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Synthesis, Spectral, and Antimicrobial Studies of 1-Butyl-3-substituted-4-(2-aryl-1*H*-indol-3-yl)-2-azetidinones

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ABSTRACT: *Ketene generated from acetyl chloride or chloroacetyl chloride adds on indolyl Schiff's base double bond to afford 1-butyl-3-substituted-4-(2-aryl-1*H*-indol-3-yl)-2-azetidinones in THF. The reaction proceeds stereospecifically via concerted* trans *[2+2] cycloaddition. The synthesized compounds have been characterized by elemental analyses and spectral data (IR, PMR, and mass). All synthesized compounds have been evaluated for antibacterial and antifungal activities, and* **4g** *to* **4l** *have shown promising results.* © 2004 Wiley Periodicals, Inc. Heteroatom Chem 15:494–501, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20052

INTRODUCTION

β-Lactam antibiotics are well known for their antimicrobial activity (e.g. penicillin and cephalosporins) [1,2], lowering cholesterol level [3,4], serine protease inhibition [5], tubercular activity, and chemotherapeutic activities [6]. Recently, β-lactams have been used as synthons in the preparation of various heterocyclic compounds of biological significance [7].

In addition to various psychopharmacological activities viz., CNS-depressant activities [8], tranquilizing effects [9], neuroplegic action [10], antitumor activity [11], and antimetastatic activity [12], indole derivatives also display a wide range of antimicrobial activities [13,14]. It is therefore considered to link the β-lactam moiety with indole moiety in search of better antimicrobial agents. Keeping these observations in view, we have undertaken a comprehensive program for developing better antimicrobial agents, and have synthesized 1-butyl-3-substitutated-4-(2-aryl-1*H*-indol-3-yl)-2-azetidinones and screened them for their antibacterial and antifungal activities.

RESULTS AND DISCUSSION

Synthesis

2-Arylindole **1** was subjected to Vilsmeier–Haack formylation [15] with $POCl_3$ and *N*,*N*-dimethyl formamide to give 2-arylindole-3-carboxaldehyde **2**. This, 3-formylindole **2** was condensed with butylamine, in refluxing toluene, to give 3-butyliminomethyl-2-arylindole (Schiff's base, 3). This 2-butyliminomethyl-2-arylindole **3** was chloroacetylated/acetylated with chloroacetyl chloride or acetyl chloride in the presence of triethylamine and THF. The four-membered ring formation takes place via concerted *trans* [2+2] thermal cycloaddition reaction to afford the desired compound **4** (Scheme 1).

The physical and analytical data of compounds (**4a–l**) are given in (Table 1).

In the IR spectra of 2-aryl-1*H*-indol-3-carboxaldehydes, >N—H absorption appears as a broad

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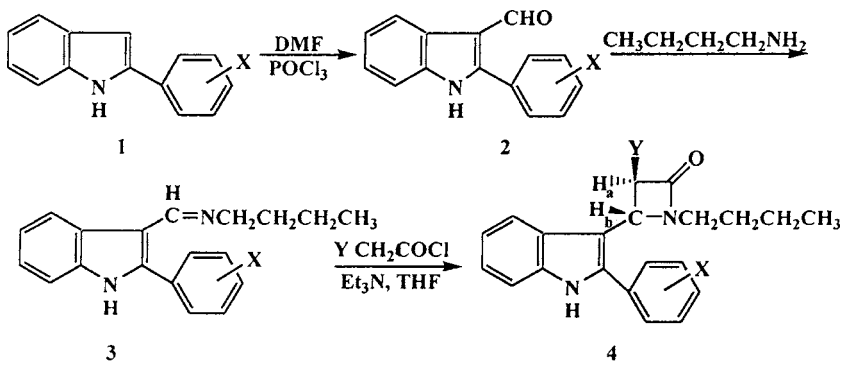


X : H; 4-Cl; 4-Br; 4-CH_3; 3-Cl, 4-F; **Y** : H, Cl

SCHEME 1

band from 3220–3140 cm^{-1}. Characteristic absorption due to >C=O of formyl group appears at 1625 cm^{-1}. This downfield shift from the normal >C=O absorption (1720 cm^{-1}) is attributed to the presence of high degree of conjugation in the formylated indole. In the ^1H NMR of 2-aryl-1*H*-indol-3-carboxaldehydes =C—H proton resonance signal of formyl group appears as a sharp singlet at δ 8.45 ppm. Aromatic and >N—H proton signals appear as multiplet from δ 6.8 to 7.7 ppm.

In the IR spectra of 3-butyliminomethyl-2-aryl-1*H*-indoles (Schiff's base), >N—H absorption appears as a broad band from 3250–3180 cm^{-1}. Characteristic absorption due to >C=N group appears at 1630–1620 cm^{-1}. In the ^1H NMR of 3-butyliminomethyl-2-aryl-1*H*-indoles, —CH=N— proton resonance signal appears as a sharp singlet at δ 8.0–8.2 ppm. This upfield shift confirms the conversion of formyl group (—CHO) into imino group (HC=N—).

TABLE 1 The Physical and Analytical Data of 1-Butyl-3-substituted-4-(2-aryl-1*H*-indol-3-yl)-2-azetidinone

Compound	*X*	*Y*	*Molecular Formula*	*Molecular Weight*	*Melting Point (°C)*	*Yield %*	*Found (Calcd) (%)*		
							C	*H*	*N*
4a	H	H	$C_{21}H_{22}N_2O$	318	67	73	78.38 (79.24)	6.73 (6.96)	8.88 (8.80)
4b	4-Br	H	$C_{21}H_{21}BrN_2O$	397	122	71	63.60 (63.63)	5.28 (5.30)	7.01 (7.07)
4c	4-Cl	H	$C_{21}H_{21}ClN_2O$	352	154	68	71.32 (71.48)	5.90 (5.95)	7.81 (7.94)
4d	4-F	H	$C_{21}H_{21}FN_2O$	336	140	75	75.04 (75.00)	6.20 (6.25)	8.30 (8.33)
4e	4-CH_3	H	$C_{22}H_{24}N_2O$	332	98	80	79.45 (79.51)	7.12 (7.22)	8.46 (8.46)
4f	3-Cl, 4-F	H	$C_{21}H_{20}ClFN_2O$	370	172	69	68.08 (68.01)	5.29 (5.39)	7.59 (7.55)
4g	H	Cl	$C_{21}H_{21}ClN_2O$	352	218	72	71.32 (71.48)	5.93 (5.95)	7.91 (7.94)
4h	4-Br	Cl	$C_{21}H_{20}BrClN_2O$	431	183	67	58.66 (58.60)	4.75 (4.65)	6.58 (6.51)
4i	4-Cl	Cl	$C_{21}H_{20}Cl_2N_2O$	386	200	68	65.15 (65.28)	5.08 (5.18)	7.20 (7.25)
4j	4-F	Cl	$C_{21}H_{20}ClFN_2O$	370	138	75	68.02 (68.01)	5.32 (5.39)	7.53 (7.55)
4k	4-CH_3	Cl	$C_{22}H_{23}ClN_2O$	366	90	81	72.01 (72.03)	6.12 (6.28)	7.62 (7.65)
4l	3-Cl, 4-F	Cl	$C_{21}H_{19}Cl_2FN_2O$	404	164	79	62.36 (62.37)	4.65 (4.70)	6.90 (6.93)

In the IR spectra of 1-butyl-3-chloro-4-[2-aryl-1*H*-indol-3-yl]-2-azetidinone and 1-butyl-4-[2-aryl-1*H*-indol-3-yl]-2-azetidinone, >N—H absorption appears as a sharp band at 3323 cm^{-1}. Characteristic absorption due to β-lactam >C=O appears at 1750 cm^{-1}. The absorption due to C—Cl and C—Br appears at 748 cm^{-1} and 499 cm^{-1}, respectively. In the ^1H NMR spectra, —CH—N< proton resonance signal appears as double doublet at δ 4.8 ppm (J_{HaHb} = 1.66 Hz). A sharp azetidinonic double doublet due to CH=Cl group appears at δ 5.0 ppm (J_{HaHb} = 1.66 Hz). This downfield shift is attributed to the highly electron withdrawing groups flanked on either side. It shows a conrotatory [2+2] cycloaddition yielding the *trans* β-lactam isomer [16]. This isomer contains two chiral centers (one carbon and another nitrogen). The >N—H proton signal of indole moiety appears as sharp singlet at δ 8.8 ppm. Aromatic proton signals appear as multiplet at δ 7.2–δ 7.5 ppm. Triplet of methyl (—CH_3) group appears at δ 0.7 ppm. CH_3—CH_2— and CH_2—CH_2—N appear as multiplets at δ 1.1 and δ 1.6 ppm respectively.

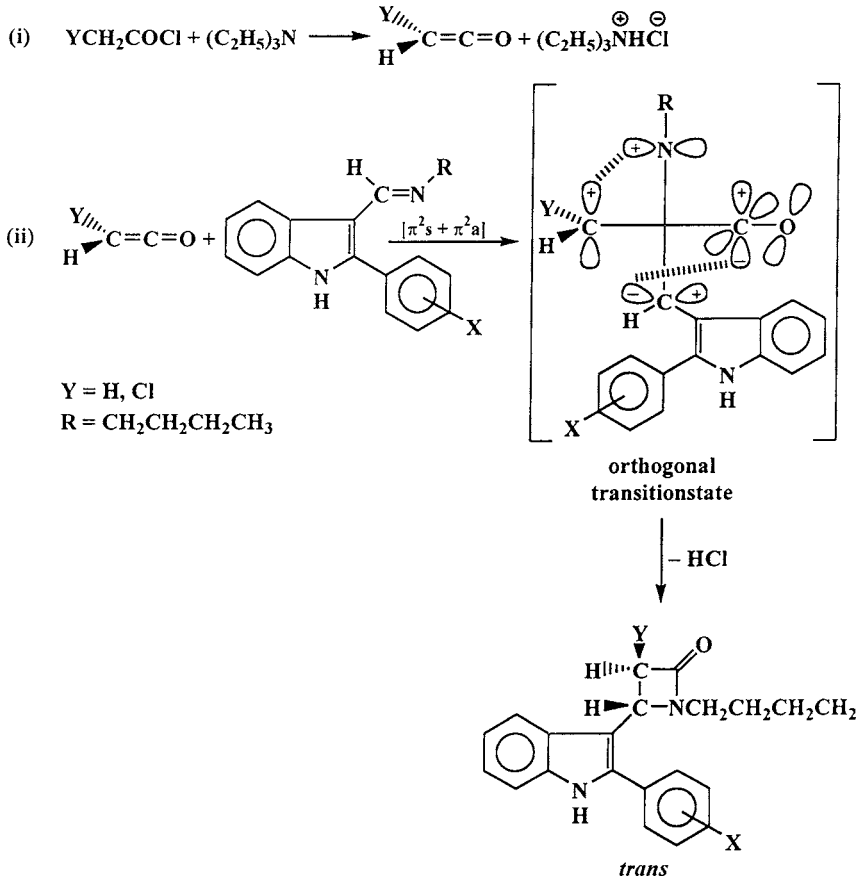
A triplet is observed downfield at δ 3.6 ppm due to methylene (—CH_2) group attached to nitrogen atom. This downfield triplet shows that methylene group is attached to azetidinone ring.

A possible mechanism is given in Scheme 2.

The IR and ^1H NMR data of 1-butyl-3-substituted-4-(2-aryl-1*H*-indol-3-yl)-2-azetidinones are summarized in Table 2.

Final confirmation is obtained from fast atomic bombardment (FAB) mass spectra as M^+ at 318 **4(a)**, 332 **4(e)**, and 432 **4(h)** that correspond to their molecular masses which are $C_{21}H_{22}N_2O$, $C_{22}H_{24}N_2O$, and $C_{21}H_{20}{}^{79}Br^{35}ClN_2O$ respectively (Table 3).

The mass fragmentation of compound **4(h)** is discussed in detail. Compound **4(h)** (Scheme 3) under FAB provides a characteristic molecular ion cluster at 430/432 **I** (100%, base peak) due to the presence of one bromine and one chlorine atom. This may fragment by two pathways A and B. In the pathway A, **I** eliminates a chlorine radical to generate a cation **II** *m/z* 395/397 (50%); removal of chlorine radical is confirmed by the peak ratio being 1:1 showing the isotopic abundance of bromine atom alone in cation **II**. Cation **II** by loss of neutral cyclopropane moiety yields cation **III** at *m/z* 353/355 (52%). Cation **III** eliminates cyclobutadiene to give cation **VI** at *m/z*



SCHEME 2

TABLE 2 Spectral Data of 1-Butyl-3-substituted-4-(2-aryl-1*H*-indol-3-yl)-2-azetidinones

Compound	*IR (KBr)ν_{max} (cm^{-1})*	*^{1}H NMR ($CDCl_3$) δ (ppm)*	*Mass m/z*
4a	3403 (NH str.), 3050 (aromatic C—H str.), 2839 (aliphatic C—H str.), 1750 (>C=O), 1657 (aromatic C=C str.), 1601 (C=C str.).	8.4 (s, NH, 1H), 7.3–7.5 (m, Ar-H, 5H), 5.1 (dd, CH—N, 1H, $J_{HaHb} = 1.68$) (trans), 5.4 (dd, CH_a—CO, 1H, $J_{HaHb} = 1.68$) (trans), 3.6 (m, N—CH_2, 2H), 1.8–2.0(m, —CH_2—CH_2, 4H), 0.09 (t, —CH_3, 3H).	318 (m^+)
4e	3416 (NH str.), 3049 (aromatic C—H), 2839 (aliphatic C—H str.), 1716 (C=O), 1657 (aromatic C=C str.), 1602 (C=C str.).	8.8 (s, NH, 1H), 7.2–7.4 (m, Ar—H), 5.6 (dd, CH—CO, 1H), 5.0 (dd, CH—N, 1H), 2.4 (t, —N—CH_2, 2H), 1.6–2.0 (m, CH_2—CH_2, 4H), 0.1 (t, —CH_3, 3H).	332 (M^+)
4h	3323 (NH str.), 2961 (aromatic C—H), 2826 (aliphatic C—H str.), 1750 (C=O), 1598 (aromatic C=C str.), 748 (C—Cl str.), 499 (C—Br str.).	8.8 (s, NH, 1H), 7.6 (d, Ar—H, 2H, $J = 8.4$ Hz), 7.5 (d, Ar—H, 2H, $J = 8.4$ Hz), 5.0 (dd, CH_a—Cl, 1H, $J_{HaHb} = 1.66$ Hz) (trans), 4.8 (dd, CH_b—N, 1H, $J_{HaHb} = 1.66$ Hz) (trans), 3.6 (m, N—CH_2, 2H), 1.1–1.6 (m, CH_2—CH_2, 4H), 0.7 (t, —CH_3, 3H).	430/432 Isotopic cluster

301 (30%) that is stablized by resonance and inturn eliminates a hydrogen radical to generate cation radical **VII** at m/z 300 (48%).

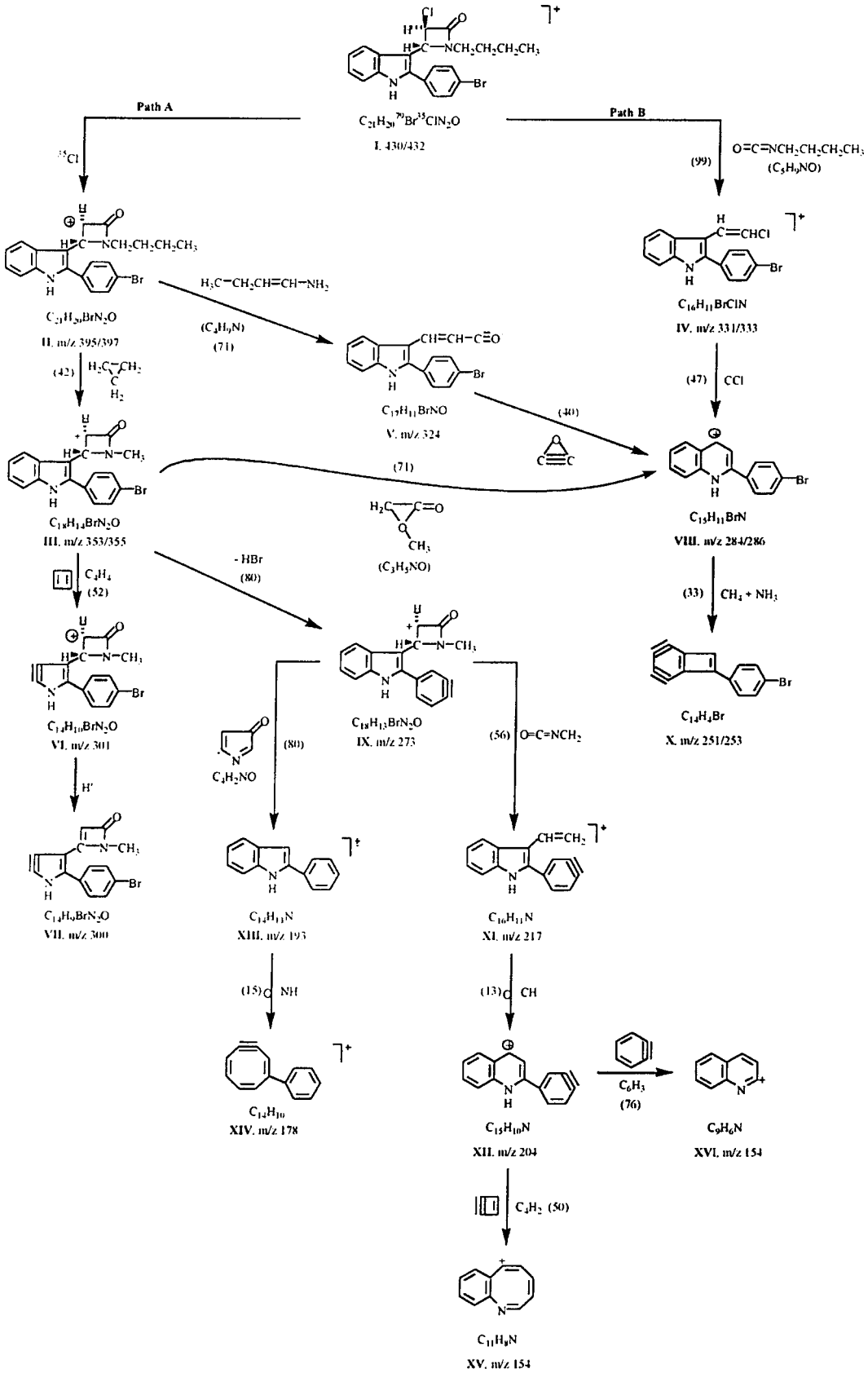
In the pathway B, cation radical **I** eliminates neutral butylisocyanate and generates cation radical **IV** at m/z 331/333 (25%). The cation radical **IV** shows isotopic cluster due to the presence of bromo and chloro groups. Cation **IV** by loss of CCl radical undergoes rearrangement to give a six-membered ring expanded cation **VIII** at m/z 284/286 (64%) that is stablized by high degree of resonance (again the peak ratio is 1:1). Cation **VIII** extruded neutral methane and ammonia moieties to give a cation **X** at m/z 251/253 (13%). Cation **II** further eliminates neutral C_4H_9N moiety to afford cation **V** at m/z 324 (30%) that is stablized by resonance.

This cation **V** further eliminates neutral moiety C_2O to give cation **VIII**. Cation **III** extruded neutral HBr moiety to give cation **IX** at m/z 273 (64%) that is stablized by resonance. Cation **IX** further eliminates C_4H_2NO radical to afford cation radical **XIII** at m/z 193 (22%). This cation radical corresponds to 2-phenylindole species that is stablized by high degree of resonance.

2-Phenylindolylcation radical **XII** eliminates neutral NH moiety and undergoes ring expansion to yield eight-membered cation radical **XIV** at m/z 178 (10%) that is stablized by resonance. Cation **IX** eliminates O=C=NCH_2 radical to afford cation radical **XI** at m/z 217 (80%) that readily loses CH radical to give ring expanded six-membered quinolinium type cation **XII** at m/z 204 (38%). It inturn further

TABLE 3 Major Mass Fragments of 1-Butyl-3-substituted-4-(2-aryl-1*H*-indol-3-yl)-2-azetidinones

Compounds	**(4a)**		**(4e)**		**(4h)**	
Fragment No.	*m/z*	*Relative Intensity (%)*	*m/z*	*Relative Intensity (%)*	*m/z*	*Relative Intensity (%)*
I	M^+, 318	10.0	M^+, 332	10	430/432	100
II	306	65.0	320	42.0	395/397	50
III	289	20.0	307	64.0	353/355	52
IV	280	12.0	290	20.0	333	25
V	264	100.0	278	100.0	324	30
VI	246	18.0	236	53.0	301	30
VII	234	20.0	220	5.0	300	48
VIII	222	98.0	208	11.0	284/286	64
IX	204	26.0	193	7.1	273	10
X	194	48.0	165	10.0	251/253	13
XI	180	12.0	154	68.0	217	80
XII	165	25.0	136	50.0	204	38
XIII	154	83.0	120	10.0	193	22
XIV	136	78.0	107	18.0	178	10



SCHEME 3 Mass fragmentation pattern of 1-butyl-3-chloro-4-[2-(4-bromophenyl)-1*H*-indol-3-yl]-2-azetidinone (**4h**).

decomposes in two ways: either elimination of benzyne radical generates quinolinium ion **XVI** at m/z 128 (9%) or loses neutral cyclobutadien-1-yne moiety to yield eight-membered ring expanded cation **XV** at m/z 154 (49%).

Antimicrobial Activity

All the synthesized compounds **4(a–l)** were screened for their antimicrobial activity against the gram-negative bacteria *Escherichia coli*, gram-positive bacteria *Klebisella pneumoniae*, and fungi *Aspergillus flavus* and *Aspergillus niger* at different concentrations by disk diffusion method [7]. Streptomycin and betadine are used as reference compounds for evaluating antibacterial and antifungal activities respectively. Compounds **4g–l** showed enhanced antibacterial and antifungal activity at 200 ppm, 400 ppm, 800 ppm, and 1000 ppm due to the presence of chlorine moiety in the β-lactam ring. The results obtained are presented in Tables 4 and 5.

EXPERIMENTAL

All the melting points were determined in open capillary tubes and are uncorrected. The IR spectra (υ_{max} in cm^{-1}) were recorded on a Perkin Elmer-557 grating infrared spectrophotometer in KBr pellets. PMR spectra were recorded on Bruker spectrometer (200 MHz) using $CDCl_3$ as a solvent. TMS was used as internal standard (chemical shift in δ, ppm). Mass spectra were recorded on Kratos 30 and 50 mass spectrometer. The purity of the compounds was checked by TLC using silica gel-G as adsorbent, UV light or iodine accomplished visualization. 2-Arylindoles were prepared by the method of Joshi et al. [18]. 2-Arylindol-3-carboxaldehydes **2** [15] and 3-butyliminomethyl-2-arylindole **3** [19] were prepared by the literature method.

*1-Butyl-3-substituted-4-(2-aryl-1*H*-indol-3-yl)-2-azetidinones* **(4)**

A mixture of 3-butyliminomethyl-2-arylindoles **3** (2 mmol) and triethylamine (4.2 mmol, 0.6 g) was

TABLE 4 Antibacterial Activity of 1-Butyl-3-substituted-4-[2-aryl-1*H*-indol-3-yl]-2-azetidinone **(4a–l)**

	Mean Value of Area of Inhibition in mm 1000 ppm IZ (IA)		*Mean Value of Area of Inhibition in mm 800 ppm IZ (IA)*		*Mean Value of Area of Inhibition in mm 400 ppm IZ (IA)*		*Mean Value of Area of Inhibition in mm 200 ppm IZ (IA)*	
Compounds	*E. coli*	*K. penumoniae*	*E. coli*	*K. penumoniae*	*E. coli*	*K. penumoniae*	*E. coli*	*K. penumoniae*
Streptomycin	8.2	7.4	8.0	7.1	7.6	6.4	6.6	5.4
4a	9.1 (1.10)	6.8 (.91)	7.2 (.90)	6.2 (.87)	6.2 (.81)	5.2 (.81)	3.4 (.51)	3.4 (.62)
4b	11.3 (1.31)	6.4 (.86)	9.8 (1.22)	5.8 (.81)	7.8 (1.02)	4.3 (.67)	4.6 (.69)	2.2 (.40)
4c	11.2 (1.36)	5.8 (.78)	10.1 (1.26)	4.2 (.59)	8.3 (1.09)	3.3 (.51)	6.3 (.95)	2.4 (.44)
4d	5.4 (.65)	4.9 (.66)	4.2 (.52)	4.1 (.57)	4.0 (.52)	3.1 (.48)	3.4 (.51)	3.0 (.55)
4e	6.8 (.82)	7.3 (.98)	5.9 (.73)	6.9 (.97)	4.7 (.61)	5.3 (.82)	4.0 (.60)	4.3 (.79)
4f	7.2 (.87)	8.2 (1.10)	6.8 (.85)	7.4 (1.04)	6.2 (.81)	6.3 (.98)	3.8 (.57)	5.2 (.96)
4g	16.4 (2.0)	11.6 (1.56)	11.2 (1.40)	10.1 (1.42)	10.7 (1.40)	8.4 (1.31)	7.2 (1.09)	7.6 (1.29)
4h	18.1 (2.20)	11.9 (1.60)	15.6 (1.95)	11.2 (1.57)	12.2 (1.60)	9.3 (1.45)	8.3 (1.25)	7.6 (1.40)
4l	15.2 (1.85)	13.2 (1.78)	13.2 (1.65)	11.9 (1.67)	11.8 (1.55)	9.8 (1.53)	9.1 (1.37)	8.2 (1.51)
4j	14.3 (1.74)	10.8 (1.45)	12.4 (1.55)	9.2 (1.29)	10.2 (1.34)	7.4 (1.15)	7.4 (1.12)	5.3 (.98)
4k	11.5 (1.40)	9.6 (1.29)	9.8 (1.22)	8.6 (1.21)	8.8 (1.15)	7.6 (1.18)	6.7 (1.01)	6.4 (1.18)
4l	10.8 (1.31)	8.4 (1.13)	8.6 (1.07)	7. (1.07)	8.1 (1.06)	6.4 (1.00)	6.2 (.93)	5.3 (.98)

IZ = Inhibition area (zone) excluding diameter of disk.
AI (activity index) = Inhibition area of sample/inhibition area of standard.

TABLE 5 Antifungal Activity of 1-Butyl-3-substituted-4-[2-aryl-1 *H*-indol-3-yl]-2-azetidinone **(4a–l)**

	Mean Value of Area of Inhibition in mm 1000 ppm IZ (IA)		*Mean Value of Area of Inhibition in mm 800 ppm IZ (IA)*		*Mean Value of Area of Inhibition in mm 400 ppm IZ (IA)*		*Mean Value of Area of Inhibition in mm 200 ppm IZ (IA)*	
Compound	*A. flavus*	*A. niger*	*A. flavus*	*A. niger*	*A. flavus*	*A. niger*	*A. flavus*	*A. niger*
Betadiene	7.2	8.1	6.8	8.0	6.6	7.6	5.9	7.3
4a	7.0 (.97)	7.6 (.93)	6.2 (0.91)	7.2 (.90)	6.0 (0.90)	5.6 (.73)	5.1 (1.86)	5.2 (0.71)
4b	6.2 (.86)	6.7 (.82)	6.0 (0.88)	6.4 (.80)	5.4 (0.81)	6.0 (.78)	4.8 (0.81)	5.4 (0.73)
4c	6.9 (0.95)	6.8 (.83)	5.8 (0.85)	6.3 (.78)	4.9 (.74)	5.9 (0.77)	4.0 (0.67)	4.2 (.57)
4d	5.6 (.77)	7.2 (.88)	5.2 (.76)	6.9 (.86)	4.6 (0.69)	6.1 (.80)	3.8 (.64)	4.8 (.65)
4e	11.2 (1.55)	10.6 (1.30)	10.0 (1.47)	9.2 (1.15)	9.2 (1.39)	8.2 (0.07)	6.9 (1.16)	6.5 (.89)
4f	9.8 (1.36)	13.0 (1.60)	8.9 (1.30)	12.6 (1.57)	7.8 (1.18)	11.3 (1.48)	7.0 (1.18)	9.2 (1.26)
4g	10.3 (1.43)	11.4 (1.40)	9.6 (1.41)	10.8 (1.35)	8.8 (1.33)	9.2 (1.22)	7.8 (1.32)	8.6 (1.17)
4h	12.4 (1.72)	10.9 (1.34)	11.3 (1.66)	9.2 (1.15)	9.1 (1.37)	8.4 (1.10)	8.1 (1.37)	8.0 (1.09)
4I	11.8 (1.63)	10.5 (1.29)	10.6 (1.55)	9.4 (1.17)	10.4 (1.57)	8.8 (1.15)	8.5 (1.44)	7.6 (1.04)
4j	10.6 (1.47)	9.9 (1.22)	9.3 (1.36)	9.3 (1.16)	9.8 (1.48)	7.2 (0.94)	7.5 (1.27)	6.8 (.93)
4k	13.2 (1.83)	12.1 (1.49)	11.2 (1.64)	11.6 (1.45)	8.4 (1.27)	10.6 (1.39)	9.1 (1.54)	9.4 (1.28)
4l	12.8 (1.77)	11.6 (1.43)	10.6 (1.55)	10.3 (1.28)	10.1 (1.53)	9.2 (1.21)	8.2 (1.38)	8.2 (1.12)

IZ = Inhibition area (zone) excluding diameter of disk.
AI (activity index) = Inhibition area of sample/inhibition area of standard.

dissoloved in tetrahydrofuran (25 mL) and cooled [2,20]. To this cooled solution, acetylchloride/ chloroacetyl chloride (2.4 mmol) was added slowly at 0°C and the mixture was stirred for 24 h and then setaside for 48 h at room temperature. The precipitated amine hydrochloride was filtered off, and tetrahydrofuran was removed under vacuum. The residue was poured into ice cold water and the resulting solid mass was suction filtered, washed with water, dried, and recrystallized from hexane.

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