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Research Article

SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF NOVEL 5-ARYLIDENE-2-IMINO-3-(2- PHENYL-1,8-NAPHTHYRIDIN-3-YL)THIAZOLIDIN-4-ONES

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ABSTRACT

Objectives: Nowadays, antimicrobial resistance represents one of the most significant challenges in the medical community. To overcome the problem, it requires the discovery of newer safe and effective molecules against infectious sickness. Synthesis and screening of 1,8-naphthyridines have attracted much attention over the decades since it plays a key role against the microorganisms.

Methods: 1,8-naphthyridine based 5-arylidene derivatives of thiazolidinone (3a-i) has been achieved by the cyclization reaction of 2-chloro-*N*-(2-phenyl-1,8-naphthyridin-3-yl)acetamide (1) with potassium thiocyanate in acetone followed by its Knoevenagel condensation reaction with appropriate arylaldehydes in ethanol. All the resulting products were confirmed using spectral and physicochemical data. Antibacterial activity was performed against different bacterial strains by agar disc diffusion method using ciprofloxacin as standard.

Results: Compound 3b showed tremendous antibacterial activity among all the tested compounds.

Conclusions: This study provides several advantages such as shorter reaction times, clean product, and good yields. Most of the final products possessed moderate to excellent antibacterial activity.

Keywords: 1,8-Naphthyridine, Thiazolidin-4-one, *N*-2-chloroacetamide, Knoevenagel, Antibacterial activity.

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INTRODUCTION

Over the decades, nitrogen and sulfur-containing heterocyclic analog synthesis have been an outstanding area of research due to their profound effect on pharmaceutical applications (Fig. 1). Besides, in the pursuit of the invention of new drugs/chemical entities obtained by the assembly of various bioactive components has gained great attention in modern medicinal chemistry. Consequently, the combination of assorted motifs into one core structure may lead to possessing new modes of therapeutic efficacy [1].

Among the different classes of heterocyclic units, the 1,8-naphthyridine unit is a privileged scaffold and widely distributed in many biologically active synthetic compounds [2]. 1,8-naphthyridine and its derivatives possess valuable pharmacological applications including antibacterial [3], antidepressant [4], antitubercular [5], anticancer [6], antihypertensive [7], and antiplatelet [8] activities. Similarly, thiazolidin-4-one and its 5-arylidene derivatives are represented as an interesting class of molecules showing a broad-spectrum of medical applications such as antimicrobial [9], anti-inflammatory [10], DPPH radical scavenger [11], antifungal [12], anticancer [13], and anticonvulsant [14] activities.

Thiazolidin-4-one ring construction is well documented [15,16], but this type of cyclization is not much explored on the 1,8-naphthyridine nucleus. By considering afore-mentioned findings and continuation of our research on 1,8-naphthyridines [17], we herein report the synthesis of novel 5-arylidene-2-imino-3-(2-phenyl-1,8-naphthyridin-3-yl)thiazolidin-4-ones and its biological screening were evaluated.

MATERIALS AND METHODS

Materials

All reagents were used as purchased from commercial sources and were used without any further purification.

Methods

Synthesis of 2-imino-3-(2-phenyl-1,8-naphthyridin-3-yl)thiazolidin-4-one (2)

2-chloro-*N*-(2-phenyl-1,8-naphthyridin-3-yl)acetamide [18] (1) (3 mmol) and potassium thiocyanate (6 mmol) were dissolved in anhydrous acetone (30 mL) to give a clear solution and refluxed for 3 h till completion of the reaction (TLC monitored). After that, the solvent was evaporated and obtained solid was washed with water (50 mL), filtered and dried. The residue was subjected to flash chromatography (ethyl acetate-hexane 2:8 v/v) to get the compound 2 as white solid. Yield 72%; mp:228°C; IR (KBr, cm^{-1}): 3284 (NH), 1720 (C=O), 1685, 1616, 1544, 698; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.81–4.05 (2H, dd, *J*=55.16, 17.11 Hz, CH_2), 7.42–7.70 (7H, m), 8.30–8.41 (2H, m), 9.19 (1H, s); ^{13}CNMR (100 MHz, DMSO-d_6) δ (ppm): 33.74 (CH_2), 121.71, 122.35, 127.43, 127.85, 128.03, 129.08, 137.01, 137.26, 138.94, 154.61, 154.94, 159.67, 160.61, 170.48 (C=O); MS: $[M+1]^+$=321. Anal. Calc. for $C_{17}H_{12}N_4OS$: C, 63.73; H, 3.78; N, 17.49; O, 4.99; S, 10.01; Found: C, 63.75; H, 3.82; N, 17.51; O, 5.02; S, 10.04.

Synthesis of 5-arylidene-2-imino-3-(2-phenyl-1,8-naphthyridin-3-yl) thiazolidin-4-one derivatives (3a-i)

A mixture of compound 2 (1 mmol), substituted benzaldehyde (1 mmol), and piperidine (2–3 drops) in ethanol (20 mL) were stirred under reflux conditions for 6–8 h. After the completion of reaction (TLC monitored), cool and diluted with ice-water (30 mL). The solid was separated by filtration, air-dried and recrystallized from 96% ethanol gave the compounds 3a-h.

5-Benzylidene-2-imino-3-(2-phenyl-1,8-naphthyridin-3-yl)thiazolidin-4-one (3a)

Light brown solid; yield:82%; mp:226–228°C; IR (KBr, cm^{-1}): 3365 (NH), 1720 (C=O), 1649, 1604, 1544, 1427, 694cm^{-1}; ^{1}H NMR (300 MHz,

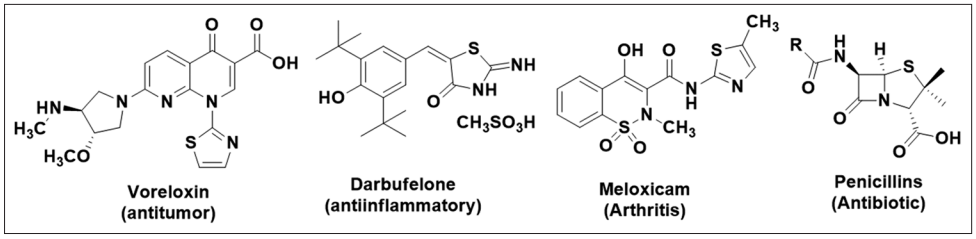


Fig. 1: Chemical structures of biologically active compounds

$CDCl_3$) δ (ppm): 7.38–7.51 (8H, m), 7.66–7.78 (3H, dd, *J*=13.89, 8.99 Hz), 7.94 (2H, s), 8.11–8.29 (2H, m), 9.07–9.09 (1H, d, *J*=4.26 Hz,); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 121.11, 121.53, 122.25, 122.35, 126.85, 128.01, 128.22, 128.45, 129.16, 129.39, 129.91, 130.18, 130.32, 132.36, 136.32, 140.68, 152.88, 153.92, 156.95, 162.80, 167.30 (C=O); MS: $[M+1]^+$= 409; Anal. Calc. for $C_{24}H_{16}N_4OS$: C, 70.57; H, 3.95; N, 13.72; O, 3.92; S, 7.85; Found: C, 70.62; H, 3.98; N, 13.75; O, 3.96; S, 7.89.

5-(4-Chlorobenzylidene)-2-imino-3-(2-phenyl-1,8-naphthyridin-3-yl) thiazolidin-4-one (3b)

Pale yellow solid; yield:79%; mp:241–243 °C; IR (KBr, cm^{-1}): 3365 (NH), 1712 (C=O), 1647, 1602, 1520, 1489, 1340, 692; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.29–7.54 (9H, m), 7.66 (1H, s, =NH), 7.76 (1H, s,–C=CH), 7.92–7.97 (2H, d, *J*=4.11 Hz), 8.17–8.23 (1H, d, *J*=7.89 Hz), 9.10–9.12 (1H, d, *J*=4.21 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):122.77 127.30, 128.93, 129.26, 129.38, 129.52, 131.44, 132.02, 134.55, 137.63, 138.40, 141.30, 151.68, 151.98, 152.54, 156.38, 167.21 (C=O); MS: $[M+1]^+$=443; Anal. Calc. for $C_{24}H_{15}N_4OSCl$: C, 65.08; H, 3.41; Cl, 8.00; N, 12.65; O, 3.61; S, 7.24; Found: C, 65.12; H, 3.45; Cl, 8.03; N, 12.70; O, 3.62; S, 7.26.

5-(2-Chlorobenzylidene)-2-imino-3-(2-phenyl-1,8-naphthyridin-3-yl) thiazolidin-4-one (3c)

Pale yellow solid; yield:77%; mp:255–257°C; IR (KBr, cm^{-1}): 3290 (NH), 1711 (C=O), 1652, 1612, 1538, 1435, 691; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 7.24–7.55 (8H, m), 7.69 (1H, s, =NH), 7.87 (1H, s,–C=CH), 8.09–8.12 (2H, d, *J*=4.10 Hz), 8.19–8.28 (2H, m), 8.77–8.79 (1H, d, *J*=4.31 Hz); ^{13}C NMR (75MHz, DMSO-d_6) δ (ppm): 121.67, 122.20, 124.94, 125.94, 127.12, 127.75, 128.25, 128.89, 129.25, 129.63, 130.06, 130.44, 132.75, 133.78, 134.97, 151.82, 152.46, 153.69, 159.38, 168.29 (C=O). MS: $[M+1]^+$=443; Anal. Calc. for $C_{24}H_{15}ClN_4OS$: C, 65.08; H, 3.41; Cl, 8.00; N, 12.65; O, 3.61; S, 7.24; Found: C, 65.11; H, 3.44; Cl, 8.02; N, 12.69; O, 3.63; S, 7.28.

2-Imino-5-(4-methoxybenzylidene)-3-(2-phenyl-1,8-naphthyridin-3-yl) thiazolidin-4-one (3d)

Pale yellow solid; yield:81%; mp:262–264°C; IR (KBr, cm^{-1}): 3309 (NH), 1718 (C=O), 1631, 1618, 1538, 1419, 692; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.78 (3H, s,–OCH_3), 7.06–7.09 (2H, m), 7.39–7.64 (8H, m), 7.75 (1H, s, –C=CH), 8.09–8.22 (3H, m), 8.76–8.79 (1H, d, *J*=4.22 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): 55.31 (OCH_3), 121.67, 122.20, 125.94, 128.25, 128.89, 129.32, 129.63, 130.06, 131.84, 132.31, 132.75, 134.97, 151.82, 152.46, 153.69, 160.76, 161.38, 167.56 (C=O); MS: $[M+1]^+$=439; Anal. Calc. for $C_{25}H_{18}N_4O_2S$: C, 68.48; H, 4.14; N, 12.78; O, 7.30; S, 7.31; found: C, 68.52; H, 4.17; N, 12.80; O, 7.33; S, 7.32.

5-(2,4-Dimethoxybenzylidene)-2-imino-3-(2-phenyl-1,8-naphthyridin-3-yl) thiazolidin-4-one (3e)

Yellow orange solid; yield:82%; mp:196–198°C; IR (KBr, cm^{-1}): 3128 (NH), 1708 (C=O), 1635, 1587, 1500, 1460, 694; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm):3.82 (d, 6H, *J*=12.04 Hz, 2–OCH_3), 6.42–6.46 (2H, m), 7.20 (1H, d, *J*=8.62 Hz), 7.40–7.49 (5H, m), 7.77 (1H, s,–C=CH), 7.94–7.97 (2H, d, *J*=3.71 Hz), 8.09–8.18 (2H, m), 9.08–9.12 (1H, d, *J*=5.64 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):55.47, 55.88 (2 –OCH_3), 98.47, 106.32, 114.32, 118.70, 124.66, 128.02, 129.22, 129.47, 129.60, 137.65, 137.95, 141.32, 152.15, 153.06, 156.25, 159.54, 162.63, 167.40 (C=O), MS: $[M+1]^+$=469; Anal. Calc. for $C_{26}H_{20}N_4O_3S$: C, 66.65; H, 4.30; N, 11.96; O, 10.24; S, 6.84; found: C, 66.68; H, 4.32; N, 12.00; O, 10.28; S, 6.87.

2-Imino-5-(4-nitrobenzylidene)-3-(2-phenyl-1,8-naphthyridin-3-yl) thiazolidin-4-one (3f)

Light yellow solid; yield:80%; mp:248–250 °C; (KBr, cm^{-1}): 3324 (NH), 1719 (C=O), 1640, 1575, 1521, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): *δ* 7.38–7.54 (9H, m), 7.64 (1H, s, =NH), 7.90 (1H, s, –C=CH), 7.96–8.12 (2H, m), 8.17–8.21 (1H, d, *J*=7.82 Hz), 9.10–9.12 (1H d, *J*=4.80 Hz); ^{13}C NMR (75 MHz, $CDCl_3$):122.75 127.32, 128.84, 129.35, 129.36, 129.43, 131.49, 132.11, 134.26, 137.69, 138.32, 141.45, 151.75, 151.94, 152.47, 156.69, 167.09 (C=O); MS: $[M+1]^+$=454; Anal. Calc. for $C_{24}H_{15}N_5O_3S$: C, 63.57; H, 3.33; N, 15.44; O, 10.58; S, 7.07; Found: C, 63.62; H, 3.36; N, 15.48; O, 10.60; S, 7.10.

2-Imino-5-(2-nitrobenzylidene)-3-(2-phenyl-1,8-naphthyridin-3-yl) thiazolidin-4-one (3g)

Pale yellow solid; yield:77%; mp:190–192°C; IR (KBr, cm^{-1}): 3299 (NH), 1713 (C=O), 1641, 1609, 1532, 1430, 695; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 7.39–7.57 (5H, m), 7.60 (1H, s, =NH), 7.66–7.75 (2H, m), 7.81 (1H, s,–C=CH), 7.86–8.13 (4H, m), 8.19–8.22 (1H, d, *J*=7.5 Hz), 9.11–9.13 (1H, d, *J*=4.93 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 121.67, 122.20, 125.57, 125.94, 127.98, 128.25, 128.89, 129.63, 129.76, 130.06, 130.52, 130.85, 132.34, 132.75, 134.97, 148.88, 151.82, 152.46, 153.69, 160.38, 170.17 (C=O); MS: $[M+1]^+$=454; Anal. Calc. for $C_{24}H_{15}N_5O_3S$: C, 63.57; H, 3.33; N, 15.44; O, 10.58; S, 7.07; found: C, 63.62; H, 3.35; N, 15.48; O, 10.60; S, 7.09.

2-Imino-5-(4-methylbenzylidene)-3-(2-phenyl-1,8-naphthyridin-3-yl) thiazolidin-4-one (3h)

Pale yellow solid; yield:78%; mp:207–209°C; (KBr, cm^{-1}): 3233 (NH), 2912, 1705 (C=O), 1634, 1580, 1529, 692; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.43 (3H, s) 7.35–7.52 (9H, m), 7.65 (1H, s, =NH), 7.89–7.93 (2H, d, *J*=3.54 Hz), 8.05 (1H, s), 8.12–8.16 (1H, d, *J*=7.49 Hz), 9.09–9.11 (1H, d, *J*=4.94 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 21.9 (CH_3), 122.64, 122.53 127.26, 128.75, 129.14, 129.85, 130.44, 131.88, 133.32, 134.34, 138.67, 139.17, 142.08, 151.90, 152.83, 153.45, 155.72, 167.23 (C=O); MS: $[M+1]^+$=423; Anal. Calc. for $C_{25}H_{18}N_4OS$: C, 71.07; H, 4.29; N, 13.26; O, 3.79; S, 7.59; found: C, 71.11; H, 4.33; N, 13.28; O, 3.82; S, 7.61.

5-(4-Hydroxybenzylidene)-2-imino-3-(2-phenyl-1,8-naphthyridin-3-yl) thiazolidin -4-one (3i)

IR (KBr, cm^{-1}): 3271 (NH), 1711 (C=O), 1628, 1614, 1523, 1422, 698; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 6.93–6.97 (1H, m), 7.39–7.59 (6H, m), 7.67 (1H, s), 7.88 (1H, s), 8.09–8.13 (2H, m), 8.19–8.34 (3H, m), 8.77–8.79 (1H, d, *J*=3.8), 8.94–8.99 (1H, d, *J* =5.41); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 116.49, 121.67, 122.20, 125.94, 127.92, 128.25, 128.89, 129.63, 130.06, 132.26, 132.39, 132.75, 134.97, 151.82, 152.46, 153.69, 159.43, 160.38, 167.18 (C=O); MS: $[M+1]^+$=425; Anal. Calc. for $C_{24}H_{16}N_4O_2S$: C, 67.91; H, 3.80; N, 13.20; O, 7.54; S, 7.55; found: C, 67.95; H, 3.83; N, 13.24; O, 7.57; S, 7.58.

RESULTS AND DISCUSSION

A two-step reaction protocol for the synthesis of novel series of compounds 3a-i is executed in Scheme 1. In the first step, the reaction

of 2-chloro-*N*-(2-phenyl-1,8-naphthyridin-3-yl)acetamide (1) was performed with KSCN in dry acetone under reflux conditions led to the formation of cyclic product 2-imino-3-(2-phenyl-1,8-naphthyridin-3-yl)thiazolidin-4-one (2) exclusively in good yield. This heterocyclization involves the thiocyanation of *N*-2-haloacetamide (2) to afford a transition intermediate (I) and followed by *in situ* intramolecular ring closure (Fig. 2). In the second step, the compound (2) was separately condensed with commercially available appropriate benzaldehydes in the presence of piperidine (Knoevenagel condensation) under reflux conditions in ethanol to provide the corresponding target products (3a-i) in excellent yields. All the synthetic compounds (2 and 3a-i) were assessed in this study by physical, spectral, and analytical data.

The IR spectra of compound 2 showed absorption bands at 3284 and 1720 cm^{-1} corresponding to imino (C=NH) and carbonyl (C=O) groups, respectively. The ^{1}H-NMR spectra of compound 2 revealed that the appearance of a doublet of doublet at the region of 3.81–4.05 ppm corresponding to the methylene protons (CH_2, thiazolidinone ring) due to deshielded by the adjacent sulfur atom and carbonyl group. The singlet signal observed at 7.60 ppm region (D_2O exchangeable) is related to imine proton. The signals appeared at the region 7.53–9.07 ppm corresponds to aromatic protons of phenyl and 1,8-naphthyridine system. In ^{13}C-NMR, the peas appeared at 33.74, 159.67, and 170.48 ppm region for active methylene (CH_2), imino (C=NH), and carbonyl (C=O) functions, respectively.

IR spectra of 3a-i were obtained at the region of 3365–3130 cm^{-1} and 1720–1705 cm^{-1}, indicated the frequencies of NH and carbonyl (C=O) functions, respectively. The arylidene compounds 3a-i can exist as geometrical *E* and *Z* forms (Fig. 3). The^{1}H-NMR spectra showed a new signal at the region of 7.76–7.95 ppm was attributed to methine proton (-C=C-H) in 3a-i. This was the higher chemical shift value than expected values, due to the deshielding effect of an adjacent carbonyl function. Accordingly, the exocyclic C=C bond was assigned *Z*-configuration [19,20]. In ^{13}C-NMR, methine carbons (=CH) of 3a-i appeared at the region of 120.58–129.34 ppm. In mass spectra, all the compounds furnished the corresponding molecular ion peaks, which were matched with the calculated molecular weight, respectively.

Antibacterial activity

From Table 1, the biological screening data of all the compounds revealed that most of the compounds displayed moderate to good bacterial inhibition. The screening studies indicated that the compounds 3b, 3d, and 3e were displayed excellent antibacterial activity against bacterial strains and 3b was the most promising analog as compared to the ciprofloxacin as a reference drug.

Biological assay

Antibacterial activity of the final analogs (3a-i) was performed against a panel of bacteria such as *Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli,* and *Pseudomonas aeruginosa* by agar disc diffusion method [21] at 50 µg/mL concentration in DMSO as a solvent. The cultures were diluted with 5% autoclaved saline and adjust the final volume concentration to ~10^5–10^6 CFU/mL. Then, the liquid form of the tested compound was soaked on to a disc (5 mm). After drying the discs, they were introduced on to the upper layer of medium evenly

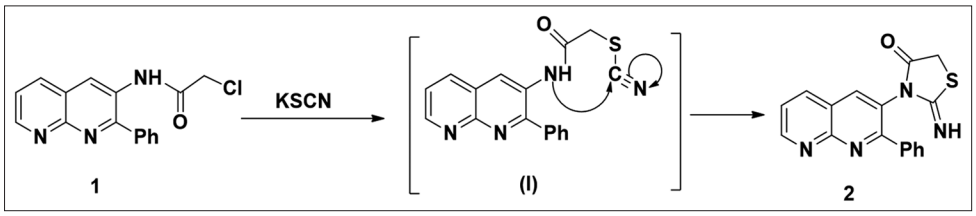
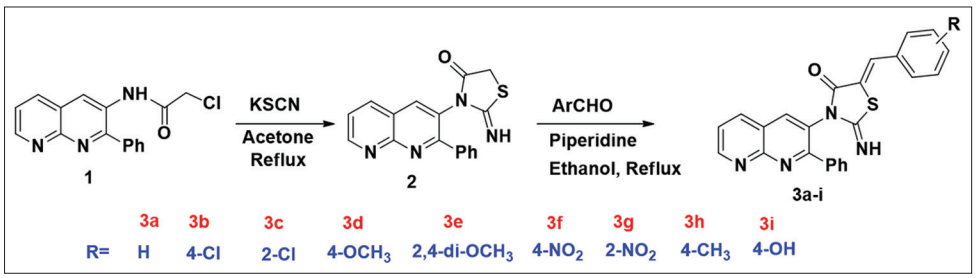


Fig. 2: Mechanistic pathway for compound 2



Scheme 1: Synthetic protocol for the final analogs 3a-i

Table 1: Biological activity of the synthetic compounds against the microorganisms

Entry	Microorganism inhibition zone diameter (mm)			
	Gram-positive bacteria		Gram-negative bacteria	
	Staphylococcus aureus	*Bacillus cereus*	*Escherichia coli*	*Pseudomonas aeruginosa*
3a	20	18	07	25
3b	28	29	28	27
3c	23	20	11	16
3d	26	25	23	23
3e	27	26	26	28
3f	08	12	07	10
3g	12	28	05	16
3h	25	18	25	26
3i	11	13	09	14
Ciprofloxacin (std.)	22	24	24	23

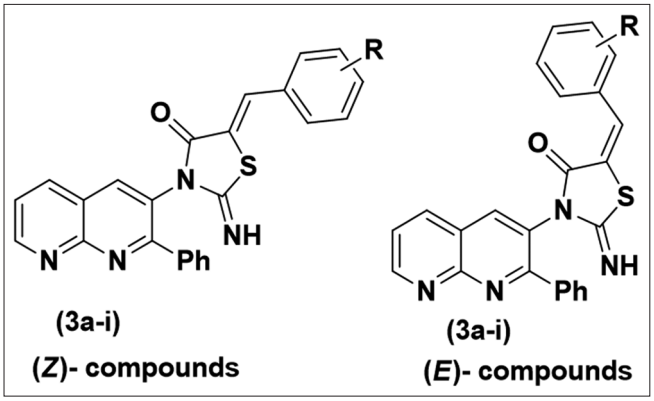


Fig. 3: E/Z isomerism of compounds 3a-i

loaded within the bacterial strain and were incubated at 37°C for 24–48 h. After the 24–48 h, the Petri dishes were examined for growth inhibition zone (mm). All determinations were performed in triplicate and the average value was taken for each compound.

CONCLUSIONS

We have developed a series of 1,8-naphthyridine based arylidene derivatives (3a-i) in good yields. The structures of newly synthesized products were fully studied by elemental and spectroscopic data. The simplicity, easier workability, applicability is reported in this approach. The preliminary results of bioassay demonstrated that the compound 3b possess remarkable antibacterial activity against the microorganisms compared with standards.

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AUTHOR'S CONTRIBUTIONS

BS (third author), who had wrote the manuscript and submitted same. Remaining authors have added value to it. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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