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Antimicrobial evaluation of spirooxindolopyrrolidine engrafted indoles against multidrug resistant ESKAPE clinical pathogens

Abstract: The synthesis of a new class of effective antibiotics and antimicrobial agents with less toxicity is highly desirable due to bacterial resistance to antibiotics has increased dramatically. In this context, molecules that embedding a spiro moiety are attractive from a medicinal chemistry point of view as these spiro heterocycles show a vital part in the development of delivery systems for antimicrobial therapies. In the present study, the synthesis and antimicrobial evaluation of structurally attractive complex hybrid heterocycles comprising spriooxindolopyrrolidine and indole heterocycles was attained in quantitative yields by cycloaddition strategy. The new class of spirocompouds were unequivocally assigned through spectroscopic analysis and the antimicrobial efficacy were assessed against six microbial pathogens. Among them, compound **4a,** bearing chlorine substituted derivative showed significant activity against tested ESKAPE pathogens. The maximum zone of inhibition observed against ESKAPE microbial pathogens causing infectious disease ranged from 6.50±0.25 to 18.90±1.05 mm, with MIC values ranging between 4.00 and <512.00 μg/ml.

Keywords: Multidrug resistant; ESKAPE pathogens; Spiropyrrolidines, Cycloaddition reaction

1. Introduction

One of the biggest societal and public health problems is the resistance of harmful bacteria to antibiotics, since bacteria and fungi account for 80-87% of all cases of health-related infections (HAIs) in the human population (Haque et al., 2011). The pathogenic potential of these bacteria is based on a number of virulence mechanisms, such as the enzymes, expression of adhesins, toxins and chemicals affecting the immune system, all of which are essential for annexation or intensification of infections (Waglechner et al., 2017; Palma et al., 2020). Current drug development process is not sufficient to support the complete eradication of antimicrobial infections (Reddy et al., 2019). Several pathogens are resistant to antibiotics and need to be treated with potentially detrimental drugs. As a result, drug discovery researchers and pharmaceutical companies have focused their efforts on finding new ways to target resistant microorganisms with lower toxicity profile (Sass et al., 2013). The preparation of novel small molecules with new mechanism of action to curing infectious disease is urgently needed.

In this context, oxygen and nitrogen containing heterocycles are very attractive in antimicrobial research as they present in substantial number of medicines as an active moiety (Stephen et al., 2015). Among them, heterocycles comprising spirooxindolopyrrolidine motif are crucial in the field of pharmaceutical chemistry since this motif are predominant in biologically potent natural products and synthetic compounds. These spirooxindole hybrids displayed diverse pharmaceutical properties *viz*. anticancer (Yang et al., 2016, Lotfy et al., 2017, Barakat et al., 2018), anti-bacterial (Chande et al., 2005), analgesic (Rajanarendar et al., 2013), local anesthetic (Kornet, et. al., 1976), anti-mycobacterial (Rajesh et al., 2011, Arumugam et al., 2021, Arumugam et al., 2021), and AChE inhibition activities (Arumugam et al., 2018, Kumar et al., 2018, Almansour et al., 2020). Owing to their unique structural profile such as inherent complex structure and three dimensionality natures, they exhibit high rigidity and the capability to expose functionality that provides a higher affinity to biological target. Finally, spiro core structures have the potential to improve solubility, a crucial attribute during the drug development process, by metabolic stability, modulating log P and having sp3 hybridization.

Recently, our research team designed and synthesized structurally diverse fused spirooxindolopyrrolidines employing multicomponent cycloaddition methodology (Arumugam et al., 2015, Arumugam et al., 2018, Arumugam et al., 2018) and these synthesized spiro compounds exhibited diverse biological profiles including antimicrobial

activities. It is important to note that some of the synthesized spiropyrrolidine heterocycles exhibited excellent activities. Remarkably, a few of hybrid with spiro unit showed higher activity than the standard drug (Arumugam et al., 2020, Arumugam et al., 2021). The biological precedents mentioned above has led to further study on the synthesis of hybrid heterocycles that embedding spiro-oxindolopyrroldines and indole into a single compound which would be of great importance for medicinal value, since the indole moiety has a significant biological profile, anticipating spiro-pyrroldine with the indole motif will enhanced biological activity (Alaqeel et al., 2022). The present study described a one-pot, synthesis of complex dispirooxindolopyrrolidines integrated indole hybrids via an intermolecular [3+2] cycloaddition cascade reaction methodology. These synthesized complex molecules were tested for their antibacterial properties against ESKAPE microbial pathogens

2. Materials and Methods

2.1. Synthesis of spirooxindolopyrrolidine fused indole, ***4a-d***

An equimolar ration of acrylate **3**, and L-tryptophan **2** and indoline-2,3-dione **1** (1 mmol) was dissolved in 20 ml of MeOH and then the reaction mixture was refluxed for 2 h. Completion of the reaction was observed by TLC and the solvent was reduced under low temperature. The product was washed with Et_2O to give the compound in quantitative yield.

Spirocompound **4a**: Pale yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 2.15 (t, J = 13.2 Hz, 1H), 2.85 (d, J = 13.2 Hz, 1H), 3.28 (d, J = 13.2 Hz, 1H), 3.45 (s, 3H), 3.69 (d, J = 13.2 Hz, 1H), 4.78-4.82 (m, 1H), 6.21 (s, 1H), 6.75-6.83 (m, 3H, ArH), 6.95 (t, J = 9.0 Hz, 1H), 7.03 (t, J = 9.0 Hz, 1H), 7.08 (s, 1H), 7.16-7.29 (m, 4H, ArH), 7.50 (s, 1H), 8.00 (d, J = 9.0 Hz, 1H), 10.26 (s, 1H), 10.33 (s, 1H), 10.67 (s, 1H); ^{13}C NMR δ_C: 29.3, 41.4, 51.3, 62.3, 64.4, 64.7, 75.2, 109.2, 110.6, 110.9, 113.2, 117.8, 119.6, 120.5, 121.1, 123.2, 124.7, 125.6, 127.5, 128.2, 129.1, 131.1, 136.1, 142.7, 143.3, 172.3, 177.8, 182.3; Mass: m/z = 556 (M^+); Anal. Calcd for $C_{30}H_{25}ClN_4O_5$: C, 64.69; H, 4.52; N, 10.06; Found C, 64.80; H, 4.64; N, 10.17.

Spirocompound **4b**: Pale yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 2.63-2.71 (m, 2H), 3.10 (s, 3H), 3.19 (d, J = 12.4 Hz, 1H), 4.6 (d, J = 1.4 Hz, 1H), 5.53-5.54 (m, 1H), 6.38 (m, 3H, ArH), 6.61-6.63 (m, 1H, ArH), 6.69-6.82 (m, 5H, ArH), 6.93-6.96 (m, 3H, ArH), 9.1 (s, 1H), 9.80 (s, 1H); ^{13}C NMR δ_C: 28.4, 39.6, 50.7, 61.8, 62.6, 64.4, 74.7, 108.8, 109.6, 117.0, 120.7, 123.2, 127.3, 127.8, 127.9, 128.3, 128.6, 129.3, 132.6, 139.6, 141.9, 143.4,

171.5, 177.4, 179.2, 182.2 ; Mass:*m/z* = 606 (M^+); Anal. Calcd for $C_{31}H_{25}F_3N_4O_6$: C, 61.39; H, 4.15; N, 9.24; Found: C, 61.50; H, 4.27; N, 9.37.

2.1. Antibacterial activity of compound ***4a-d***

The well diffusion method established by CLSI was used to test four (4a-d) synthetic compounds for their antibacterial activity against ESKAPE pathogens. These bacterial pathogens were grown in nutrient broth and allowed to thrive for 24 h at 37° C. Before, being kept on the MHA plates, the dissolved compounds were impregnated on a 6.00 mm blank sterile disc and dried under sterile conditions. McFarland standards (1.00 x10^8 CFU/mL) of each ESKAPE pathogen were swabbed on to MHA plates as microbial inoculum. The positive and negative control was amoxicillin (30 mcg) and DMSO, respectively. After that, an impregnated dry disc was placed on surface of the culture plates and incubated twenty four hour at 37° C. The preliminary antibiotic test was performed in triplicate.

After preliminary screening, the significant compound **4a** selected for it antibacterial activity evaluation by agar well diffusion method (Bonev et al., 2008). 0.1 ml of the respective ESKAPE pathogens were streaked onto the plates containg MHA plates. 6 mm diameter wells were made in MHA plates using a sterilized steel drill that filled with 25.00, 50.00, 75.00 and 100.00 μl of the compound (**4a**). Amoxicillin and DMSO and were used as a positive and negative controls. The diameter of inhibition zone was calculated after 24 h of incubation.

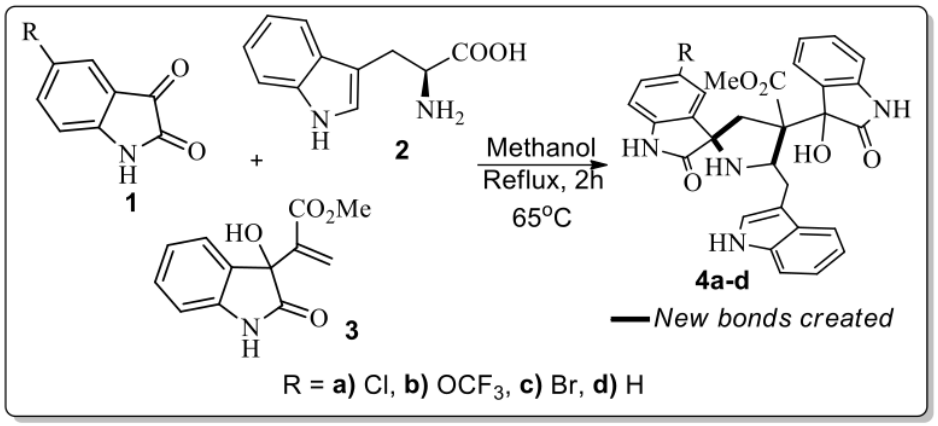
2.2. MIC determination by Broth Microdilution Assay

MIC values of compound **4a** was evaluated using broth micro dilution method (Winn et al., 2006). MIC assay evaluations were completed by three times with potential lead compound **4a**. The compound **4a** was assayed for their growth control activity against ESKAPE pathogens and amoxicillin. The compound **4a** was dissolved in DMSO for MIC assay. After 24 h of incubation at 37° C, the ESKAPE pathogens were attained from Mueller Hinton broth (MHB). The inoculum of test ESKAPE pathogens were fixed to attain the MacFarland standard (0.5) turbidity of an inoculum size was 1.0x10^8 CFU/mL for MIC assays. The MIC test was performed with MHB at pH 7 using the doubling dilution technique. Microtiter well (last well) containing only inoculation broth was earmarked as a control, and no growth of ESKAPE pathogen was stated as the MIC value in µg/mL. The compound **4a** and amoxicillin were diluted with MHB and arranged at concentrations of 2.00, 4.00, 8.00, 16.00, 32.00, 64.00, 128.00, 256.00 and 512.00 μg/mL, respectively (Abusetta et al., 2020). The experiment was repeated three times to find mean MIC value.

3. Results

3.1. synthesis of spirooxindolopyrrolidine fused indole

The Baylis-Hillman adduct (BHA) such as methyl 2-(3-hydroxy-2-oxoindolin-3-yl) acrylate **3** was synthesized from isatin and acrylate, DABCO was used as catalyst through Baylis-Hillman reaction (Mi Chung et al., 2002). With the BHA in hand and it has been utilized as dipolarophile under optimized reaction conditions, we carried out the three-component cycloaddition of **3** with ylide generated from indoline-2,3-dione **1** and L-tryptophan under reflux condition. An equimolar mixture of **1, 2** and **3** in refluxing methanol (10 mL, 60 min) afforded the spirooxindolopyrrolidine tethered indole hybrids **4** as single product in good yield (86%). The reaction was performed initially with different solvents system such as MeOH, EtOH, CH_3CN, 1,4-Dioxane, toluene and reaction furnished the cycloadduct in 86, 79, 75, 74, 46% yields respectively and found that methanol is appropriate solvent for this three-component reaction. Consequently, the entire subsequent reaction was carried out under these similar optimized conditions.

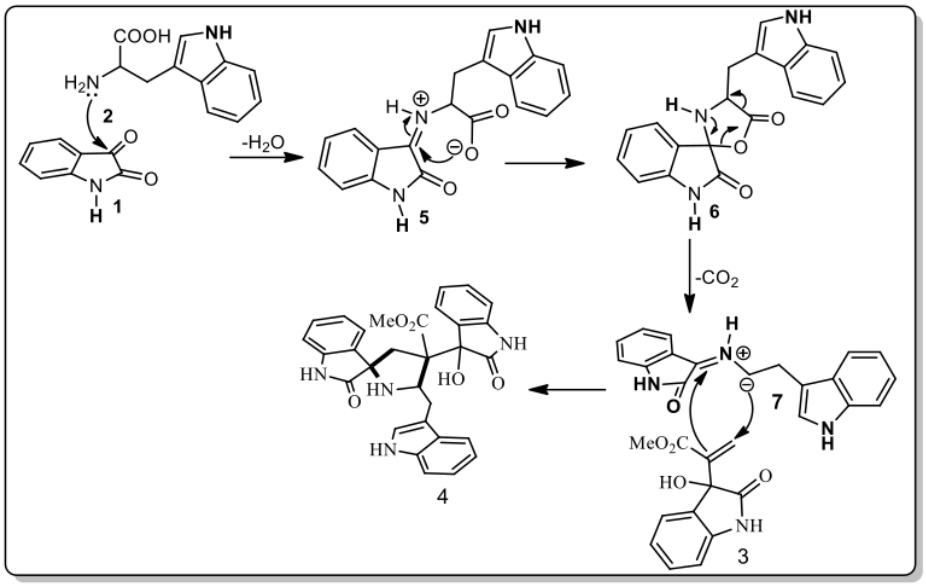


Scheme 1. Preparation spirooxindolopyrrolidine incorporated indoles, **4a-d**

The structure of mono-spirooxindolopyrrolidine integrated indole hybrids **4** was elucidated by spectroscopic analysis as illustrated for a representative compound **4a**. In the ^1H NMR spectrum of **4a**, a multiplet at δ 4.78-4.82 ppm is ascribable to H-5 hydrogen and two doublets at δ 3.28 ppm and δ 2.85 ppm were attributed to H-3 hydrogens of pyrrolidine rings. The triplet and doublet at δ 2.15 and δ 3.69 ppm were belong to indole adjacent hydrogens (H-6). A signal at δ 3.46 as singlet was assigned to ester methyl hydrogens. The aromatic

signals as multiple in the region δ 6.75 to 8.00 ppm. The signals at δ 10.27 and 10.33 ppm were assigned to oxindole NH hydrogens and a signal at δ 10.67 ppm was assignable to indole hydrogen. The carbon signal at δ 75.2 ppm due to the OH group attached oxindole quaternary carbon (C-7). The signals at δ 64.7 and 41.4 ppm were assignable to spiro carbon (C-2) and methylene carbon (C-3) respectively. The carbon signals at 62.3 and 64.4 ppm were attributed to methylene (C-5) and quaternary carbons (C-4) respectively. The methylene carbon (C-6) resonated at δ 41.4 ppm. The ester methyl carbon exhibited at δ 51.3 ppm. The two oxindole carbonyl carbons resonated at δ 177.8 and182.3 ppm, respectively and the signal at 172.3 was assignable to ester carbonyl carbon.

A rational mechanism for the construction of spirooxindolopyrrolidines tethered indole **4** is depicted in Scheme 2. Firstly, the ylide created *in situ* by the reaction of isatin **1** and L-tryptophan **2** through iminium ion **5** and **6** *via* spontaneous dehydration and decarboxylation. Subsequently, ylide **7** adds to exocyclic double bond of **3** regioselectively to form compound **4** in good yields. Other possible regioiomer could not observed even in trace due to the polarization of the dipolarophile **3** that preferentially trap with the electron-rich carbon of the **7** furnishing **4** in good yields. The cycloaddition reaction generated up to four adjoined stereocenter out of four, one is spiro carbon and two quaternary carbons via two C-C and one C-N bonds in one-pot synthetic method.



Scheme 2. The formation of spirooxindolopyrrolidine engrafted indoles

3. Discussion

3.2. Antibacterial activity

The above synthesized spirooxindolopyrrolidine integrated indole hybrids **4a-d** were assayed for their antimicrobial potency against multidrug resistant microbial pathogens such as *S. aureus*, *K. pneumoniae*, *E. faecium*, *A. baumannii*, *P. aeruginosa*, and *Enterobacter* (ESKAPE) species using agar well diffusion method. Antibiotics sensitivity profile (ASP) of tested ESKAPE pathogens outcomes were presented in Table S1 (*vide* supplementary data). The overall ASP results indicated that the maximum resistant was observed in seven antibiotics and minimum of four antibiotics against tested microbial pathogens. Among the tested ESKAPE pathogens *A. baumannii* was resistant to seven tested antibiotics whereas, *Enterobacter* sp., showed only four antibiotics. But the *E. faecium* and *K. pneumoniae* displayed maximum of five antibiotics. The two antibiotics such as ampicillin and gentamycin were showed resistant to maximum numbers tested pathogens.

Compounds **4a-d** showed efficient anti-bacterial activity against ESKAPE bacterial pathogens and amoxicillin was used as drug of standard. The results of the preliminary antimicrobial testing of the compounds **(4a-d)** are shown in Table 1. The overall, the inhibitory potency of synthesized compounds **4a-d** showed efficient antibacterial activity against ESKAPE pathogens. Amongst, compound **4a** which carrying chlorine atom on the phenyl ring showed significant inhibitory activities against tested ESKAPE pathogens (Table 2). The maximum and minimum inhibition zone was observed towards *Enterobacter* sp. (18.50±1.05 mm) and *A. baumannii* (6.50±0.25 mm), and results was compared with standard amoxicillin drug (19.75±0.50 mm).

Table 1: Antibacterial activity of spiroxoindopyrroles **4a-d** against ESKAPE pathogens by Kirby Bauer (disc diffusion) method

ESKAPE pathogens	**Compounds concentration (mg/mL)/ Zone of inhibition (mm)**				
	4a	**4b**	**4c**	**4d**	**AMC$^{\$}$**
E. faecium	14.30±0.50	13.75±0.30	11.20±0.18	9.15±0.30	17.00±0.35
S. aureus	17.85±1.00	14.60±0.35	12.45±0.70	11.00±0.15	20.50±0.75
K. pneumoniae	14.60±0.18	13.05±0.20	11.00±0.50	8.50±0.55	19.20±0.30
A. baumannii	12.55±0.08	10.75±1.10	8.10±0.40	6.50±0.25	15.00±1.25

P. aeruginosa	16.85±0.25	13.00±1.00	10.60±0.35	9.00±0.45	21.00±1.85
Enterobacter sp.	18.50±1.05	13.30±0.15	12.65±0.40	11.00±1.25	19.75±0.50

[$] - Amoxicillin (AMC)- (positive control), DMSO - negative control

Table 2: Antibacterial efficacy of spirooxindopyrrolidine **4a** against ESKAPE pathogens by agar well diffusion method

ESKAPE pathogens	**Compound 4a concentrations (μg/mL)/ Zone of inhibition (mm)**				
	25.00	**50.00**	**75.00**	**100.00**	**AMC***
E. faecium	9.25±0.25	10.15±0.05	12.00±0.15	14.70±0.45	15.00±0.15
S. aureus	6.75±0.40	7.50±0.30	14.05±0.65	17.05±0.20	17.00±0.20
K. pneumoniae	0.00	7.85±1.05	12.10±0.10	13.80±0.30	16.50±0.35
A. baumannii	0.00	6.50±0.35	11.25±0.20	12.00±0.40	14.15±0.50
P. aeruginosa	7.05±1.00	7.05±1.00	15.35±0.75	15.85±0.65	18.00±0.80
Enterobacter sp.	8.10±0.25	8.10±0.25	17.60±0.55	19.50±1.15	20.15±0.45

[*] - AMC - Amoxicillin

3.3. **MIC determination**

The lowermost concentration of the compound **4a** at which no growth of ESKAPE pathogens were detected upon manual examination after incubation at 37° C for 24 h is deliberated the MIC value (Table 3). Even if the wells were clear of turbidity, pellets formed on the bottom of the wells were considered bacterial growth. The bottom most MIC value of **4a** was observed at 16.00 μg/mL and the uppermost MIC value of >256 μg/mL were detected against *Enterobacter* sp., and *A. baumannii* respectively (Table 3).

However, the most anti-microbial agents in therapeutic usage exert their antimicrobial activities by interfering with biosynthetic pathways such as protein, DNA and RNA synthesis and also disturb the cytoplasmic membrane (O'Neill et al., 2004). In this study, compound **4a** exert its antimicrobial efficiency by disturbance cell membrane integrity (Oliva et al., 2004, Randall et al., 2013) thereby inhibiting the bacterial pathogens.

Table 3: Compound **4a** MIC values against ESKAPE pathogens.

ESKAPE pathogens	**MIC value (μg/mL)**	
	4a	**AMC**

E. faecium	32.00	5.00
S. aureus	64.00	5.00
K. pneumoniae	128.00	10.00
A. baumannii	>256.00	15.00
P. aeruginosa	64.00	10.00
Enterobacter sp.	16.00	5.00

Molecular docking and characterization

Molecular docking studies of the selective antimicrobial target protein of RNA polymerase (6VJS) involved through biological transcription mechanism were executed to extend the observation and understanding the lead (chemical compound) interaction (Dhanaraj et al., 2021). The best resolution X-RD target protein structure of Escherichia coli RNA polymerase were downloaded and verified to confirm the structural characterization of primary and secondary and tertiary features. To recognize the atomic interaction and stearic binding site on the active biomolecule's backbone and amino acid functional groups (Dhanaraj et al., 2018). The proposed ligand important biological medicinal properties can be predicted by using the docking results parameters viz. energy score, Emodel, hydrogen bonding, and G-score. The identified ligand and compound structure were optimized and minimized before it uses for the flexible glide docking. The structural ligand binding site were selected based on the existed pdb molecular properties and by literature reference active site were confirmed. The preprocessed macromolecule and optimized ligand were processed primary SP Glide docking followed by XP glide flexible docking was excecated. The G score values of the ligand protein were predicted as -7.804 with interacting energy of -37.492, glide evdw -29.702, glide ecoul -10.796, glide emodel score -44.655, XP hydrogen bonding score of -0.9. The protein active binding site amino acid molecule of PHE 1270, GLY 1271, LEU 1291, GLU 1272 were interacted with ligand by hydrogen bonding with the chemical bonding

phenomenon of electron donating and acceptance. Interaction of molecules was revealed through gscore and other docking parameters with strong hydrogen bonding interaction.

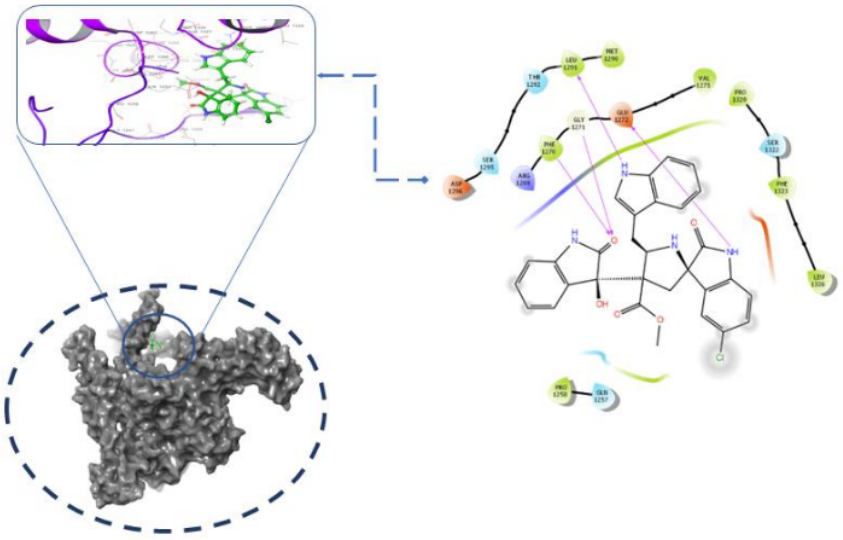


Figure 1. Molecular Binding interaction of RNA Ploymerase enzyme and ligand hydrogen bonding pose with binding site amino acids of (PHE 1270, GLY 1271, LEU 1291,GLU 1272)

Table 5. Molecular interaction Score docking parameters with unit of KJ/mol

S.No	Protein ID	Energy	glide gscore	glide evdw	glide ecoul	glide energy	glide emodel	XP HBond	Aminoacid interaction Interaction	Bonding Information
1	6VJS	-37.492	-7.804	-29.702	-10.796	-32.646	-44.655	-0.9	PHE 1270,GLY 1271,LEU 1291,GLU 1272	Hydrogen bond

4. Conclusions

A new class of dispirooxindolopyrrolidine integrated indole hybrids was obtained in good to excellent yields by the [3+2] cycloaddition cascade methodology. The rare class of non-stabilized ylide azomethine derived from L-tryptophan and isatin via decarboxylative/dehydration cycloaddition process and it is pertinent to note that the azomethine ylide are relatively meagre in literature. The synthesized

spirooxindolopyrrolidines were displayed potent antibacterial efficacy against ESKAPE bacterial pathogens. Among them compound that bearing chlorine atom on the oxindole moiety had most effective activity against ESKAPE pathogens. The maximum inhibition zone against designated infectious disease-causing ESKAPE pathogens has been determined to range from 6.50±25 to 18.90±1.05 mm, with MIC values from 4.00 to 512.00 μg/ml.

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