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Short communication

Isoxazoles incorporated N-substituted decahydroquinolines: A precursor to the next generation antimicrobial drug

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ABSTRACT

We report here a simple entry into N-substituted decahydroisoxazoloquinoline system with substituents at position 3 and 4 from the readily available substrates for the first time. The synthesized isoxazoloquinolines were evaluated against six bacterial and four fungal strains. The results suggest that the decahydroisoxazolo[4,3-*c*]quinoline scaffold has the potential to be developed into therapeutically useful antimicrobial agents.

1. Introduction

The search for novel and an effective antimicrobial drug is a prolonged continuing process due to adverse effects of the existing drugs [1–3]. Further, the emergence of new microbial strains resistance to the currently employed antimicrobial drugs necessiates the development of next generation antimicrobial agents. The chemistry of isoxazoles occupies an extremely important niche possessing diverse pharmacological activities [4–10] and isoxazolidine moiety forms the basic unit of a variety of potentially useful therapeutic agents [11].

We are interested to synthesise a new tri- or tetracyclic fused isoxazoles, and there were also reports suggesting that some fused isoxazoloquinolinones [12–14] reported, exist as a biologically attractive tricyclic systems which serve as inhibitors of P-38 mitogenactivated protein (MAP) kinase [15,16] benzodiazepine ligand receptors [17] and selective multidrug resistance proteins [18]. Encouraged by the diverse biological activities exhibited by decahydroquinolines [19], we anticipate that the hybrid emanating from the incorporation of isoxazolidine moiety into *trans*-1,2-decahydroquinoline might exhibit clinically useful antimicrobial activity.

As the synthesis of novel tri- or tetracyclic system is the main target of this synthetic program, here, we have reported the synthesis and antimicrobial activity of novel series of 3-aryl-4-phenyl-5-benzyl-1,3,4,5,5a,6,7,8,9,9a-decahydroisoxazolo[4,3-*c*] quinolines (**3a**–**l**) from its readily accessible putative precursor 1-benzyl-2-phenyloctahydroquinolin-4(1H)-one **1** (Scheme 1).

2. Chemistry

The reaction sequence for the synthesis of various title compounds (**3a**–**l**) is outlined in Scheme 1. Condensation of 1-acetylcyclohexene with benzaldehyde and benzylamine in the presence of catalytic amount of piperidine gave 1-benzyl-2-phenyloctahydroquinolin-4(1*H*)-one **1**. Reaction of an alcoholic solution of **1** with various substituted benzaldehydes/heterocyclic aldehydes in the presence of catalytic amount of piperidine-pyridine resulted in the formation of 1-benzyl-2-phenyl-3-arylideneoctahydroquinolin-4(1*H*)-one (**2a**–**l**), which on refluxing with an aqueous alcoholic solution of hydroxylamine hydrochloride in the presence of anhydrous sodium acetate furnished 3-aryl-4-phenyl-5-benzyl-1,3,4,5,5a,6,7,8,9,9a-decahydro- isoxazolo[4,3-*c*] quinolines (**3a**–**l**). The purity of the compounds was assessed by TLC and the structures of the intermediates and the final products were established by IR, ^{1}H NMR, ^{13}C NMR, DEPT spectroscopic data.

3. Antimicrobial evaluation

The newly synthesized compounds (**3a**–**l**) were screened for their antibacterial activity against six *bacterial* strains (*Pseudomonas*

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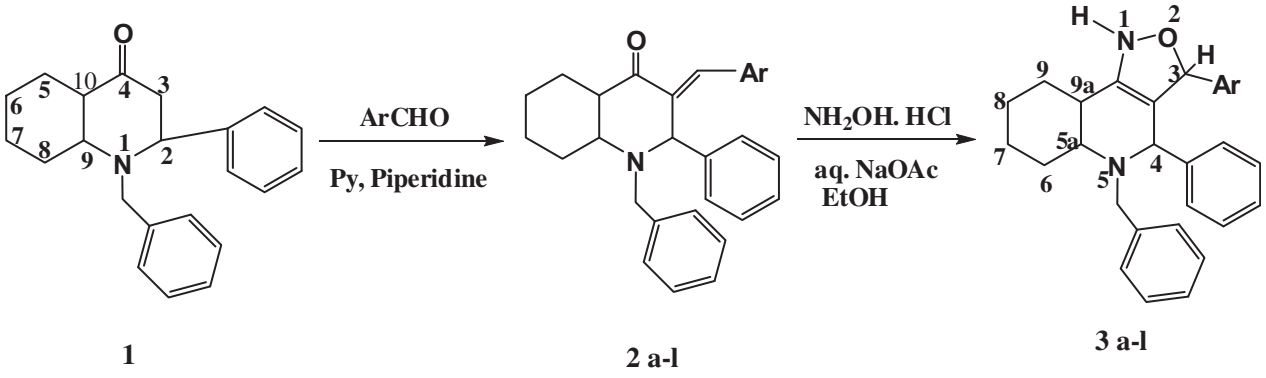

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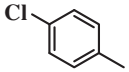
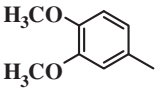
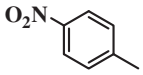
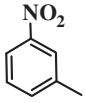
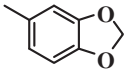
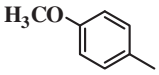
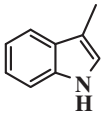
a		e		i	
b		f		j	
c		g		k	
d		h		l	

Scheme 1. Synthetic route to title compounds **3a**–**l**.

aeruginosa ATCC 9027, *Escherichia coli* ATCC 35218, *Salmonella typhi* ATCC 6539, *Staphylococcus aureus* ATCC 6538, *Bacillus subtilis* ATCC 6631 and *Bacillus shaericus* ATCC 7031) by disc diffusion method [20,21] using MH medium (Mueller–Hinton medium) and against four fungal strains (*Candida albicans* ATCC 90028, *C. albicans PYCC 3436*, *Aspergillus niger* ATCC 16404 and *Aspergillus fumigatus* ATCC 28212) by agar cup plate method [22,23]. Ciprofloxacin (the antibacterial drug) and Ketoconazole (the antifungal drug) were used as reference standards.

4. Results and discussion

4.1. Chemistry

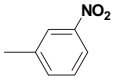
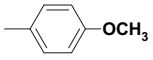
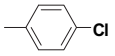
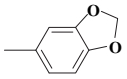
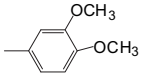
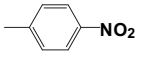
A comparison of the spectroscopic data of **3a** with that of **2a** established the formation of isoxazolidine ring beyond doubt. In the ^{1}H NMR spectrum of **2a**, (a representative example) a two proton singlet at δ 3.6 is assigned to methylene protons of N-benzylic group, while the one proton singlet at δ 4.6 is ascribed to N-benzylic methine proton; the downfield one-proton singlet at δ 6.4 is assigned to benzylidene proton () based on DEPT spectral data. The upfield complex multiplet (10 H) in the region δ 1.0–2.6 and the downfield multiplet (15H) in the region δ 7.2–7.7 are due to aliphatic (methylene and methine) and aromatic protons respectively. The downfield carbon signal at δ 196.7 revealed the presence of a carbonyl group, the presence of which is also supported by an IR band at 1710 cm^{-1}.

The ^{1}H NMR spectrum of **3a** displayed in addition to signals due to –N–CH$_2$–Ph (δ 3.6) and –N–CH–Ph (δ 4.2) groups, a one proton singlet at δ 5.4 and a downfield one proton singlet at δ 8.5 which exchanged with D$_2$O and disappeared on acetylation (Ac$_2$O/Py); the former and latter signals are assigned to protons of O–CH and –N–H of dihydroisoxazole moiety respectively. The absence of signals due to C=O and benzylidene proton of **2a** and the appearance of new signals due to O–C<u>H</u> and N–<u>H</u> protons established beyond doubt the formation of isoxazolidine ring in **3a**. That the downfield one proton signal is not due to OH of the oxime itself is ruled out by comparing the chemical shift of the oxime hydroxyl (δ 11.0) of **1** (prepared for this purpose) with that **3a**. The physical and analytical data of the synthesized compounds (**3a**–**l**) are listed in Table 1.

4.2. In vitro antibacterial activity

The data generated from this study (Table 2) revealed that the majority of the synthesized compounds (**3a**–**l**) showed variable inhibition activities against the tested strains and all of them showed moderate to good antibacterial activity as compared to that of the standard. Of all the compounds in series, **3b** and **3k** showed significant inhibition against *Gram-negative* strains and **3b**, **3e** and **3k** against *Gram-positive* strains. Compounds **3b**, **3d**, **3e**, **3j** and **3k**

Table 1
Physical and analytical data of the compounds **3a**–**l**.

S. No	Substrate (Ar)	Time hrs	Yield (%)	Mp. (°C)	Mol. formula	Elemental analysis[a] (calculated %/found %)	
						C	H
a.		2.0	82	124–125	$C_{29}H_{32}N_2O$	82.04/82.07	7.60/7.62
b.		2.5	78	131–132	$C_{29}H_{31}N_2OCl$	75.88/75.86	6.81/6.82
c.		3.5	72	115–118	$C_{29}H_{31}N_3O_3$	74.18/74.19	6.67/6.65
d.		3.0	75	117–120	$C_{30}H_{34}N_2O_2$	79.27/79.26	7.54/7.51
e.		4.0	79	112–113	$C_{29}H_{31}N_2OCl$	75.88/75.84	6.81/6.83
f.		3.0	70	130–132	$C_{27}H_{30}N_2O_2$	78.23/78.27	7.29/7.26
g.		4.0	71	143–144	$C_{29}H_{31}N_2O_3$	76.46/76.48	6.86/6.83
h.		3.5	81	156–158	$C_{31}H_{33}N_3O$	80.31/80.33	7.17/7.20
i.		2.5	80	137–139	$C_{31}H_{36}N_2O_3$	76.83/76.80	7.49/7.50
j.		3.0	76	161–163	$C_{29}H_{31}N_3O_3$	74.18/74.20	6.65/6.67
k.		3.5	84	129–130	$C_{28}H_{31}N_3O$	79.02/79.05	7.34/7.35
l.		3.5	80	113–115	$C_{28}H_{31}N_3O$	79.02/79.04	7.34/7.37

[a] Elemental analysis for C and H were within ±0.4% of the theoretical value.

showed significant inhibitory activity against all bacterial strains, whereas compounds **3f** and **3g** displayed low inhibitory activity in comparison to that of the standard.

4.3. In vitro antifungal activity

The antifungal screening data (Table 3) revealed that all the tested compounds showed significant fungal inhibition at a concentration of 10 μg/mL. Compounds **3b**, **3c** and **3e** exhibited very high antifungal activity against all fungal strains, compounds **3b** and **3c** exhibited similar activity against *C. albicans* ATCC 90028 as compared to that of the standard (Table 3). Substitution by **3b** (2-chloro) and **3c** (3-nitro) groups results in an increase in activity against *C. albicans* ATCC 90028 and the activity was found to be higher than that of the standard ketoconazole. Thus, compounds **3b**, **3c**, **3e**, **3k** and **3l** have emerged as the most effective antifungal agents, whereas compounds **3a** and **3f** showed low inhibitory activities.

A scrutiny of results of antimicrobial study of decahydroisoxazoloquinolines (**3a**–**l**) (Tables 2 and 3) emphasised that the substitution of 3-benzene ring by electron-withdrawing groups (Cl, NO_2, OMe) increased the antimicrobial activity (especially antifungal activity) of the parent compound **3a**. The effect of the electron-withdrawing groups in increasing the activity is obvious, since in the absence of direct conjugation between 3-phenyl group and the isoxazolidine moiety, the nuclear substituents can exert only electron-withdrawing inductive (–I effect)/field effects irrespective of the position on the nucleus and their electron-donating resonance effect (IR effect) is either negligible or very small. (*eg.* OMe). Thus, the observed order of antifungal activity **3c** (*m*-NO_2, $\sigma = 1.09$ & $\pi = 0.11$) > **3b** (*o*-Cl, $\sigma = 0.86$ & $\pi = 0.76$) > **3e** (*p*-Cl, $\sigma = 0.69$ & $\pi = 0.93$) > **3g** (3,4- methylenedioxy, $\sigma = 0.54$ & $\pi = 0.82$) > **3d** (*p*-OMe, $\sigma = 0.41$ & $\pi = -0.12$) reflects the relative magnitudes of electron-withdrawing abilities of the nuclear substituents as evidenced by their Hammet σ constants [24]. Thus, there appears to be an empirical correlation between antifungal

Table 2
In vitro antibacterial activity of compounds **3a**–**l**.

Compd.	*Gram-positive* bacteria						*Gram-negative* bacteria					
	S. aureus		*B. subtilis*		*B. shaericus*		*P. aeruginosa*		*E. coli*		*S. typii*	
	ATCC 6538		ATCC 6631		ATCC 7031		ATCC 9027		ATCC 35218		ATCC 6539	
	X	Y	X	Y	X	Y	X	Y	X	Y	X	Y
3a	100	10	100	4	100	11	100	3	100	4	>100	3
3b	50	12	50	5	50	13	25	6	25	7	>100	9
3c	100	8	50	6	100	9	25	5	50	5	>100	8
3d	50	14	100	5	100	7	100	4	25	6	100	11
3e	50	14	50	6	25	16	25	5	50	4	>100	9
3f	100	5	50	5	50	12	50	4	100	3	>100	2
3g	100	8	100	5	50	11	25	5	50	4	>100	7
3h	50	11	>100	3	100	6	25	5	25	7	>100	7
3i	100	9	50	7	100	9	25	4	50	6	100	12
3j	50	11	100	4	50	14	12.5	6	50	5	100	10
3k	50	12	50	6	25	16	12.5	7	25	7	50	11
3l	50	11	100	3	50	13	50	4	100	4	100	11
Ciprofloxacin	25	17	25	9	20	24	12.5	8	18	9	50	39

Minimum Inhibitory Concentration (MIC) in μg/mL (**X**)/Zone of inhibition in mm (**Y**) at 10 μg/mL > 100 = No inhibition even at a higher concentration of 100 μg/mL.

activity and Hammet σ values, on the other hand there is poor correlation between the activity and hydrophobic constant π [24].

The higher activity of **3k** (2-pyridyl) over that of **3l** (3-pyridyl) may be explained on the assumption that 2-pyridyl group exerts greater −I effect than 3-pyridyl does.

5. Conclusion

A series of novel and hitherto unknown 3-aryl-4-phenyl-5-benzyl-1,3,4,5,5a,6,7,8,9,9a-decahydroisoxazolo[4,3-*c*]quinolines (**3a**–**l**) have been synthesized successfully in appreciable yields and evaluated them for *in vitro* antimicrobial activity against six bacterial and four fungal strains. From the activity studies, it was concluded that among all isoxazolidine derivatives, compounds **3b**, **3e** and **3k** registered high inhibitory activity against all bacterial strains and **3b**, **3c**, **3e**, **3k** and **3l** exhibited very high antifungal activity against *C. albicans*, whereas compound **3b** showed overall significant activity against both the bacterial and fungal strains. To the best of our knowledge, this is the first record of synthesis and antimicrobial evaluation of 3-aryl-4-phenyl-5-benzyl-1,3,4,5,5a,6,7,8,9,9a-decahydroisoxazolo[4,3-*c*]quinolines (**3a**–**l**). The results of *in vitro* antimicrobial evaluation emphasised that the hybrid generated from the incorporation of isoxazole moiety into decahydroquinoline core have high potential as useful antimicrobial agents. These preliminary results should pave the way for further studies in developing new decahydroisoxazoloquinolines as clinically useful antimicrobial agents.

Table 3
In vitro antifungal activity of compounds **3a**–**l**.

Compd.	*C. albicans*		*A. fumigatus*		*A. niger*		*C. albicans*	
	ATCC 90028		ATCC 28212		ATCC 16404		PYCC 3436	
	X	Y	X	Y	X	Y	X	Y
3a	>100	7	100	2	>100	4	50	10
3b	25	22	25	5	100	14	25	16
3c	25	24	12.5	5	100	21	25	16
3d	50	14	100	3	>100	7	50	12
3e	25	21	50	4	100	16	12.5	18
3f	100	12	50	4	>100	4	100	4
3g	50	16	50	4	100	11	100	6
3h	100	13	25	5	>100	9	50	11
3i	50	15	12.5	6	100	14	50	9
3j	50	19	12.5	6	100	13	50	12
3k	50	18	12.5	7	100	10	12.5	18
3l	50	17	12.5	6	>100	8	12.5	17
Ketoconazole	25	22	7	10	50	25	7.8	22

Minimum Inhibitory Concentration (MIC) in μg/mL(**X**)/Zone of inhibition in mm (**Y**) at 10 μg/mL. > 100 = No inhibition even at a higher concentration of 100 μg/mL.

6. Experimental

6.1. Chemistry

Melting points were determined in open capillary tubes and are uncorrected. The purity of the compounds was checked on a silica gel-G plate and visualised using iodine/UV lamp. IR spectra were recorded on a Schimadzu FT–IR spectrophotometer using KBr pellets. ^{1}H NMR spectra were recorded on a Bruker Avance 300 MHz NMR spectrometer in $CDCl_3$ and DMSO-d_6 using TMS as an internal standard. Elemental analyses were carried out with Elementer-Vario EL III elemental analyzer.

6.2. Synthesis of 1-benzyl-2-phenyloctahydroquinolin-4(1H)-one (*1*)

To an ethanolic solution of 1-acetylcyclohexene (0.01 mol), benzylamine (0.01 mol), benzaldehyde (0.01 mol) and catalytic amount of piperidine were added and the reaction mixture was refluxed for 5 h. After the completion of the reaction (as monitored by TLC), the contents were concentrated, cooled and poured into crushed ice. The resulting mass was extracted with chloroform, washed with water, dried and concentrated *in vacuo*; crystallisation from aq. ethanol gave pure compound **1**.

Mp. 165–167 °C; ^{1}H NMR ($CDCl_3$): δ 1.0–2.7 (m, 12H, 4CH_2 & 2CH, –CO$\underline{CH}_2$), 3.5 (dd, 1H, J = 8Hz, 1.5 Hz, –N–$\underline{CH}\varphi$), 3.7 (s, 2H, -N–$\underline{CH}_2$–Ph), 7.2–7.4 (m, 10H, Ar–H); ^{13}C NMR: 25.6, 29.3 (–CO$\underline{CH}_2$), 49.5, 55.6 (–NCH–9), 61.5 (–N–$\underline{CH}\varphi$), 65.7 (–N–$\underline{CH}_2\varphi$), 125.6, 128.8, 139.5, 146.9, 198.2 (C=O). DEPT-135: δ 25.69 (↓), 28.62 (↓), 49.36 (↓), 55.50 (↑) (–NCH–9), 59.56 (↑) (N–CHφ), 68.40 (↓) (–N–$CH_2\varphi$), 125.67 (↑), 126.28 (↑), 129.56 (↑), 134.00 (↑), 139.14 (↑).

6.3. Synthesis of 1-benzyl-2-phenyl-3-arylideneoctahydroquinoline-4(1H)-ones (*2a*–*l*)

To an alcoholic solution of compound **1** (0.01 mol), appropriate aromatic aldehydes (0.01 mol) and catalytic amount of pyridine and piperidine were added and the mixture was refluxed for 3 h. The excess of alcohol was distilled off and the resulting residue was treated with cold water, and extracted with chloroform; it was

washed with water, dried and evaporated. The residue on crystallisation from ethanol–water mixture (2:1) afforded compounds (**2a**–**l**).

*6.3.1. 1-Benzyl-2-phenyl-3-benzylideneoctahydroquinoline-4(1H)-one (**2a**)*

Mp. 143–145 °C; IR (KBr): 3060 (aromatic C–H str.), 1710 (C=O str. in ring), 1220–1076 (aliphatic C–N str.), 880–720 (aromatic C–H def.); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.0–2.6 (m, 10H, 4CH_2 & 2CH), 3.6 (s, 2H, –N–CH_2φ), 4.6 (s, 1H, –N–CHφ), 6.4 (s, 1H, = CHφ), 7.2–7.7 (m, 15H, Ar–H); ^{13}C NMR: 22.6, 24.6, 28.6, 32.4, 41.6, 53.2, 56.5, 68.4, 125.6, 126.0, 126.2, 134.0, 135.3, 136.4 (=CH–Ar), 137.4, 196.7 (C=O); DEPT-135: δ 22.45 (↓), 25.62 (↓), 26.35 (↓), 33.42 (↓), 41.65 (↑), 55.34 (↑) (–N–CHφ), 59.52 (↓) (–N–CH_2φ), 65.72 (↑), 123.02 (↑), 125.94 (↑), 127.75 (↑), 133.04 (↑), 136.53 (↑) (=CH–Ar).

*6.3.2. 1-Benzyl-2-phenyl-3-(2-chlorobenzylidene)octahydroquinolin-4-one (**2b**)*

Mp. 171–172 °C (methanol); yield: 86%; IR (KBr, cm^{-1}): 3066 (aromatic C–H str.), 1718 (CO str. in ring); ^{1}H NMR (300 MH_Z, $CDCl_3$): δ 1.2–2.8 (m, 10H, 4× CH_2 & 2× CH), 3.6 (s, 2H, –NCH_2φ), 4.5 (s, 1H, –NCHφ), 6.7 (s, 1H,=CHAr), 7.2–7.8 (m, 14H, ArH); ^{13}C NMR (75 MH_Z, $CDCl_3$): δ 22.1, 25.4, 28.0, 31.9, 41.5, 53.8 (–N–CHφ), 57.9(–N–CH_2φ), 69.4, 126.3, 127.2, 128.2, 136.0, 137.3, 137.9 (=CHAr), 138.4, 198.5 (CO).

*6.3.3. 1-Benzyl-2-phenyl-3-(3-nitrobenzylidene)octahydroquinolin-4-one (**2c**)*

Mp. 143–145 °C (aq. ethanol); yield: 81%; IR (KBr, cm^{-1}): 3071 (aromatic C–H str.), 1711 (CO str.); ^{1}H NMR (300 MH_Z, $CDCl_3$): δ 1.1–2.8 (m, 10H, 4× CH_2 & 2× CH), 3.7 (s, 2H, –NCH_2φ), 4.6 (s, 1H, –NCHφ), 6.6(s, 1H,=CHAr), 7.2–7.5 (m, 14H, ArH); ^{13}C NMR (75 MH_Z, $CDCl_3$): δ 22.1, 24.4, 28.1, 32.4, 41.9, 54.2 (–N–CHφ), 56.5 (–N–CH_2φ), 67.3, 125.6, 126.5, 127.8, 134.0, 136.3(=CHAr),137.8, 142.7, 197.8 (CO).

*6.3.4. 1-Benzyl-2-phenyl-3-(4-methoxybenzylidene)octahydroquinolin-4-one (**2d**)*

Mp. 186–187 °C (aq. ethanol); yield: 87%; IR (KBr, cm^{-1}): 3078 (aromatic C–H str.), 1722 (CO str.); ^{1}H NMR (300 MH_Z, $CDCl_3$): δ 1.1–2.5 (m, 10H, 4× CH_2 & 2× CH), 3.4 (s, 2H, –NCH_2φ), 3.8 (s, 3H, –OCH_3), 4.7 (s, 1H, –NCHφ), 6.1(s, 1H,=CHAr), 6.9–7.5 (m, 14H, ArH); ^{13}C NMR (75 MH_Z, $CDCl_3$): δ 23.5, 24.1, 28.9, 32.4, 41.9, 52.3 (–NCHφ), 58.6 (–NCH_2φ), 67.1, 125.6, 126.2, 127.8, 128.1, 129.0, 134.0, 135.3, 136.4 (=CHAr), 137.4, 156.7 (–OCH_3), 198.3 (CO).

*6.3.5. 1-Benzyl-2-phenyl-3-(4-chlorobenzylidene)octahydroquinolin-4-one (**2e**)*

Mp. 179–181 °C (aq. ethanol); yield: 89%; IR (KBr, cm^{-1}): 3069 (aromatic C–H str.), 1717 (CO str.); ^{1}H NMR (300 MH_Z, $CDCl_3$): δ 1.3–2.7 (m, 10H, 4× CH_2 & 2× CH), 3.6 (s, 2H, –NCH_2φ), 4.6 (s, 1H, –NCHφ), 6.5(s, 1H,=CHAr), 7.2–7.6 (m, 14H, ArH); ^{13}C NMR (75 MH_Z, $CDCl_3$): δ 22.6, 24.7, 28.2, 32.4, 41.6, 52.5 (–NCHφ), 56.8 (–NCH_2φ), 68.5, 125.6, 126.2, 127.1, 128.8, 133.4, 135.3, 136.4 (=CHAr), 138.1, 197.5 (CO).

*6.3.6. 1-Benzyl-2-phenyl-3-(furan-2-ylmethylene)octahydroquinolin-4-one (**2f**)*

Mp. 152–153 °C (methanol); yield: 78%; IR (KBr, cm^{-1}): 3054 (aromatic C–H str.), 1706 (CO str.); ^{1}H NMR (300 MH_Z, $CDCl_3$): δ 1.3–2.7 (m, 10H, 4× CH_2 & 2× CH), 3.6 (s, 2H, –NCH_2φ), 4.5 (s, 1H, –NCHφ), 6.8 (s, 1H,=CHAr), 7.2–8.17 (m, 13H, ArH); ^{13}C NMR (75 MH_Z, $CDCl_3$): δ 22.5, 24.6, 25.3, 31.4, 40.9, 51.5 (–NCHφ), 59.1 (–NCH_2φ), 67.2, 101.2, 109.3, 121.2, 126.2, 128.7, 137.8 (=CHAr), 138.1, 143.4, 152.0, 197.3 (CO).

*6.3.7. 1-Benzyl-2-phenyl-3-(benzo[d][1,3]dioxol-5-ylmethylene) octahydroquinolin-4-one (**2g**)*

Mp. 149–150 °C (aq. ethanol); yield: 81%; IR (KBr, cm^{-1}): 3066 (aromatic C–H str.), 1716 (CO str.); ^{1}H NMR (300 MH_Z, $CDCl_3$): δ 1.1–2.7 (m, 10H, 4× CH_2 & 2× CH), 3.6 (s, 2H, –NCH_2φ), 4.6 (s, 1H, –NCHφ), 6.1 (s, 3H, –OCH_2O), 6.7(s, 1H,=CHAr), 7.1–7.3 (m, 13H, ArH); ^{13}C NMR (75 MH_Z, $CDCl_3$): δ 22.4, 24.2, 26.3, 32.2, 41.5, 52.3 (–NCHφ), 58.1 (–NCH_2φ), 65.4, 99.8, 106.3 (–O–CH_2–O), 124.6, 126.2, 127.9, 129.2, 134.0, 136.3, 136.7 (=CHAr), 137.4, 148.6, 197.2 (CO).

*6.3.8. 1-(Benzyl-2-phenyl-3-(1H-indol-3-yl)methylene)octahydroquinolin-4-one (**2h**)*

Mp. 167–169 °C (aq. ethanol); yield: 79%; IR (KBr, cm^{-1}): 3051(aromatic C–H str.), 1704 (CO str.); ^{1}H NMR (300 MH_Z, $CDCl_3$): δ 1.2–2.8 (m, 10H, 4× CH_2 & 2× CH), 3.6 (s, 2H, –NCH_2), 4.6 (s, 1H, –NCHφ), 6.7 (s, 1H,=CHAr), 7.1–7.8 (m, 15H, ArH), 10.8 (s, 1H, –NH); ^{13}C NMR (75 MH_Z, $CDCl_3$): δ 22.5, 24.7, 24.9, 33.2, 40.8, 53.2 (–N–CHφ), 59.3 (–NCH_2φ), 68.4, 112.6, 120.7, 122.5, 125.6, 126.8, 127.4, 128.0, 135.5, 137.4, 137.8 (=CHAr), 138.5, 146.1, 196.8 (CO).

*6.3.9. 1-Benzyl-2-phenyl-3-(3,4-dimethoxybenzylidene)octahydroquinolin-4-one (**2i**)*

Mp., 211–212 °C (aq. ethanol); yield: 70%; IR (KBr, cm^{-1}): 3074 (aromatic C–H str.), 1719 (CO str.); ^{1}H NMR (300 MH_Z, $CDCl_3$): δ 1.1–2.7 (m, 10H, 4× CH_2 & 2× CH), 3.6 (s, 2H, –NCH_2φ), 3.9 (s, 6H, 2× OCH_3), 4.6 (s, 1H, –N–CHφ), 6.7 (s, 1H,=CHAr), 6.9–7.4 (m, 13H, ArH); ^{13}C NMR (75 MH_Z, $CDCl_3$): δ 22.7, 24.1, 25.6, 32.3, 41.2, 53.5 (–N–CHφ), 56.3 (–N–CH_2φ), 56.7 (–OCH_3), 67.5, 112.5, 123.6, 127.8, 128.5, 134.4, 135.5, 136.3 (=CHAr), 137.4, 149.6, 196.9 (CO).

*6.3.10. 1-Benzyl-2-phenyl-3-(4-nitrobenzylidene)octahydroquinolin-4-one (**2j**)*

Mp. 164–165 °C (aq. ethanol); yield 64%; IR (KBr, cm^{-1}): 3070 (aromatic C–H str.), 1720 (CO str.); ^{1}H NMR (300 MH_Z, $CDCl_3$): δ 1.1–2.7 (m, 10H, 4× CH_2 & 2× CH), 3.6 (s, 2H, –NCH_2φ), 4.6 (s, 1H, –NCHφ), 6.5 (s, 1H,=CHAr), 6.9–7.3 (m, 14H, ArH); ^{13}C NMR (75 MH_Z, $CDCl_3$): δ 22.4, 24.8, 25.3, 32.5, 41.6, 52.2 (–N–CHφ), 56.2 (–N–CH_2φ), 68.7, 123.6, 127.1, 128.3, 128.9, 135.1, 136.4, 137.4 (=CHAr), 138.6, 147.2, 198.1 (CO).

*6.3.11. 1-Benzyl-2-phenyl-3-(pyridin-2-ylmethylene)octahydroquinolin-4-one (**2k**)*

Mp. 170–172 °C (aq. ethanol); yield 61%; IR (KBr, cm^{-1}): 3070 (aromatic C–H str.), 1721 (CO str.); ^{1}H NMR (300 MH_Z, $CDCl_3$): δ 1.0–2.6 (m, 10H, 4× CH_2 & 2× CH), 3.6 (s, 2H, –NCH_2), 4.6 (s, 1H, –NCHφ), 6.5 (s, 1H,=CHAr), 7.2–8.2 (m, 14H, ArH); ^{13}C NMR (75 MH_Z, $CDCl_3$): δ 22.8, 24.3, 26.1, 32.4, 40.5, 53.6 (–N–CHφ), 55.8(–N–CH_2φ), 66.4, 122.6, 124.8, 126.7, 128.3, 136.5 (=CHAr), 138.3, 146.4, 152.4, 196.8 (CO).

*6.3.12. 1-Benzyl-2-phenyl-3-(pyridin-3-ylmethylene)octahydroquinolin-4-one (**2l**)*

Mp. 158–159 °C (aq. ethanol); yield 72%; IR (KBr): 3063 (aromatic C–H str.), 1714 (CO str.); ^{1}H NMR (300 MH_Z, $CDCl_3$): δ 1.1–2.8 (m, 10H, 4× CH_2 & 2× CH), 3.6 (s, 2H, –NCH_2φ), 4.7 (s, 1H, –NCHφ), 6.7 (s, 1H,=CHAr), 7.2–8.3 (m, 14H, ArH); ^{13}C NMR (75 MH_Z, $CDCl_3$): δ 22.3, 24.5, 25.6, 32.8, 41.2, 52.3 (–N–CHφ), 55.2 (–N–CH_2φ), 67.1, 123.6, 127.1, 128.2, 132.7, 136.6, 137.0 (=CHAr), 138.4, 142.8, 143.7, 149.2, 198.3 (CO).

*6.4. General procedure for the synthesis of compounds (**3a**–**l**)*

To an ethanolic solution of compounds (**2a**–**l**) (0.01 mol), an aqueous solution of hydroxylamine hydrochloride (0.10 mol) in

minimum amount of water and an aqueous solution of NaOAc in minimum amount of water were added and the reaction mixture was refluxed for 4 h on a water bath and the course of the reaction was followed by TLC. After completion of the reaction, excess of alcohol was evaporated and the resulting residue was treated with ice–water. The compounds (**3a**–**l**) that separated were filtered, dried and crystallised from ethanol.

*6.4.1. 3,4-Diphenyl-5-benzyl-1,3,4,5,5a,6,7,8,9,9a-decahydroisoxazolo [4,3-c]quinoline (**3a**)*

IR (KBr): 3290 (N–H str.), 2924 (aromatic C–H str.) cm^{-1}; ^1H NMR (300 MH_Z, $CDCl_3$): δ 1.1–1.5 (m, 10H, $4CH_2$ & 2CH), 3.6 (s, 2H, N–$CH_2\varphi$), 4.2 (s, 1H, N–CHφ), 5.4 (s, 1H, O–CHAr), 7.1–7.4 (m, 15H, Ar–H), 8.5 (s, 1H, –NH); ^{13}C NMR (75 MH_Z, $CDCl_3$): 23.3, 27.5, 31.9, 38.4, 56.1 (–N–$\underline{C}H_2\varphi$), 62.1 (–N–$\underline{C}H\varphi$), 67.5, 84.7 (O–$\underline{C}HAr$), 113.9, 125.2, 128.7, 129.2, 137.4, 143.9; DEPT-135 (75 MH_Z, $CDCl_3$): δ 23.35 (↓), 26.62 (↓), 34.58 (↓), 38.45 (↓), 55.34 (↓) (N–$CH_2\varphi$), 61.23 (↑) (N–CHφ), 67.52 (↑), 83.55 (↑) (O–$\underline{C}HAr$), 123.01 (↑), 125.94 (↑), 127.75 (↑), 128.71 (↑), 129.02 (↑).

*6.4.2. 3-(2-chlorophenyl)-4-phenyl-5-benzyl-1,3,4,5,5a,6,7,8,9,9a-decahydro- isoxazolo[4,3-c]quinoline (**3b**)*

IR (KBr): 3310 (N–H str.), 2921(aromatic C–H str.) cm^{-1}; ^1H NMR (300 MH_Z, $CDCl_3$): δ 1.0–2.5 (m, 10H, $4CH_2$ & 2CH), 3.6 (s, 2H, N–$CH_2\varphi$), 4.4 (s, 1H, N–CHφ), 5.2 (s, 1H, O–$\underline{C}HAr$), 7.2–7.8 (m, 14H, Ar–H), 8.7 (s, 1H, –NH); ^{13}C NMR (75 MH_Z, $CDCl_3$): 24.4, 25.2, 30.8, 33.7, 56.4 (–N–$\underline{C}H_2\varphi$), 60.2 (–N–$\underline{C}H\varphi$), 64.3, 82.6 (O–$\underline{C}HAr$), 127.5, 128.2.

*6.4.3. 3-(3-nitrophenyl)-4-phenyl-5-benzyl-1,3,4,5,5a,6,7,8,9,9a-decahydro-isoxazolo-[4,3-c]quinoline (**3c**)*

IR (KBr): 3280 (N–H str.), 2929 (aromatic C–H str.) cm^{-1}; ^1H NMR (300 MH_Z, $CDCl_3$): δ 1.0–2.7 (m, 10H, $4CH_2$ & 2CH), 3.6 (s, 2H, N–$CH_2\varphi$), 4.2 (s, 1H, N–CHφ), 5.4 (s, 1H, O–CHAr), 7.2–8.2 (m, 14H, Ar–H), 8.7 (s, 1H, –NH); ^{13}C NMR (75 MH_Z, $CDCl_3$): 24.3, 25.5, 34.7, 37.4, 56.2 (–N–$\underline{C}H_2\varphi$), 59.2 (–N–$\underline{C}H\varphi$), 64.3, 82.4 (O–$\underline{C}HAr$), 127.1, 128.0, 133.6, 137.8, 138.3, 145.1.

*6.4.4. 3-(4-methoxyphenyl)-4-phenyl-5-benzyl-1,3,4,5,5a,6,7,8, 9,9a-decahydro-isoxazolo[4,3-c]quinoline (**3d**)*

IR (KBr): 3385 (N–H str.), 3161 (aromatic C–H str.) cm^{-1}; ^1H NMR (300 MH_Z, $CDCl_3$): δ 1.0–2.5 (m, 10H, $4CH_2$ & 2CH), 3.5 (s, 2H, N–$CH_2\varphi$), 3.9 (s, 3H, O–CH_3), 4.3 (s, 1H, –N–CHφ), 5.2 (s, 1H, O–CHAr), 6.9–7.4 (m, 14 H, Ar–H), 8.6 (s, 1H, –NH); ^{13}C NMR (75 MH_Z, $CDCl_3$): 24.5, 25.6, 30.7, 33.5, 55.23 (O–CH_3), 55.7 (–N–$\underline{C}H_2\varphi$), 57.2 (–N–$\underline{C}H\varphi$), 64.2, 82.3 (O–$\underline{C}HAr$), 127.4, 128.5, 133.8, 137.6, 138.3, 145.4.

*6.4.5. 3-(4-chlorophenyl)-4-phenyl-5-benzyl-1,3,4,5,5a,6,7,8,9,9a-decahydro-isoxazolo[4,3-c]quinoline (**3e**)*

IR (KBr): 3250 (N–H str.), 3080(aromatic C–H str.) cm^{-1}; ^1H NMR (300 MH_Z, $CDCl_3$): δ 1.0–2.6 (m, 10H, $4CH_2$ & 2CH), 3.4 (s, 2H, –N–$CH_2\varphi$), 4.3 (s, 1H, –N–CHφ), 5.3 (s, 1H, O–CHAr), 7.2–7.4 (m, 14H, Ar–H), 8.8 (s, 1H, –NH); ^{13}C NMR (75 MH_Z, $CDCl_3$): 24.4, 25.1, 30.2, 33.1, 55.3 (–N–$\underline{C}H_2\varphi$), 56.6 (–N–$\underline{C}H\varphi$), 64.2, 83.4 (O–$\underline{C}HAr$), 126.4, 125.8, 134.3, 137.4, 138. 3, 143.4.

*6.4.6. 3-(furan-2-yl)-4-phenyl-5-benzyl-1,3,4,5,5a,6,7,8,9,9a-decahydro-isoxazolo-[4,3-c]quinoline (**3f**)*

IR (KBr): 3382 (N–H str.), 2996 (aromatic C–H str.)cm^{-1}; ^1H NMR (300 MH_Z, $CDCl_3$): δ 1.0–2.5 (m, 10H, $4CH_2$ & 2CH), 3.5 (s, 2H, N–$CH_2\varphi$), 4.7 (s, 1H, –N–CHφ), 5.5 (s, 1H, O–CHAr), 6.6–7.4 (m, 13H, Ar–H), 8.6 (s, 1H, –NH); ^{13}C NMR (75 MH_Z, $CDCl_3$): 24.3, 25.3, 30.2, 33.1, 55.4 (–N–$\underline{C}H_2\varphi$), 56.2 (–N–$\underline{C}H\varphi$), 64.2, 82.4 (O–$\underline{C}HAr$), 127.4, 128.8, 133.4, 137.2, 138.1, 145.4.

*6.4.7. 3-(3,4-Methylenedioxyphenyl)- 4-phenyl-5-benzyl-1,3,4,5, 5a,6,7,8,9,9a-decahydroisoxazolo[4,3-c]quinoline (**3g**)*

IR (KBr): 3210 (N–H str.), 3064 (aromatic C–H str.) cm^{-1}; ^1H NMR (300 MH_Z, $CDCl_3$): δ 1.0–2.4 (m, 10H, $4CH_2$ & 2CH), 3.5 (s, 2H, N–$CH_2\varphi$), 4.5 (s, 1H, –N–CHφ), 5.4 (s, 1H, O–CHAr), 6.1 (s, 1H, –O–CH_2–O–), 6.9–7.5 (m, 13H, Ar–H), 8.7 (s, 1H, –NH); ^{13}C NMR (75 MH_Z, $CDCl_3$): 24.3, 25.3, 30.2, 33.1, 55.2 (–N–$\underline{C}H_2\varphi$), 56.2 (–N–$\underline{C}H\varphi$), 64.2, 82.4 (O–$\underline{C}HAr$), 104.4 (–O–CH_2–O), 127.4, 128.8, 133.4, 137.2, 138.1, 145.4.

*6.4.8. 3-(1H-indol-2-yl)-4-phenyl-5-benzyl-1,3,4,5,5a,6,7,8,9,9a-decahydroisoxazolo-[4,3-c]quinoline (**3h**)*

^1H NMR (300 MH_Z, $CDCl_3$): δ 1.0–2.5 (m, 10H, $4CH_2$ & 2CH), 3.4 (s, 2H, N–$CH_2\varphi$), 4.1 (s, 1H, N–CHφ), 5.1 (s, 1H, O–CHAr), 7.0–7.6 (m, 15H, Ar–H), 8.9 (s, 1H, –NH), 10.4 (s, 1H, –NH of indole); ^{13}C NMR (75 MH_Z, $CDCl_3$): 24.3, 25.3, 30.2, 33.1, 55.6 (–N–$\underline{C}H_2\varphi$), 56.2 (–N–$\underline{C}H\varphi$), 64.2, 82.4 (O–$\underline{C}HAr$), 127.4, 128.8, 133.4, 137.2, 138.1, 145.4.

*6.4.9. 3-(3,4-dimethoxyphenyl)-4-phenyl-5-benzyl-1,3,4,5,5a,6,7,8, 9,9a-decahydroisoxazolo[4,3-c]quinoline (**3i**)*

IR (KBr): 3330 (N–H str.), 3072 (aromatic C–H str.) cm^{-1}; ^1H NMR (300 MH_Z, $CDCl_3$): δ 1.0–2.5 (m, 10H, $4CH_2$ & 2CH), 3.5 (s, 2H, N–$CH_2\varphi$), 3.9 (s, 6H, 2× O–CH_3), 4.2 (s, 1H, N–CHφ), 5.1 (s, 1H, O–CHAr), 6.8–7.3 (m, 13H, Ar–H), 8.5 (s, 1H, –NH); ^{13}C NMR (75 MH_Z, $CDCl_3$): 24.3, 25.3, 30.2, 33.1, 55.12, 55.4 (–N–$\underline{C}H_2\varphi$), 56.2 (–N–$\underline{C}H\varphi$), 64.2, 82.4 (O–$\underline{C}HAr$), 127.4, 128.8, 133.4, 137.2, 138.1, 145.4.

*6.4.10. 3-(4-nitrophenyl)-4-phenyl-5-benzyl-1,3,4,5,5a,6,7,8,9,9a-decahydro-isoxazolo[4,3-c]quinoline (**3j**)*

IR (KBr): 3240 (N–H str.), 3045 (aromatic C–H str.) cm^{-1}; ^1H NMR (300 MH_Z, $CDCl_3$): δ 1.0–2.6 (m, 10H, $4CH_2$ & 2CH), 3.6 (s, 2H, N–$CH_2\varphi$), 4.1(s, 1H, N–CHφ), 5.2 (s, 1H, O–CHAr), 7.2–8.2 (m, 14H, Ar–H), 9.2 (s, 1H, –NH); ^{13}C NMR (75 MH_Z, $CDCl_3$): 24.3, 25.3, 30.2, 33.1, 55.4 (–N–$\underline{C}H_2\varphi$), 56.7 (–N–$\underline{C}H\varphi$), 64.2, 82.4 (O–$\underline{C}HAr$), 127.4, 128.8, 133.4, 137.2, 138.1, 145.4.

*6.4.11. 3-(pyridin-2-yl-4-phenyl-5-benzyl-)-1,3,4,5,5a,6,7,8,9,9a-decahydro-isoxazolo-[4,3-c]quinoline (**3k**)*

^1H NMR (300 MH_Z, $CDCl_3$): δ 1.0–2.5 (m, 10H, $4CH_2$ & 2CH), 3.6 (s, 2H, N–$CH_2\varphi$), 4.1 (s, 1H, N–CHφ), 5.2 (s, 1H, O–CHAr), 7.1–8.4 (m, 14H, Ar–H), 8.7 (s, 1H, –NH); ^{13}C NMR (75 MH_Z, $CDCl_3$): 24.3, 25.3, 30.2, 33.1, 55.4 (–N–$\underline{C}H_2\varphi$), 56.2 (–N–$\underline{C}H\varphi$), 64.2, 82.4 (O–$\underline{C}HAr$), 127.4, 128.8, 133.4, 137.2, 138.1, 145.4.

*6.4.12. 3-(pyridin-3-yl)- 4-phenyl-5-benzyl-1,3,4,5,5a,6,7,8,9,9a-decahydro-isoxazolo-[4,3-c]quinoline (**3l**)*

IR (KBr): 3290(N–H str.), 3038 (aromatic C–H str.) cm^{-1}; ^1H NMR (300 MH_Z, $CDCl_3$): δ 1.0–2.5 (m, 10H, $4CH_2$ & 2CH), 3.5 (s, 2H, N–$CH_2\varphi$), 4.3 (s, 1H, NCHφ), 5.2 (s, 1H, O–CHAr), 7.2–8.6 (m, 14H, Ar–H), 8.6 (s, 1H, –NH); ^{13}C NMR (75 MH_Z, $CDCl_3$): 24.3, 25.3, 30.2, 33.1, 55.4(–N–$\underline{C}H_2\varphi$), 56.2 (–N–$\underline{C}H\varphi$), 64.2, 82.4 (O–$\underline{C}HAr$), 127.4, 128.8, 133.4, 137.2, 138.1, 145.4.

6.5. Antibacterial assay

Discs measuring 6.25 mm in diameter were punched from Whatmann no. 1 filter paper. Batches of 10 discs were dispensed to each screw capped bottle and sterilized by dry heat at 140 °C for an hour. The test compounds were prepared with a concentration of 0.5% using methanol. The discs of each concentration were placed in triplicate in meat peptone agar medium and seeded with fresh bacterial culture separately and incubated at 37 °C for 24 h. The zone of inhibition was measured in millimetres using 10 μg/mL concentrations of synthesized compounds (**3a**–**l**); methanol was used both as a solvent and as a control. No zone of inhibition was observed in control (i.e. in methanol).

6.6. Antifungal assay

Potato dextrose agar (PDA) was used as basal medium for test fungi. Glass petridishes used were sterilized and sterilized melted PDA medium (~45 °C) was poured at the rate of 15 mL into each petridish (90 mm). After solidification of the medium, small portions of the mycelium of each fungus were spread carefully over the centre of each PDA plate with the help of sterilized needles. Then, each fungus was transferred to a number of PDA plates, which were then incubated and ready for use after five days of incubation. Prepared discs of samples were placed gently on solidified agar plates, freshly seeded with the test organisms with sterile forceps.

A control disc was also placed on the test plates to compare the effect of the test samples and to nullify the effect of solvent respectively. The plates were then kept in a refrigerator at 4 °C for 24 h so that the materials had sufficient time to diffuse over a considerable area of the plates. After this, the plates were incubated at 25 °C for 72 h. Methanol (0.5%) was used as solvent to prepare desired solution of the compounds and also to maintain proper control. The zone of inhibition was measured in millimetres using 10 μg/mL concentration of synthesized compounds (**3a**–**l**); no zone of inhibition was observed in control (i.e. in methanol).

The MIC values were determined by two fold serial dilution technique. The compounds were dissolved in methanol to give a concentration of 100 μg/mL, which was serially diluted to give concentrations of 50.0, 25.0, 12.5, 6.25, 3.125 μg/mL in culture tubes containing 1 mL of nutrient medium. The MIC was recorded in each case as the minimum concentration of compound, which inhibited the growth of (99%) of tested microorganism.

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Appendix. Supplementary material

Supplementary data related to this article can be found online at doi:10.1016/j.ejmech.2011.10.045.

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