Hz, 1H, furyl), 6.06–6.04 (d, $J = 8.04$ Hz, 1H, CH), 4.14 (s, 3H, –OCH_3) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 148.0$, 144.0, 116.9, 114.1 (furyl ring), 137.2 (CH in imidazole), 137.8, 128.9, 126.2, 126.1, 125.7 (phenyl ring), 134.3 (HC=N), 128.0 (CH in imidazole), 120.5 (CH in imidazole), 71.9 (CH), 55.9 (OCH_3) ppm; EI-MS: *m*/*z* (%) = 296.89 (49).

4-[[2-(Furan-2-ylmethylene)hydrazinyl](1H-imidazol-1-yl)methyl]-N,N-dimethylaniline (**6**, $C_{17}H_{19}N_5O$)
Yield: 89 %; light yellow solid; m.p.: 113 °C; IR (KBr): $\overline{V} = 3028$ (aromatic C–H str), 2970 (NH), 1651 (C=N), 1067 (N–CH–N) cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta = 8.17$ (s, 1H, HC=N), 7.70–7.67 (d, $J = 6.56$ Hz, 1H, furyl), 7.69 (s, 1H, imidazole),7.40–7.38 (d, $J = 8.17$ Hz, 1H, NH), 7.18–7.15 (d, $J = 11.09$ Hz, 1H, HC=CH in imidazole), 7.07–6.80 (dd, $J = 4.67$, 4.89 Hz, 4H, Ph), 6.94–6.92 (d, $J = 6.51$ Hz, 1H, furyl H), 6.70–6.67 (d, $J = 11.16$ Hz, 1H, HC=CH in imidazole), 6.49–6.44 (dd, $J = 6.67$ Hz, 1H, furyl H), 6.19–6.17 (d, $J = 8.06$ Hz, 1H, CH), 2.80 (s, 6H, –N(CH_3)$_2$) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 148.2$, 144.1, 117.0, 112.9 (furyl ring), 138.1, 128.0, 126.9, 126.7, 126.0 (phenyl ring), 137.7 (CH in imidazole), 134.3 (HC=N), 128.7 (CH in imidazole), 120.8 (CH in imidazole), 71.9 (CH), 40.9 (N ($C\underline{H}_3$)$_2$) ppm; EI-MS: *m*/*z* (%) = 309.01 (12).

1-[(2-Benzylidenehydrazinyl)(phenyl)methyl]-1H-imidazole (**7**, $C_{17}H_{16}N_4$)
Yield: 83 %; yellow solid; m.p.: 134 °C; IR (KBr): $\overline{V} = 3023$ (aromatic C–H str), 2971 (NH), 1661 (C=N), 1057 (N–CH–N) cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta = 8.32$ (s,

Table 7 Larvicidal profile of compounds **1–24** on second instar larvae of *Culex* sp.

Comp	Mortality/%				LD_{50}
	Concentration/μg/cm^3				
	10	20	30	40	
1	36 ± 4.1	54 ± 40	82 ± 4.4	100 ± 0.0	15.48
2	50 ± 4.8	71 ± 4.2	100 ± 0.0	–	10.80
3	42 ± 4.0	86 ± 2.5	100 ± 0.0	–	12.88
4	42 ± 4.1	82 ± 4.0	100 ± 0.0	–	11.00
5	52 ± 4.8	73 ± 4.2	100 ± 0.0	–	8.34
6	38 ± 1.9	66 ± 4.8	100 ± 0.0	–	14.79
7	32 ± 2.1	63 ± 2.0	89 ± 1.8	100 ± 0.0	15.90
8	21 ± 1.4	43 ± 1.0	86 ± 1.2	100 ± 0.0	23.13
9	35 ± 1.9	51 ± 1.0	78 ± 1.0	100 ± 0.0	19.10
10	47 ± 1.0	67 ± 2.0	81 ± 1.3	100 ± 0.0	13.16
11	41 ± 2.9	52 ± 1.9	84 ± 2.3	100 ± 0.0	18.07
12	59 ± 1.0	63 ± 2.0	88 ± 1.8	100 ± 0.0	8.23
13	75 ± 4.6	100 ± 0.0	–	–	0.7
14	32 ± 3.7	53 ± 4.9	89 ± 5.3	100 ± 0.0	16.7
15	41 ± 2.2	57 ± 3.6	83 ± 4.8	100 ± 0.0	11.3
16	54 ± 2.7	76 ± 4.1	100 ± 0.0	–	9.4
17	47 ± 5.6	63 ± 5.2	81 ± 3.8	100 ± 0.0	12.8
18	54 ± 4.4	79 ± 1.1	100 ± 0.0	–	8.4
19	59 ± 5.1	85 ± 2.8	100 ± 0.0	–	7.3
20	67 ± 3.9	100 ± 0.0	–	–	6.4
21	31 ± 3.6	46 ± 4.8	57 ± 2.1	100 ± 0.0	24.6
22	48 ± 4.3	70 ± 4.0	100 ± 0.0	–	13.2
23	47 ± 4.1	53 ± 5.2	76 ± 4.8	100 ± 0.0	12.9
24	52 ± 3.2	60 ± 1.8	88 ± 3.7	100 ± 0.0	9.5

Value were the means of three replicates ± SD

1H, HC=N), 7.97 (s, 1H, imadzole), 7.57–7.22 (m, 5H, Ph), 7.33–7.22 (m, 5H, Ph), 7.20–7.16 (d, $J = 11.22$ Hz, 1H, HC=CH in imidazole), 6.88–6.84 (d, $J = 11.24$ Hz, 1H, HC=CH in imidazole), 6.13–6.10 (d, $J = 9.19$ Hz, 1H, CH), 2.41–2.40 (d, $J = 9.10$ Hz, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 144.1$ (HC=N), 138.2, 124.9, 127.9, 133.9 (phenyl ring), 137.8 (CH in imidazole), 128.1, 126.0, 136.0, 126.9 (phenyl), 128.5 (CH in imidazole), 120.3 (CH in imidazole), 73.8 (CH) ppm; EI-MS: *m/z* (%) = 266.34 (56).

1-[[2-(4-Chlorobenzylidene)hydrazinyl](phenyl)methyl]-1H-imidazole (**8**, $C_{17}H_{15}ClN_4$)
Yield: 82 %; yellow solid; m.p.: 146 °C; IR (KBr): $\overline{V} = 3020$ (aromatic C–H str), 2967 (NH), 1667 (C=N), 1051 (N–CH–N), 846 (C–Cl) cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta = 8.30$ (s, 1H, HC=N), 7.93 (s, 1H, imadzole), 7.67–7.50 (m, 5H, Ph), 7.32–7.27 (dd, 4H, Ph-Cl), 7.18–7.14 (d, $J = 11.24$ Hz, 1H, HC=CH in imidazole), 6.81–6.78 (d, $J = 11.28$ Hz, 1H, HC=CH in imidazole), 6.10–6.06 (d, $J = 9.11$ Hz, 1H, CH), 2.45–2.41 (d, $J = 9.15$ Hz, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 144.7$ (HC=N), 138.6, 128.1, 130.2, 131.9 (Ph-Cl), 137.8 (CH in imidazole), 128.8, 126.9, 135.7, 126.1 (phenyl), 127.5 (CH in imidazole), 122.6 (CH in imidazole), 74.1 (CH) ppm; EI-MS: *m/z* (%) = 310.67 (45).

4-[[2-[(1H-Imidazol-1-yl)(phenyl)methyl]hydrazono]methyl]phenol (**9**, $C_{17}H_{16}N_4O$)
Yield: 84 %; light yellow solid; m.p.: 139 °C; IR (KBr): $\overline{V} = 3376$ (OH), 3024 (aromatic C–H str), 2974 (NH), 1667 (C=N), 1055 (N–CH–N) cm^{-1}; ^{1}H NMR (DMSO-d_6):

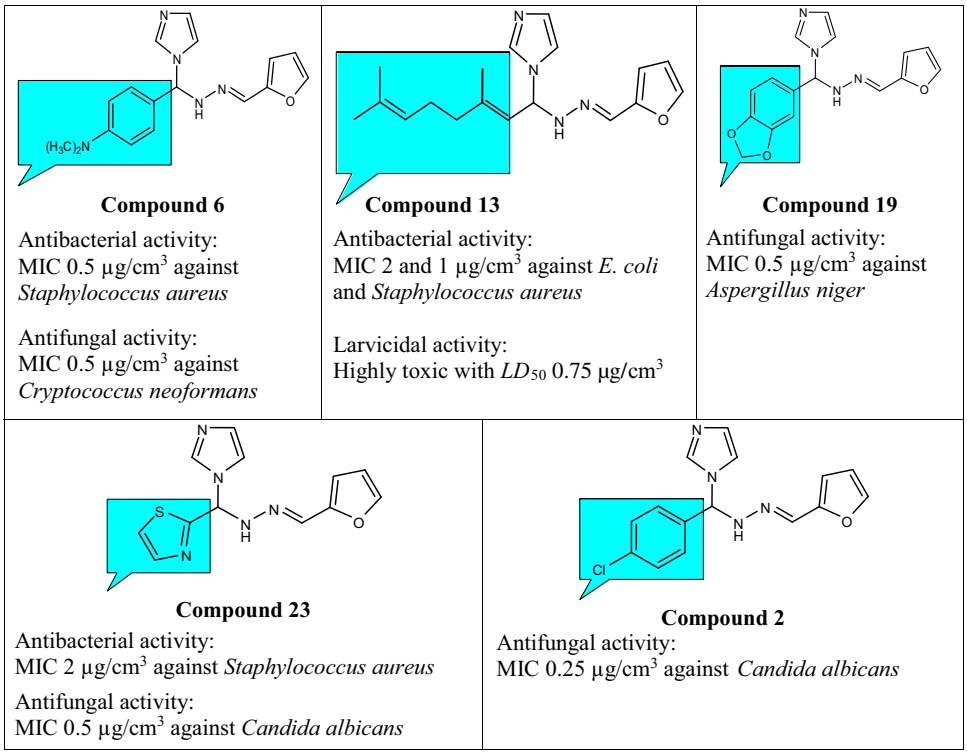


Fig. 2 Highly bioactive synthetic compounds

δ = 9.37 (s, 1H, Ph-OH), 8.36 (s, 1H, HC=N), 7.91 (s, 1H, imadzole), 7.67–7.50 (m, 5H, Ph), 7.31–7.42 (dd, 4H, Ph-OH), 7.16–7.13 (d, J = 11.29 Hz, 1H, HC=CH in imidazole), 6.84–6.81 (d, J = 11.24 Hz, 1H, HC=CH in imidazole), 6.16–6.12 (d, J = 9.12 Hz, 1H, CH), 2.47–2.44 (d, J = 9.16 Hz, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 144.1 (HC=N), 137.2, 127.0, 129.5, 132.2 (Ph-OH), 136.8 (CH in imidazole), 128.3, 126.7, 135.6, 126.4 (phenyl), 128.1 (CH in imidazole), 121.4 (CH in imidazole), 73.8 (CH) ppm; EI-MS: m/z (%) = 292.13 (33).

1-[[2-(4-Nitrobenzylidene)hydrazinyl](phenyl)methyl]-1H-imidazole (**10**, $C_{17}H_{15}N_5O_2$)
Yield: 80 %; light yellow solid; m.p.: 147 °C; IR (KBr): $\overline{V}$ = 3027 (aromatic C–H str), 2975 (NH), 1665 (C=N), 1603 (NO_2), 1064 (N–CH–N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 8.38 (s, 1H, HC=N), 7.92 (s, 1H, imadzole), 7.81-7.45 (m, 5H, Ph), 7.52–7.43 (dd, 1H, Ph), 7.24–7.21 (d, J = 11.26 Hz, 1H, HC=CH in imidazole), 6.88–6.82 (d, J = 11.29 Hz, 1H, HC=CH in imidazole), 6.13–6.07 (d, J = 9.19 Hz, 1H, CH), 2.41–2.38 (d, J = 9.10 Hz, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 143.7 (HC=N), 137.6, 125.1, 126.3, 134.2 (phenyl ring), 137.1 (CH in imidazole), 128.6, 126.1, 137.8, 127.3 (phenyl), 128.1 (CH in imidazole), 120.7 (CH in imidazole), 73.1 (CH) ppm; EI-MS: m/z (%) = 321.33 (24).

1-[[2-(4-Methoxybenzylidene)hydrazinyl](phenyl)methyl]-1H-imidazole (**11**, $C_{18}H_{18}N_4O$)
Yield: 78 %; light yellow solid; m.p.: 140 °C; IR (KBr): $\overline{V}$ = 3021 (aromatic C–H str), 2978 (NH), 1657 (C=N), 1053 (N–CH–N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 8.37 (s, 1H, HC=N), 7.98 (s, 1H, imadzole), 4.11 (s, 3H, CH_3O), 7.81–7.57 (m, 5H, Ph), 7.33–7.22 (dd, J = 4.56, 4.98 Hz, 4H, Ph-Cl), 7.20–7.14 (d, J = 11.35 Hz, 1H, HC=CH in imidazole), 6.83–6.91 (d, J = 11.42 Hz, 1H, HC=CH in imidazole), 6.19–6.12 (d, J = 9.23 Hz, 1H, CH), 2.47–2.41 (d, J = 9.15 Hz, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 144.9 (HC=N), 138.6, 125.3, 128.1, 134.1 (phenyl ring), 137.8 (CH in imidazole), 128.8, 125.9, 137.5, 127.0 (phenyl), 128.9 (CH in imidazole), 127.4 (CH in imidazole), 73.3 (CH), 55.1 (OCH_3) ppm; EI-MS: m/z (%) = 306.15 (16).

4-[[2-[(1H-Imidazol-1-yl)(phenyl)methyl]hydrazono]methyl]-N,N-dimethylaniline (**12**, $C_{19}H_{21}N_5$)
Yield: 76 %; light yellow solid; m.p.: 152 °C; IR (KBr): $\overline{V}$ = 3029 (aromatic C–H str), 2967 (NH), 1657 (C=N), 1052 (N–CH–N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 8.89 (s, 1H, HC=N), 7.91 (s, 1H, imadzole), 7.78–7.50 (m, 5H, Ph), 7.33–7.22 (d, 4H, Ph), 7.20–7.17 (d, J = 11.78 Hz, 1H, HC=CH in imidazole), 6.80–6.71 (d, J = 11.67 Hz, 1H, HC=CH in imidazole), 6.19–6.11 (d, J = 9.19 Hz, 1H, CH), 2.38–2.35 (d, J = 9.10 Hz, 1H, NH), 2.80 (s, 6H,

$N(CH_3)_2$) ppm; ^{13}C NMR (DMSO-d_6): δ = 148.1 (HC=N), 138.7, 124.1, 127.5, 132.1 (phenyl ring), 136.9 (CH in imidazole), 127.3, 126.0, 135.1, 126.5 (phenyl), 127.1 (CH in imidazole), 120.8 (CH in imidazole), 73.9 (CH), 40.8 ($N(CH_3)_2$) ppm; EI-MS: *m/z* (%) = 319.18 (56).

1-[1-[2-(Furan-2-ylmethylene)hydrazinyl]-3,7-dimethyl-octa-2,6-dienyl]-1H-imidazole (**13**, $C_{18}H_{24}N_4O$)
Yield: 89 %; light yellow solid; m.p.: 128 °C; IR (KBr): $\overline{V}$ = 2913 (NH), 1624 (C=N), 1062(N–CH–N) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 8.23 (s, 1H, HC=N), 7.94–7.89 (d, J = 11.71 Hz, 1H, HC=CH in imidazole), 6.66–6.70 (d, J = 11.77 Hz, 1H, HC=CH in imidazole), 7.70–7.67 (d, J = 6.45 Hz, 1H, furyl), 7.20–7.17 (d, J = 12.8 Hz, 1H, NH), 6.93–6.89 (dd, J = 6.34 Hz, 1H, furyl), 7.71 (s, 1H, imidazole), 6.54–6.50 (d, J = 6.43 Hz, 1H, furyl), 5.78–5.74 (d, J = 10.65 Hz, 1H, –HC=CH), 5.32 (t, 1H, CH=$C(CH_3)_2$), 4.39–4.37 (dd, J = 12.3 Hz, 1H, CH), 2.16–2.12 (tt, J = 10.76 Hz, 2H, CH_2–CH_2), 1.86 (s, 3H, CH_3), 1.84 (s, 3H, CH_3), 1.72 (s, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 149.2 (furyl ring), 145.3 (furyl ring), 138.2 (HC=C–), 135.9 (HC=N), 133.8 (HC=$C(CH_3)_2$), 129.7 (CH in imidazole), 128.5 (CH in imidazole), 124.5 (HC=C–), 123.1 (HC=$C(CH_3)_2$), 118.4 (furyl ring), 115.4 (furyl ring), 120.2 (CH in imidazole), 71.0 (CH), 38.2 (CH_2), 30.9 (CH_2), 26.5 (CH_2), 24.8 (HC=C($CH_3)_2$), 18.4 (HC=C($CH_3)_2$), 17.1 (HC=C–CH_3) ppm; EI-MS: *m/z* (%) = 312.21 (15).

1-[1-(2-Benzylidenehydrazinyl)-3,7-dimethylocta-2,6-dienyl]-1H-imidazole (**14**, $C_{20}H_{26}N_4$)
Yield: 89 %; light yellow solid; m.p.: 124 °C; IR (KBr): $\overline{V}$ = 3028 (aromatic C–H str), 2970 (NH), 1651 (C=N), 1067 (N–CH–N) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 8.12 (s, 1H, HC=N), 7.90–7.96 (d, J = 11.67 Hz, 1H, HC=CH in imidazole), 6.77–6.71 (d, J = 11.81 Hz, 1H, HC=CH in imidazole), 7.52–7.49 (m, 5H), 7.23 (s, 1H, imidazole), 7.21 (d, J = 12.1 Hz, 1H, NH), 5.75–5.70 (t, J = 10.55 Hz, 1H, –CH=$C(CH_3)_2$), 5.32–5.29 (d, J = 12.1 Hz, 1H, HC=CH), 4.37–4.29 (dd, J = 12.1 Hz, 1H, CH), 2.12–2.10 (tt, 2H, CH_2–CH_2), 1.89 (s, 3H, CH_3), 1.81 (s, 3H, CH_3), 1.74 (s, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 138.5 (HC=C–), 135.0 (HC=N), 133.1 (HC=$C(CH_3)_2$), 132.0, 130.1, 129.6, 128.0 (phenyl), 120.19 (CH in imidazole), 128.6 (CH in imidazole), 127.9 (CH in imidazole), 124.0 (HC=C–), 123.6 (HC=$C(CH_3)_2$), 71.6 (CH), 37.1 (CH_2), 30.2 (CH_2), 24.1 (HC=C($CH_3)_2$), 18.0 (HC=C($CH_3)_2$), 17.6 (HC=C–CH_3) ppm; EI-MS: *m/z* (%) = 312.21 (15).

3-[[2-(Furan-2-ylmethylene)hydrazinyl](1H-imidazol-1-yl)methyl]-1H-indole (**15**, $C_{17}H_{15}N_5O$)
Yield: 89 %; light yellow solid; m.p.: 146 °C; IR (KBr): $\overline{V}$ = 3067 (aromatic C–H str), 2985 (NH), 1661 (C=N), 1058 (N–CH–N) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 10.84 (s, 1H, NH indole), 8.27 (s, 1H, HC=N), 7.82 (s, 1H, CH imidazole), 7.71–7.68 (d, J = 6.35 Hz, 1H, furyl), 7.60–7.58 (d, J = 8.87 Hz, 1H, Ph), 7.32 (dd, 1H, Ph), 7.23–7.23 (d, J = 11.41 Hz, 1H, NH), 7.18 (d, J = 11.37 Hz, 1H, HC=CH in imidazole), 7.11–7.07 (t, J = 8.66 Hz, 1H, Ph), 6.90–6.88 (d, J = 6.98 Hz, 1H, furyl), 6.70–6.67 (d, J = 11.32 Hz, 1H, HC=CH in imidazole), 6.50–6.48 (t, J = 6.07 Hz, 1H, furyl), 6.19–6.15 (d, J = 11.45 Hz, CH) ppm; ^{13}C NMR (DMSO-d_6): δ = 148.2, 144.5, 117.5, 114.5 (furyl ring), 135.7 (CH in imidazole), 134.1, 128.3, 119.7, 118.1, 117.8, 110.4 (indole), 133.7 (HC=N), 128.7 (CH in imidazole), 120.1 (CH in imidazole), 72.2 (CH) ppm; EI-MS: *m/z* (%) = 305.39 (12).

3-[(2-Benzylidenehydrazinyl)(1H-imidazol-1-yl)methyl]-1H-indole (**16**, $C_{19}H_{17}N_5$)
Yield: 89 %; light yellow solid; m.p.: 148 °C; ^1H NMR (DMSO-d_6): δ $\overline{V}$ = 10.80 (s, 1H, NH indole), 8.22 (s, 1H, HC=N), 7.83 (s, 1H, CH imidazole), 7.81–7.52 (m, 5H, Ph), 7.48–7.45 (d, J = 8.56 Hz, 1H, Ph), 7.32–7.27 (d, J = 8.08 Hz, 1H, Ph), 7.21–7.18 (d, J = 11.41 Hz, 1H, NH), 7.16–7.14 (d, J = 11.87 Hz, 1H, HC=CH in imidazole), 7.12–7.14 (t, 1H, Ph), 6.18–6.15 (d, J = 11.45 Hz, CH), 6.69–6.63 (d, J = 11.78 Hz, 1H, HC=CH in imidazole) ppm; ^{13}C NMR (DMSO-d_6): δ = 135.7 (CH in imidazole), 133.1 (HC=N), 120.8 (CH in imidazole), 128.8 (CH in imidazole), 135.3, 128.7, 119.1, 118.6, 117.0, 110.8 (indole), 133.1, 128.9, 127.9, 132.9 (phenyl ring), 72.2 (CH) ppm; EI-MS: *m/z* (%) = 315.01 (12).

1-[(Furan-2-yl)[2-(furan-2-ylmethylene)hydrazinyl]methyl]-1H-imidazole (**17**, $C_{13}H_{12}N_4O_2$)
Yield: 89 %; light yellow solid; m.p.: 124 °C; IR (KBr): $\overline{V}$ = 3035 (aromatic C-H str), 2967 (NH), 1658 (C=N), 1060 (N–CH–N) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 8.31 (s, 1H, HC=N), 7.89 (s, 1H, imidazole), 7.71–7.67 (d, J = 6.60 Hz, 1H, furan), 7.61–7.58 (d, J = 6.55 Hz, 1H, furan), 7.46–7.40 (d, J = 11.61 Hz, 1H, NH), 7.28–7.24 (d, J = 11.04 Hz, 1H, HC=CH in imidazole), 6.72–6.69 (d, J = 11.87 Hz, 1H, HC=CH in imidazole), 6.52 (d, 1H, furan), 6.44 (dd, 1H, furan), 6.92 (d, 1H, furan), 6.26 (d, 1H, furan), 6.19–6.17 (d, J = 11.65 Hz, 1H, CH) ppm; ^{13}C NMR (DMSO-d_6): δ = 156.8, 142.5, 112.4, 109.5 (furan ring), 149.9, 148.3, 118.1, 112.3 (furan ring), 138.6 (CH in imidazole), 134.9 (HC=N), 128.7 (CH in imidazole), 120.8 (CH in imidazole), 74.9 (CH) ppm; EI-MS: *m/z* (%) = 256.65 (12).

1-[(2-Benzylidenehydrazinyl)(furan-2-yl)methyl]-1H-imidazole (**18**, $C_{15}H_{14}N_4O$)
Yield: 89 %; light yellow solid; m.p.: 134 °C; IR (KBr): $\overline{V}$ = 3035 (aromatic C–H str), 2967 (NH), 1658 (C=N), 1060 (N–CH–N) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 8.34 (s,

1H, HC=N), 7.89 (s, 1H, imidazole), 7.82–7.51 (m, 5H, phenyl ring), 7.71–7.68 (d, $J = 6.45$ Hz, 1H, furan), 7.28–7.24 (d, $J = 11.36$ Hz, 1H, HC=CH in imidazole), 6.72–6.69 (d, $J = 11.56$ Hz, 1H, HC=CH in imidazole), 6.52 (dd, 1H, furan), 6.29–6.25 (d, $J = 11.67$ Hz, 1H, CH), 6.28–6.24 (d, $J = 6.78$ Hz, 1H, furyl H), 2.46–2.40 (d, $J = 11.52$ Hz, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 138.6$ (CH in imidazole), 156.8, 142.5, 112.4, 109.5 (furan ring), 134.9 (HC=N), 120.8 (CH in imidazole), 133.1, 131.7, 129.8, 128.6 (phenyl ring), 128.7 (CH in imidazole), 74.9 (CH) ppm; EI-MS: *m/z* (%) = 266.34 (12).

1-[(Benzo[d] [1,3] dioxol-5-yl)[2-(furan-2-ylmethylene)-hydrazinyl]methyl]-1H-imidazole (**19**, $C_{16}H_{14}N_4O_3$)
Yield: 89 %; light yellow solid; m.p.: 146 °C; IR (KBr): $\overline{V} = 3045$ (aromatic C–H str), 2965 (NH), 1667 (C=N), 1062 (N–CH–N) cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta = 8.34$ (s, 1H, HC=N), 7.74–7.72 (d, $J = 6.17$ Hz, 1H, furan), 7.69 (s, 1H, imidazole), 7.56–7.51 (d, $J = 12.02$ Hz, 1H, NH), 7.18–7.14 (d, $J = 6.55$ Hz, 1H, HC=CH in imidazole), 6.94–6.90 (d, $J = 6.47$ Hz, 1H, furan), 6.89 (s, 1H, Ph), 6.78–6.74 (d, $J = 14.02$ Hz, 1H, Ph), 6.70–6.64 (d, $J = 6.41$ Hz, 1H, HC=CH in imidazole), 6.59–6.54 (dd, $J = 6.61$ Hz, 1H, furan), 6.17 (s, 2H, CH_2), 6.13–6.10 (d, $J = 14.06$ Hz, 1H, Ph), 6.08 (d, $J = 12.02$ Hz, CH) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 148.2$, 144.1, 117.0, 112.9 (furan ring), 146.6, 145.4, 131.7, 120.2, 112.9, 112.8 (phenyl), 137.7 (CH in imidazole), 134.5 (HC=N), 128.7 (CH in imidazole), 120.8 (CH in imidazole), 102.5 (CH_2), 73.1 (CH) ppm; EI-MS: *m/z* (%) = 310.01 (31).

1-[(Benzo[d] [1,3] dioxol-5-yl)(2-benzylidenehydrazinyl)-methyl]-1H-imidazole (**20**, $C_{18}H_{16}N_4O_2$)
Yield: 89 %; light yellow solid; m.p.: 176 °C; IR (KBr): $\overline{V} = 3028$ (aromatic C–H str), 2970 (NH), 1651 (C=N), 1067 (N–CH–N) cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta = 8.39$ (s, 1H, HC=N), 7.83–7.52 (m, 5H, Ph), 7.48 (s, 1H, imidazole), 7.16–7.13 (d, $J = 11.42$ Hz, 1H, HC=CH in imidazole), 6.92 (s, 1H, Ph), 6.84–6.81 (d, $J = 12.89$ Hz, 1H, CH), 6.75–6.72 (d, $J = 5.44$ Hz, 1H, phenyl ring), 6.70–6.65 (d, $J = 11.41$ Hz, 1H, HC=CH in imidazole), 6.65–6.61 (d, $J = 5.55$ Hz, 1H, Ph), 6.19 (s, 2H, CH_2), 2.56–2.53 (d, $J = 12.72$ Hz, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 149.4$, 146.5, 132.5, 120.9, 112.8 (phenyl), 137.7 (CH in imidazole), 134.5 (HC=N), 128.9 (C=C in imidazole ring), 103.5 (CH_2), 128.7 (CH in imidazole), 129.2–133.7 (phenyl ring), 120.8 (C=C in imidazole), 73.9 (CH) ppm; EI-MS: *m/z* (%) = 320.01 (31).

2-[[2-(Furan-2-ylmethylene)hydrazinyl](1H-imidazol-1-yl)methyl]pyridine (**21**, $C_{14}H_{13}N_5O$)
Yield: 89 %; light yellow solid; m.p.: 134 °C; IR (KBr): $\overline{V} = 3042$ (aromatic C–H str), 2988 (NH), 1648 (C=N), 1065 (N–CH–N) cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta = 8.41$ (d, 1H, pyridine), 8.38 (s, 1H, HC=N), 7.74 (d, 1H, furan), 7.70–7.67 (dd, $J = 4.43$ Hz, 1H, pyridine), 7.40–4.37 (d, $J = 4.22$ Hz, 1H, pyridine), 7.38–7.33 (d, $J = 4.65$ Hz, 1H, HC=CH in imidazole), 7.34 (s, 1H, imidazole), 7.30–7.28 (dd, $J = 4.54$ Hz, 1H, pyridine), 7.07–7.01 (d, $J = 11.98$ Hz, 1H, NH), 6.90–6.87 (d, $J = 6.37$ Hz, 1H, furan), 6.73–6.69 (d, $J = 11.27$ Hz, 1H, HC=CH in imidazole), 6.56–6.51 (dd, $J = 6.77$ Hz, 1H, furan), 6.23 (d, $J = 11.90$ Hz, 1H, CH) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 134.3$ (HC=N), 138.9 (CH in imidazole), 121.8 (CH in imidazole), 127.7 (CH in imidazole), 135.9, 120.9, 124.0, 146.7, 158.9 (pyridine), 118.4, 112.4, 145.6, 148.9 (furan ring), 73.4 (CH) ppm; EI-MS: *m/z* (%) = 267.36 (22).

2-[(2-Benzylidenehydrazinyl)(1H-imidazol-1-yl)methyl]-pyridine (**22**, $C_{16}H_{15}N_5$)
Yield: 89 %; light yellow solid; m.p.: 167 °C; IR (KBr): $\overline{V} = 3035$ (aromatic C–H str), 2978 (NH), 1659 (C=N), 1087 (N–CH–N) cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta = 8.45$ (s, 1H, HC=N), 8.37–8.34 (d, $J = 4.07$ Hz, 1H, pyridine), 7.83–7.80 (d, $J = 5.22$ Hz, 2H, Ph), 7.81 (s, 1H, imidazole), 7.74–7.69 (dd, $J = 4.92$ Hz, 1H, pyridine), 7.55–7.51 (dd, $J = 5.17$ Hz, 1H, Ph), 7.52–7.48 (d, $J = 5.17$ Hz, 2H, Ph), 7.42–4.39 (d, $J = 4.87$ Hz, 1H, pyridine), 7.10–7.07 (d, $J = 11.09$ Hz, 1H, HC=CH in imidazole), 7.32–7.28 (dd, 1H, pyridine), 6.70–6.67 (d, $J = 11.19$ Hz, 1H, HC=CH in imidazole), 6.19–6.16 (d, $J = 12.08$ Hz, 1H, CH), 2.87–2.84 (d, $J = 12.10$ Hz, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 158.1$, 146.7, 136.0, 126.9, 120.0 (pyridine), 136.7 (CH in imidazole), 134.3 (HC=N), 129.0, 128.2, 133.6, 130.9 (Ph), 128.7 (CH in imidazole), 120.8 (CH in imidazole), 73.9 (CH) ppm; EI-MS: *m/z* (%) = 277.01 (12).

5-[[2-(Furan-2-ylmethylene)hydrazinyl](1H-imidazol-1-yl)methyl]thiazole (**23**, $C_{12}H_{11}N_5OS$)
Yield: 89 %; light yellow solid; m.p.: 113 °C; IR (KBr): $\overline{V} = 3049$ (aromatic C-H str), 2969 (NH), 1658 (C=N), 1088 (N–CH–N) cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta = 8.24$ (s, 1H, HC=N), 2.12 (d, $J = 12.13$ Hz, 1H, NH), 6.22–6.19 (d, $J = 12.20$ Hz, 1H, CH), 6.91–6.87 (d, $J = 6.67$ Hz, 1H, furan), 6.44–6.40 (dd, $J = 6.61$ Hz, 1H, furan), 7.63–7.60 (d, $J = 6.60$ Hz, 1H, furan), 7.82 (s, 1H, imidazole), 6.17–6.14 (d, $J = 11.12$ Hz, 1H, HC=CH in imidazole), 7.72–7.69 (d, $J = 11.10$ Hz, 1H, HC=CH in imidazole), 8.91 (s, 1H, thiazole H), 7.48 (s, 1H, thiazole) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 153.1$, 141.2, 132.8 (thiazole ring), 144.7, 149.1, 118.9, 112.0 (furan), 133.9 (HC=N), 127.9 (CH in imidazole), 122.2 (CH in imidazole), 121.6 (CH in imidazole), 73.6 (CH) ppm; EI-MS: *m/z* (%) = 273.34 (12).

5-[(2-Benzylidenehydrazinyl)(1H-imidazol-1-yl)methyl]thiazole (**24**, $C_{14}H_{13}N_5S$)

Yield: 89 %; light yellow solid; m.p.: 135 °C; IR (KBr): $\overline{V}$ = 3049 (aromatic C–H str), 2969 (NH), 1658 (C=N), 619 (C–S–C), 1088 (N–CH–N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 8.92 (s, 1H, thiazole), 8.21 (s, 1H, HC=N), 7.90 (s, 1H, imidazole), 7.86–7.84 (d, J = 7.89 Hz, 1H, HC=CH in imidazole), 7.81–7.30 (m, 5H, Ph), 7.28 (s, 1H, thiazole), 6.24–6.21 (d, J = 12.41 Hz, 1H, CH), 6.18–6.14 (d, J = 7.76 Hz, 1H, HC=CH in imidazole), 2.13–2.10 (d, J = 12.45 Hz, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 153.9, 142.5, 133.0 (thiazole ring), 138.1, 128.0, 126.9, 126.7, 126.0 (Ph), 133.9 (HC=N), 128.6 (CH in imidazole), 121.4 (CH in imidazole), 120.7 (CH in imidazole), 73.8 (CH) ppm; EI-MS: *m/z* (%) = 283.7 (16).

In vitro antibacterial screening

The compounds **1**–**24** were evaluated for their in vitro antibacterial activity against *S. aureus* (ATCC-25923), *Klebsiella pneumonia* (recultured), *E. coli* (ATCC-25922), *P. aeruginosa* (ATCC-27853) by agar diffusion [32, 33], using Mueller–Hinton agar (Hi-Media) medium. Each compound was tested at a concentration of 100 μg/cm^3 in DMSO. Ciprofloxacin was used as the standard. The zone of inhibition was measured after 24 h incubation at 37 °C. The minimum inhibitory concentration (MIC) was measured to be the lowest concentration that completely inhibited growths on agar plates.

In vitro antifungal screening

The compounds **1**–**24** were evaluated for their in vitro antifungal activity such as *A. niger*, *C. albicans*, *M. audouinii*, and *C. neoformans* (recultured) using an agar diffusion method [34–36] with sabouraud's dextrose agar (Hi-Media). Each compound was tested at a concentration of 100 μg/cm^3 in DMSO. Clotrimazole was used as a standard. The zone of inhibition (mm) was measured incubated at 37 °C for 24 h. The minimum inhibitory concentration (MIC) was measured as lowest concentration, which completely inhibited growths on agar plates. Selected synthesized compounds **2** and **6** where determined by minimal inhibitory concentration (MIC) at concentration of 64 μg/cm^3. The twofold dilutions of the solution were prepared (64, 32, … 0.5 μg/cm^3). The microorganism suspensions at 106 CFU/cm^3 (colony forming unit/cm^3) concentrations were inoculated to the corresponding wells. The plates were incubated at 36 °C at 24 h. The MIC values were measured as the lowest concentration that completely inhibited visible growth of the microorganisms.

Larvicidal activity

The persistence of larvicidal activity of synthesized compounds **1**–**24** were tested beside the urban mosquito larvae (*C. quinquefasciatus*) using standard bio assay protocol. Eggs of *C. quinquefasciatus* were obtained from drainage system. Eggs were placed in clean water and kept at room temperature for hatching. Larval development was monitored for 7 days. The second stage larvae were collected at the tip of a pasture pipette and pleased in cotton bud to remove excess water and transferred to the test vial. The larval mortality was observed using various concentrations (10, 20, 30, and 40 μg/cm^3) of synthesized compounds **1**–**24**. The susceptibility or resistance of the mosquito larvae (*C. quinquefasciatus*) to the selected concentration of the synthesized compounds **1**–**24** was carried out by adopting standard bioassay protocol [37–39].

Acknowledgments We are very grateful to Saudi Biological Society and Prince Sultan Research Chair for Environment and Wildlife, Department of Botany and Microbiology, College of Sciences, King Saud University (KSU), Riyadh, Saudi Arabia for encouragement.

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