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Original article

Microwave-induced synthesis and anti-microbial activities of 7,10,11,12-tetrahydrobenzo[*c*]acridin-8(9*H*)-one derivatives

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ABSTRACT

Some new substituted tetrahydroacridin-8-ones and diverse derivatives were synthesized by uncatalysed multi-component reaction of dimedone or cyclohexan-1,3-dione, α-naphthylamine and various (*o*,*p*,*m*)-substituted benzaldehydes. The in vitro anti-microbial activities of the prepared compounds were evaluated against some bacteria and fungi strains. The results suggested that, the products **2a**–**g** and **4a**–**g** exhibited good inhibitory effect against most of the tested organisms. Especially, **2f**, **2g**, **4f** and **4g** were shown to be most effective against *Rhodotorula rubra* and *Aspergillus parasiticus* and compounds **2a**, **2c**, **2g**, **4f** and **4g** proved to be effective with MIC values in the range of 3.9–7.8 μg/ml.

1. Introduction

Acridine derivatives have been known since the 19th century where they were first used as pigments and dyes [1]. Their antiseptic activity has been discovered in the early 1900s and some derivatives were extensively used during First World War for their antibacterial and anti-malarial activities. In the 1920s, their potential in the fight against cancer was first noted. The synthetic research on acridine derived antimalarial experienced a renaissance during the middle of 1960s. Wide ranges of acridines were tested for anti-malarial activities [2] and among them the introduction of benzo analogue is one of the types of nuclei variation, that has received a considerable attention [3,4].

1,4-Dihydropyridines (DHPs) are well known compounds because of their pharmacological profile as calcium channel modulations [5,6]. In fact, it is well established that slight structural modification on the DHP ring may bring significant change in pharmacological activities [7–9]. With an 1,4-DHPs parent nucleus, acridines are well known therapeutic agent [10,11]. The use of acridine derivatives as therapeutic agent has been the subject of numerous studies [12–14]. Therefore, the synthesis of new tetracyclic acridine compounds has increased rapidly in last few years [15–20].

Recently, synthesis of organic compounds assisted by microwaves [21] under solvent free conditions [22,23], is an improved technique. Due to greater selectivity, rapid transfer of energy, significant practical simplicity and pure products, microwave-assisted reactions have greater advantages over conventional homogeneous methods. The coupling of microwave technology with one-pot multi-component condensation reactions has received significant attention [24] since two or more steps in the synthetic sequence can be carried out without the isolation of intermediates. This leads to reduction of time and energy and constitutes overall an economical way of developing new pharmaceutically important compounds [25].

Some methods are available in the literature for the synthesis of acridine compounds containing 1,4-dihydropyridines, from dimedone, aldehyde and different anilines or ammonium acetate via traditional heating in organic solvents [26], in water catalyzed by TEBAC [27], under microwave irradiation [28] and using ionic liquids [29]. Nowadays, to avoid the use of toxic organic solvents, ionic liquids are emerging as effective solvents for green processes. However, the high cost of most conventional ionic liquids and their toxicity prompted us to explore other clean method. Hence, we now report an efficient, solvent free, no catalyst, microwave-assisted multi-component synthesis of some substituted 7,10,11,12-tetrahydrobenzo[*c*]acridin-8(9*H*)-one derivatives and evaluation of anti-microbial activities of the prepared compounds.

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2. Results and discussion

2.1. Chemistry

Irradiation of a mixture of dimedone (**1**), α-naphthylamine and salicylaldehyde (Scheme 1) containing no catalyst or solvent, under microwaves at 160 W gave a yellow solid (91.9%) within 3 min time. The product was identified as 10,10-dimethyl-7-(*o*-hydroxyphenyl)-7,10,11,12-tetrahydrobenzo[*c*]acridin-8(9*H*)-one (**2a**). IR spectrum of **2a** showed a strong band at 1587 cm^{-1} for carbonyl group and broadband in the region 3100–3500 cm^{-1} for NH and OH groups. The ^1H NMR spectrum revealed two singlets at δ 1.03 and 1.09 for gem dimethyl protons, two fine doublets at δ 2.06–2.29 and 2.61–2.71 for C_9–H and C_{11}–H, singlet at δ 5.87 for C_7–H, multiplet in the region δ 6.99–7.73 for aromatic protons, doublet at δ 8.18 for C_6–H, a singlet at δ 8.93 for NH proton and broad singlet at 13.03 for OH proton. The mass spectrum of **2a** exhibited a molecular ion peak at *m*/*z* 369 ($M^{+\bullet}$) and its base peak at *m*/*z* 276, similar to known 7-phenyltetarahydrobenzo[*c*]acridin-8(9*H*)-ones [30].

Extension of this technique to different aldehydes provided some known and new benzo[*c*]acridin-8(9*H*)-one derivatives (Scheme 1). The known compounds **2b**, **2c**, **2e**, **2f** and **2g** were identical in all respects (mp, mmp, IR, ^1H NMR and Mass) with authentic samples prepared [30,31] and new compounds **2a** and **2d** were completely characterized by IR, ^1H NMR, Mass spectral data and elemental analysis.

In order to apply this reaction to a library synthesis, cyclohexan-1,3-dione (**3**) was treated with α-naphthylamine and various aldehydes which successfully yielded the corresponding 7-(substituted phenyl)-7,10,11,12-tetrahydrobenzo[*c*]acridin-8(9*H*)-ones **4a**–**g** (Scheme 2). The expected products were formed in quantitative yields and purity (Table 1). The IR spectra of compounds (**4a**–**g**) showed intense bands in the region 1587–1591 cm^{-1} due to carbonyl stretching and broad bands in the region 3100–3300 cm^{-1} due to NH stretching.

The ^1H NMR spectra were recorded in DMSO-d_6 support the proposed structure of the compounds. The CH_2 protons (C_9, C_{10} and C_{11}) of **4a**–**g** appeared as a multiplet at δ 1.81–2.85 ppm and the CH proton (C_7) appeared as a singlet at δ 5.64–5.86 ppm. The entire aromatic protons showed multiplet at δ 6.78–8.47 ppm. The NH proton resonance at 9.20–9.35 was disappeared after addition of D_2O. The mass spectra of all compounds (**4a**–**g**) showed molecular ion peaks confirming their molecular weight; moreover their fragmentation pathways are similar to **2a**–**g**. The known compound **4e** was identical in all respects (mp, mmp, IR, ^1H NMR and Mass) with authentic sample prepared [32].

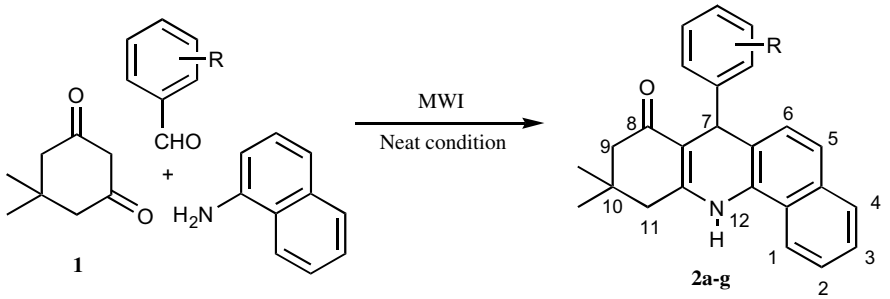
2.2. Anti-microbial activity

All the synthesized compounds were screened for their anti-bacterial and anti-fungal activities. For preliminary screening, the anti-microbial tests were carried out by disc-diffusion method [33]. One hundred microlitres of suspension containing 10^8 CFU/ml of bacteria, 10^6 CFU/ml of fungi were spread on Mueller–Hinton agar medium (MHA) and Sabouraud's dextrose agar (SDA) medium, respectively. The discs (6 mm in diameter), impregnated with 10 μl of the test compounds (500 μg/disc and 1000 μg/disc) at the concentration of 50 and 100 mg/ml were placed on the inoculated agar. Negative controls were prepared using the same solvent (DMSO) employed to dissolve the test compounds. Ofloxacin (5 μg/disc) and Clotrimazole (10 μg/disc) were used as positive reference standard to determine the sensitivity of each microbial species tested. The inoculated plates were incubated at 37 °C for 24 h and 27 °C for 72 h for bacteria and fungi strains, respectively. Anti-microbial activity was evaluated by measuring the diameter of zone of inhibition against test organisms.

The results of the anti-microbial screening are given in Tables 2 and 3. From the results obtained, it is obvious that most of the compounds showed promising activity against bacteria and fungi. The compounds **2a**–**g** showed significant inhibition effect on the growth of bacteria like *Escherichia coli*, *Klebsiella aerogenes*, *Salmonella typhimurium*, *Bacillus subtilis and Bacillus cereus* (Table 2) and moderate activity against *Pseudomonas aeruginosa*, *Vibrio fischeri*, *Corynebacterium rubrum*, *Staphylococcus albus* and *Proteus vulgaris*. Among the compounds **2a**–**g**, **2c**, **2f** and **2g** showed activity against all the bacteria, which might be due to the presence of chlorine and hydroxyl groups in *p*-position and nitro group in *o*-position in phenyl ring. These compounds also showed very good anti-fungal activity. For instance, the growth of fungi like *Aspergillus flavus*, *Rhodotorula rubra*, *Aspergillus parasiticus* and *Trichoderma viridie* was very much affected by **2a**–**g** and **2f** indicated maximum activity of 21 and 23 mm at 500 and 1000 μg/disc, respectively, against *Rhodotorula rubra* which is greater than the standard inhibition value (Table 2). These compounds (**2a**–**g**) showed moderate activity against other fungi (Table 2).

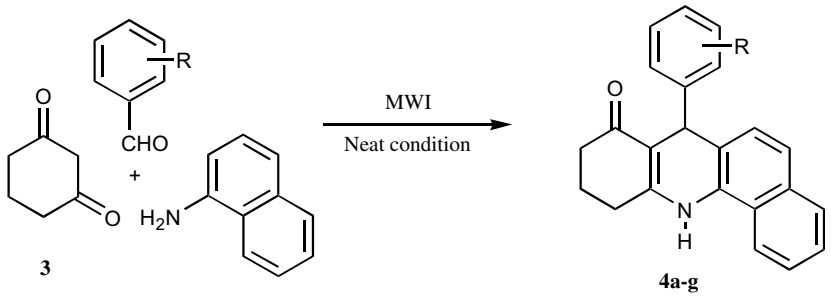
The anti-microbial activity of compounds **4a**–**g** is similar to **2a**–**g** (Table 3). Among them, **4c**, **4f** and **4g** showed activity against all bacteria and fungi, whereas compounds **4a**, **4b**, **4d** and **4e** showed activity only against *Escherichia coli*, *Bacillus subtilis* and *Bacillus cereus*. The compounds **4a**–**g** have a pronounced effect on the growth of fungi like *Aspergillus flavus*, *Rhodotorula rubra*, *Aspergillus parasiticus* and *Trichoderma viridie* and moderate activity against other fungi (Table 3).

Minimum inhibitory concentration (MIC) of the compounds was also estimated by broth dilution assay [34] for the microorganisms, which were determined as sensitive to the compounds in disc-diffusion assay. Nutrient broth (NB) and Sabouraud's dextrose broth (SDB) were used to estimate the MIC values of the test compounds against bacteria and fungi, respectively. Two fold serial dilutions of test compounds were followed with 1 ml of sterile broth in test tubes to provide various concentration range from 3.9 to 1000



2a: R = *o*-OH, **2b**: R = *o*-Cl, **2c**: R = *p*-Cl, **2d**: R = *m*-Cl,
2e: R = H, **2f**: R = *p*-OH, **2g**: R = *m*-NO_2

Scheme 1.



3 4a-g

4a: R = *o*-OH, **4b**: R = *o*-Cl, **4c**: R = *p*-Cl, **4d**: R = *m*-Cl, **4e**: R = H, **4f**: R = *p*-OH, **4g**: R = *m*-NO_2

Scheme 2.

μg/ml of the test compounds. Ten microlitres of the test organism were added to each tube and incubated at 37 °C for 24 h and 27 °C for 72 h for bacteria and fungi strains, respectively. The highest dilution of the test compound completely inhibiting the test organism was considered as MIC value of the test compound, respectively. The results of the MIC values of the compounds have been listed in Table 4. The MIC values of the compounds **2a**–**g** and **4a**–**g** range between 3.9 and 125 μg/ml, in most of the cases. Among the compounds **2a**–**g**, **2a**, **2c** and **2f** showed MIC values as 3.9 and 7.8 μg/ml against *Aspergillus parasiticus*, whereas **2g** showed 3.9, 7.8 and 15.6 μg/ml against *Escherichia coli*, *Aspergillus parasiticus*, *Rhodotorula rubra* and *Bacillus cereus*. The compounds **4b**, **4c**, **4f** and **4g** also showed 3.9 μg/ml as MIC value against some bacteria and fungi.

3. Experimental

All reagents used were AR grade. Melting points (mp) were determined using Boetius microheating table and are uncorrected. Infrared spectra (cm^{-1}) were recorded on Shimadzu-8201 spectrophotometer as pallets on KBr discs. The ^1H NMR (400 MHz) spectra were recorded on Bruker AMX-400 spectrometer in DMSO-d_6 using TMS as an internal reference (Chemical shifts in δ, ppm) unless otherwise stated. The splitting patterns are designated as follows: s, singlet, d, doublet, t, triplet, m, multiplet, dd, doublet of doublet. Elemental analyses were performed on Perkin Elmer CHN-analyzer. Mass spectra were recorded on Shimadzu GCMS-QP5050A (70 eV) mass spectrometer. The reactions were monitored by thin layer chromatography (TLC) using glass plates coated with Silica gel-G containing 13% calcium sulphate as binder. Column chromatography was performed on silica gel (60–120 mesh). For microwave irradiation a Kenstar (OM-20ESP, 2450 MHz) domestic microwave oven was used.

*3.1. Synthesis of 10,10-dimethyl-7-(substituted phenyl)-7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-ones (**2a**–**g**) and 7-(substituted phenyl)-7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-ones (**4a**–**g**)*

General procedure: a mixture of α-naphthylamine (0.1432 g, 1 mmol), dimedone (0.1402 g, 1 mmol) (or) cyclohexan-1,3-dione (**3**) (0.1121 g, 1 mmol), and respective aldehydes (1 mmol) was taken in a 100 ml beaker and the mixture was placed inside the microwave oven and irradiated at an output of 160 W under neat condition for the specified times (Table 1). After completion of reaction, the mixture was poured into ice; the precipitate formed was filtered and purified by column chromatography using petroleum ether and ethyl acetate as an eluant.

Table 1
Microwave synthesis of **2a**–**g** and **4a**–**g** at 160 W under microwave irradiation

Compound	Time (min)	Yield (%)	mp (°C)	Compound	Time (min)	Yield (%)	mp (°C)
2a	3	91.9	220–222	**4a**	5	93.8	1196–198
2b	4	95.8	265–266	**4b**	4	92.4	256–258
2c	3	98.1	290–292	**4c**	3	96.0	205–206
2d	3	96.8	270–272	**4d**	3	94.6	240–241
2e	2	93.5	258–259	**4e**	3	95.4	246–248
2f	4	93.5	280–282	**4f**	4	94.1	228–230
2g	2	92.9	238–240	**4g**	4	92.4	202–203

*3.1.1. 10,10-Dimethyl-7-(o-hydroxyphenyl)-7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one **2a***

IR (ν_{max}): 1587 (C=O), 3100–3500 (NH and OH); ^1H NMR (DMSO-d_6): 1.03 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 2.06–2.29 (dd, 2H, C_9–H), 2.61–2.71 (dd, 2H, C_{11}–H), 5.87 (s, 1H, C_7–H), 6.99–7.73 (m, 9H, Ar–H), 8.18 (d, 1H, C_6–H), 8.93 (s, 1H, NH), 13.03 (s, 1H, OH); Ms (*m*/*z*): 369; Anal. Calc. ($C_{25}H_{23}NO_2$): C, 81.27, H, 6.27, N, 3.79; found: C, 81.25, H, 6.27, N, 3.77.

*3.1.2. 10,10-Dimethyl-7-(o-chlorophenyl)-7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one **2b***

IR (ν_{max}): 1587 (C=O), 3300 (NH); ^1H NMR (DMSO-d_6): 1.00 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.03–2.24 (dd, 2H, C_9–H), 2.52–2.71 (dd, 2H, C_{11}–H), 6.04 (s, 1H, C_7–H), 6.87–7.82 (m, 9H, Ar–H), 8.42 (d, 1H, C_6–H), 9.23 (s, 1H, NH); Ms (*m*/*z*): 387; Anal. Calc. ($C_{25}H_{22}NOCl$): C, 77.41, H, 5.72, N, 3.61; found: C, 77.50, H, 5.74, N, 3.60.

*3.1.3. 10,10-Dimethyl-7-(p-chlorophenyl)-7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one **2c***

IR (ν_{max}): 1589 (C=O), 3307 (NH); ^1H NMR (DMSO-d_6): 0.98 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 2.04–2.28 (dd, 2H, C_9–H), 2.58–2.70 (dd, 2H, C_{11}–H), 5.43 (s, 1H, C_7–H), 7.18–7.83 (m, 9H, Ar–H), 8.46 (d, 1H, C_6–H), 9.35 (s, 1H, NH); Ms (*m*/*z*): 387; Anal. Calc. ($C_{25}H_{22}NOCl$): C, 77.41, H, 5.72, N, 3.61; found: C, 77.49, H, 5.71, N, 3.58.

*3.1.4. 10,10-Dimethyl-7-(m-chlorophenyl)-7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one **2d***

IR (ν_{max}): 1591 (C=O), 3340 (NH); ^1H NMR (DMSO-d_6): 1.05 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 2.03–2.29 (dd, 2H, C_9–H), 2.60–2.71 (dd, 2H, C_{11}–H), 5.80 (s, 1H, C_7–H), 6.68–7.48 (m, 9H, Ar–H), 8.40 (d, 1H, C_6–H), 9.25 (s, 1H, NH); Ms (*m*/*z*): 387; Anal. Calc. ($C_{25}H_{22}NOCl$): C, 77.41, H, 5.72, N, 3.61; found: C, 77.49, H, 5.72, N, 3.60.

*3.1.5. 10,10-Dimethyl-7-phenyl-7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one **2e***

IR (ν_{max}): 1599 (C=O), 3309 (NH); ^1H NMR (DMSO-d_6): 0.99 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.02–2.22 (dd, 2H, C_9–H), 2.59–2.75 (dd, 2H, C_{11}–H), 6.04 (s, 1H, C_7–H), 6.85–7.52 (m, 9H, Ar–H), 7.77 (d, 1H, C_5–H), 8.41 (d, 1H, C_6–H), 9.23 (s, 1H, NH); Ms (*m*/*z*): 353; Anal. Calc. ($C_{25}H_{23}NO$): C, 84.95, H, 6.56, N, 3.96; found: C, 84.95, H, 6.56, N, 3.98.

Table 2
In vitro anti-microbial activity of **2a–g** (μg/disc) by disc-diffusion assay

Microorganisms	Diameter of zone of inhibition in mm															
	2a (μg/disc)		**2b** (μg/disc)		**2c** (μg/disc)		**2d** (μg/disc)		**2e** (μg/disc)		**2f** (μg/disc)		**2g** (μg/disc)		A (μg/disc)	B (μg/disc)
	500	1000	500	1000	500	1000	500	1000	500	1000	500	1000	500	1000	5	10
Escherichia coli (NCIM 2065)[a]	–	8	7	8	7	9	7	8	7	10	7	12	10	15	23	NT
Pseudomonas aeruginosa (NCIM 2200)[a]	–	–	–	–	7	9	–	–	–	–	7	9	7	8	22	NT
Klebsiella aerogenes (NCIM 2239)[a]	7	10	–	9	8	11	–	9	–	–	9	12	8	11	24	NT
Salmonella typhimurium (NCIM 2501)[a]	10	11	10	13	9	11	8	10	9	10	9	11	10	13	21	NT
Bacillus subtilis (NCIM 2063)[a]	–	9	7	8	8	10	–	9	8	11	7	10	9	11	24	NT
Bacillus cereus (NCIM 2155)[a]	7	10	8	11	10	13	9	10	9	12	9	11	10	13	19	NT
Vibrio fischeri (NCIM 2154)[a]	–	8	7	9	7	9	7	9	–	8	7	9	7	10	27	NT
Corynebacterium rubrum (NCIM 2252)[a]	–	–	–	–	7	10	7	8	–	–	7	10	8	9	25	NT
Staphylococcus albus (NCIM 2178)[a]	–	–	–	–	7	9	–	–	–	–	7	8	7	9	21	NT
Proteus vulgaris (NCIM 2027)[a]	–	–	–	–	9	10	–	–	–	–	7	9	7	9	19	NT
Aspergillus niger (NCIM 1196)[b]	–	–	–	–	–	–	–	–	–	–	8	10	–	–	NT	16
Aspergillus flavus (NCIM 535)[b]	9	10	8	10	7	8	9	10	9	10	9	12	9	13	NT	16
Rhodotorula rubra (NCIM 3174)[b]	10	14	10	13	9	13	7	9	10	12	21	23	10	15	NT	17
Aspergillus fumigatus (NCIM 902)[b]	–	–	–	8	–	8	–	9	–	10	–	–	8	10	NT	18
Aspergillus parasiticus (NCIM 904)[b]	10	16	8	10	12	17	11	12	7	10	12	14	10	16	NT	18
Penicillium chrysogenum (NCIM 707)[b]	–	–	–	–	–	–	7	10	–	–	–	9	8	11	NT	21
Lipomyces lipofera (NCIM 3252)[b]	–	–	7	10	–	–	–	8	–	–	7	10	8	11	NT	18
Trichoderma viridie (NCIM 1195)[b]	10	12	7	8	7	9	10	13	9	12	10	12	10	12	NT	19

A = Ofloxacin, B = Clotrimazole, –, no inhibition, NT – not tested.
[a] Bacteria.
[b] Fungi.

3.1.6. *10,10-Dimethyl-7-(*p*-hydroxyphenyl)-7,10,11,12-tetrahydrobenzo[*c*]acridin-8(9*H*)-one* ***2f***

IR (ν_{max}): 1590 (C═O), 3290–3400 (NH and OH); ^{1}H NMR (DMSO-d_6): 1.02 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 2.04–2.24 (dd, 2H, C_9–H), 2.50–2.73 (dd, 2H, C_{11}–H), 5.82 (s, 1H, C_7–H), 6.94–7.80 (m, 9H, Ar–H), 8.44 (d, 1H, C_6–H), 9.08 (s, 1H, NH), 12.93 (s, 1H, OH); Ms (*m*/*z*): 369; Anal. Calc. ($C_{25}H_{23}NO_2$): C, 81.27, H, 6.27, N, 3.79; found: C, 81.28, H, 6.25, N, 3.76.

3.1.7. *10,10-Dimethyl-7-(*m*-nitrophenyl)-7,10,11,12-tetrahydrobenzo[*c*]acridin-8(9*H*)-one* ***2g***

IR (ν_{max}): 1590 (C═O), 3310 (NH); ^{1}H NMR (DMSO-d_6): 1.03 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 2.04–2.25 (dd, 2H, C_9–H), 2.58–2.71 (dd, 2H, C_{11}–H), 5.65 (s, 1H, C_7–H), 7.00–8.14 (m, 9H, Ar–H), 8.44 (d, 1H, C_6–H), 9.17 (s, 1H, NH); Ms (*m*/*z*): 398; Anal. Calc. ($C_{25}H_{22}N_2O_3$): C, 75.36, H, 5.57, N, 7.03; found: C, 75.36, H, 5.55, N, 7.00.

3.1.8. *7-(*o*-Hydroxyphenyl)-7,10,11,12-tetrahydrobenzo[*c*]acridin-8(9*H*)-one* ***4a***

IR (ν_{max}): 1591 (C═O), 3100–3300 (NH and OH); ^{1}H NMR (DMSO-d_6): 1.90–2.85 (m, 6H, C_9–H, C_{10}-H and C_{11}–H), 5.74 (s, 1H, C_7–H), 7.03–7.80 (m, 9H, Ar–H), 8.47 (d, 1H, C_6–H), 9.20 (s, 1H, NH), 10.36 (s, 1H, OH); Ms (*m*/*z*): 341; Anal. Calc. ($C_{23}H_{19}NO_2$): C, 80.91, H, 5.61, N, 4.10; found: C, 80.90, H, 5.59, N, 4.10.

3.1.9. *7-(*o*-Chlorophenyl)-7,10,11,12-tetrahydrobenzo[*c*]acridin-8(9*H*)-one* ***4b***

IR (ν_{max}): 1590 (C═O), 3270 (NH); ^{1}H NMR (DMSO-d_6): 1.82–2.50 (m, 6H, C_9–H, C_{10}–H and C_{11}–H), 5.86 (s, 1H, C_7–H), 6.92–7.32 (m, 10H, Ar–H), 9.35 (s, 1H, NH); Ms (*m*/*z*): 359; Anal. Calc. ($C_{23}H_{18}NOCl$): C, 76.77, H, 5.04, N, 3.89; found: C, 76.87, H, 5.02, N, 3.88.

Table 3
In vitro anti-microbial activity of **4a–g** (μg/disc) by disc-diffusion assay

Microorganisms	Diameter of zone of inhibition in mm															
	4a (μg/disc)		**4b** (μg/disc)		**4c** (μg/disc)		**4d** (μg/disc)		**4e** (μg/disc)		**4f** (μg/disc)		**4g** (μg/disc)		A (μg/disc)	B (μg/disc)
	500	1000	500	1000	500	1000	500	1000	500	1000	500	1000	500	1000	5	10
Escherichia coli (NCIM 2065)[a]	8	9	–	8	7	8	7	9	8	9	7	9	9	12	23	NT
Pseudomonas aeruginosa (NCIM 2200)[a]	–	–	–	–	7	10	–	–	–	–	7	9	–	–	22	NT
Klebsiella aerogenes (NCIM 2239)[a]	–	–	–	–	–	9	–	9	–	–	7	10	7	9	24	NT
Salmonella typhimurium (NCIM 2501)[a]	–	–	–	–	9	11	–	–	–	–	7	9	7	10	21	NT
Bacillus subtilis (NCIM 2063)[a]	8	10	7	10	8	12	8	11	8	10	9	11	10	12	24	NT
Bacillus cereus (NCIM 2155)[a]	7	8	–	–	10	13	–	–	8	9	–	–	7	10	19	NT
Vibrio fischeri (NCIM 2154)[a]	–	–	7	9	8	9	9	10	–	–	7	9	7	9	27	NT
Corynebacterium rubrum (NCIM 2252)[a]	–	–	7	8	7	8	7	9	–	–	7	9	7	8	25	NT
Staphylococcus albus (NCIM 2178)[a]	–	–	–	–	8	10	–	–	–	–	8	10	8	11	21	NT
Proteus vulgaris (NCIM 2027)[a]	–	–	–	–	7	9	–	–	–	–	7	9	7	9	19	NT
Aspergillus niger (NCIM 1196)[b]	–	9	–	–	8	10	–	–	–	–	9	10	7	9	NT	16
Aspergillus flavus (NCIM 535)[b]	8	11	7	9	7	10	9	11	9	10	7	8	8	12	NT	16
Rhodotorula rubra (NCIM 3174)[b]	11	13	13	16	12	16	8	10	8	12	12	14	10	14	NT	17
Aspergillus fumigatus (NCIM 902)[b]	–	12	–	9	8	10	8	12	–	11	–	–	–	9	NT	18
Aspergillus parasiticus (NCIM 904)[b]	9	10	8	10	10	12	12	13	7	9	12	13	11	13	NT	18
Penicillium chrysogenum (NCIM 707)[b]	–	9	–	–	7	8	–	–	–	–	9	10	–	–	NT	21
Lipomyces lipofera (NCIM 3252)[b]	–	–	–	–	–	9	–	–	–	–	10	11	8	10	NT	18
Trichoderma viridie (NCIM 1195)[b]	9	10	9	10	–	8	8	10	11	12	10	11	9	10	NT	19

A = Ofloxacin, B = Clotrimazole, –, no inhibition, NT – not tested.
[a] Bacteria.
[b] Fungi.

Table 4
Minimum inhibitory concentration values of **2a–g** and **4a–g** (μg/ml) against the microorganisms tested in broth dilution assay

Microorganisms	2a	2b	2c	2d	2e	2f	2g	4a	4b	4c	4d	4e	4f	4g
Escherichia coli (NCIM 2065)[a]	125	125	62.5	125	62.5	31.2	3.9	125	125	62.5	62.5	125	125	31.2
Pseudomonas aeruginosa (NCIM 2200)[a]	–	–	62.5	–	–	62.5	125	–	–	62.5	–	–	125	–
Klebsiella aerogenes (NCIM 2239)[a]	62.5	125	62.5	125	–	31.2	31.2	–	–	125	125	–	62.5	125
Salmonella typhimurium (NCIM 2501)[a]	31.2	31.2	31.2	62.5	62.5	31.2	15.6	–	–	62.5	–	–	125	62.5
Bacillus subtilis (NCIM 2063)[a]	62.5	62.5	31.2	62.5	31.2	62.5	31.2	62.5	62.5	31.2	31.2	62.5	31.2	31.2
Bacillus cereus (NCIM 2155)[a]	62.5	31.2	15.6	62.5	31.2	31.2	15.6	125	–	15.6	–	125	–	62.5
Vibrio fischeri (NCIM 2154)[a]	125	62.5	62.5	125	125	125	62.5	–	125	62.5	62.5	–	125	125
Corynebacterium rubrum (NCIM 2252)[a]	–	–	62.5	125	–	62.5	125	–	125	125	125	–	125	125
Staphylococcus albus (NCIM 2178)[a]	–	–	125	–	–	125	125	–	–	62.5	–	–	62.5	62.5
Proteus vulgaris (NCIM 2027)[a]	–	–	62.5	–	–	125	125	–	–	125		–	125	125
Aspergillus niger (NCIM 1196)[b]	–	–	–	–	–	62.5	–	125	–	62.5	–	–	62.5	125
Aspergillus flavus (NCIM 535)[b]	62.5	62.5	125	62.5	62.5	31.2	15.6	31.2	62.5	62.5	62.5	62.5	125	31.2
Rhodotorula rubra (NCIM 3174)[b]	7.8	15.6	15.6	62.5	31.2	3.9	7.8	15.6	3.9	3.9	62.5	31.2	7.8	3.9
Aspergillus fumigatus (NCIM 902)[b]	–	125	125	62.5	62.5	–	62.5	62.5	62.5	62.5	31.2	62.5	–	125
Aspergillus parasiticus (NCIM 904)[b]	3.9	62.5	3.9	31.2	62.5	7.8	3.9	62.5	62.5	31.2	15.6	62.5	15.6	15.6
Penicillium chrysogenum (NCIM 707)[b]	–	–	–	62.5	–	125	62.5	125	–	125	–	–	125	–
Lipomyces lipofera (NCIM 3252)[b]	–	125	–	125	–	62.5	62.5	–	–	125	–	–	62.5	62.5
Trichoderma viridie (NCIM 1195)[b]	31.2	125	62.5	15.6	31.2	31.2	31.2	62.5	62.5	125	125	31.2	31.2	62.5

– Not tested.
[a] Bacteria.
[b] Fungi.

3.1.10. 7-(p-Chlorophenyl)-7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one **4c**

IR (ν_{max}): 1588 (C═O), 3280 (NH); ^{1}H NMR (DMSO-d_6): 1.85–2.53 (m, 6H, C_9–H, C_{10}–H and C_{11}–H), 5.80 (s, 1H, C_7–H), 6.86–7.19 (m, 10H, Ar–H), 9.22 (s, 1H, NH); Ms (*m*/*z*): 359; Anal. Calc. ($C_{23}H_{18}NOCl$): C, 76.77, H, 5.04, N, 3.89; found: C, 76.88, H, 5.04, N, 3.86.

3.1.11. 7-(m-Chlorophenyl)-7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one **4d**

IR (ν_{max}): 1590 (C═O), 3220 (NH); ^{1}H NMR (DMSO-d_6): 1.82–2.55 (m, 6H, C_9–H, C_{10}–H and C_{11}–H) 5.64 (s, 1H, C_7–H), 6.96–7.40 (m, 10H, Ar–H), 9.32 (s, 1H, NH); Ms (*m*/*z*): 359; Anal. Calc. ($C_{23}H_{18}NOCl$): C, 76.77, H, 5.04, N, 3.89; found: C, 76.88, H, 5.02, N, 3.88.

3.1.12. 7-Phenyl-7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one **4e**

IR (ν_{max}): 1587 (C═O), 3280 (NH); ^{1}H NMR (DMSO-d_6): 1.81–2.45 (m, 6H, C_9–H, C_{10}–H and C_{11}–H), 5.84 (s, 1H, C_7–H), 6.78–7.19 (m, 11H, Ar–H), 9.24 (s, 1H, NH); Ms (*m*/*z*): 325; Anal. Calc. ($C_{23}H_{19}NO$): C, 84.89, H, 5.89, N, 4.31; found: C, 84.95, H, 5.85, N, 4.28.

3.1.13. 7-(p-Hydroxy)-7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one **4f**

IR (ν_{max}): 1591 (C═O), 3100–3300 (NH and OH); ^{1}H NMR (DMSO-d_6): 1.98–2.55 (m, 6H, C_9–H, C_{10}–H and C_{11}–H), 5.64 (s, 1H, C_7–H), 6.92–7.11 (m, 10H, Ar–H), 9.20 (s, 1H, NH), 10.32 (s, 1H, OH); Ms (*m*/*z*): 341; Anal. Calc. ($C_{23}H_{19}NO_2$): C, 80.91, H, 5.61, N, 4.10; found: C, 80.90, H, 5.60, N, 4.08.

3.1.14. 7-(m-Nitrophenyl)-7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one **4g**

IR (ν_{max}): 1587 (C═O), 3200 (NH); ^{1}H NMR (DMSO-d_6): 1.86–2.46 (m, 6H, C_9–H, C_{10}–H and C_{11}–H), 5.80 (s, 1H, C_7–H), 6.89–7.80 (m, 10H, Ar–H), 9.33 (s, 1H, NH); Ms (*m*/*z*): 370; Anal. Calc. ($C_{23}H_{18}N_2O_3$): C, 74.58, H, 4.90, N, 7.56; found: C, 74.58, H, 4.90, N, 7.55.

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