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Design, synthesis and antimicrobial evaluation of novel 1-benzyl 2-butyl-4-chloroimidazole embodied 4-azafluorenones via molecular hybridization approach

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ABSTRACT

A series of novel 1-benzyl-2-butyl-4-chloroimidazole embodied 4-azafluorenone hybrids, designed via molecular hybridization approach, were synthesized in very good yields using one pot condensation of 1-benzyl-2-butyl-4-chloroimidazole-5-carboxaldehyde, 1,3-indanedione, aryl/heteroaryl methyl ketones and ammonium acetate. All the synthetic derivatives were fully characterized by spectral data and evaluated for antimicrobial activity by disc diffusion method against selected bacteria and fungal strains. Among the 15 new compounds screened, 4-(1-benzyl-2-butyl-4-chloro-1*H*-imidazol-5-yl)-2-(furan-2-yl)-5*H*-indeno[1,2-*b*]pyridin-5-one(**10k**) has pronounced activity with higher zone of inhibition (ZoI) against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Aspergillus flavus* and *Candida albicans*. Also 4-(1-benzyl-2-butyl-4-chloro-1*H*-imidazol-5-yl)-2-(dibenzo[*b*,*d*]thiophen-2-yl)-5*H*-indeno [1,2-*b*]pyridin-5-one (**10n**) and 4-(1-benzyl-2-butyl-4-chloro-1*H*-imidazol-5-yl)-2-(3-tosyl-3*H*-inden-1-yl)-5*H*-indeno[1,2-*b*]pyridin-5-one (**10o**) showed selective higher inhibitory activity against *Aspergillus flavus* and *Candida albicans*. The results demonstrated potential importance of molecular hybridization in the development of **10k** as potential antimicrobial agent.

With the emergence and development of resistant, multidrug resistant and even extremely drug resistant microbial strains, the battle of humankind against infections is never ending in this 'Plethora of microbes'.[1,2] This has created an urgent need to devote our continuous efforts for the discovery and development of new antimicrobials with broader spectrum of activity and lower toxicity. Many structural frameworks have been described as privileged structures[3] and in particular the five member heterocyclic imidazole nucleus is endowed with various biological activities due to the presence of ring nitrogens.[4,5] The valuable therapeutic properties of the imidazole related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents such as ketoconazole, miconazole, tioconazole, clotrimazole and sulconazole etc.[6] However, with the emergence of resistance mechanisms, there is a need for newer antimicrobial agents to combat resistance developed against widely used antimicrobial drugs.[1,6]

4-Azafluorenones (5*H*-indeno[1,2-*b*]pyridin-5-one; Fig. 1) are the naturally occurring alkaloids isolated from the root of the plant *Polyalthia debilis* (Pierre) belonging to the family of *Annonaceae*, the root water decoction of which has been traditionally used for treatment of antimicrobial infections.[7–16] The isolated compound Onychine (**1**) with azafluorenone architecture is active against *Candida albicans* in micro molar concentrations.[8] In addition, **1** also exhibited antimicrobial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Saccharomyces* in the range of 50–100 μM· concentration.[9]

Other 4-azafluorenone derivatives **2**–**5** are found to exhibit antimalarial, adenosine A2a receptor binding and phosphodiesterase inhibiting activities for the treatment of neurodegenerative disorders, calcium antagonistic agents and inflammation related diseases.[11–16] The unique structural feature of these bioactive natural and synthetic analogs.[17,18] (Fig. 1 is due the presence of 4-azafluorenone moiety playing a vital role exhibiting wide spectrum pharmacological properties.

We therefore envisaged that integrating natural 4-azafluorenone and pharmacophoric imidazole moieties in one molecular platform (molecular hybridization)[19,20] could generate potential new scaffolds for biological evaluation. The choice of 1-benzyl-2-butyl-4-chloroimidazole as pharmacophore for modification arises from recent reports, wherein 2-butyl-4-chloroimidazole was conjugated to isoxazolidine, which exhibited enhanced

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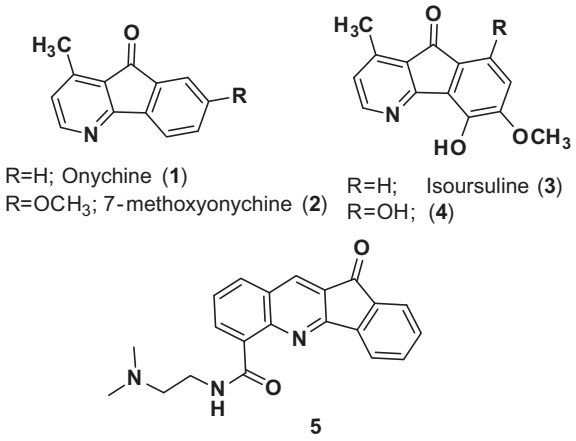


Figure 1. Examples of bioactive natural (**1**–**4**) and synthetic (**5**) azafluorenones.

antimicrobial activity.[21–23] As a part of our ongoing research aiming on the development of novel bioactive hybrid molecules through one-pot multicomponent reactions,[24–26] we report herein one-pot synthesis and antimicrobial evaluation of novel 1-benzyl-2-butyl-4-chloroimidazole embodied 4-azafluorenones. Antimicrobial evaluation of these new derivatives resulted in the identification of 4-(1-benzyl-2-butyl-4-chloro-1*H*-imidazol-5-yl)-2-(furan-2-yl)-5*H*-indeno[1,2-*b*]pyridin-5-one **10k** as most active antimicrobial agent. 4-(1-Benzyl-2-butyl-4-chloro-1*H*-imidazol-5-yl)-2-(dibenzo[*b*,*d*]thio phen-2-yl)-5*H*-indeno[1,2-*b*]pyridin-5-one (**10n**) and 4-(1-benzyl-2-butyl-4-chloro-1*H*-imidazol-5-yl)-2-(3-tosyl-3*H*-ind en-1-yl)-5*H*-indeno[1,2-*b*]pyridin-5-one (**10o**) also exhibited selective higher inhibitory activity against fungal strains *Aspergillus flavus* and *Candida albicans*.

The design strategy adopted here for library generation is based on most recent molecular hybridization approach.[19,20] Molecular hybridization is a strategy of rational design based on the recognition of pharmacophoric sub-units in the molecular structure of two or more known bioactives. The adequate fusion of these sub-units, lead to the design of new hybrid architecture that maintain pre-selected characteristics of the original template (Fig. 2). Considering antimicrobial Onychine **1** as a basic bioactive unit of natural 4-azafluorenone, the modifications were introduced on 4-azafluorenone nucleus through hybridization with chosen imidazole pharmacophore (1-benzyl-2-butyl-4-chloroimidazole).

As a starting point for the study, 2-butyl-4-chloroimidazole-5-carboxaldehyde **6** was prepared from valeronitrile by following the procedure developed in our laboratory.[25,27] N-Benzylation of **6** using benzyl bromide, K_2CO_3 in DMF gave benzyl derivative **7** in very good yield (92.0%).[28] Compound **7** was characterized by ^{1}H NMR and mass spectral analysis.[28] With requisite imidazole derivative **7** in hand, initially, it was reacted with 1,3-indanedione, acetophenone and ammonium acetate in various solvents (methanol, 2-propanol, acetonitrile, THF, water, DMF and glycol)

Table 1
Optimization of reaction conditions[a]

Entry	Solvent[b]	Reaction Temp (°C)	Time (h)	Product Yield (%)[c]
1	Methanol	40	8	20
2	Methanol	Reflux	8	42
3	2-Propanol	60	8	25
4	2-Propanol	Reflux	8	46
5	Glycol	60	8	30
6	Glycol	120	8	74
7	DMF	60	8	48
8	DMF	120	3	82
9	Acetonitrile	Reflux	8	54
10	Water	100	8	15
11	THF	Reflux	8	28
12	Neat	120	8	64
13	DMF	100	3	76
14	DMF	110	3	82
15	DMF	130	3	84

[a] 1-Benzyl-2-butyl-4-chloroimidazole carboxaldehyde 7 (1 mmol), 1,3-indanedione (1 mmol), acetophenone (1 mmol) and ammonium acetate (2.5 mmol).
[b] The volume of solvent is 5 mL.
[c] Isolated yield.

and temperatures ranging from 60 °C to 130 °C by modifying the related literature protocols,[29,30] After a series of experiments (Table 1), the reaction was found to be most efficient when **7** was reacted with equimolar amounts of 1,3-indanedione (**8**), acetophenone (**9a**) and 2.5 equiv of ammonium acetate in DMF at 120 °C to give 4-azafluorenone **10a** in very good yield (82%; Scheme 1).

Further, to expand the series, imidazole embodied 4-azafluorenone analogs **10a**–**o** were prepared through one-pot condensation between 1-benzyl-2-butyl-4-chloroimidazole carboxaldehyde (**7**), aryl/heteroaryl methyl ketones **9a**–**o** (Fig. 3), 1,3-Indanedione (**8**) and ammonium acetate (Scheme 1 and Table 2).[31] All the reactions proceeded well in 3.0–4.0 h to give products in very good yields (77–86%). The results also revealed that aryl methyl ketones bearing electron withdrawing groups (entry 5) gave slightly higher yield compared with aryl methyl ketones bearing electron releasing groups (entries 4 and 6). The reactions are also progressed well with heterocyclic methyl ketones (entries 9–15) to give 4-azafluorenone derivatives **10i**–**o** in very good yields. All the compounds were purified through silica gel column chromatography and were fully characterized by IR, ^{1}H NMR, ^{13}C NMR, Electrospray ionization (ESI) and High resolution mass spectral (HRMS) analysis.[32] The single crystal X-ray diffraction studies of **10h** unambiguously confirmed the structure (Fig. 4).[33] A plausible mechanism for the formation of 4-azafluorenones **10** is depicted in Figure 5. Based on the above data and literature precedents,[30] initially, 1-benzyl-2-butyl-4-chloroimidazole carboxaldehyde **7** condenses with 1,3-indanedione to form intermediate **11** which further undergoes in situ Michael addition with 1-arylethenamine **12**, obtained by reacting aromatic ketone with ammonium acetate, to yield intermediate **13**, which then cyclized and subsequently dehydrogenated to afford 4-azafluorenone **10**.

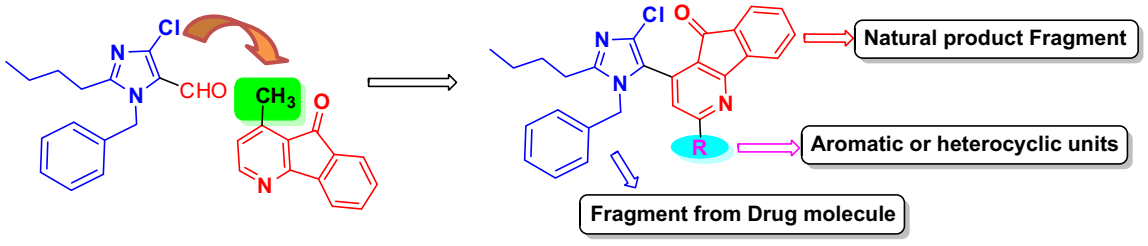
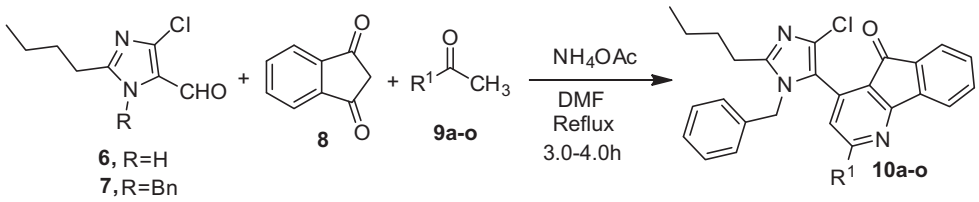


Figure 2. Illustration of design strategy for library generation.



Scheme 1. Synthesis of 4-azafluorenone hybrids **10a–o**.

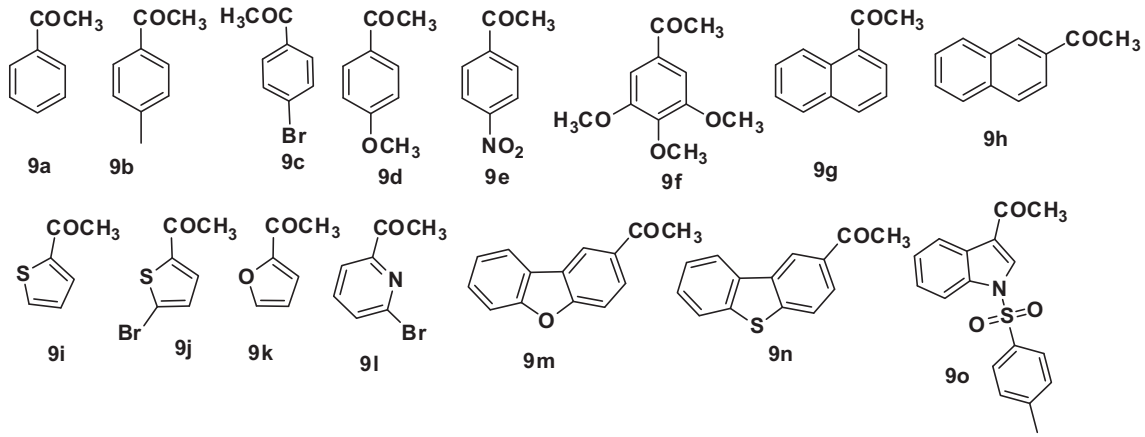


Figure 3. Aryl/heteroayl methyl ketones **9a–o** used in the present study.

Table 2
Synthesis of 2-butyl-4-chloro-1-benzylimidazole derived 4-azaflourenone **10a–o**

Entry	Ketones **9**	Reaction time (h)	Product **10**	Yield (%)[a]
1	**9a**	3.0	**10a**	82
2	**9b**	3.5	**10b**	80
3	**9c**	4.0	**10c**	81
4	**9d**	4.0	**10d**	79
5	**9e**	3.0	**10e**	86
6	**9f**	4.0	**10f**	77
7	**9g**	3.5	**10g**	84
8	**9h**	3.5	**10h**	85
9	**9i**	3.5	**10i**	86
10	**9j**	3.5	**10j**	84
11	**9k**	4.0	**10k**	85
12	**9l**	3.5	**10l**	83
13	**9m**	3.5	**10m**	81
14	**9n**	4.0	**10n**	86
15	**9o**	4.0	**10o**	85

[a] Isolated yield.

Fifteen newly synthesized 1-benzyl-2-butyl-4-chloroimidazole embodied 4-azafluorenones **10a–o** were evaluated for their in vitro antibacterial activity against two gram positive bacteria namely *Bacillus subtilis* (MTCC 121) and *Staphylococcus aureus* (MTCC 1430) and three gram negative bacteria namely *Escherichia coli* (MTCC 1573), *Klebsiella pneumoniae* (MTCC 618) and *Pseudomonas aeruginosa* (MTCC 2453) by disc diffusion method,[34,35] using gentamicin as the reference drug. The results were recorded for each tested compound (10 μg/disc) as an average diameter of zone of inhibition (ZoI) in millimeters (zone lacking the bacterial growth) surrounding the disc. Antibacterial evaluation data revealed that, in general all the tested compounds **10a–o** (10 μg/disc) possessed good deal of antibacterial activity against selected gram positive (*Staphylococcus aureus*) and gram negative bacteria (*Klebsiella pneumoniae* and *Pseudomonas aeruginosa*) as compared to the standard drug gentamicin (Table 3). On the basis of zone of inhibition (ZoI) against test bacterium *S. aureus*, nine compounds

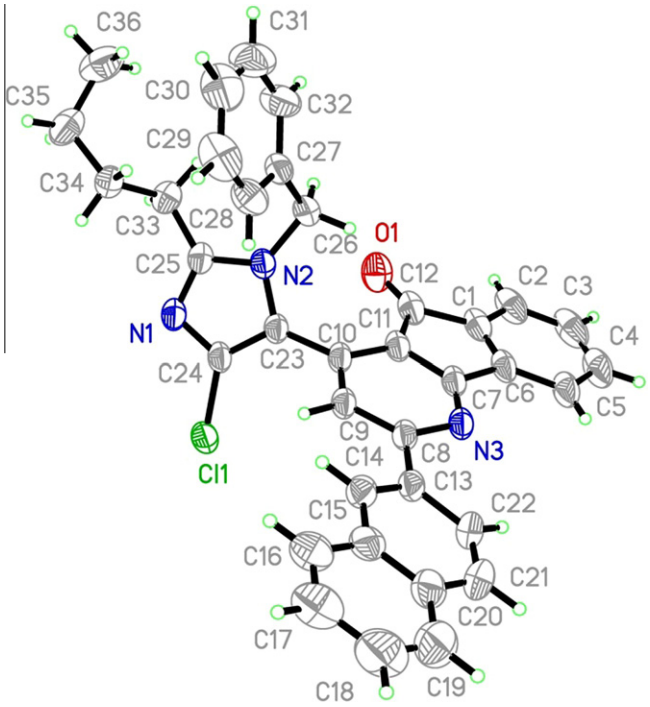


Figure 4. ORTEP representation of compound **10h** with thermal displacement ellipsoids drawn at the 30% probability.[33]

10a, **10c**, **10f**, **10g**, **10h**, **10j**, **10k**, **10l** and **10n** (10 μg/disc) exhibited good activity with higher zone of inhibition ⩾12.0 mm as compared to standard gentamicin which showed ZoI of 15.0 mm. It is noteworthy that, among the nine active compounds one compound **10k** was found to be the most potent member producing ZoI of 15.0 mm against *S. aureus* equal to that of the standard antibiotic gentamicin (Table 3).

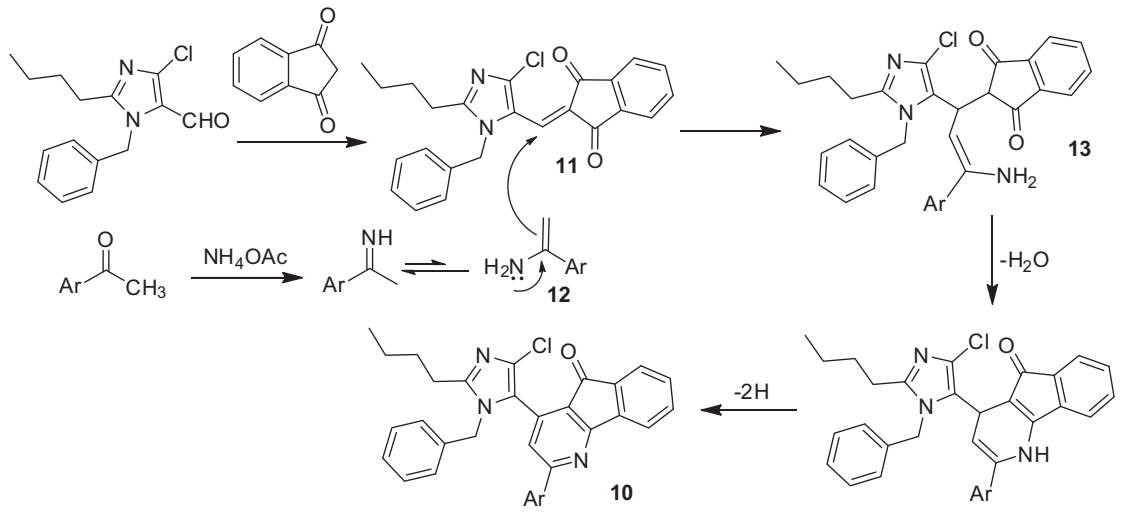


Figure 5. Plausible mechanism for the formation of 4-azafluorenone **10**.

Table 3
Inhibitory action of 10a-o against the selected bacterial strains (gram positive and gram negative bacteria) and fungal strains determined as zone of inhibition (in mm) by the disc diffusion method[a]

Compounds	Gram positive bacteria1		Gram negative bacteria			Fungal strains	
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*K. pneumoniae*	*A. flavus*	*C. albicans*
10a	8	12	9	10	11	8	10
10b	8	10	9	8	11	7	10
10c	9	12	9	6	12	7	10
10d	9	10	8	9	11	6	12
10e	10	10	8	10	10	6	11
10f	9	12	9	7	11	6	10
10g	10	12	9	6	12	5	12
10h	9	12	8	13	12	6	10
10i	10	10	9	11	10	5	10
10j	9	12	8	13	12	7	9
10k	8	15	8	14	15	10	13
10l	8	12	9	12	9	9	11
10m	9	11	9	13	13	7	10
10n	9	12	8	7	11	10	14
10o	7	10	8	7	12	11	13
Gentamicin	14	15	12	15	19	–	–
Nystatin	–	–	–	–	–	9	8
DMSO	–	–	–	–	–	–	–

A. flavus: *Aspergillus flavus*, *B. subtilis*: *Bacillus subtilis*, *S. aureus*: *Staphylococcus aureus*, *C. albicans*: *Candida albicans E. coli*: *Escherichia coli*, *P. aeruginosa*: *Pseudomonas aeruginosa*, *K. pneumoniae*: *Klebsiella pneumoniae*.
– indicates no activity.
[a] The experiment was carried out in triplicate and the values represent average zone of inhibition.

Similarly, based on the measurement of ZoI at a concentration of 10 μg/disc, five compounds **10h**, **10j**, **10k**, **10l** and **10m** were found to be most effective against gram negative bacteria *P. aeruginosa* showing maximum ZoI $\geqslant$ 12 mm compared to the zone of inhibition of standard drug gentamicin (15 mm). Here also, **10k** was found to be most active compound producing ZoI of 14.0 mm. In case of *Klebsiella pneumoniae*, all the compounds except **10e**, **10i** and **10l**, exhibited moderate to good activity with ZoI in the range of 11–15 mm. Among them, compound **10k** showed maximum zone of inhibition (15 mm) when compared to standard drug gentamicin (19 mm) and resulted as the most active compound in the series against *K. pneumoniae*. However, all the compounds **10a–o** showed lower antibacterial activity against the bacteria; *Bacillus subtilis* (a gram positive bacteria) and *E. coli* (gram negative bacteria) producing ZoI $\leqslant$ 10 as shown in Table 3. On the whole among all the compounds evaluated against gram positive and gram negative bacteria, **10k** exhibited significantly greater antibacterial activity against *S. aureus*, *P. aeruginosa* and *K. pneumoniae* with higher ZoI comparable to standard drug gentamicin.

1-Benzyl-2-butyl-4-chloroimidazole embodied 4-azafluorenones **10a–o** were also evaluated for their in vitro antifungal activity against two fungal strains namely *Aspergillus flavus* (MTCC 8188) and *Candida albicans* (MTCC 7253) by disc diffusion method. Nystatin was used as the reference antifungal drug for comparison. Results of the in vitro antifungal activity (Table 3) for the tested compounds (10 μg/disc) showed that **10d**, **10e**, **10f**, **10g**, **10h** (ZoI $\leqslant$ 6), **10b**, **10c**, **10j**, **10m** (ZoI = 7), 10a (ZoI = 8), and **10k**, **10l**, **10n** and **10o** (ZoI $\geqslant$ 9) produced moderate to higher antifungal activity against *Aspergillus flavus* compared to standard drug as described in Table 3. However, all the compounds tested against another fungal strain, *Candida albicans* showed greater inhibitory activity than the standard drug Nystatin (ZoI = 8). Among them, three compounds **10k**, **10n**, **10o** (ZoI $\geqslant$13) were found to be most potent members showing higher zone of inhibition against *Candida albicans* even greater than standard drug Nystatin (ZoI = 8 mm,

Table 3). Together with antibacterial and antifungal evaluations, **10k** was found to be the most potent antimicrobial agent with higher inhibitory activity against bacterial and fungal strains: *S. aureus*, *P. aeruginosa*, *K. pneumoniae*, *A. flavus* and *C. albicans*. The compounds **10n** and **10o** also showed higher selective antifungal activity against fungal strains *A. flavus* and *C. albicans*.

In summary, a series of novel 1-benzyl-2-butyl-4-chloroimidazole embodied 4-azafluorenone hybrids, designed via molecular hybridization approach, were prepared in very good yields using one pot condensation of 1-benzyl-2-butyl-4-chloroimidazole-5-carboxaldehyde, 1,3-indanedione, aryl/hetero aryl methyl ketones and ammonium acetate. Antimicrobial evaluation data revealed that, in general all the tested compounds **10a–o** (10 μg/disc) possessed good deal of antibacterial activity against selected gram positive (*Staphylococcus aureus*), gram negative bacteria (*Klebsiella pneumoniae* and *Pseudomonas aeruginosa*) and antifungal activity against fungal strains (*A. flavus* and *C. albicans*) as compared to the standard drugs. On the whole among all the compounds tested, compound **10k** exhibited significantly greater antibacterial activity among the tested series against *S. aureus*, *P. aeruginosa* and *K. pneumoniae* with higher zone of inhibition comparable to standard drug Gentamicin and anti fungal activity against *A. flavus* and *C. albicans* with an inhibitory activity even greater than standard drug Nystatin. Compounds **10n** and **10o** also exhibited significantly higher antifungal activity against *A. flavus* and *C. albicans* with greater zone of inhibition than the reference drug. Since *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Candida albicans* are well known opportunistic pathogens and known to cause severe nosocomial and/or secondary infections, the compounds can be tested in combination with the known antibiotics in vitro for effective treatment to avoid development of resistance mechanisms by these microbes.

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Supplementary data

Supplementary data associated with this article can be found, in online version, at http://dx.doi.org/10.1016/j.bmcl.2012.10.042. Copies of ^{1}H, ^{13}C NMR and mass (ESI-MS and HR-MS) spectra of all the new compounds. CCDC 885580 (for **10h**) contain the crystallographic data and can be obtained free of charge from the Cambridge Crystallographic Data centre via www.ccdc.cam.ac.uk/data_request/cif.

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28. *1-Benzyl-2-butyl-4-chloroimidazole carboxaldehyde* (**7**). 2-Butyl-4-chloroimidazole carboxaldehyde 627 (5.0 g, 26.9 mmol) in DMF was added potassium carbonate (4.08 g, 29.56 mmol) and benzyl bromide (3.15 mL, 26.9 mmol) with stirring at 0 °C for 1 h and then at RT for 3 h. The reaction mixture was poured in ice cold water, extracted with ethyl acetate (3 × 25 mL), combined organic extract was dried over anhydrous sodium sulphate and evaporated under vacuum. The crude residue thus obtained was chromatographed over silica gel (hexane/ethyl acetate, 9:1) to give 1-benzyl-2-butyl-4-chloroimidazole carboxaldehyde 7 (6.53 g, 92%) as pale yellow syrup. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74(s, 1H), 7.29 (m, 3H), 7.01 (d, J = 8.3 Hz, 2H), 5.53 (s, 2H), 2.59 (t, J = 7.5Hz, 2H), 1.60-1.70 (m, 2H), 1.25-1.37 (m, 2H), 0.88(t, J = 7.5Hz, 3H). MS (ESI) m/z 277 $[M+H]^+$.
29. Tu, S.; Jiang, B.; Jiang, H.; Zhang, Y.; Jia, R.; Zhang, J.; Shao, Q.; Li, C.; Zhou, D.; Cao, L. *Tetrahedron* **2007**, *63*, 5406.
30. Tu, S.; Jiang, B.; Jia, R.; Zhang, J.; Zhang, Y. *Tetrahedron Lett.* **2007**, *48*, 1369.
31. *General procedure for the synthesis of 4-(1-benzyl-2-butyl-4-chloro-1H-imidazol-5-yl)-2-substituted-5H-indeno[1,2-b]pyridin-5-one* (**10a–o**). 1-Benzyl-2-butyl-4-chloroimidazole carboxaldehyde 7 (0. 250 g, 0.90 mmol), acetophenones **9a–o** (0.906 mmol), 1,3-indanedione 8 (0.132 g, 0.906 mmol) and ammonium acetate (0.174 g, 2.26 mmol) in DMF (5 mL) was heated at 120 °C for 3.0–4.0 h. After completion (by tlc), the reaction mixture was cooled to room temperature, poured in ice cold water, filtered and washed with water (2 × 5 mL) to give crude solid residue. Column chromatography over silica gel (hexane/ethyl acetate, 8:2) gave **10a–o** as pale yellow solids.
32. *4-(1-Benzyl-2-butyl-4-chloro-1H-imidazol-5-yl)-2-phenyl-5H-indeno[1,2-b] pyridine -5-one* (**10a**). Mp:110–113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95–8.01 (m, 3H), 7.70 (d, J = 7.55 Hz, 1H), 7.60 (t, J = 7.55 Hz, 1H), 7.42–7.48 (m, 6H), 7.14–7.22 (m, 2H), 6.80 (d, J = 7.55 Hz, 2H), 5.11 (d, J = 16.6 Hz, 1H), 4.93 (d, J = 16.6 Hz, 1H), 2.58–2.69 (m, 2H), 1.66–1.85 (m, 2H), 1.33–1.46 (m, 2H), 0.93 (t, J = 6.79 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.1, 166.2, 161.5, 149.7, 143.3, 137.9, 136.4, 135.5, 134.9, 134.5, 131.1, 130.3, 128.9, 128.8, 127.8, 127.5, 126.0, 123.9, 121.8, 121.2, 48.9, 29.7, 27.2, 22.5, 13.9. IR (KBr) 2924, 2860, 1710, 1556, 1454, 1253, 1169, 1078, 748, 692 cm^{-1}. MS (ESI) m/z 504 $[M+H]^+$; HR-MS (ESI) Calcd for $C_{32}H_{27}N_3OCl$ $[M+H]^+$: 504.1842, found: 504.1857. *4-(1-Benzyl-2-butyl-4-chloro-1H-imidazol-5-yl)-2-p-tolyl-5H-indeno[1,2-b]pyridin-5-one* (**10b**) Mp:122–125 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76–7.91 (m, 3H), 7.62 (t, J = 7.55 Hz, 1H), 7.49–7.56 (m, 1H), 7.35–7.42 (m, 2H), 7.11–7.21 (m, 5H), 6.78 (d, J = 7.55 Hz, 2H), 5.17 (d, J = 16.6 Hz, 1H), 4.91 (d, J = 16.6 Hz, 1H), 2.50–2.65 (m, 2H), 2.38 (s, 3H), 1.64–1.79 (m, 2H), 1.32–1.45 (m, 2H), 0.90 (t, J = 7.55 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.1, 166.1, 161.4, 149.5, 143.1, 140.3, 136.2, 135.3, 134.9, 134.7, 134.2, 130.9, 129.4, 128.8, 127.7, 125.9, 123.6, 122.9, 121.1, 121.0, 48.7, 29.6, 27.0, 22.3, 21.4, 13.8. IR (KBr) 2922, 2852, 1704, 1561, 1452, 1340, 1248, 1174, 917, 826, 750, 730 cm^{-1}. MS (ESI) m/z 518 $[M+H]^+$; HR-MS (ESI) Calcd for $C_{33}H_{29}N_3OCl$ $[M+H]^+$: 518.1999, found: 518.2011. *4-(1-Benzyl-2-butyl-4-chloro-1H-imidazol-5-yl)-2-(4-bromophenyl)-5H-indeno[1,2-b]pyridin-5-one* (**10c**) Mp: 133–135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 7.55 Hz, 1H), 7.84 (d, J = 8.30 Hz, 2H), 7.68 (d, J = 7.55 Hz, 1H), 7.56–7.61 (m, 3H), 7.41–7.47 (m, 2H), 7.15–7.24 (m, 3H), 6.79 (d, J = 6.80 Hz, 2H), 5.11 (d, J = 17.3 Hz, 1H), 4.90 (d, J = 17.3 Hz, 1H), 2.54–2.66 (m, 2H), 1.60–1.80 (m, 2H), 1.34–1.44 (m, 2H), 0.92 (t, J = 7.55 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.9, 166.2, 160.1, 149.9, 143.0, 136.6, 136.3, 135.4, 134.9, 134.5, 131.9, 131.5, 131.2, 130.7, 128.9, 128.9, 127.9, 125.9, 125.8, 125.1, 123.9, 121.4, 121.2, 48.8, 29.7, 27.1, 22.4, 13.9. IR (KBr) 2922, 2851, 1711, 1562, 1493, 1455, 1381, 1261, 1071, 1007, 916, 832, 749 cm^{-1}. MS (ESI) m/z 582 [M+H]+; HR-MS (ESI) Calcd for $C_{32}H_{26}N_3OClBr$ $[M+H]^+$: 582.0947, found: 582.0976. *4-(1-Benzyl-2-butyl-4-chloro-1H-imidazol-5-yl)-2-(4-methoxyphenyl)-5H-indeno [1,2-b]pyridin-5-one* (**10d**) Mp: 139–141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88–7.95 (m, 3H), 7.64 (d, J = 7.36 Hz, 1H), 7.54 (t, J = 7.36 Hz, 1H), 7.36–7.40 (m, 2H), 7.10–7.20 (m, 3H), 6.90 (d, J = 8.68Hz, 2H), 6.80 (d, J = 6.79Hz, 2H), 5.09 (d, J = 16.9 Hz, 1H), 4.93 (d, J = 16.9 Hz, 1H), 3.83 (s, 3H), 2.51–2.67 (m, 2H), 1.65–1.83 (m, 2H),

1.34–1.46 (m, 2H), 0.91 (t, J = 7.36 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.3, 166.2, 161.8, 161.2, 149.6, 143.1, 136.3, 135.4, 134.8, 134.3, 131.0, 130.3, 128.9, 128.8, 127.8, 125.9, 123.7, 122.1, 121.0, 120.7, 114.2, 55.3, 48.8, 29.7, 27.1, 22.4, 13.8. IR (KBr) 2925, 2854, 1703, 1562, 1454, 1256, 1170, 1028, 917, 831, 752 cm^{-1}. MS (ESI) m/z 534 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{33}H_{29}N_3O_2Cl$ [M+H]$_+$: 534.1948, found:534.1971. *4-(1-Benzyl-2-butyl-4-chloro-1H-imidazol-5-yl)-2-(4-nitrophenyl)-5H-indeno[1,2-b]pyridin-5-one* (**10e**) Mp: 163–166 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23–8.32 (m, 2H), 8.12 (d, J = 9.06 Hz, 2H), 7.95–8.02 (m, 2H), 7.70–7.82 (m, 1H), 7.65 (t, J = 7.55Hz, 1H), 7.46–7.51(m, 2H), 7.19–7.34(m, 2H), 6.84 (d, J = 6.79Hz, 2H), 5.17 (d, J = 16.6 Hz, 1H), 4.96 (d, J = 16.6 Hz, 1H), 2.60–2.72 (m, 2H), 1.63–1.85 (m, 2H), 1.34–1.48 (m, 2H), 0.84–0.95 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.7, 166.2, 158.4, 155.0, 150.2, 148.6, 143.3, 142.6, 136.1, 135.2, 134.7, 131.5, 129.6, 129.4, 128.9, 128.0, 127.9, 127.5, 125.8, 124.0, 123.8, 122.5, 121.2, 48.8, 29.6, 27.0, 22.3, 13.7. IR (KBr) 2922, 2851, 1715, 1593, 1516, 1452, 1344, 1275, 1253, 1083, 916, 862, 750 cm^{-1}. MS (ESI) m/z 549 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{32}H_{20}N_4O_3Cl$ [M+H]$^+$: 549.1693, found:549.1687. *4-(1-Benzyl-2-butyl-4-chloro-1H-imidazol-5-yl)-2-(3,4,5-trimethoxyphenyl)-5H-indeno[1,2-b]pyridin-5-one* (**10f**) Mp: 143–144 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, J = 7.36 Hz, 2H), 7.71 (d, J = 7.36 Hz, 1H), 7.62 (q, J = 7.36 Hz, J = 7.36 Hz, 2H), 7.43–7.53 (m, 1H), 7.38 (s, 1H), 7.23 (s, 2H), 6.81 (d, J = 6.79 Hz, 3H), 5.11 (d, J = 16.9 Hz, 1H), 4.95 (d, J = 16.9 Hz, 1H), 3.95 (s, 6H), 3.89 (s, 3H), 2.58–2.66 (m, 2H), 1.67–1.80 (m, 2H), 1.34–1.47 (m, 2H), 0.88–0.96 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.9, 166.1, 161.2, 153.6, 149.6, 143.1, 136.4, 135.5, 134.7, 134.5, 133.1, 132.1, 131.1, 128.9, 128.8, 127.9, 124.0, 123.9, 121.4, 121.2, 105.1, 60.7, 56.2, 48.9, 29.7, 27.2, 22.4, 13.9. IR (KBr) 2924, 2854, 1715, 1542, 1446, 1377, 1256, 1174, 1088, 1020, 812, 750, 664 cm^{-1}. MS (ESI) m/z 594 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{35}H_{33}N_3O_4Cl$ [M+H]$^+$: 594.2159, found: 594.2151. *4-(1-Benzyl-2-butyl-4-chloro-1H-imidazol-5-yl)-2-(naphthalen-1-yl)-5H-indeno[1,2-b]pyridin-5-one* (**10g**) Mp: 138–139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 7.55 Hz, 1H), 7.87 (t, J = 7.55 Hz, 3H), 7.70 (d, J = 6.79 Hz, 1H), 7.61 (d, J = 6.79 Hz, 1H), 7.35–7.57 (m, 6H), 7.12–7.19 (m, 3H), 6.77 (d, J = 7.55 Hz, 2H), 5.12 (d, J = 16.6 Hz, 1H), 4.97 (d, J = 16.6 Hz, 1H), 2.56–2.70 (m, 2H), 1.65–1.85 (m, 2H), 1.34–1.46 (m, 2H), 0.92 (t, J = 6.79 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.4, 166.0, 163.7, 149.8, 143.2, 137.0, 136.2, 135.0, 134.0, 133.9, 131.1, 130.8, 129.9, 128.8, 127.9, 127.8, 126.8, 126.7, 126.0, 125.3, 125.1, 123.8, 123.1, 121.8, 121.3, 48.8, 29.7, 27.1, 22.3, 13.8. IR (KBr) 2927, 2859, 1712, 1563, 1454, 1352, 1256, 1152, 1048, 967, 916, 823, 755, 717 cm^{-1}. MS (ESI) m/z 554 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{36}H_{29}N_3OCl$ [M+H]$^+$: 554.1999 found: 554.1977. *4-(1-Benzyl-2-butyl-4-chloro-1H-imidazol-5-yl)-2-(naphthalen-2-yl)-5H-indeno[1,2-b]pyridin-5-one* (**10h**); Mp: 130–131 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.10 (d, J = 8.30 Hz, 1H), 8.02 (d, J = 7.17 Hz, 1H), 7.81–7.89 (m, 3H), 7.70 (d, J = 7.17 Hz, 1H), 7.61 (s, 2H), 7.42–7.51 (m, 3H), 7.11–7.25 (m, 3H), 6.83 (d, J = 6.42 Hz, 2H), 5.13 (d, J = 16.6 Hz, 1H), 4.95 (d, J = 16.6 Hz, 1H), 2.55–2.69 (m, 2H), 1.65–1.83 (m, 2H), 1.33–1.48 (m, 2H), 0.94 (t, J = 7.17 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.2, 161.4, 149.8, 143.2, 136.3, 135.5, 135.1, 134.9, 134.5, 134.3, 133.3, 131.1, 129.0, 128.6, 127.9, 127.7, 127.5, 127.2, 126.5, 126.0, 124.5, 123.9, 122.0, 121.3, 48.9, 29.7, 27.2, 22.5, 13.9. IR (KBr) 2927, 2859, 1712, 1563, 1454, 1352, 1256, 1154, 1048, 967, 916, 823, 755, 717 cm^{-1}. MS (ESI) m/z 554 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{36}H_{29}N_3OCl$ [M+H]$^+$: 554.1999, found 554.1998. *4-(1-Benzyl-2-butyl-4-chloro-1H-imidazol-5-yl)-2-(thiophen-2-yl)-5H-indeno[1,2-b]pyridin-5-one* (**10i**) Mp: 153–155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 7.36 Hz, 1H), 7.68 (d, J = 7.17 Hz, 1H), 7.57–7.61 (m, 2H), 7.39–7.52 (m, 3H), 7.35 (s, 1H), 7.14–7.22 (m, 2H), 7.11 (t, J = 4.91 Hz, 1H), 6.80(d, J = 6.79 Hz, 2H), 5.12 (d, J = 16.8 Hz, 1H), 4.93 (d, J = 16.8 Hz, 1H), 2.54–2.68 (m, 2H), 1.66–1.84 (m, 2H), 1.35–1.44 (m, 2H), 0.93 (t, J = 7.17 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.5, 165.8, 16.08, 158.4, 155.0, 148.8, 142.0, 141.0, 136.5, 135.5, 134.5, 130.1, 129.0, 127.9, 126.9, 126.4, 126.0, 123.8, 123.6, 121.4, 119.7, 48.9, 29.8, 27.2, 22.5, 13.9. IR (KBr) 2924, 2852, 1716, 1561, 1432, 1381, 1256, 1159, 916, 786, 747, 728 cm^{-1}. MS (ESI) m/z 510 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{30}H_{25}N_3OSCl$ [M+H]$^+$: 510.1406, found: 510.1399. *4-(1-Benzyl-2-butyl-4-chloro-1H-imidazol-5-yl)-2-(5-bromothiophen-2-yl)-5H-indeno [1,2-b]pyridin-5-one* (**10j**) Mp: 162–164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 7.36 Hz, 1H), 7.68 (d, J = 7.36 Hz, 1H), 7.60 (t, J = 7.36 Hz, 1H), 7.37–7.47 (m, 2H), 7.15–7.28 (m, 3H), 7.06 (d, J = 3.77 Hz, 1H), 6.93(dd, J = 3.96 Hz, J = 3.71 Hz, 1H), 6.79 (d, J = 7.55 Hz, 2H), 5.09 (d, J = 16.05 Hz, 1H), 4.89 (d, J = 16.05 Hz, 1H), 2.58–2.65 (m, 2H), 1.62–1.82 (m, 2H), 1.37–1.47 (m, 2H), 0.93 (t, J = 7.17 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.2, 162.8, 158.4, 153.0, 149.9, 143.8, 142.6, 134.8, 134.7, 130.7, 129.0, 126.6, 126.0, 124.7, 123.9, 121.4, 119.0, 115.6, 49.0, 29.8, 27.2, 22.5, 14.0. IR (KBr) 2922, 2851, 1715, 1566, 1435, 1273, 1082, 915, 807, 749, 729 cm^{-1}. MS (ESI) m/z 588 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{30}H_{24}N_3OSClBr$ [M+H]$^+$:588.0511, found:588.0502. *4-(1-Benzyl-2-butyl-4-chloro-1H-imidazol-5-yl)-2-(furan-2-yl)-5H-indeno[1,2-b]pyridin-5-one* (**10k**); Mp: 137–138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 7.55 Hz, 1H), 7.69 (d, J = 7.55 Hz, 1H), 7.56–7.62 (m, 2H), 7.42–7.49 (m, 2H), 7.28 (d, J = 3.77 Hz, 1H), 7.13–7.21 (m, 3H), 6.79 (d, J = 6.75 Hz, 2H), 6.57(dd, J = 1.51 Hz, J = 1.51 Hz, 1H), 5.07 (d, J = 16.6 Hz, 1H), 4.93 (d, J = 16.6 Hz, 1H), 2.53–2.69 (m, 2H), 1.66–1.83 (m, 2H), 1.33–1.46 (m, 2H), 0.92 (t, J = 7.55 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.8, 166.4, 153.0, 152.8, 149.8, 144.7, 142.8, 136.2, 135.5, 134.8, 134.6, 131.2, 128.9, 127.8, 126.0, 123.8, 119.4, 112.7, 112.4, 48.9, 29.7, 27.2, 22.4, 13.9. IR (KBr) 2954, 2869, 1715, 1560, 1483, 1277, 1256, 1054, 912, 882, 748, 728 cm^{-1}. MS (ESI) m/z 494 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{30}H_{25}N_3O_2Cl$ [M+H]$^+$: 494.1635, found:494.1654. *4-(1-Benzyl-2-butyl-4-chloro-1H-imidazol-5-yl)-2-(6-bromopyridin-2-yl)-5H-indeno[1,2-b]pyridin-5-one* (**10l**). Mp: 161–163 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, J = 7.74 Hz, 1H), 8.23 (s, 1H), 7.87 (d, J = 7.36 Hz, 1H), 7.67 (t, J = 7.36 Hz, 2H), 7.57 (t, J = 7.55 Hz, 1H), 7.49 (d, J = 7.93 Hz, 1H), 7.43 (t, J = 7.36 Hz, 1H), 7.08–7.21 (m, 3H), 6.83 (d, J = 7.17 Hz, 2H), 5.09 (d, J = 16.6 Hz, 1H), 4.97 (d, J = 16.6 Hz, 1H), 2.54–2.65 (m, 2H), 1.64–1.81 (m, 2H), 1.33–1.45 (m, 2H), 0.91 (t, J = 7.17 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.5, 165.7, 160.0, 158.0, 155.7, 149.8, 142.9, 141.9, 138.9, 136.0, 135.4, 134.9, 131.2, 129.0, 127.9, 126.0, 124.0, 122.8, 121.0, 120.7, 48.3, 29.6, 27.2, 22.5, 13.9. IR (KBr) 2954, 2854, 1713, 1605, 1562, 1495, 1426, 1378, 1272, 1181, 1126, 917, 799, 734 cm^{-1}. MS (ESI) m/z 583 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{31}H_{25}N_4OClBr$ [M+H]$^+$: 583.0900, found:583.0891. *4-(1-Benzyl-2-butyl-4-chloro-1H-imidazol-5-yl)-2-(dibenzo[b,d]furan-2-yl)-5H-indeno[1,2-b]pyridin-5-one* (**10m**) Mp: 197–198 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, J = 1.51Hz, 1H), 7.96 (m, 3H), 7.72 (d, J = 7.55Hz, 1H), 7.46–7.66 (m, 6H), 7.35–7.42 (m, 1H), 7.18–7.25 (m, 3H), 6.87 (d, J = 7.55Hz, 2H), 5.15 (d, J = 16.6 Hz, 1H), 4.99 (d, J = 16.6 Hz, 1H), 2.63–2.70 (m, 2H), 1.68–1.87 (m, 2H), 1.35–1.47 (m, 2H), 0.85–0.95 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.4, 166.3, 161.4, 157.5, 156.7, 149.9, 142.9, 136.1, 135.0, 134.3, 132.7, 131.2, 128.9, 127.8, 127.6, 126.8, 125.9, 123.8, 123.0, 121.5, 121.1, 120.9, 119.9, 111.9, 111.8, 48.8, 29.6, 27.1, 22.4, 13.7. IR (KBr) 2924, 2853, 1710, 1596, 1560, 1451, 1420, 1256, 1198, 1120, 917, 749, 731 cm^{-1}. MS (ESI) m/z 594 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{38}H_{29}N_3O_2Cl$ [M+H]$^+$: 594.1948, found: 594.1969. *4-(1-benzyl-2-butyl-4-chloro-1H-imidazol-5-yl)-2-(dibenzo[b,d]thiophen-2-yl)-5H-indeno[1,2-b]pyridin-5-one* (**10n**) Mp: 181–183 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.23 (t, J = 3.77Hz,1H), 8.00–8.04 (m, 2H), 7.81–7.88 (m, 2H), 7.69 (d, J = 7.55Hz, 1H), 7.57–7.63 (m, 2H), 7.42–7.49(m, 4H), 7.14–7.23(m, 2H), 6.83 (d, J = 6.79Hz, 2H), 5.13 (d, J = 16.6 Hz, 1H), 4.95 (d, J = 16.6 Hz, 1H), 2.55–2.70 (m, 2H), 1.66–1.86 (m, 2H), 1.36–1.46 (m, 2H), 0.94 (t, J = 6.79Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.2, 166.4, 161.4, 149.8, 143.1, 141.8, 139.8, 135.5, 135.4, 134.9, 134.5, 134.3, 131.8, 128.9, 127.9, 127.1, 126.0, 125.7, 124.6, 123.9, 121.6, 121.3, 48.9, 29.7, 27.2, 22.5, 13.9. IR (KBr) 2922, 2851, 1705, 1604, 1557, 1451, 1349, 1247, 1080, 1022, 916, 878, 780, 726 cm^{-1}. MS (ESI) m/z 610 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{38}H_{29}N_3OSCl$ [M+H]$^+$: 610.1719, found:610.1692. *4-(1-Benzyl-2-butyl-4-chloro-1H-imidazol-5-yl)-2-(3-tosyl-3H-inden-1-yl)-5H-indeno[1,2-b]pyridin-5-one* (**10o**) Mp: 148–150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, J = 6.79Hz, 1H), 8.05 (s, 1H), 7.94–8.00 (m, 2H), 7.82 (d, J = 8.30Hz, 2H), 7.70 (d, J = 7.17Hz, 1H), 7.57–7.65 (m, 1H), 7.43–7.53(m, 1H), 7.30–7.39 (m, 2H), 7.18–7.25 (m, 6H), 6.83 (d, J = 6.42Hz, 2H), 5.13 (d, J = 16.9 Hz, 1H), 4.94 (d, J = 16.6 Hz, 1H), 2.55–2.67 (m, 2H), 2.36 (s, 3H), 1.66–1.83 (m, 2H), 1.33–1.46 (m, 2H), 0.83–0.91 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.6, 166.1, 157.4, 149.8, 145.1, 143.0, 135.9, 135.4, 135.1, 134.8, 132.1, 131.1, 130.1, 130.0, 128.9, 128.7, 128.0, 127.6, 127.0, 126.0, 125.9, 125.2, 124.1, 123.8, 122.4, 121.9, 121.1, 113.5, 48.8, 29.7, 27.1, 22.7, 21.6, 13.8. IR (KBr) 2952, 2855, 1712, 1568, 1450, 1382, 1348, 1256, 1103, 909, 753, 734 cm^{-1}. MS (EI) m/z 661 [M-35]$^+$; Calcd for $C_{41}H_{34}N_4O_3SCl$.

33. Sheldrick G.M. A short history of SHELX, *Acta Crystallogr.* **2008** *A64*, 112. Bruker (2001) SAINT (Version 6.28a) & SMART (Version 5.625). Bruker AXS Inc., Madison, Wisconsin, USA. Crystal data for **10h**: $C_{36}H_{28}ClN_3O$, M = 554.06, triclinic, space group $P\bar{1}$, a = 8.5222(8) Å, b = 12.0029 (11) Å, c = 14.2893(13) Å, α = 80.268(2)°, β = 87.545(2)°, γ = 84.525(2)°, V = 1433.5(2) Å^3, Z = 2, D_{calcd} = 1.284 mg m^{-3}, T = 294(2) K, μ = 0.168 mm^{-1}, $F(000)$ = 580, λ = 0.71073 Å. Data collection yielded 13815 reflections resulting in 5014 unique, averaged reflections, 3866 with $I>2(I)$. Full-matrix least-squares refinement led to a final R = 0.0421, wR = 0.1130 and GOF = 1.033.
34. Cruikshank, R.; Duguid, J. P.; Marion, B. P.; Swain, R. H. A. *Medicial Microbiology*, 12th ed.; Churchill Livingstone: London, 1975, Vol. II, 196–202. Collins A. H., Eds., Microbiology Methods, 2nd ed. Butterworth: London, 1976.
35. Evaluation of in vitro antimicrobial activity: For evaluation of antibacterial activity, a standard inoculum of 0.5Mac Farland was introduced on to the surface of nutrient agar plates and evenly distributed with the aid of a sterile L-Shaped glass spreader. Discs of 5mm diameter were prepared from Whatmann No1 filter paper and sterilized by dry heat in a hot air oven at 160 °C for 2 h. These sterile discs with the test compounds in DMSO at a concentration of 10 μg/disc, were gently placed onto the nutrient agar plates. The plates were then incubated for 24 h at 37 °C. Gentamicin was used as a reference standard for antibacterial evaluation. The zones of inhibition were measured in triplicate in each case and compared with that of control and standard drug. Table 3 summarizes the results of the in vitro antibacterial activities of the compounds **10a**–**10o** expressed as Zone of inhibition in mm. Similarly, antifungal activity was determined using standard procedure in which a loopful of each of the fungal strain was made as a suspension in saline and transferred to Yeast extract potato dextrose agar plates. Nystatin was used as a reference standard for antifungal evaluation. The inoculum was evenly distributed with the aid of a sterile glass spreader. The sterile discs (5 mm diameter) with the test compounds in DMSO at a concentration of 10 μg/disc, were gently placed onto the Yeast extract potato dextrose agar plates. The plates were then incubated for 2–3 days at room temperature. The zones of inhibition were measured in each case and compared with that of control and standard drug. Table 3 summarizes the results of the in vitro antifungal activities of the compounds **10a**–**10o** expressed as Zone of inhibition in mm.