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SYNTHESIS, MOLECULAR PROPERTIES PREDICTION AND BIOLOGICAL ACTIVITY OF 2-PHENYLINDOLIZIN ACETAMIDE DERIVATIVES

Balusu Phani Kumar[1], V. S. R. Prasad[1] and A. Jaya Shree*[2]

[1]Mylan Labs Limited, Hyderabad, Telangana, India.
[2]Centre for Chemical Sciences and Technology, JNTUH, Hyderabad, Telangana, India, 500085.

***Author for Correspondence: A. Jaya Shree**
Centre for Chemical Sciences and Technology, JNTUH, Hyderabad, Telangana, India, 500085.

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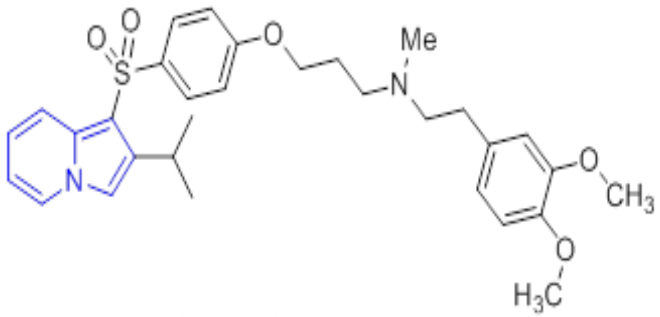
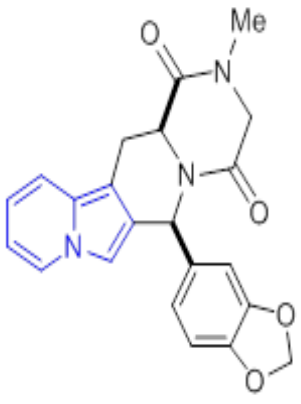
ABSTRACT
The discovery of camptothecin and its analogs was the major breakthrough through which 'Indolizine moiety' came into limelight. A novel compounds, 2-Phenylindolizin acetamide derivatives (8a-8k) has beensynthesized by the reaction of 2-oxo-2-(2-phenylindolizin-3-yl)acetyl chloride(6) with different aromatic compounds (7a-7h) in presence of triethyl amine in DCM.The synthesis and screened for their Antimicrobial activities of novel class of 2-Phenylindolizin acetamide scaffolds are described by variation in therapeutic effects of parent molecule. Result revealed, the target compounds 8a, 8band8f exhibited a remarkable increase of antimicrobialactivity than CPF against in three medically relevant organismslike *staphylococcus aureus, escherichia coli, pseudomonas aeruginosa* is observed. Further,8d and 8ashowed better activity against antifungal starins *candida albicans, aspergillus flavus* and *aspergillus fumigates*. In present investigation, the target compounds 8a-8h were subjected to insilico molecular properties prediction and drug likeness by employing Molinspiration (Molinspiration, 2014) and Mol-Soft (MolSoft, 2007) property explorer toolkits for predicting their high oral bioavailability.

KEYWORDS: Indolizines, Antimicrobial activity, Molinspiration, Molsoft.

INTRODUCTION
Premeditated introduction of functional substituents at variouspositions of core chemical skeletons at will is veryimportant in medicinal chemistry with respect to drugdiscovery. For instance, as illustrated in Figure 1, someindolizines were reported to exhibit different biologicalactivities with therapeutic likely depending on thereplacement patterns of the core structure.[1] Therefore,development of new synthetic methods to install diversefunctional groups at suitable positions around an indolizine[2] core should further extend versatility of this scaffold in manydifferent medicinal areas.Indolizines are aromatic organic compounds containing condensed five and six-membered ringswith bridging nitrogen (isomer of indole).[3] Heterocycles, possessing indolizine core have also foundnumerous biological and pharmacological activities, such as anti-inflammatory,[4,5] antiviral,[6] aromatase inhibitory,[7] analgestic,[8] antitumor activities.[9,10]



L-type calcium channel blocker



PDE5A inhibitor

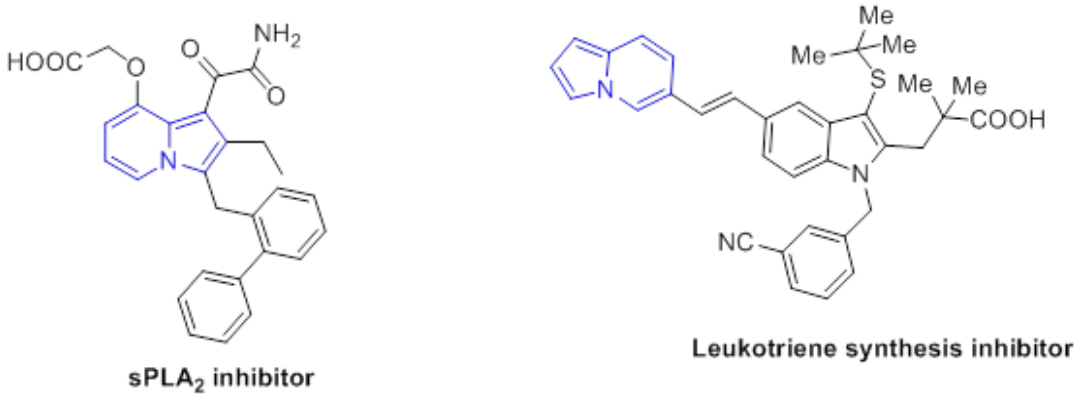


Figure 1: A number of indolizines were described to exhibit altered biological activities.

Bestevaluations on indolizines define the interaction and mixture of indolizine byproducts. In a currentevaluation bySingh and Mmatli, novelistsabsorbedmostly on the growth in combination, and a limitednatural activities of indolizinederivatives from 2000 to 2010 were stated.[11] In a newevaluation by Vemula et al,[12] insufficientaccomplishments of indolizine derivatives were conversed. Though, these appraisalsrequired a thorough biologicalactivity study of indolizine derivatives. As the significance of indolozine nucleus and the deficiency of any importantcriticism on its biological activities, this criticismhighpoints the biological activity of characteristic indolizine derivatives, keynatural observations of the primary studies, mechanism of action, and current and forthcomingprojectionscorrelated to indolizine derivatives.As part of our research interest on nitrogen-fused bicycles, we have recently reported mild and simplistic syntheses ofindolizines and indolizinones, retaining a strategy where initiationof alkene permits for consequent intermolecular ring closure by nucleophilic attack on 2nd position of indolizine ring is a highly efficient manner.

Synthesized and observedrecentlymanufactured indolizine byproducts for their antimicrobial inactivitybeside thirteen bacterial and three fungous strains.[13] Compound I exhibited twofold antibacterial and antifungalactivity with MIC values in the series of 500–1,000 µg/ml against fungalstrains *A.niger*, *C.albicans*, and *C.tropicalis*, while for bacterial strains MIC values were in the range of32–500 µg/ml (Figure 2). According to the revision, the authors concluded that the phenyl moiety in compound II might be responsiblefor its antimicrobial properties against a gram-negative bacterium (*escherichia coli*), a gram-positive bacterium (*staphylococcus aures*), while their antifungal potential was assessed against *candida albicans* and *aspergillus flavus.*[14] (Figure 2).Acceptable to discoverthe antimycobacterial prospective of indolizine,[15] produced and confirmed 1-substituted indolizinederivatives for their motionbeside Mycobacteriumtuberculosis $H_{37}Rv$. Interestingly, the novelists claimed compound III as the first antimycobacterial indolizine withMIC value matched to 6.25 µg/ml.Among the synthesized compounds,compoundIVexposedmajor activity (MIC:16 µg/ml) besidemycobacterium tuberculosis.[16] (Figure 2)

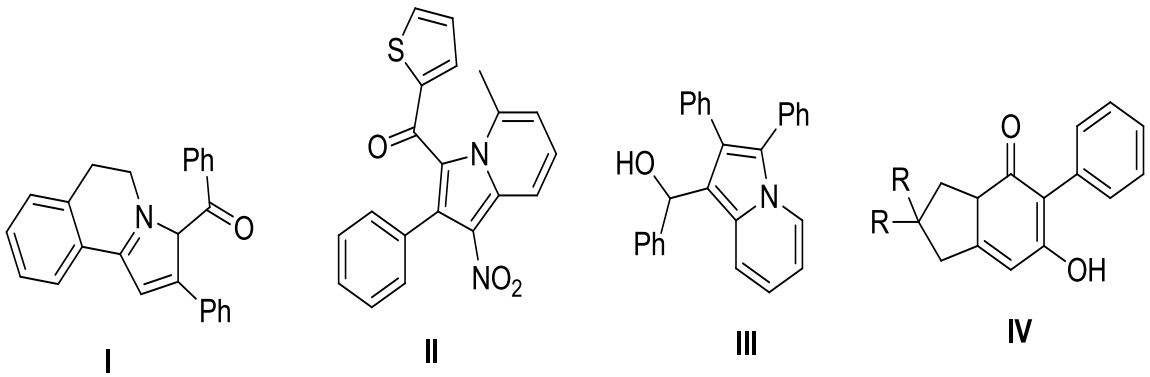
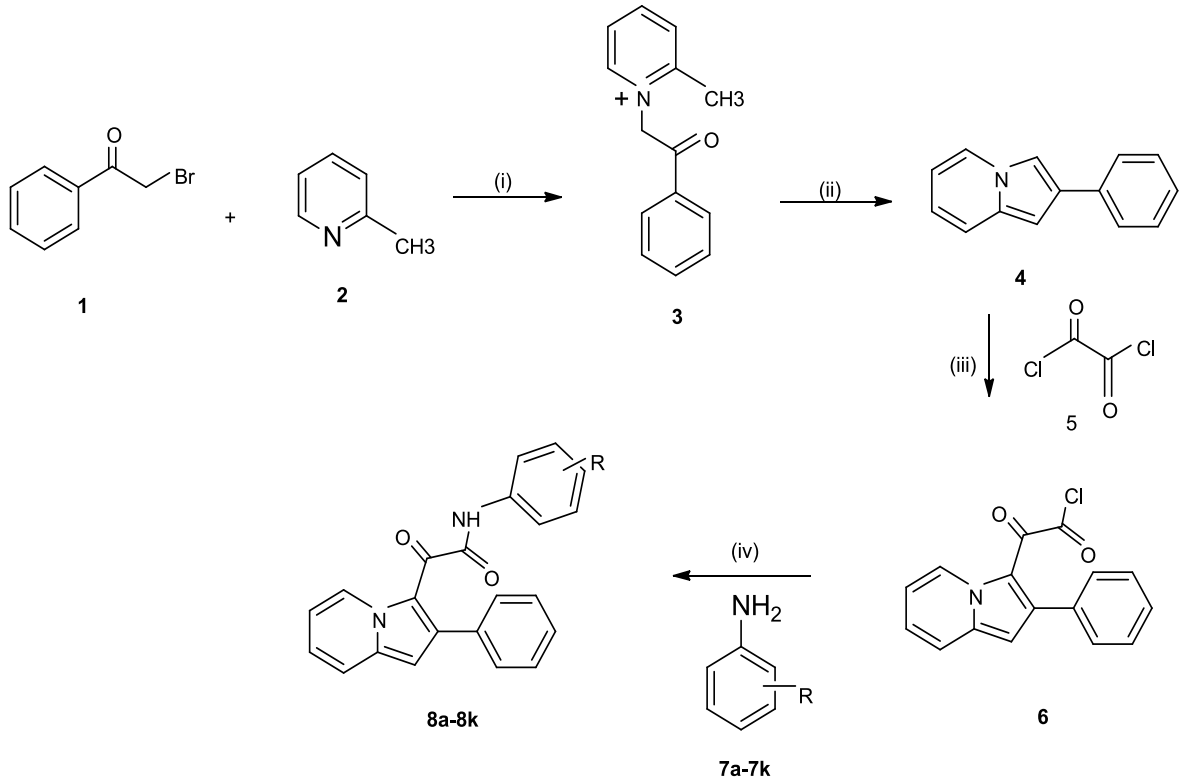


Figure 2: Compounds against mycobacterium tuberculosis (I-IV)

Tuberculosis (TB) is an infectious disease produced by *mycobacterium tuberculosis* (MTB), which affects the lungs and other organs of the body. Due to emergence of multidrug-resistant strains of *mycobacterium tuberculosis* underscores the need of constant developments on new, efficient, novel antimicrobial molecules against multi-drug resistance TB. Tuberculosis (TB) is an aerial contagious disease

produced by species found in Mycobacterium tuberculosis complex that includes M. tuberculosis (Mtb). The number of cases of MDR-TB have been increased in 27 high burden countries in 2011 and 20% of previously treated cases were estimated to have MDR-TB.[17] About 9 million new cases are estimated each year with almost two million death tolls.[18,19] Thus, tuberculosis becomes a significant threat to global health. So, the novel therapeutics are necessary to treat both drug susceptible TB and progressively common drug resistant strains since, no new chemical entities are emerged in the past 4 decades for the treatment of TB.[20-21]

In spite ofpresencemainpharmaceutical moiety, a completeanalysis on the biologically active possible of indolizine derived is absent. To the superlative of our awareness, forgoingperiodicals on indolizine byproductsprimarily focused on their sympathyalsoproduction. The existingworkdiscourses the valuable nature of indolizine derivatives and their probableappliance of action. Important SAR points are discussed with each study to high spot the justification behind the study. Furthermore, the currentstudy also deliversdata about modern/comingforecasts of the topic and different indolizine byproducts in scientifictribunals and synthesized various 2-Phenylindolizin acetamide derivatives carried out the antimicrobial activity of newly synthesized targets8a-8h (Scheme 1).



Scheme 1: Synthesis of 2-phenylindolizin acetamide derivatives(8a-8k)

Reagent and Conditions: (i) MeOH, Reflux, 2 hr(ii) aq $NaHCO_3$,Reflux, 3 hr (iii) Toluene, THF, 4 hr (iv) DCM, Et_3N, 6 hr, 25°C, yield 28-83%.

Experimental section

Research laboratory chemicals remainedproviding by Rankem India Ltd. and Ficher Scientific Ltd. Melting points were determined by the open tube capillary technique and are not right. The purity of the compounds was determined by thin layer chromatography (TLC) plates (silica gel G) in the solvent system Ethyl acetate–Hexane (6:4). The spots were observed by contact to iodine vapours or by UV light or P-anisaldehyde Stain Solution. The IR spectra were established by perkineElmer 1720 FT-IR spectrometer (KBr pellets). The ^{1}H NMR &^{13}C NMR spectra weregot by Bruker Advance II 300 spectrometer using TMS because the internal standard in $CDCl_3$. Commercial chemicals were distilled from CaH_2 and degassed (freeze and thaw) three times prior to use; THF, Ethylacetate, hexanes distilled from Na/benzophenone.

General procedure for synthesis of target compounds (8a-8k)

2-(2-methylpyridin-1(2H)-yl)-1-phenylethanone (3): To a solution of 2-bromo-1-phenylethanone1(3.0g, 0.241 mol), 2-methylpyridine2(0.8g, 0.150 mol) soluble in MeOH reflux for 2 hr to give the desired product 3. The compound 3 was added $NaHCO_3$ reflux for 3 hr to give desired product 4. 2-phenylindolizine (4)was treated with oxalyl dichloride 5 in the presence Toluene, Tetra hydrofuran at room temperature for 4 hrto obtained the

complex2-oxo-2-(2-phenylindolizin-3-yl)acetyl chloride (6). The reaction intermediate 6 was condensation with aromatic amines (7a-7k) inmethylene dichloride (8ml) was cooled to 0 ˚C and was added Et_3N (2.3ml, 0.290mol) and stirred for6 hr. Reaction completion was observed by TLC. Water was added to the reaction mixture and separated the organic layer (2X 300ml). The combined organic layer was washed with brine solution and was dried over anhydrous Na_2SO_4. Organic layer was concentrated under reduced pressure to give target compounds (8a-8k). The crude material was purified by column chromatography, yield 50.0 g, 93 %.

Methyl-3-(2-oxo-2-(2-phenylindolizin-3-yl)acetamido)benzoate(8a)
Physical state: Solid, Color: Yellowish green, Melting point: Not recorded, HPLC conditions.
Column: Zorbax SB C-18 (4.6 x 250) mm, l *max:* 210 nm, *Mobile phase:* A: 0.01 M NaH_2PO_4 B: Acetonitrile (30:70), *Flow rate:* 1.0 mL/min, *Retention time:* 5.24 min, *Purity:* 97.8%

To an ice-cold solution of 2-oxo-2-(2-phenylindolizin-3-yl)acetyl chloride (6) (0.5g, 1.76mmol),and methyl 3-aminobenzoate (0.3g, 1.93mmol),in Methylene dichloride (10ml) was added triethylamine (1ml, 7.03mmol). The reaction mixture was agitated at rt for 2 hr. The solvent was impassivebelow vacuum to give the crude compound. The crude compound attained was purified by silica gel column chromatographyspending ethyl acetate–hexane (1:4) as eluent to yield (8a)*TLC system:* Ethyl acetate–Hexane (1:1)$R_f$value: 0.55, Yield: 0.4g (57.1%), Nature of the compound: Yellowish green solid

Methyl-3-(2-oxo-2-(2-phenylindolizin-3-yl)acetamido)benzoate (8a)
IR (KBR): 3450cm^{-1}, 3259cm^{-1}, 3084cm^{-1}, 1718cm^{-1}, (C=O) 1681cm^{-1}, 1658 cm^{-1}, (C=C)1596 cm^{-1}, 1572cm^{-1}, 1452cm^{-1}, 1422cm^{-1}, 1336cm^{-1}, 1287cm^{-1}, 1243cm^{-1} 1172.51cm^{-1}. ^{1}H-NMR, $CDCl_3$) δ_{ppm}9.77 (d, *J*=7.5, 1H, Ar-H), 8.25 (s, 1H, N-H), 7.75 (m, 2H, Ar-H), 7.61 (dd, *J*=7.0, 1H, Ar-H), 7.52-7.41(m, 3H, Ar-H), 7.22-7.33 (m, 5H, Ar-H),7.0 (t, *J*=8.0, 1H, Ar-H), 6.65 (1H, s, Ar-H), 3.91 (3H, s, OCH_3);^{13}C-NMR δ 165.94, 157.44, 153.21, 145.21, 138.24, 132.68, 130.63, 129.92, 129.85, 123.85, 121.58, 120.77, 117.28, 114.12, 100.83, 55.19.LC-MS (m/z): 398 (M^+), 399.2 (M+H).

Butyl-4-(2-oxo-2-(2-phenylindolizin-3-yl)acetamido)benzoate(8b)
Physical state: Solid, Color: Yellow, Melting point: Not recorded, HPLC conditions: *Column:* Kromasil 100 C-18 (4.6 x 250) mm, λ *max:* 265 nm, *Mobile phase:* 0.01 M NaH2PO4 (pH: 3.0): Acetonitrile (20:80), Flow rate*:* 1.0 ml/min, Retention time*:* 7.63min, *Purity:* 94.2%

To an ice-cold solution of 2-oxo-2-(2-phenylindolizin-3-yl)acetyl chloride (6) (0.3g, 1.05 mmol),and n-butyl-4-aminobenzoate (0.22g, 1.16 mmol),in DCM (5mL) was added triethylamine (3 mL, 2.11 mmol),. The reaction mixture was stirred at rt for 1 h. The solvent was evaporated in vacuum to give the crude compound.The crude compound obtained was purified by silica gel column chromatography using ethyl acetate–hexane (1: 4) as eluent to yield (8b) *TLC system:* Ethyl acetate–Hexane (1:1) $R_f$value: 0.63, *Yield:* 0.25 g (62.5%), *Nature of the compound:* Yellow solid, HPLC Purity: (94.2%) Please refer to the attached chromatogram.

IR (KBR): 3476cm^{-1}, 3249cm^{-1}, 3185 cm^{-1}, 3109cm^{-1}, 2958cm^{-1}, 1705cm^{-1}, 1688cm^{-1}, (C=O) 1601 cm^{-1}, 1571cm^{-1}, (C=C) 1540cm^{-1}, 1455cm^{-1}, 1423cm^{-1}, 1314cm^{-1}, 1280cm^{-1}, 1175.4cm^{-1}. ^{1}H-NMR, $CDCl_3$) δ_{ppm}9.67 (d, *J*=7.5, 1H, Ar-H), 8.23 (s, 1H, N-H), 7.94 (dd, *J*=7.6, 2H, Ar-H), 7.84 (dd, *J*=7.6, 1H, Ar-H), 7.60 (dd, *J*=8.0, 1H, Ar-H), 7.42 (m, 2H, Ar-H), 7.22-7.35 (m, 5H, Ar-H), 7.01 (t, *J*=7.5, 1H, Ar-H), 6.52 (1H, s, Ar-H), 4.32 (2H, s, OCH_2), 1.72 (2H, p, CH_2), 1.45 (2H, *J*=7.5, q, CH_2), 1.10 (3H, *J*=7.0, t, CH_3); ^{13}C-NMR δ 164.21, 158.12, 152.20, 144.45, 139.78, 130.60, 132.12, 130.78, 128.45, 122.78, 120.60, 118.45, 113.78, 102.78, 54.12.LC-MS (m/z): 440 (M^+), 441.2 (M+H).

N-(2,4-dimethoxyphenyl)-2-oxo-2-(2-phenylindolizin-3-yl)acetamide (8c)

Physical state: Solid, Color: Yellow, Melting point: Not recorded, HPLC conditions: Column: Zorbax SB C-18 (4.6 x 250)mm l max: 210 nm, Mobile phase: 0.01 M NaH_2PO_4: Acetonitrile (30:70), Flow rate: 1.0 ml/min, Retention time: 6.46 min, Purity: 99.6%

To an ice-cold solution of 2-oxo-2-(2-phenylindolizin-3-yl)acetyl chloride (6) (0.3g, 1.05mmol),and 2,4-dimethoxyaniline (0.18g, 1.16mmol),in Methylene dichloride (10 mL) was added triethylamine (0.6mL, 4.24mmol),. The reaction mixture was stirred at rt for 2 h. The solvent was evaporated under vacuum to give the crude compound. The crude compound was purified by silica gel column chromatography using ethyl acetate–hexane (3: 22) as eluent to yield (8c) *TLC system:* Ethyl acetate–Hexane (3:7) $R_f$value: 0.42, *Yield:* 0.35g (82.7%), *Nature of the compound:* Yellow solid, HPLC Purity: (99.6%) Please refer to the attached chromatogram.

IR (KBR): 3389cm^{-1}, 3061cm^{-1}, 2999cm^{-1}, 2931cm^{-1}, 2835cm^{-1}, 1682cm^{-1}, 1603cm^{-1}, (C=O) 1587 cm^{-1}, (C=C) 1529cm^{-1}, 1495cm^{-1}, 1454cm^{-1}, 1411cm^{-1}, 1341cm^{-1}, 1158cm^{-1}. ^{1}H-NMR, 400 MHz, $CDCl_3$) δ_{ppm}9.82 (d, *J*=7.5, 1H, Ar-H), 8.61 (s, 1H, N-H), 7.52-7.62 (m, 2H, Ar-H), 7.42-7.47 (m, 2H, Ar-H), 7.54 (m, 5H, Ar-H), 7.98 (t, *J*=7.5, 1H, Ar-H), 6.64 (1H, s, Ar-H), 6.46 (d, *J*=8.0, 1H, Ar-H), 6.32 (dd, *J*=7.5, 1H, Ar-H), 3.72 (3H, s, OCH_3), 3.84 (3H, s, OCH_3); ^{13}C-NMR(75 MHz, $CDCl_3$) δ_{ppm} 162.78, 159.47, 151.72, 145.12, 140.78, 135.62, 131.22, 130.80, 128.40, 123.80, 121.58, 118.40, 115.80, 103.80, 59.85.LC-MS (m/z): 400 (M^+), 401.2 $(M+H)^+$.

2-oxo-2-(2-phenylindolizin-3-yl)-N-(pyridin-3-yl)acetamide(8d0029

Physical state: Solid, Color: Green, Melting point: Not recorded, HPLC conditions,*Column:* Kromasil 100 C-18 (4.6 x 250)mm, l *max:* 235 nm, *Mobile phase:* 0.01 M NaH_2PO_4 (pH: 3.0): Acetonitrile (30:70), Flow rate: 1.0 ml/min, Retention time*:* 4.9 min, *Purity:* 98.4%.

To an ice-cold solution of 2-oxo-2-(2-phenylindolizin-3-yl)acetyl chloride (6) (1g, 3.52mmol),and 3-aminopyridine (0.32g, 3.39mmol),in Methylene dichloride (15ml) was added triethylamine (1.0ml, 7.17mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated under vacuum to give the crude compound *2-oxo-2-(2-phenylindolizin-3-yl)-N-(pyridin-3-yl)acetamide*(8d). The crude compound obtained was purified by silica gel column chromatography using ethyl acetate-hexane (1: 4) as eluent to yield (8d). TLC system: Ethyl acetate–Hexane (1:1) Rf value: 0.43, Nature of the compound: Green solid Yield: 0.180g (15%). (98.4%) Please refer to the attached chromatogram.

IR (KBR): 3173cm^{-1}, 3028cm^{-1}, 1685cm^{-1}, 1583cm^{-1} (C=O), 1529cm^{-1}, (C=C) 1413cm^{-1}, 1343 cm^{-1}, 1301cm^{-1}, 1242cm^{-1}. ^{1}H-NMR(300 MHz, $CDCl_3$) δ_{ppm}9.80 (d, *J*=7.5, 1H, Ar-H), 8.82 (s, 1H, N-H), 8.41 (dd, *J*=7.5, 1H, Ar-H), 8.26 (dd, *J*=7.0, 2H, Ar-H), 7.82 (t, *J*=8.0, 1H, Ar-H), 7.56 (m, 3H, Ar-H), 7.42 (m, 2H, Ar-H), 7.30 (t, *J*=8.0, 1H, Ar-H), 7.22 (m, 2H, Ar-H), 7.14 (t, *J*=7.8, 1H, Ar-H), 7.02 (m, 2H, Ar-H), 6.62 (s, 1H, Ar-H).^{13}C-NMR (75 MHz, $CDCl_3$) δ_{ppm}167.94, 159.44, 153.21, 149.42, 146.98, 136.38, 136.03, 135.83, 134.11, 132.68, 130.63, 129.92, 129.85, 123.85, 121.58, 120.77, 114.12, 113.83, 50.78.LC-MS (m/z): 341 (M^+), 342 (M+H).

2-oxo-2-(2-phenylindolizin-3-yl)-N-(pyridin-4-yl)acetamide (8e)

Physical state: Solid, Color: Yellow, *Column:* Kromasil 100 C-18 (4.6 x 250) mm, l *max:* 235 nm, *Mobile phase:* 0.01 M NaH2PO4 (pH: 3.0): Acetonitrile (50:50), *Flow rate:* 1.0 ml/min, *Retention time:* 5.6 min, *Purity:* 99.8%

To an ice-cold solution of 2-oxo-2-(2-phenylindolizin-3-yl)acetyl chloride (6) (0.5g, 1.76mmol),and 4-aminopyridine (0.18g, 1.93 mmol),in dichloromethane (6ml) was added triethylamine (0.5ml, 3.52mmol). The reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated under vacuum to give the crude compound *2-oxo-2-(2-phenylindolizin-3-yl)-N-(pyridin-4-yl)acetamide*(8e). The crude compound obtained was purified by silica gel column chromatography using methanol–chloroform as eluent to yield (8e). TLC system: Methanol–Chloroform (1:9) $R_f$value: 0.57, Nature of the compound: Yellow solid Yield: 0.450g (75%). (99.8%) Please refer to the attached chromatogram.

IR (KBR): 3478cm^{-1}, 3031cm^{-1}, 1673cm^{-1}, 1591cm^{-1} (C=O), 1554cm^{-1}, (C=C) 1486cm^{-1}, 1451 cm^{-1}, 1418cm^{-1}, 1337cm^{-1}, 1305cm^{-1}, 1242cm^{-1}. (^{1}H-NMR, $CDCl_3$) δ_{ppm}9.78 (d, *J*=7.5, 1H, Ar-H), 8.31-8.40 (m, 3H, N-H, Ar-H), 7.58-7.70 (m, 2H, Ar-H), 7.42 (m, 2H, Ar-H), 7.24-7.36 (m, 5H, Ar-H), 7.16(t, *J*=7.6, 1H, Ar-H), 7.02 (t, *J*=8.0, 1H, Ar-H), ^{13}C-NMR δ 167.94, 159.42, 153.20, 149.40, 145.78, 135.42, 136.25, 134.24, 132.89, 130.34, 129.24, 127.26, 123.80, 121.60, 120.70, 114.22, 113.45, 51.28. LC-MS (m/z): 341 (M^+), 342 (M+H).

N-(6-methoxypyridin-3-yl)-2-oxo-2-(2-phenylindolizin-3-yl)acetamide (8f)
Physical state: Solid, Color: Yellow, *Column:* Zorbax SB C-18 (4.6 x 250) mm, l *max:* 210 nm
Mobile phase: H2O: Acetonitrile (40:60), *Flow rate:* 1.0 ml/min, *Retention time:* 5.8min, *Purity:* 99.1%

To an ice-cold solution of 2-oxo-2-(2-phenylindolizin-3-yl)acetylchloride (6) (0.5g, 1.76mmol), and 5-amino-2-methoxypyridine (0.2g, 1.61mmol), in Methylene dichloride (10 mL) was added triethylamine (0.5mL, 3.58mmol). The reaction mixture was stirred at rt for 1 h. The solvent was evaporated under vacuum to give the crude compound *N-(6-methoxypyridin-3-yl)-2-oxo-2-(2-phenylindolizin-3-yl)acetamide*(8f). The crude compound obtained was purified by silica gel column chromatography using ethyl acetate –hexane (3: 7) as eluent to yield (8f). *TLC system:* Ethyl acetate–Hexane (1:1) *Rf* value: 0.46, *Nature of the compound:* Yellow solid *Yield:* 0.150g (22.93%). (99.1%) Please refer to the attached chromatogram.

IR (KBR): 3262cm^{-1}, 3117cm^{-1}, 3087cm^{-1}, 2944cm^{-1}, 1649cm^{-1}, 1588cm^{-1} (C=O), 1550cm^{-1}, (C=C) 1488cm^{-1},1416cm^{-1}, 1383cm^{-1}, 1335cm^{-1}, 1304cm^{-1}, 1269cm^{-1}, 1240cm^{-1}. (^{1}H-NMR, $CDCl_3$) δ_{ppm}9.68 (d, *J*=7.6, 1H, Ar-H), 8.14 (s, 1H, N-H), 7.94 (d, *J*=7.6, 1H, Ar-H), 7.61 (dd, *J*=7.6, 1H, Ar-H), 7.40-7.51 (m, 3H, Ar-H), 7.26-7.32 (m, 4H, Ar-H), 7.01 (t, *J*=8.0,1H, Ar-H), 6.61 (m, 2H, Ar-H), 3.82 (s, 3H, OCH_3).; LC-MS (m/z): 371 (M^+), 372 (M+H).

methyl 5-(2-oxo-2-(2-phenylindolizin-3-yl)acetamido) thiophene-3-carboxylate (8g)
Physical state: Solid, Color: Yellow, *Column:* Zorbax SB C-18 (4.6 x 250) mm, l *max:* 220 nm
Mobile phase: H2O: Acetonitrile (30:70), *Flow rate:* 1.0 ml/min, *Retention time:* 4.97 min
Purity: 96.2%

To an ice-cold solution of 2-oxo-2-(2-phenylindolizin-3-yl)acetyl chloride (6) (0.5g, 1.76mmol) and 5-Aminothiophene-3-carboxylic acid methylester(0.3g, 1.9mmol) in DCM (10ml) was added triethylamine (1ml, 7.03mmol). The reaction mixture was stirred at rt for 2 h. The solvent was evaporated under vacuum to give the crude compound *methyl 5-(2-oxo-2-(2-phenylindolizin-3-yl)acetamido)thiophene-3-carboxylate* (8g). The crude compound obtained was purified by silica gel column

chromatography using ethyl acetate–hexane (1: 3) as eluent to yield (8g). *TLC system:* Ethyl acetate–Hexane (1:1) *Rf* value: 0.51, *Nature of the compound:* Yellow solid *Yield:* 0.20g (28.16%). (96.2%) Please refer to the attached chromatogram.

IR (KBR): 3290cm^{-1}, 3100cm^{-1}, 3026cm^{-1}, 2926cm^{-1}, 1710cm^{-1}, 1671cm^{-1}, 1628cm^{-1}, 1598cm^{-1} (C=O), 1556cm^{-1},1511cm^{-1}, (C=C) 1416cm^{-1}, 1343cm^{-1}, 1311cm^{-1}, 1247cm^{-1}, 1235cm^{-1}. (^{1}H-NMR, $CDCl_3$) δ_{ppm}9.78 (d, *J*=7.5,1H, Ar-H), 9.01 (s, 1H, N-H), 7.64 (m, 2H, Ar-H), 7.41-7.52 (m, 2H, Ar-H), 7.30-7.41 (m, 2H, Ar-H), 7.02(m,2H, Ar-H), 6.84(s, 1H, Ar-H), 3.82 (s, 3H, OCH_3).; LC-MS (m/z): 404 (M^+), 405 (M+H).

2-oxo-2-(2-phenylindolizin-3-yl)-N-(3,4,5-trimethoxyphenyl)acetamide (8h)

Physical state: Solid, Color: Yellow, Melting point: Not recorded, HPLC conditions: Column: Zorbax SB C-18 (4.6 x 250) mm l max: 210 nm, Mobile phase: 0.01 M NaH_2PO_4: Acetonitrile (30:70), Flow rate: 1.0 mL/min, Retention time: 6.46 min, Purity: 96.6%

To an ice-cold solution of 2-oxo-2-(2-phenylindolizin-3-yl)acetyl chloride (6) (0.2 g, 1.15 mmol),and 3,4,5-trimethoxyaniline (0.2 g, 1.12 mmol),in DCM (15 mL) was added triethylamine (0.5 mL, 4.20 mmol),. The reaction mixture was stirred at rt for 2 h. The solvent was evaporated under vacuum to give the crude compound *2-oxo-2-(2-phenylindolizin-3-yl)-N-(3,4,5-trimethoxyphenyl)acetamide* (8h). The crude compound was purified by silica gel column chromatography using ethyl acetate–hexane (3: 22) as eluent to yield (8h) *TLC system:* Ethyl acetate–Hexane (3:7) $R_f$value: 0.44, *Yield:* 0.35g (83.8%), *Nature of the compound:*Yellow solid, HPLC Purity: (99.5%) Please refer to the attached chromatogram.

IR (KBR): 3428cm^{-1}, 3072cm^{-1}, 2986cm^{-1}, 2924cm^{-1}, 2835cm^{-1}, 1680cm^{-1}, 1613cm^{-1}, (C=O) 1567 cm^{-1}, (C=C) 1530cm^{-1}, 1490cm^{-1}, 1452cm^{-1}, 1415cm^{-1}, 1352cm^{-1}, 1160cm^{-1}. ^{1}H-NMR, $CDCl_3$) δ_{ppm}9.81 (d, *J*=6.5, 1H, Ar-H), 8.60 (s, 1H, N-H), 7.56 (m, 2H, Ar-H), 7.40-7.48 (m, 2H, Ar-H), 7.35-7.30 (m, 5H, Ar-H), 7.22 (t, *J*=7.5, 1H, Ar-H), 6.64 (1H, s, Ar-H), 6.45 (d, *J*=8.0, 1H, Ar-H), 6.30 (dd, *J*=7.6, 1H, Ar-H), 3.70 (9H, s, OCH_3),; LC-MS (m/z): 430 (M^+), 431.1 (M+H).

Methyl-6-(2-oxo-2-(2-phenylindolizin-3-yl)acetamido)nicotinate(8i)

Physical state: Solid, Color: Light Yellow, *Column:* Kromasil 100 C-18 (4.6 x 250) mm, l *max:* 235 nm, *Mobile phase:* 0.01 M NaH_2PO_4 (pH: 3.0): Acetonitrile (50:50), *Flow rate:* 1.0 ml/min, *Retention time:* 5.9 min, *Purity:* 99.6%.

To an ice-cold solution of 2-oxo-2-(2-phenylindolizin-3-yl)acetyl chloride (6) (0.5 g, 1.86 mmol),and methyl-6-aminonicotinate (0.14 g, 1.90 mmol),in dichloromethane (10 mL) was added triethylamine (0.6 mL, 3.51 mmol). The reaction mixture was stirred at ambient temperature for 2 h. The solvent was vaporized under vacuum to give the crude compound Methyl-6-(2-oxo-2-(2-phenylindolizin-3-yl)acetamido)nicotinate (8i). The crude compound obtained was purified by silica gel column chromatography using methanol–chloroform as eluent to yield (8i). TLC system: Methanol–Chloroform (1:9) R_f value: 0.59, Nature of the compound: Light Yellow solid Yield: 0.450g (75%). (99.6%) Please refer to the attached chromatogram.

IR (KBR): 3470cm^{-1}, 3039cm^{-1}, 2984cm^{-1}, 2894cm^{-1}, 1670cm^{-1}, 1591cm^{-1} (C=O), 1550cm^{-1}, (C=C) 1482cm^{-1},1445cm^{-1}, 1415cm^{-1},1330cm^{-1}, 1289cm^{-1},; (^{1}H-NMR, $CDCl_3$) δ_{ppm}9.80 (d, *J*=8.0, 1H, Ar-H), 8.28-8.35 (m, 3H, N-H, Ar-H), 7.55-7.68 (m, 2H, Ar-H), 7.40 (m, 2H, Ar-H), 7.22-7.34 (m, 5H, Ar-H), 7.14 (t, *J*=7.5, 1H, Ar-H), 7.08 (t, *J*=7.6, 1H, Ar-H), 3.68 (3H, s, OCH_3),; LC-MS (m/z): 399 (M^+), 400 (M+H).

Ethyl-3-(2-oxo-2-(2-phenylindolizin-3-yl)acetamido)benzoate (8j)

Physical state: Solid, Color: Yellow, Melting point: Not recorded, HPLC conditions: *Column:* Kromasil 100 C-18 (4.6 x 250) mm, λ *max:* 265 nm, *Mobile phase:* 0.01 M NaH2PO4 (pH: 3.0): Acetonitrile (20:80), *Flow rate:* 1.0 ml/min, *Retention time:* 7.63 min, *Purity:* 94.2%

To an ice-cold solution of 2-oxo-2-(2-phenylindolizin-3-yl)acetyl chloride (6) (0.3g, 1.05mmol),and ethyl 3-aminobenzoate (0.20g, 1.16mmol),in DCM (5ml) was added triethylamine (3ml, 2.11mmol),. The reaction mixture was stirred at rt for 1 h. The solvent was evaporated in vacuum to give the crude compound. The crude compound obtained was purified by silica gel column chromatography using ethyl acetate–hexane (1: 4) as eluent to yield (8j) *TLC system:* Ethyl acetate–Hexane (1:1) R_f value: 0.63, Yield:0.25 g (62.5%), Nature of the compound:Yellow solid, HPLC Purity: (94.2%) Please refer to the attached chromatogram.

IR (KBR): 3476cm^{-1}, 3249cm^{-1}, 3185cm^{-1}, 3109cm^{-1}, 2958cm^{-1}, 1705cm^{-1}, 1688cm^{-1}, (C=O) 1601 cm^{-1}, 1571cm^{-1}, (C=C) 1540cm^{-1}, 1455cm^{-1}, 1423cm^{-1}, 1314cm^{-1}, 1280cm^{-1}, 1175.4cm^{-1}. ^{1}H-NMR, $CDCl_3$) δ_{ppm}9.67 (d, *J*=7.5, 1H, Ar-H), 8.23 (s, 1H, N-H), 7.94 (dd, *J*=7.6, 2H, Ar-H), 7.84 (dd, *J*=7.6, 1H, Ar-H), 7.60 (dd, *J*=8.0, 1H, Ar-H), 7.42 (m, 2H, Ar-H), 7.22-7.35 (m, 5H, Ar-H), 7.01 (t, *J*=7.5, 1H, Ar-H), 6.52 (1H, s, Ar-H), 4.32 (2H, s, OCH_2), 1.72 (2H, p, CH_2), 1.45 (2H, *J*=7.5, q, CH_2), 1.10 (3H, *J*=7.0, t, CH_3); ^{13}C-NMR δ 164.21, 158.12, 152.20, 144.45, 139.78, 130.60, 132.12, 130.78, 128.45, 122.78, 120.60, 118.45, 113.78, 102.78, 54.12.LC-MS (m/z): 412 (M^+), 413.1 (M+H).

2-oxo-2-(2-phenylindolizin-3-yl)-N-(pyridin-2-yl)acetamide (8k)

Physical state: Solid, Color: Yellow, *Column:* Kromasil 100 C-18 (4.6 x 250)mm, l *max:* 235nm, *Mobile phase:*

0.01 M NaH2PO4 (pH: 3.0): Acetonitrile (50:50), *Flow rate:* 1.0 ml/min, *Retention time:* 5.6 min, *Purity:* 99.8%

To an ice-cold solution of 2-oxo-2-(2-phenylindolizin-3-yl)acetyl chloride (6) (0.5g, 1.76mmol),and pyridin-2-amine (0.18g, 1.93mmol),in dichloromethane (6ml) was added triethylamine (0.5 ml, 3.52mmol). The reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated under vacuum to give the crude compound *2-oxo-2-(2-phenylindolizin-3-yl)-N-(pyridin-2-yl)acetamide*(8k). The crude compound obtained was purified by silica gel column chromatography using methanol–chloroform as eluent to yield (8k). TLC system: Methanol–Chloroform (1:9) R_f value: 0.57, Nature of the compound: Yellow solid Yield: 0.450g (75%). (99.8%) Please refer to the attached chromatogram.

IR (KBR): 3478cm^{-1}, 3031cm^{-1}, 1673cm^{-1}, 1591cm^{-1} (C=O), 1554cm^{-1}, (C=C) 1486cm^{-1},1451cm^{-1}, 1418cm^{-1}, 1337cm^{-1}, 1305cm^{-1}, 1242cm^{-1}. (^{1}H-NMR, $CDCl_3$) δ_{ppm}9.78 (d, *J*=7.5, 1H, Ar-H), 8.31-8.40 (m, 3H, N-H, Ar-H), 7.58-7.70 (m, 2H, Ar-H), 7.42 (m, 2H, Ar-H), 7.24-7.36 (m, 5H, Ar-H), 7.16 (t, *J*=7.6, 1H, Ar-H), 7.02 (t, *J*=8.0, 1H, Ar-H), ^{13}C-NMR δ 167.94, 159.42, 153.20, 149.40, 145.78, 135.42, 136.25, 134.24, 132.89, 130.34, 129.24, 127.26, 123.80, 121.60, 120.70, 114.22, 113.45, 51.28. LC-MS (m/z): 341 (M^+), 342 (M+H).

ANTI-MICROBIAL ACTIVITY

MEDIA AND CHEMICALS

Nutrient Broth, Nutrient agar and 5 mm width antibiotic assay were attained from Hi-Media Laboratories Limited, India. Barium chloride dehydrate GR, concentrated sulphuric acid GR, Dimethyl sulphoxideGR, Sodium chloride AR and Potassiumdichromate were found from Ranbaxy Laboratories Ltd, Chemical Division, India. The normalinfective and fungiform strains were bought from National Centre from Cell Science (NCCS), Pune, India. The infectiveinvolved two Gram helpfulinfectiveinsulates Staphylococcus aureus NCCS 2079 and Bacillus cereus NCCS 2106 and two Gram undesirableinfectiousinsulates Escherichia coli NCCS2065 and Pseudomonas aeruginosa NCCS 2200. The fungicidal organisms involved were Aspergillus nigeri NCCS 1196 (AN) and Candida albicans NCCS 3471(CA). The bacteria were fully-fledged and continued on nutrient agar (Hi-Media, Mumbai) and were subgroupafteressential.

Glass wares and Apparatus

Glass petridish, Cut-glass tubes, Beakers, Erlenmeyer bottles, Infective loop and calculatingchamber. All the glass wares were of Borosilicate grade. Numericalmicrochip technologyequilibrium (Shankar Scientific supplies, India), Yorco Horizontal Laminar air flow bench (Yorco sales Pvt. Ltd, New Delhi, India), Ausco incubator, Zone reader (Cintex industrial Corporation, India), hot air oven, autoclave and UV/Visible spectrophotometer (Shimadzu corporation, Japan).

Antibacterial activity

The antisepticaction of formedcomplexes was premeditated by the disc diffusion method beside the next pathogenic viruses. The gram-optimisticinfectiveseparated were Staphylococcus aureus NCCS 2079 (SA) and Bacillus cereus NCCS 2106 (BC). The gram negative microbialdividedwere Escherichia coli NCCS 2065 (EC) and Pseudomonas aeruginosa NCCS 2200 (PA). The completecomposites were used at the concentration of 250 µg/ml and 500 µg/ml using DMSO as a solvent. The amoxicillin 10 µg/disc and Streptomycin 30 µg/disc were used as a normal (Himedia laboratories limited, Mumbai).

Disc Diffusion Method

A interruption of Staphylococcus aureus (SA) was additional to sterilized nutrient agar at 45ºC. The combination was stirred to sterilizedPetri dishes to give a bottomlessness of 3 to 4 mm and acceptable to congeal. Supplies were observed to lessenunbrokencoat of average on the plate. Sterilized discs 5mm in width (made from Whatman Filter paper) were immersed in the resolutions of makemixtures (250µg/ml) and continue an organic control sample for evaluation. Consent the plates to standpoint for 1hour at room temperature as a period of reintubationdispersal to minimize the effects of changes in dissimilar time. Then the plates were incubated at 37ºC for 24 hours and experimental for antiseptic activity. The width of the zone of backup was restrained for each plate in which the zone of inhibition was observed. The normal zone of inhibition was designed and linked with that of standard. A similar process was accepted for revising the antibacterial activity against the additional organisms.

Antifungal activity

The antifungal movement of syntheticcomplexes were strategic by disc diffusion method beside the viruses of Aspergillus nigeri NCCS 1196 (AN) and Candida albicans NCCS 3471(CA). Mixtures were treated at the absorptions of 250 µg/ml using DMSO as a solvent. The ordinary used was Ketaconazole 50 µg/ml and Griseofulvin 50 µg/ml beside both the organisms.

Disc Diffusion Method

A interruption of Aspergills nigeri NCCS 1196 (AN) was additional to a sterilized sabouraud dextrose agar at 45ºC. The mixture was shifted to sterilizedPetri dishes and suitable to solidify. Sterilized discs 5 mm in warmth (made from Whatmann Filter paper) occupied in the resolutions of formedmixtures and resistor were sited on the artificial of agar middle with tongs and pressedunimportantly to approve even contact. Approval the plates to stand for 1 hr at room temperature as a period of reintubationdistribution to minimalize the

effects of variance at 37 ºC for 13 hr and practical for antibacterial commotion. The breadths of the zone of deputy were restrained for the plates in which the zone of reserve was noticed. The average zone of inhibition was calculated with that of normal.

A number of 2-phenylindolizin acetamidederivatives (8a-8k) were manufactured and gauged for gram confident and gram undesirable bacteria and the complex with unlike p-substituted on the phenyl group there group appraised for *invitro* antibacterial events, and this multiple QSAR revisionsoverharshstudyshowed a linear joining of the movement with electronic supply along with stereosrestrictions. Small electron-donor groups with hydrophilic belongingsrise the *invitro* activity against G+, G- microorganisms. Additional the boardmixtures8a-8k were also display good movementbeside fungal types like *C. albicans A. flavus and A.fumigatus.*

Antimicrobial evaluation of novel compounds 8a-8k

Table 2: Antimicrobial movement and antifungal action of manufacturedmixtures8(a-k)

Compounds	Zone of inhibition in mm					
	Antibacterial activity			Antifungal activity		
	S.aureus	*E.coli*	*P.aeruginosa*	*C. albicans*	*A. flavus*	*A.fumigatus*
8a	24	22	23	12	10	11
8b	23	21	22	11	9	10
8c	21	18	19	10	9	10
8d	19	17	17	11	10	11
8e	20	17	18	10	9	10
8f	22	20	21	10	9	10
8g	16	15	19	13	ND	9
8h	ND	18	ND	ND	11	8
8i	22	20	21	10	10	11
8j	21	18	19	20	10	11
8k	17	16	20	14	ND	10
Ampicillin	20	21	22	21	ND	ND
Flucanazole	ND	ND	ND	20	20	22

ND: No zone of inhibition

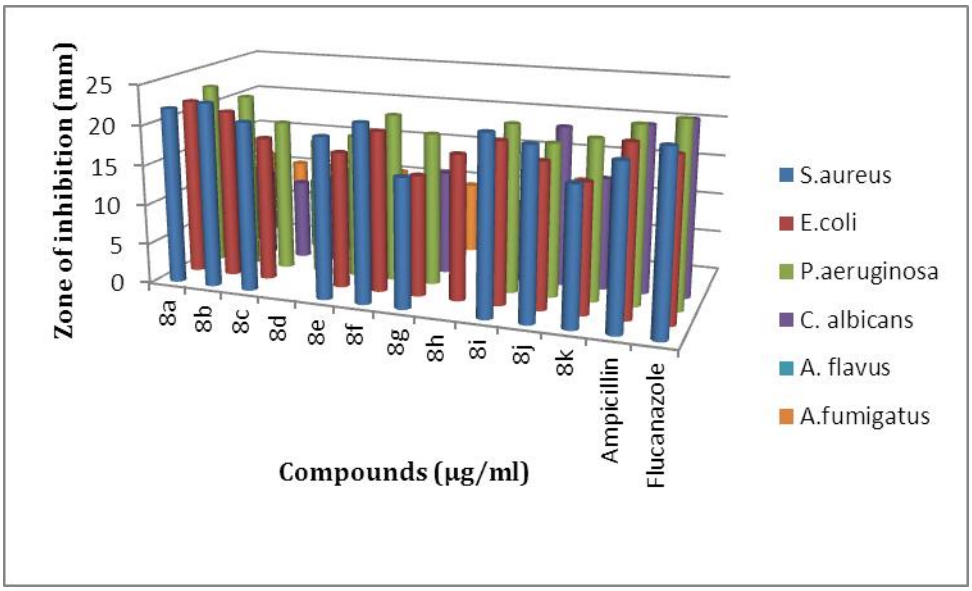


Figure 3 Antimicrobial activity and antifungal activity of target compounds 8(a-k)

ANTI-MYCOBACTERIAL[23-25]

Procedure

Mycobacterium smegmatis is considered as an appropriate model for study of Anti-tubercular activity of compounds as it shares considerable homology with *Mycobacterium tuberculosis*. Thus, the series of compounds synthesized were evaluated to ascertain their Anti Mycobacterial capacity on *M.smegmatis* (*MC*^{2} 155) strain. Primarily the activity was determined in the form of percentage inhibition following which the MIC was calculated for the compounds showing 30% or more growth inhibition. Initially, 10mm stock concentrations of the compounds were diluted with the required 100% (v/v) DMSO solution to achieve a working concentration

of 1.5 mM. The assay was performed in a 96 well format plate. 100 µL of inoculum was incubated with 2% compound (1.5 mM), making the final concentration of compound as 30 µM. The inoculum of *M. smegmatis* was maintained in Middlebrook 7H9 broth supplemented with ADS (Albumin-Dextrose-Saline). Rifampicin and Isoniazid as positive controls of inhibition of *Mycobacterium smegmatis*.

Table 3. Physicochemical Properties and tuberculosis of synthesized 2-phenylindolizin acetamide derivatives

Comp.	Mol.Formula	Mol.Wt	M.p. (˚C)	Rf	% yield	Antimycobacterial MIC (µM) *M.smegmatis*
8a	C24H18N2O4	398.41				>100
8b	C27H24N2O4	440.49				71.40
8c	C24H20N2O4	400.42				69.89
8d	C21H15N3O2	341.36				>100
8e	C21H15N3O2	341.36				>100
8f	C22H17N3O3	371.38				32.26
8g	C22H16N2O4S	404.43				60.37
8h	C25H22N2O5	430.45				[c]
8i	C23H17N3O4	399.39				>100
8j	C25H20N2O4	412.43				90.14
8k	C21H15N3O2	341.36				46.80
Ref						[a]
						[b]

[a]Rifampicin—2.43 µg/mL; [b]isoniazid—18 µg/mL, [c]Not determined

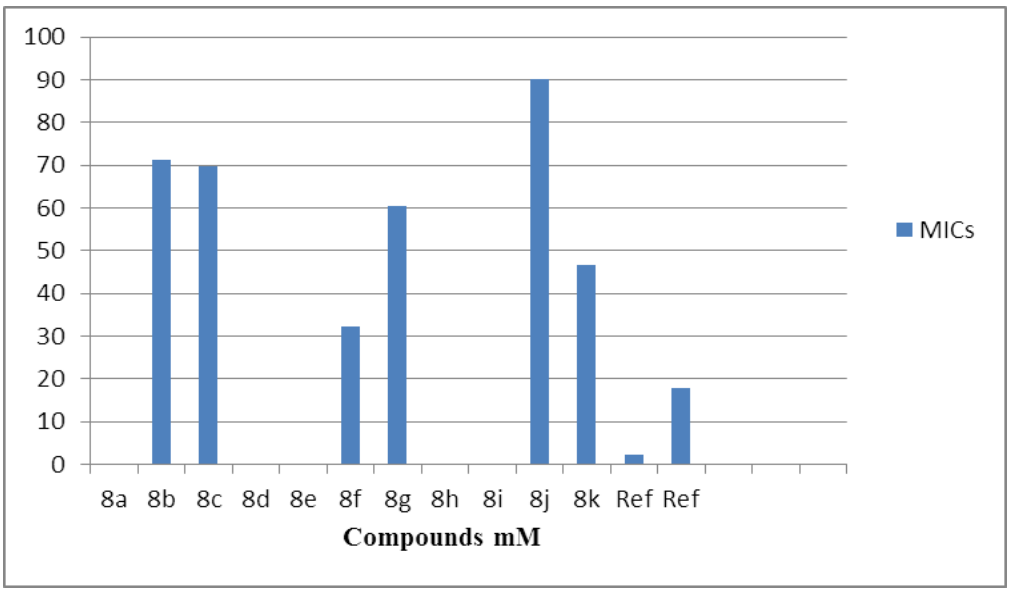


Figure 4: antitubercular activity of synthesized 2-phenylindolizin acetamide derivatives (8a-8k)

RESULTS AND DISCUSSION

Biological Activity

The consequences of organiceducations of latelymanufactured compounds (8a-8k) disclose that the mixturesownimportantanti-bacterial and anti-fungal activities. Additionally the series of compounds were tested to ascertain their antibacterial, antifungal capacity and are summarized in Table 2. From the assay it was evident that, some compounds from the series were found to be associated with promising antibacterial, anti-fungal properties. From anti-bacterial and anti-fungal activity showingoutcomes, that has been detected that mixtures8b, 8a, 8fand 8jkeepexcellent movement.In the series compounds 8b, 8a and 8fexhibited best antibacterial activity against *S.aureus*with mm values at 23, 22 and 22, respectively. Further, compound 8a, 8b showed very good antibacterial activity against *P.aeruginosa* with mm values of 23, 22 mm. Furthermore compounds 8c,8e, 8g and 8k showed moderate *invitro* anti-bacterial activity against Gram (+), Gram (-) bacteria (*S.aureus*, *E.coli*, *P.aeruginosa*). Compounds 8jand 8d in the series show excellent antifungal activity against organism's *C. albicans,A. flavus* with mm values 20, 10 and 11, 10 and 8a, 8i, 8j active against *A.fumigatus*with 11 mm respectively.

ANTI-MYCOBACTERIAL

A series of 2-phenylindolizin acetamide 8a–8k have been synthesised and screened for *invitro* antimycobacterial activity against Mycobacterium smegmatis MC-155. Additionally the series of compounds were tested to ascertain their anti-mycobacterial capacity and are

summarized in Table 1. Thus, the compounds were analysed with *M. smegmatis*. From the assay it was evident that, some compounds from the series were found to be associated with promising anti-mycobacterial properties. In the series compounds 8f and 8k exhibited best anti-mycobacterial activity with MIC values at 32.26µM and 46.80 µM, respectively. Further, compound 8g showed very good anti-mycobacterial activity with MIC values of 60.32 µM. Furthermore compounds 8b,8c, and 8j showed moderate anti-mycobacterial activity with MIC values of 71.40 µM, 69.89 µM, and 90.14 µM, respectively. Compounds 8a, 8d, 8e, and 8i in the series did not show any growth inhibition against bacteria even at highest concentration tested and we could not observe linear effect depending on concentration of the compound. Therefore we could not determine effect of the compounds for 90% growth inhibition.

CONCLUSION

The present study provides the data about present/upcomingprojections of the theme and dissimilar indolizine byproducts in clinical trials and synthesized various 2-phenylindolizin acetamide derivatives carried out the antibacterial, antitubercular activity of newly synthesized targets (8a-8k). From anti-bacterial and anti-fungal activity transmission results, it has been practical that mixtures8b, 8a, 8f and 8jpossess excellent movement. In the series compounds 8b, 8a and 8f exhibited best antibacterial activity against *S.aureus* with mm values at 23, 22 and 22, respectively. Compounds 8j and 8d in the series show excellent antifungal activity against organism's *C. albicans*,*A. flavus* with mm values 20, 10 and 11, 10 and 8a, 8i, 8j active against *A. fumigatus* with 11 mm respectively.

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