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Original article

Amberlite–IRA-402 (OH) ion exchange resin mediated synthesis of indolizines, pyrrolo [1,2-a] quinolines and isoquinolines: Antibacterial and antifungal evaluation of the products

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ABSTRACT

A number of indolizines and pyrrolo[1,2-a]quinolines/isoquinolines were prepared from phenacyl pyridinium, quinolinium and isoquinolinium salts derived fromthe reaction of the heterocycles with 2-bromo acetophenone with alkynes and alkenes using amberlite–IRA-402 (OH) ion exchange resin as the base. Antibacterial and antifungal studies were carried out against thirteen bacterial and four fungal strains, which revealed that three derivatives (**4a**, **4b**, **7a**) out of fifteen are effective against all the thirteen strains and one derivative, **10**, showed dual antibactericidal and antifungal efficacy.

1. Introduction

A great deal of research in heterocyclic chemistry is concerned with the discovery of new methods of ring formation since more than half of the biologically active compounds produced by nature contain a heterocyclic moiety as a fundamental unit in their structure [1].

The heterocyclic aromatic compound indolizine (isomer of indole) forms the structural core of a variety of alkaloids such as swainsonine and monomorine [2,3], which were prepared for both practical and theoretical reasons [4]. Indolizine derivatives containing a variety of functional groups are being used due to their interesting biological activities like antibacterial [5], antiviral and antileishmanial [6], antiinflamatory [7], analgesic [8], antitumor [9], antioxidant [10], aromatase inhibitory [11], calcium entry blocking [12], and histamine H_3 receptor antagonist [13] and also evaluated as agrochemical [14]. As such, the indolizines are important synthetic targets for developing new pharmaceuticals or agrochemicals.

It is small wonder therefore that great efforts have been made to discover and optimize new reactions that facilitate the construction of indolizine derivatives. One of the most important methods for the preparation of indolizines (and benzoindolizines) is 1,3 dipolar cycloaddition of pyridinium and related heteroaromatic ylides, e.g. quinolinium or isoquinolinium ylides, with alkynes [15]. Recently various metal catalyzed reactions of heteroaryl halide with propargyl amine or of heteroaromatic aldehydes with amines and alkynes followed by cyclization have been developed [16]. The scope of all these procedures has been limited to the use of alkynes, very few of which are commercially available. As an alternative to the alkynes, the olefinic dipolarophiles have been utilized to play the pivotal role in this strategy, although there remain some difficulties, as the intermediate tetrahydroindolizines formed are unstable and reversibly transform into a betaine intermediate followed by decomposition [17]. To overcome this problem fluoroalkenes, fluoroiodo alkenes, and fluorinated vinyl tosylates are being used in the cycloaddition where hydrogen fluoride or TSOH is eliminated to prepare fluorinated or unfluorinated indolizines [18–20]. Also the tetrahydroindolizines can be aromatized into indolizines *in situ* via dehydrogenative

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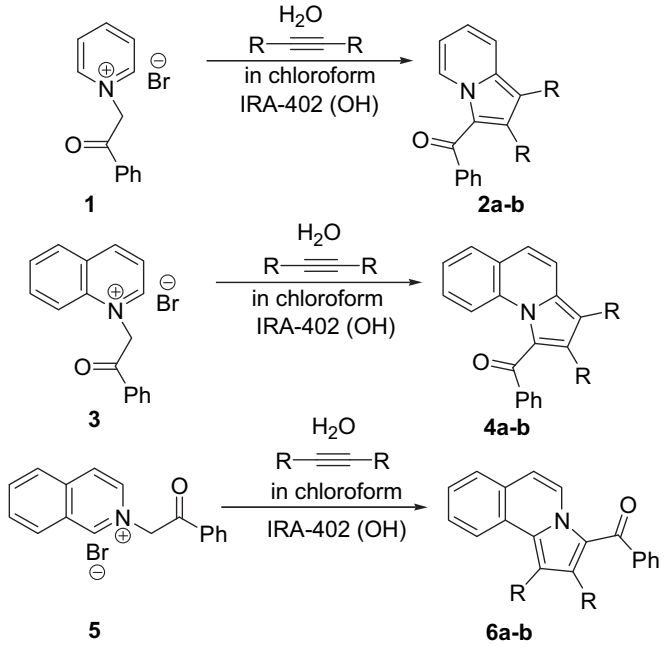
aromatization in a one-pot sequence [21] using a mild dehydrogenative oxidant like TPCD or MnO_2.

Very recently, we reported the synthesis of bioactive heterocycles via azomethine ylide cycloaddition [22]. We felt that this approach can be judiciously extended for the syntheses of indolizines and pyrrolo[1,2-a]quinolines/isoquinolines. We also intended to utilize the advantages of Amberlite–IRA-402(OH) ion-exchange resin [23] as a base cum catalyst in this biphasic system in lieu of bases like Et_3N, DBU etc. Since newer antibiotics and chemotherapeutic agents are being steadily synthesized in controlling many infections but the success depends on non-development of drug resistance [24]. In this endeavor our approach is centered with the synthesis of new chemical entities for the search of newer antimicrobial agents. Herein, we wish to report in detail the syntheses of indolizines, pyrrolo[1,2-a]quinolines/isoquinolines using amberlite resin along with the results of investigation on their bactericidal and fungicidal properties.

2. Results and discussion

2.1. Chemistry

Isoquinolinium, quinolinium or pyridinium salts were prepared by the reaction of isoquinoline or quinoline or pyridine with 2-bromo acetophenone in diethylether at room temperature. For the cycloaddition reaction, the salts were dissolved in water and a solution of dipolarophile in chloroform was added. Then amberlite–IRA-402 (OH) ion exchange resin (as the base) and DDQ (as the oxidizing agent) were added to the reaction mixture. Initially we reacted with pyridinium, quinolinium and isoquinolinium salts with alkynic dipolarophile. The reactions proceeded smoothly and became complete within 5 h with 65–70% yield. However, addition of DDQ was not mandatory for oxidation in case of alkynic dipolarophiles like DMAD/DEAD (Scheme 1). Without DDQ, the reaction was complete within 5–6 h and the yield of the products was quite similar (Table 1, entry 1–6). But the reaction of olefinic dipolarophiles with pyridinium or quinolinium salts in presence of DDQ took almost 9–10 h to complete and generated only moderate yields (Scheme 2, Table 1, entry 7–11), though with isoquinolinium salts it took 6–7 h producing a convincing yield (Table 1, entry 12–14). Using TPCD as the oxidizing agent, pyrrolo[1,2-a]quinolines were not formed from quinoliniums, rather the indolizine derivatives were produced due to oxidation of the quinoline ring. However, using MnO_2 as the oxidizing agent the expected pyrrolo [1,2-a]quinolines were isolated in low yields [25], on the other hand, replacing MnO_2 with DDQ, in presence of Amberlite resin the pyrrolo [1,2-a] quinolines yield was quite satisfactory.



Scheme 1. Synthesis of indolizines, pyrrolo [1,2-a] quinolines, pyrrolo [1,2-a] isoquinolines using alkynes.

In case of isoquinolinium salt the yield with alkynic or olefinic dipolarophile is higher than in case of quinolinium or pyridinium salt (Table 1, entry 5–6, 12–14). This might be due to the fact that the C-1 of isoquinoline is more electrophilic in nature than C-2 of quinoline or pyridine where electrophilicity is distributed in between C-2 and C-4. The compounds were characterized on the basis of spectral analysis like IR, ^1H and ^{13}C NMR and also by MS. Besides the spectral studies, the structure of **9c** was unambiguously established by single crystal X-ray crystallography (Fig. 1).

It is noteworthy that the reaction of isoquinolinium salt with trans-beta-nitrostyrene yielded no expected cycloaddition product when carried out following similar reaction protocol rather we were able to isolate a product **10** whose structure was established with the help of spectroscopic analysis and also confirmed by single crystal X-ray crystallography (Fig. 2). It is a cyclized product and appears to have formed by the self condensation of the salt with its enol form (Scheme 3) (Table 1, entry 15). Although there appears a similar report on self condensation of pyridinium salt with its enol form [20b], however, we were unable isolate similar product from the reaction of quinolinium salt. The reaction of isoquinolinium salt in the presence of amberlite and DDQ without a dipolarrophile, the yield of **10** was quite good.

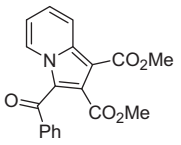
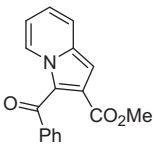
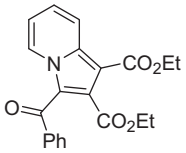
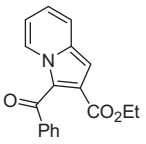
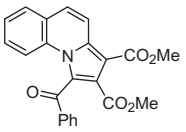
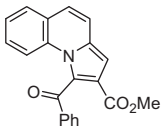
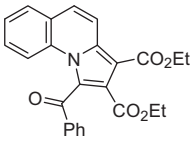
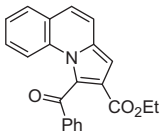
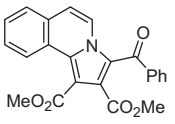
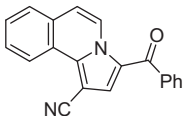
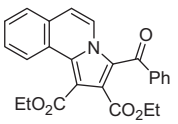
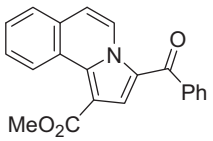
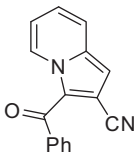
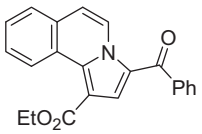
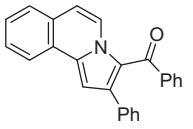
To establish the effectiveness of Amberlite resin we also performed reactions in presence of other bases like Et_3N, DBU etc in homogenous as well as biphasic conditions. In each case it took 8–10 h to complete the reaction and the yield was quite good. It is noteworthy that in these cases some colored material was also produced. On the other hand, using resin, which is reusable after simple washing with solvent and NaOH solution, the formation of colored material was checked.

2.2. Pharmacology

The synthesized compounds were tested for their antimicrobial and antifungal studies *in vitro*. The microorganisms used in this study consisted of 13 strains of bacteria namely: *Bacillus subtilis UC564*, *Staphylococcus aureus 25923*, *Streptococcus faecalis 29212*, *Micrococcus luteus AGD1*, *Escherichia coli ATCC25938*, *Klebsiella pneumoniae J/l/4*, *Pseudomonas aeruginosa ATCC27853*, *Vibrio cholera 7201*, *Vibrio parahaemolyticus 72016*, *Shigella dysenteriae 3*, *Shigella flexneri DN13*, *Salmonella typhi DIRW*, and *Salmonella typhimurium 11*. Antifungal studies were carried out on four strains of fungi, *viz. Aspergillus niger*, *Candida albicans*, *Candida tropicalis*, and *Cryptpcoccus neoformans*. The results of the antimicrobial activity testing are shown in Table 2, which demonstrates that out of the tested compound six (**4a**, **4b**, **7a**, **9a**, **9c** and **10**) possess significant antibacterial activity. Compounds **4a**, **4b**, and **7a** demonstrated activity against all the 13 Gram-positive and Gram-negative strains.

The MIC tests revealed that **7a** had MIC between 16 and 128 μg/ml against five bacterial strains (*V. cholera 7201*, *B. subtilis UC 564*, *S. aureus ATCC 25923*, *K. pneumoniae J/1/4*, and *S. dysenteriae 3*) and their zone diameters were found within 8–12 mm. Similarly, **4a** and **4b** had MIC between 16 and 128 μg/ml and the bacterial strains for **4a** were *S. dysenteriae 3*, *B. subtilis UC 564*, *S. faecalis 29212*, *K. pneumoniae J/1/4*, *S. typhimurium 11* and that for **4b** were *B. subtilis UC 564*, *S. dysenteriae 3*, *P. aeruginosa ATCC 27853*, *S. aureus ATCC*

Table 1
Structure and yield of the products.

Entry	Products	Structure	Yields	Entry	Products	Structure	Yields
1.	**2a**		65	8.	**7b**		53
2.	**2b**		63	9.	**7c**		52
3.	**4a**		65	10.	**8a**		50
4.	**4b**		62	11.	**8b**		51
5.	**6a**		84	12.	**9a**		75
6.	**6b**		85	13.	**9b**		73
7.	**7a**		54	14.	**9c**		75
				15.	**10**		75

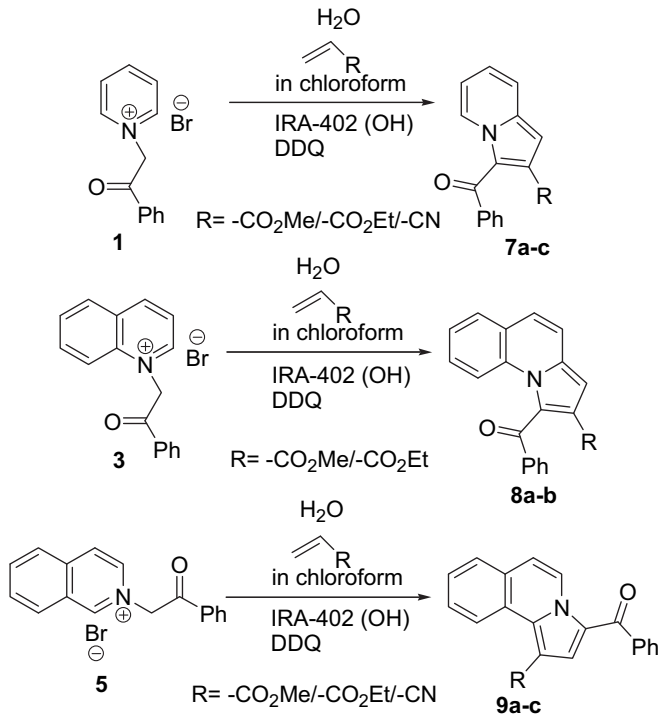
25923, *V. parahaemolyticus 72016*, *V. cholera 7201*. Likewise, compound **10** had MIC value 32–128 μg/ml against seven bacterial strains (*B. subtilis UC 564*, *E. coli ATCC 25938*, *K. pneumoniae J/1/4*, *V. cholera 7201*, *S. aureus ATCC 25923*, *P. aeruginosa ATCC 27853*, *S. dysenteriae 3*) and their zone diameters were within 8–12 mm (Table 3).

The data presented in Table-2 summarizes the effect of all types of ring system along with their substituent. The parent indolizine or benzo-fused indolizines are more or less active against 4–5 types of bacterial strain. The presence of the ester group (methyl/ethyl) seemed to be quite beneficial and also the nitrile (**7a**, **9a**) and phenyl ring (**10**) was found to be effective. However, structural features of the active compounds revealed that the compounds with ester or nitrile substituent adjacent to the benzoyl group is somehow more active than the compounds where the substituent is one carbon away from the benzoyl group. In case of pyrrolo quinoline the presence of two ester groups is beneficial (**4a**, **4b**) rather than the pyrrolo isoquinoline where the presence of one extra ester group diminishes its activity (**6a**, **6b**).

Among all the compounds, the compound **10** shown sensitivity towards three fungi i.e *A. niger*, *C. albicans*, *C. tropicalis* which had MIC value 500–1000 μg/ml (Table 4) and the zone diameter of inhibition *are* 12, 30 and 10 mm respectively. However, it showed no recognizable antifungal activity against *C. neoformans*.

Further study was conducted to determine minimum bactericidal concentration (MBC)/minimum fungicidal concentration (MFC) of the effective compounds (**4a**, **4b**, **7a** and **10**) against four susceptible bacterial and two fungal strains at different concentrations.

The MIC of compound **7a** against *S. aureus ATCC25923*, *B. subtilis UC564*, *V. cholera 7201* was found to be 16–32 μg/ml. So double folded drug dilutions were added to the nutrient broth culture of *S. aureus*, *B. subtilis*, and *V. cholera* at the logarithmic growth phase. Similarly, for compounds **4a** and **4b**, double folded dilutions were added to the broth culture of *B. subtilis UC564*, *S. dysenteriae 3*, *E. coli*



Scheme 2. Synthesis of indolizines, pyrrolo [1,2-a] quinolines, pyrrolo [1,2-a] isoquinolines using alkenes.

ATCC 25938, and *P. aerugenosa ATCC27853* and then colony count was done on nutrient agar plates, this did not show any colony at the highest concentrations. So, the compounds **4a**, **4b** and **7a** were concluded to show bactericidal action against respective Gram-positive and Gram-negative bacterial strains (Fig. 3a,b and c).

Among all the compounds tested, compound **10** showed significant sensitivity to *A. niger* and *C. albicans*. So dilutions of **10** were added to the fungi suspension and the growth of the fungi was determined by dry weight calculation. The results showed that the growth of these organisms decreased on increasing the concentration of the drug, and complete inhibition occurred at the highest concentrations (Fig. 4).

Thus, the drugs **4a**, **4b**, **7a** and **10** exhibited bacteriostatic or fungistatic activity at lower but bactericidal at higher concentrations.

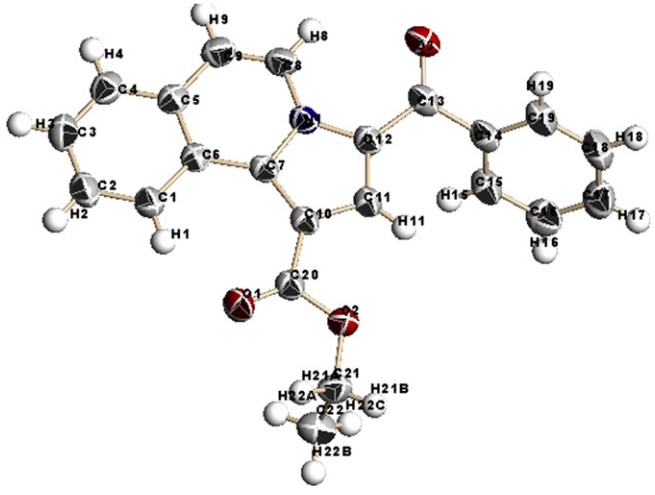


Fig. 1. ORTEP diagram of compound **9c**, displacement ellipsoids are drawn at 50% probability level.

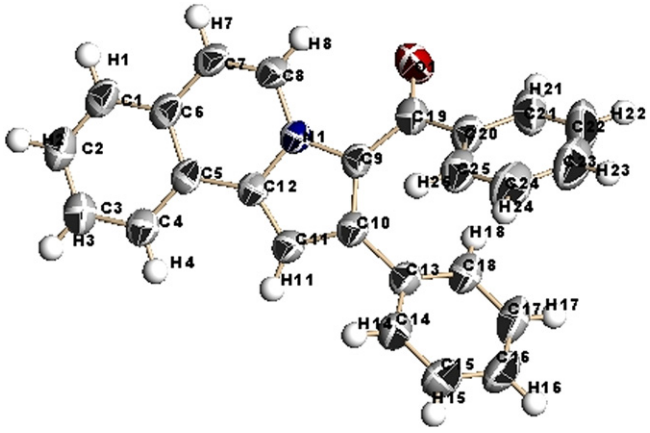


Fig. 2. ORTEP diagram of compound **10**, displacement ellipsoids are drawn at 50% probability level.

The minimum bactericidal concentration (MBC) was always found to be 2–4 folds higher than MIC values. At this stage we are not certain about the exact mechanism of bactericidal/fungicidal activity of the compounds at ultrastructural level, which needs further concerted investigation on this aspect. However, we believe that the compounds should have inhibitory effect on the growth of biofilm-associated microorganisms and that may be by their penetration and chemical reaction into biofilm matrix, the extracellular polymeric material.

Newer antibiotics and chemotherapeutic agents are being steadily synthesized in controlling many infections but the success depends on non-development of drug resistance. So, the search for antimicrobials using different approaches has been done with worthwhile antimicrobial action in few compounds.

3. Conclusion

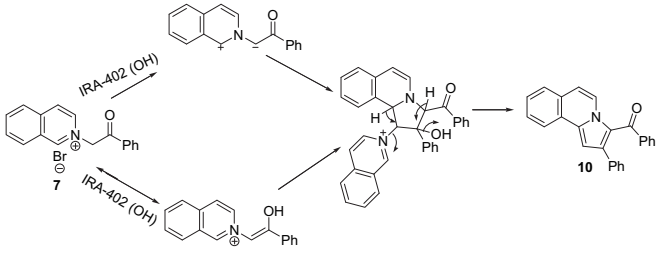
In summary, we have developed a novel methodology for the syntheses of indolizines and pyrrolo[1,2-a]quinolines/isoquinolines using amberlite–IRA-402 (OH) ion exchange resin as the base and DDQ as the oxidizing agent in one-pot sequence. Of the 15 compounds three showed significant antibacterial actions and one showed very significant antifungal activity. The identified four compounds (**4a**, **4b**, **7a** and **10**) exhibited bacteriostatic or fungistatic activity and may be developed as newer antimicrobial agents.

4. Experimental section

4.1. Chemistry

4.1.1. General methods

Melting points were determined with a capillary melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO FTIR (model 410) in KBr pellets. ESI-MS (positive) was



Scheme 3. Self cycloaddition of isoquinolinium salt.

Table 2
Antimicrobial activity of the test compounds.

Name of bacteria	Minimum inhibitory concentration (μg/ml) of test compounds and standard antibiotics																
	2a	**2b**	**4a**	**4b**	**6a**	**6b**	**7a**	**7b**	**7c**	**8a**	**8b**	**9a**	**9b**	**9c**	**10**	Gentamycin	Amoxicillin
Escherichia coli	>500	>500	>500	>500	256	128	>500	>500	>500	>500	>500	256	500	64	32	0.25	0.50
Klebsiella pneumoniae J/1/4	>500	>500	64	256	500	128	64	>500	>500	>500	>500	32	256	256	64	2	128
Staphylococcus aureus ATCC 25923	>500	>500	500	64	256	500	32	>500	>500	>500	>500	256	128	256	128	1	0.50
Pseudomonas aeruginosae ATCC 27853	500	>500	>500	32	500	500	>500	>500	>500	>500	>500	64	128	64	128	2	256
Vibrio cholera 7201	>500	>500	500	128	500	500	16	>500	>500	>500	>500	32	256	32	64	0.5	256
Bacillus subtilis UC 564	>500	>500	32	16	>500	256	16	>500	>500	>500	>500	128	256	64	32	4	0.50
Shigella dysenteriae 3	>500	>500	16	32	>500	>500	128	>500	>500	>500	>500	>500	256	128	128	1	64
Streptococcus faecalis 29212	>500	>500	64	500	>500	>500	500	>500	>500	>500	>500	>500	256	256	500	0.50	0.25
Shigella flexneri DN13	>500	>500	500	>500	>500	256	500	>500	>500	>500	>500	>500	128	256	500	1	128
Salmonella typhi DIRW	>500	>500	128	500	>500	128	500	>500	>500	>500	>500	>500	256	>500	>500	1	128
Vibrio parahaemolyticus 72016	>500	>500	>500	64	256	128	256	>500	>500	>500	>500	>500	256	256	500	1	256
Micrococcus luteus AGD1	>500	>500	>500	500	>500	>500	256	>500	>500	>500	>500	>500	>500	500	500	8	0.5
Salmonella typhimurium 11	>500	>500	500	>500	256	>500	500	>500	>500	>500	>500	>500	500	256	>500	1	>1000

conducted using LC-ESI-Q-TOF micro Mass spectrometer. ^{1}H and ^{13}C NMR spectra were taken on a Bruker 300 MHz DPX spectrometer at 300 and 74.99 MHz, respectively, with tetramethylsilane as internal standard and the chemical shifts are reported in δ units. Pyridine, quinoline, isoquinoline and the alkynes and alkenes were purchased from Aldrich Chemical Ltd (USA). Organic solvents used for the chemical synthesis and for chromatography were acquired from E. Merck (India) were of analytical grade. All chromatographic purifications were performed with silica gel (60–120 mesh) obtained from SRL (India). Thin layer chromatography was performed on pre-coated silica gel 60 F_{254} aluminum sheets (E. Merck, Germany) using 10–30 % ethyl acetate in petroleum–ether (60–80 °C) as solvent and the spots were developed using iodine or Liebermann–Burchard reagent.

4.1.2. General method of preparation

Compound **1** (0.9 mmol, 250 mg) or **3** (0.76 mmol, 250 mg) or **5** (0.76 mmol, 250 mg) was dissolved in 20 ml of water. To this 20 ml of chloroform was added. Then methyl acrylate (0.9 mmol, 0.08 ml/0.76 mmol, 0.07 ml) or ethyl acrylate (0.9 mmol, 0.10 ml/0.76 mmol, 0.08 ml) was added to this mixture followed by 300 mg of Amberlite–IRA-402 (OH) ion exchange resin and DDQ (0.9 mmol, 191 mg/0.76 mmol, 161 mg). The mixture was stirred vigorously at room temperature for about 8–10 h. After completion of the reaction as evident from TLC, the chloroform layer was separated and evaporated in vacuum. The crude product was subjected to column chromatography and eluted with 15% ethyl acetate-petroleum–ether mixture. The product was crystallized from chloroform-hexane mixture.

*4.1.3. 3-Benzoyl-indolizine-1,2-dicarboxylic acid dimethyl ester (**2a**)*

Yellowish solid, mp 160–162 °C; IR (KBr, ν_{max}) 1739, 1698, 1624, 1451, 1217 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.31 (3H, s, CH_3), 3.88 (3H, s, CH_3), 7.11 (1H, m), 7.45 (3H, m), 7.56 (1H, t, $J = 7.5$ Hz), 7.69 (2H, d, $J = 7.2$ Hz), 8.39 (1H, d, $J = 8.7$ Hz), 9.64 (1H, d, $J = 6.9$ Hz); ^{13}C NMR ($CDCl_3$) δ 51.6 (OMe), 52.1 (OMe), 103.9 (C), 115.9 (CH), 119.8 (CH), 120.7 (C), 127.9 (CH), 128.0 (2× CH), 128.4 (CH), 128.5 (2× CH), 131.5 (C), 131.7 (CH), 138.1 (C), 139.5 (C), 163.2 (C═O), 165.1 (C═O), 186.6 (C═O); MS (ESI-MS, positive ion) *m/z* 360 $[M + Na]^+$.

*4.1.4. 3-Benzoyl-indolizine-1,2-dicarboxylic acid diethyl ester (**2b**)*

Yellowish solid, mp 91–93 °C; IR (KBr, ν_{max}) 1739, 1705, 1607, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.06 (3H, t, $J = 7.2$ Hz, CH_3), 1.34 (3H, t, $J = 7.2$ Hz, CH_3), 3.65 (2H, q, $J = 7.2$ Hz, CH_2), 4.34 (2H, q, $J = 7.2$ Hz, CH_2), 7.10 (1H, t, $J = 6.9$ Hz), 7.45 (3H, m), 7.55 (1H, t, $J = 7.5$ Hz), 7.70 (2H, m), 8.42 (1H, d, $J = 9$ Hz), 9.63 (1H, d, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$) δ 13.4 (Me), 14.1 (Me), 60.3 (CH_2), 61.5 (CH_2), 104.1 (C), 115.8 (CH), 119.8 (CH), 120.5 (C), 127.8 (CH), 127.9 (2× CH), 128.4 (CH), 128.6 (2× CH), 131.6 (C), 131.8 (CH), 138.3 (C), 139.5 (C), 162.8 (C═O), 164.8 (C═O), 186.6 (C═O); MS (ESI-MS, positive ion) *m/z* 388 $[M + Na]^+$.

*4.1.5. Dimethyl-1-benzoyl-pyrrolo[1,2-a]quinoline-2,3-dicarboxylate (**4a**)*

Yellow solid, mp 188–190 °C; IR (KBr, ν_{max}) 1737, 1698, 1632, 1445, 1258 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.43 (3H, s, CH_3), 3.91 (3H, s, CH_3), 7.44 (2H, m), 7.50 (2H, t, $J = 7.5$ Hz), 7.62 (3H, m), 7.79 (1H, m), 7.97 (2H, d, $J = 7.2$ Hz), 8.26 (1H, d, $J = 9.3$ Hz); ^{13}C NMR ($CDCl_3$) δ 51.7 (OMe), 52.2 (OMe), 105.4 (C), 117.8 (CH), 118.9 (CH), 125.2 (2× C), 125.6 (CH), 126.3 (C), 127.9 (CH), 128.6 (2× CH), 128.9 (CH), 129.1

Table 3
Zone of inhibition of the tested active compounds.

Name of bacteria	Diameter of zone inhibition in mm					
	4a	**4b**	**7a**	**9a**	**9c**	**10**
Escherichia coli ATCC 25938	12.1 ± 0.1	8.1 ± 0.12	–[a]	8.0 ± 0.1	11.2 ± 0.4	10.0 ± 0.01
Klebsiella pneumonia J/1/4	10.0 ± 0.06	8.6 ± 0.06	8.9 ± 0.1	11.0 ± 0.25	8.5 ± 0.17	10.5 ± 0.12
Staphylococcus aureus ATCC25923	–	10.2 ± 0.01	12.1 ± 0.7	7.5 ± 0.3	8.3 ± 0.1	8.5 ± 0.2
Pseudomonas aerugenosa ATCC27853	–	9.7 ± 0.2	–	9.5 ± 0.5	11 ± 0.3	8.1 ± 0.25
Vibrio cholera 7201	–	7.7 ± 0.1	10.0 ± 0.2	11.0 ± 0.4	10.2 ± 0.2	9.0 ± 0.02
Vibrio cholera 720	–	7.7 ± 0.1	10.0 ± 0.2	11.0 ± 0.4	10.2 ± 0.2	9.0 ± 0.02
Bacillus subtilis UC564	10.2 ± 0.17	10 ± 0.15	9.7 ± 0.2	7.5 ± 0.4	11.4 ± 0.2	10.2 ± 0.1
Shigella dysenteriae 3	11.5 ± 0.12	11.1 ± 0.2	9.0 ± 0.2	–	9.7 ± 0.3	8.0 ± 0.17
Streptococcus faecalis 29212	12 ± 0.14	–	–	–	7 ± 0.25	–
Shigella flexneriDN13	–	–	–	–	7.1 ± 0.2	–
Salmonella typhi DI RW	7.5 ± 0.03	–	–	–	–	–
Vibrio parahaemolyticus 72016	–	9.3 ± 0.13	7.5 ± 023	–	8.0 ± 0.7	–
Micrococcus luteus AGD1	–	–	7.5 ± 0.17	–	8.1 ± 0.1	–
Salmonella typhimurium 11	–	–	–	–	–	–

[a] '–' shows no measurable zone of inhibion.

Table 4
Antifungal activity of compound **10** taking Fluconazole as a standard.

Name of organism	MIC μg/ml		Zone of inhibition
	10	Fluconazole	**10**
Aspergillus niger	500	10	12
Candida albicans	500	4	30
Candida tropicalis	1000	8	10
Cryptpcoccus neoformans	–	8	–

(CH), 129.8 (2× CH), 132.3 (C), 133.8 (CH), 137.0 (C), 137.5 (C), 163.5 (C═O), 165.1 (C═O), 187.6 (C═O); MS (ESI-MS, positive ion) *m/z* 410 $[M + Na]^+$.

4.1.6. Diethyl-1-benzoyl-pyrrolo[1,2-a]quinoline-2,3-dicarboxylate (**4b**)

Yellow solid, mp 158–160 °C; IR (KBr, ν_{max}) 1726, 1698, 1633, 1440, 1256 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (3H, t, $J = 7.2$ Hz, CH_3), 1.37 (3H, t, $J = 7.2$ Hz, CH_3), 3.85 (2H, q, $J = 7.2$ Hz, CH_2), 4.37 (2H, q, $J = 7.2$ Hz, CH_2), 7.48 (4H, m), 7.61 (3H, m), 7.78 (1H, m), 8.00 (2H, d, $J = 6.9$ Hz), 8.29 (1H, d, $J = 9.3$ Hz); ^{13}C NMR ($CDCl_3$) δ 13.6 (Me), 14.2 (Me), 60.5 (CH_2), 61.5 (CH_2), 105.7 (C), 117.9 (CH), 119.0 (CH), 125.2 (C), 125.6 (CH), 126.1 (C), 127.8 (CH), 128.2 (C), 128.6 (2× CH), 128.9 (CH), 129.2 (CH), 130.0 (2× CH), 132.4 (C), 133.9 (CH), 137.2 (C), 137.7 (C), 163.2 (C═O), 164.8 (C═O), 187.7 (C═O); MS (ESI-MS, positive ion) *m/z* 438 $[M + Na]^+$.

4.1.7. Dimethyl- 3-benzoyl-pyrrolo[2,1-a]isoquinoline-1,2-dicarboxylate (**6a**)

Orange solid, mp 155–157 °C; IR (KBr, ν_{max}) 1731, 1624, 1508, 1358 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.43 (3H, s, CH_3), 3.91 (3H, s, CH_3), 7.44 (2H, t, $J = 3.9$ Hz), 7.50 (2H, t, $J = 7.5$ Hz), 7.62 (3H, m), 7.79 (1H, m), 7.97 (2H, d, $J = 7.2$ Hz), 8.26 (1H, d, $J = 9.3$ Hz); ^{13}C NMR ($CDCl_3$) δ 51.9 (OMe), 52.5 (OMe), 109.6 (C), 115.8 (CH), 122.9 (C), 123.6 (CH), 124.2 (C), 125.6 (CH), 127.1 (CH), 128.3 (CH), 128.4 (2× CH), 128.9 (2× CH, −C), 129.0 (CH), 129.5 (C), 132.3 (C), 132.6 (CH), 139.7 (C), 164.6 (C═O), 165.9 (C═O), 187.2 (C═O); MS (ESI-MS, positive ion) *m/z* 410 $[M + Na]^+$.

4.1.8. Diethyl- 3-benzoyl-pyrrolo[2,1-a]isoquinoline-1,2-dicarboxylate (**6b**)

Orange solid, mp 118–120 °C; IR (KBr, ν_{max}) 1726, 1622, 1356, 1225 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (3H, t, $J = 7.2$ Hz, CH_3), 1.37 (3H, t, $J = 6.9$ Hz, CH_3), 3.66 (2H, q, $J = 6.9$, 14.1 Hz, CH_2), 4.44 (2H, q, $J = 6.9$, 14.1 Hz, CH_2), 7.16 (1H, d, $J = 7.5$ Hz), 7.47 (2H, t, $J = 7.2$ Hz), 7.59 (3H,

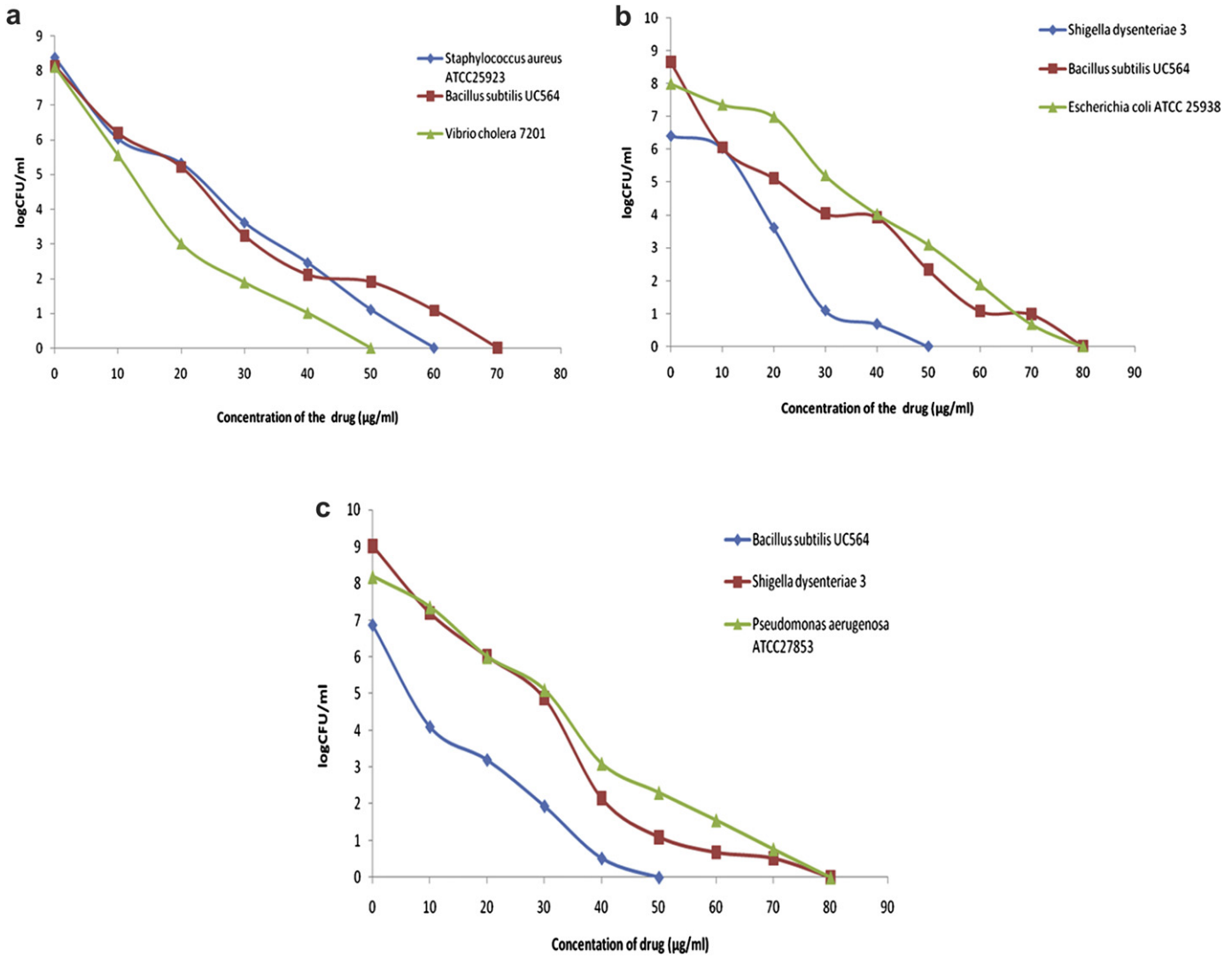


Fig. 3. a) Mode of action of drug **7a** on three different bacteria *S. aureus ATCC25923*, *B. subtilis UC564*, *V. cholera 7201*. b) Mode of action of drug **4a** on three different bacteria *B. subtilis UC564, S. dysenteriae 3* and *E. coli ATCC 25938*. c) Mode of action of drug **4b** on three different bacteria *B. subtilis UC564, S. dysenteriae 3* and *P. aerugenosa*.

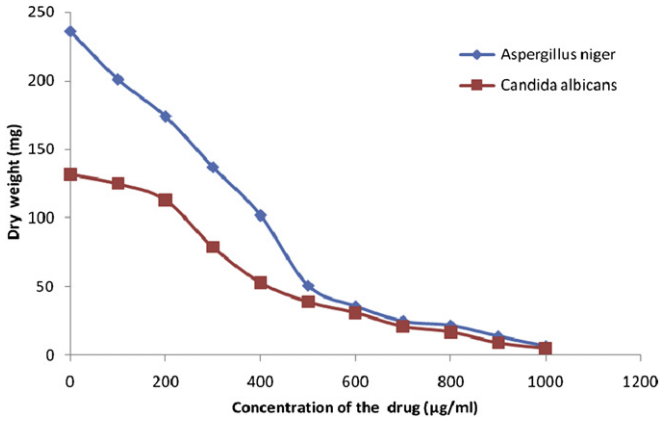


Fig. 4. Mode of action of drug **10** on *in vitro* growth of two fungi *A. niger* and *C. albicans*.

m), 7.72 (1H, m), 7.81 (2H, d, J = 7.5 Hz), 8.88 (2H, m); ^{13}C NMR ($CDCl_3$) δ 13.5 (Me), 13.9 (Me), 61.4 (CH_2), 61.6 (CH_2), 110.0 (C), 115.7 (CH), 122.7 (C), 123.6 (CH), 124.3 (C), 125.6 (CH), 127.1 (CH), 127.2 (C), 128.2 (CH), 128.4 (2× CH), 128.9 (CH), 129.2 (2× CH), 129.5 (C), 132.2 (C), 132.7 (CH), 139.7 (C), 164.3 (C═O), 165.5 (C═O), 187.1 (C═O); MS (ESI-MS, positive ion) m/z 438 $[M + Na]^+$.

*4.1.9. 3-Benzoyl-indolizine-2-carbonitrile (**7a**)*

White solid, mp 124–126 °C; IR (KBr, ν_{max}) 2222, 1621, 1479, 1342 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.17 (1H, t, J = 6.6 Hz), 7.52 (3H, m), 7.61 (2H, m), 7.82 (3H, m), 9.96 (1H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 84.7 (C), 115.1 (C), 115.8 (CH), 117.4 (CH), 122.8 (C), 127.8 (CH), 128.4 (2× CH), 128.8 (2× CH), 129.2 (CH), 129.4 (CH), 131.9 (CH), 139.1 (C), 141.1 (C), 185.0 (C═O); MS (ESI-MS, positive ion) m/z 269 $[M + Na]^+$.

*4.1.10. 3-Benzoyl-indolizine-2-carboxylic acid methyl ester (**7b**)*

Greenish white solid, mp 157–159 °C; IR (KBr, ν_{max}) 1698, 1623, 1341, 1209 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.90 (3H, s, CH_3), 7.11 (1H, t, J = 6.3 Hz), 7.53 (4H, m), 7.81 (3H, m), 8.40 (1H, d, J = 8.7 Hz), 9.98 (1H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 51.2 (OMe), 105.8 (C), 115.3 (CH), 119.3 (CH), 122.4 (C), 127.7 (CH), 128.3 (2× CH), 128.8 (2× CH), 128.9 (CH), 129.1 (CH), 131.4 (CH), 139.7 (C), 139.8 (C), 164.3 (C═O), 185. 5 (C═O); MS (ESI-MS, positive ion) m/z 302 $[M + Na]^+$.

*4.1.11. 3-Benzoyl-indolizine-2-carboxylic acid ethyl ester (**7c**)*

White solid, mp 81–83 °C; IR (KBr, ν_{max}) 1696, 1613, 1343, 1215 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40 (3H, t, J = 6.9 Hz, CH_3), 4.38 (2H, q, J = 6.6, 13.8 Hz), 7.10 (1H, m), 7.51 (4H, m), 7.82 (3H, m), 8.40 (1H, d, J = 8.7 Hz), 9.98 (1H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 14.4 (Me), 60.0 (CH_2), 106.1 (C), 115.1 (CH), 119.3 (CH), 122.3 (C), 127.5 (CH), 128.2 (2× CH), 128.8 (3× CH), 129.0 (CH), 131.3 (CH), 139.7 (C), 139.8 (C), 163.9 (C═O), 185.4 (C═O); MS (ESI-MS, positive ion) m/z 316 $[M + Na]^+$.

*4.1.12. 1-Benzoyl-pyrrolo[1,2-a]quinoline-2-carboxylic acid methyl ester (**8a**)*

Yellowish white solid, mp 154–156 °C; IR (KBr, ν_{max}) 1705, 1624, 1452, 1234 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.90 (3H, s, CH_3), 7.54 (4H, m), 7.64 (1H, s), 7.69 (2H, m), 7.82 (1H, d, J = 7.8 Hz), 8.09 (3H, m), 8.33 (1H, d, J = 9.3 Hz); ^{13}C NMR ($CDCl_3$) δ 51.3 (OMe), 107.2 (–C), 117.5 (CH), 120.1 (CH), 125.0 (C), 125.4 (CH), 128.1 (C), 128.4 (2× CH), 128.6 (CH), 128.8 (CH), 129.0 (CH), 129.5 (CH), 130.1 (2×CH), 132.8 (CH), 133.0 (C), 138.3 (C), 140.2 (C), 164.4 (C═O), 184.8 (C═O); MS (ESI-MS, positive ion) m/z 352 $[M + Na]^+$.

*4.1.13. 1-Benzoyl-pyrrolo[1,2-a]quinoline-2-carboxylic acid ethyl ester (**8b**)*

Yellowish white solid, mp 164–166 °C; IR (KBr, ν_{max}) 1690, 1629, 1453, 1210 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.39 (3H, t, J = 6.9 Hz, CH_3), 4.38 (2H, q, J = 6.6 Hz), 7.53 (4H, m), 7.68 (3H, t, J = 9.6 Hz), 7.82 (1H, d, J = 7.5 Hz), 8.08 (3H, m), 8.34 (1H, d, J = 9.3 Hz); ^{13}C NMR ($CDCl_3$) δ 14.5 (Me), 60.1 (CH_2), 107.6 (C), 117.6 (CH), 120.1 (CH), 125.0 (C), 125.3 (CH), 128.0 (C), 128.4 (2× CH), 128.6 (CH), 128.8 (CH), 128.9 (CH), 129.4 (CH), 130.1 (2× CH), 132.8 (CH), 133.1 (C), 138.3 (C), 140.2 (C), 164.0 (C═O), 184.8 (C═O); MS (ESI-MS, positive ion) m/z 366 $[M + Na]^+$.

*4.1.14. 3-Benzoyl-pyrrolo[2,1-a]isoquinoline-1-carbonitrile (**9a**)*

White solid, mp 198–200 °C; IR (KBr, ν_{max}) 2221, 1628, 1344 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.29 (1H, m), 7.55 (3H, m), 7.63 (1H, m), 7.71 (2H, m), 7.84 (3H, m), 8.97 (1H, d, J = 4.5 Hz), 9.56 (1H, d, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 85.7 (C), 115.7 (CH), 117.0 (C), 123.5 (C), 123.9 (CH), 124.3 (C), 125.1 (CH), 127.1 (CH), 128.5 (2× CH), 128.7 (CH), 128.8 (CH), 129.1 (2× CH), 129.7 (C), 129.9 (CH), 132.2 (CH), 137.7 (C), 139.0 (C), 185.4 (C═O); MS (ESI-MS, positive ion) m/z 319 $[M + Na]^+$.

*4.1.15. 3-Benzoyl-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid methyl ester (**9b**)*

Greenish white solid, mp 183–185 °C; IR (KBr, ν_{max}) 1704, 1617, 1455, 1187 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.92 (3H, s, CH_3), 7.30 (1H, d, J = 7.5 Hz), 7.57 (3H, m), 7.68 (2H, m), 7.83 (4H, m), 9.67 (1H, d, J = 7.5 Hz), 9.86 (1H, m); ^{13}C NMR ($CDCl_3$) δ 51.8 (Me), 109.7 (–C), 115.5 (CH), 123.3 (C), 124.5 (C), 125.0 (CH), 126.7 (CH), 127.8 (CH), 128.1 (CH), 128.4 (2× CH), 129.2 (2× CH), 129.3 (CH), 130.1 (CH), 130.5 (C), 131.7 (CH), 137.0 (C), 139.8 (C), 164.9 (C═O), 185.9 (C═O); MS (ESI-MS, positive ion) m/z 352 $[M + Na]^+$.

*4.1.16. 3-Benzoyl-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester (**9c**)*

Yellowish white solid, mp 138–140 °C; IR (KBr, ν_{max}) 1704, 1623, 1525, 1176 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40 (3H, t, J = 7.2 Hz, CH_3), 4.40 (2H, q, J = 6.9, 14.1 Hz, –CH_2), 7.28 (1H, d, J = 7.8 Hz), 7.61 (5H, m), 7.77 (1H, m), 7.82 (1H, s), 7.87 (2H, m), 9.66 (1H, d, J = 7.5 Hz), 9.83 (1H, m); ^{13}C NMR ($CDCl_3$) δ 14.4 (Me), 60.5 (CH_2), 110.1 (C), 115.4 (CH), 123.2 (C), 124.4 (C), 124.9 (CH), 126.6 (CH), 127.6 (CH), 128.0 (CH), 128.3 (2× CH), 129.2 (3× CH), 129.9 (CH), 130.4 (C), 131.6 (CH), 136.8 (C), 139.8 (C), 164.5 (C═O), 185.8 (C═O); MS (ESI-MS, positive ion) m/z 366 $[M + Na]^+$.

*4.1.17. 3-Benzoyl- 2-phenyl-pyrrolo[2,1-a]isoquinoline (**10**)*

Yellow solid, mp 191–193 °C; IR (KBr, ν_{max}) 1605, 1402, 1340 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.06 (6H, m), 7.17 (4H, m), 7.55 (4H, m), 7.71 (1H, m), 8.18 (1H, m), 9.30 (1H, d, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 104.0 (CH), 113.4 (CH), 122.4 (C), 123.8 (CH), 125.1 (C), 125.7 (CH), 127.0 (CH), 127.3 (CH), 127.9 (2× CH), 128.0 (2× CH), 128.1 (CH), 128.3 (CH), 129.3 (C), 130.2 (2× CH), 130.5 (2× CH), 131.6 (CH), 135.2 (C), 136.2 (C), 138.5 (C), 140.1 (C), 187.9 (C═O); MS (ESI-MS, positive ion) m/z 370 $[M + Na]^+$.

*4.1.18. Crystal data for **9c***

$C_{22}H_{17}NO_3$, Mr = 343.37, greenish rectangular shaped crystals were grown from chloroforme-hexane. Space group Triclinic P-1. Lattice constants (A°): a = 8.4125(6), b = 9.9415(7), c = 11.0268(8), α = 65.643(4), β = 84.421(4), γ = 87.463(4), cell volume V = 836.13 (10) $A^{\circ 3}$, formula units/cell Z = 2, Number of independent reflections 2935, after convergence R_1 = 0.0430, wR_2 = 0.1219.

*4.1.19. Crystal data for **10***

$C_{25}H_{17}NO$, Mr = 347.40, yellowish-green rambohedral shaped crystals were grown from chloroforme-hexane. Space group Monoclinic $P2_1/c$. Lattice constants (A°): a = 18.6732(15), b = 13.1118(12), c = 7.4589(8), α = 90, β = 98.697(7), γ = 90, cell volume V = 1805.2(3) $A^{\circ 3}$, formula units/cell Z = 4, Number of

independent reflections 3181, after convergence $R_1 = 0.0759$, $wR_2 = 0.1942$.

4.2. Pharmacological studies

4.2.1. Materials and methods

4.2.1.1. Microorganisms. The microorganisms used in this study consisted of 13 strains of bacteria namely: *B. subtilis UC564*, *S. aureus 25923*, *S. faecalis 29212*, *M. luteus AGD1*, *E. coli ATCC25938*, *K. pneumoniae J/l/4*, *P. aeruginosa ATCC27853*, *V. cholera 7201*, *V. parahaemolyticus 72016*, *S. dysenteriae 3*, *Shigella flexnarae DN13*, *S. typhi DIRW*, and *S. typhimurium 11*. Antifungal studies were also carried out on four strains of fungi namely, *A. niger*, *C. albicans*, *C. tropicalis*, and *C. neoformans*. All the strains were clinical isolates from human beings. The strains were identified using Barrow and Feltham's method [26]. These were obtained from Division of Microbiology, Department of Pharmaceutical Technology, Jadavpur University, Kolkata-32, India. The bacterial strains were grown in Mueller–Hinton Agar (Merck India Ltd.) at 37 °C for 24 h while the fungi were grown on Sabouraud dextrose agar at 28 °C for 3–5 days.

4.2.1.2. Preparation of inoculums. Active cultures for experiments were prepared by transferring a loopful of inoculum from the stock cultures to Mueller–Hinton Broth (MHB) for bacteria and Sabouraud dextrose broth (SDB) for fungi that were incubated without stirring for 24 h at 37 °C and for 72 h at 28 °C respectively. The cultures were diluted with sterile normal saline to achieve the surface viable counting [27] corresponding to 2.0×10^6 colony forming units (CFU/ml) for bacteria and 2.0×10^5 spore/ml for fungi strains.

4.2.1.3. Preparation of stock solution. The compounds, **2a**–**b**, **4a**–**b**, **6a**–**b**, **7a**–**c**, **8a**–**b**, **9a**–**c** and **10**, screened for their antimicrobial activity were dissolved either in Tween 80 or in propylene glycol. **6a**, **9b**, **6b**, and **9c** were dissolved in 4% Tween 80 and the remaining ones were dissolved in 4% of propylene glycol to get the concentration of 1 mg/ml and were used as stock solution.

4.2.1.4. Antimicrobial assay. Antimicrobial sensitivity tests were performed by disc diffusion method following the NCCLS protocol [28]. For sensitivity testing 0.1 ml of bacterial suspension (2×10^6 cfu/ml) and 0.1 ml of fungal spore suspension (2×10^5 spores/ml) were transferred to freshly prepared Mueller–Hinton Agar plates and Sabouraud dextrose plates respectively. Then sterile paper discs (6 mm diameter) impregnated into prepared solution of the compounds at concentrations of 1–1000 μg/ml for bacteria and 1–1500 μg/ml for fungi, were placed aseptically on sensitivity plates [29]. The plates were then incubated at 37 °C overnight for bacteria and 28 °C for 96 h for fungi. The sensitivity was recorded by measuring the clear zone of inhibition on agar surface around the discs.

4.2.1.5. Determination of minimum inhibitory concentration (MIC). MIC was determined by agar dilution and broth dilution methods [30]. For broth dilution assay, 0.1 ml standardized suspension of bacteria (2×10^6 cfu/ml) or fungal spores (2×10^5 spores/ml) were added to Mueller–Hinton broth for bacteria & Sabouraud dextrose broth for fungi containing test drug concentration 1–1000 μg/ml for bacteria and 1–1500 μg/ml for fungi with appropriate antibiotic control and incubated at 37 °C overnight for bacteria and 28 °C for 96 h for fungi. For agar dilution assay, previously prepared drug dilutions of the test drug, with appropriate antibiotic control were prepared in Mueller–Hinton Agar and Sabouraud dextrose agar. Prepared agar plates using serial dilutions of the drug and control antibiotics as above, were spot inoculated (2×10^6 cfu/spot for bacteria and 2×10^5 spores/spot for fungi). The inoculated plates were then incubated at 37 °C for 24 h for bacteria and 28 °C for 96 h for fungi. The lowest concentration of tube or plate which did not show any visible growth after macroscopic evaluation was considered as the MIC.

4.2.1.6. Determination of minimal bactericidal concentration (MBC) and minimum fungicidal concentration (MFC). The test drugs (**4a**, **4b**, **7a** and **10**), which exhibited considerable antibacterial and antifungal activity, were diluted double fold with Mueller–Hinton broth for bacterial strains and Sabouraud dextrose broth for fungi in a series of test tubes. An aliquot of 1 ml of the bacterial suspension (2×10^6 cfu/ml) and fungal spores (2×10^5 spores/ml) were inoculated into each tube. The control tubes were inoculated with same quantity of broth culture only. All tubes were incubated at 37 °C for 24 h and 28 °C for 96 h with shaking on a platform shaker at 200 rpm. The test drugs were added to the mid-logarithmic phase of growth and aliquots of 1.0 ml were withdrawn for determination of colony count [31] while the growth of the fungi was determined by dry weight of the sample at 60°c for 20 h for 3 days [32].

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Appendix. Supplementary data

^1H and ^{13}C NMR spectra of all compounds associated with this article can be found in the online version. Crystallographic data in CIF format are available free of charge via the Internate at **CCDC 767293** and **767294**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

Appendix. Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.ejmech.2011.02.066.

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