Original Article

Synthesis and Antimicrobial Activity of Naphthylamine Analogs Having Azetidinone and Thiazolidinone Moiety

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Abstract

Background and Objective: To synthesize 2-naphthylamine analogs containing azetidin-2-one (4a–g) and thiazolidin-4-one (5a–g) ring moiety, with the aim of finding new potent antimicrobial agents.

Methods: The antimicrobial activities (antibacterial and antifungal) of the newly-prepared compounds were tested *in vitro* against bacterial cultures (*Bacillus subtilis, Staphylococcus aureus, Escherichia coli,* and *Pseudomonas aeruginosa*) and fungal culture (*Candida albicans*) using agar plate diffusion antimicrobial bioassay. The structures of the title compounds were supported by their spectral data (IR, ^{1}H NMR and ^{13}C NMR).

Results: The synthetic methodology used for the synthesis of the title compounds is shown in Scheme 1 in the paper. Among all the prepared analogs, four compounds (4a, 4e, 4g and 4f) exhibited broad spectrum activity, as compared to the standard drug (ampicillin). Another three compounds (3b, 5b and 5e) showed remarkable antifungal activity, as compared with the standard drug (amphotericin B).

Conclusions: The present investigation led to the synthesis and biological evaluation of naphthylamine analogs having azetidin-2-one and thiazolidin-4-one heterocyclic nucleus/moiety.

Introduction

The discovery, development and identification of biologically active antimicrobial compounds have gained a lot of importance in recent years, even though there are a considerable number of adverse effects. Medicinal chemists have always been tried to design drug molecules that possess maximum therapeutic application while having minimum toxicity profile. Moreover, because of excessive use of antibacterial antibiotics, immunosuppressants and cytotoxins, opportunistic mycosis has become prominent. To combat the increasing number of fungal pathogens and the growing burden of resistance, there is a need to develop new antimicrobial compounds.

Naphthalene analogs occupy a central place among medicinally important compounds, due to their diverse and interesting antibiotic properties.[1] Napthalene is the simplest and the most important member of the arene class, in which two benzene rings are fused in ortho positions. The effectiveness of this structural feature is demonstrated by β-naphthol having almost the same carbon skeleton; it is commonly used as a dye, and reported to possess very good antimicrobial property.[2] Several naphthalene nucleus-containing drugs are also available, such as nafacillin, naftifine, tolnaftate, terbinafine, etc. (Fig. 1), all of which play a vital role in the control of microbial infection.[1]

On the other hand, the imine and azomethine groups (–N=CH–) have been found, respectively, in various natural, natural-derived and non-natural compounds (Fig. 2) and have been shown to be critical to their biological activities.[3–5] They occupy a central place among medicinally important compounds due to their wide spectrum of biological properties, including antimicrobial,[6] anti-inflammatory,[7] analgesic,[8] anti-tubercular,[8,9] antimycobacterial,[10] antioxidant,[11] antiviral,[12] inhibitory,[13] cytotoxic,[14] anticonvulsant,[15] anti-proliferative,[16] anticancer,[17] and antifungal activities.[18] Schiff bases of aromatic aldehydes with effective conjugation system are more stable than the aliphatic aldehydes.

Keywords: Antimicrobial; 2-Azetidinone; 4-Thiazolidinone; Schiff bases; Naphthalene.

Abbreviations: FTIR, Fourier-transform infrared spectroscopy; IR, infrared; Natom, number of atoms other than hydrogen; NMR, nuclear magnetic resonance; nOHNH, number of H– bond acceptor; nON, number of hydrogen bond donor; TMS, tetramethylsilane; TPSA, topological polar surface area; ZOI, zone of inhibition.

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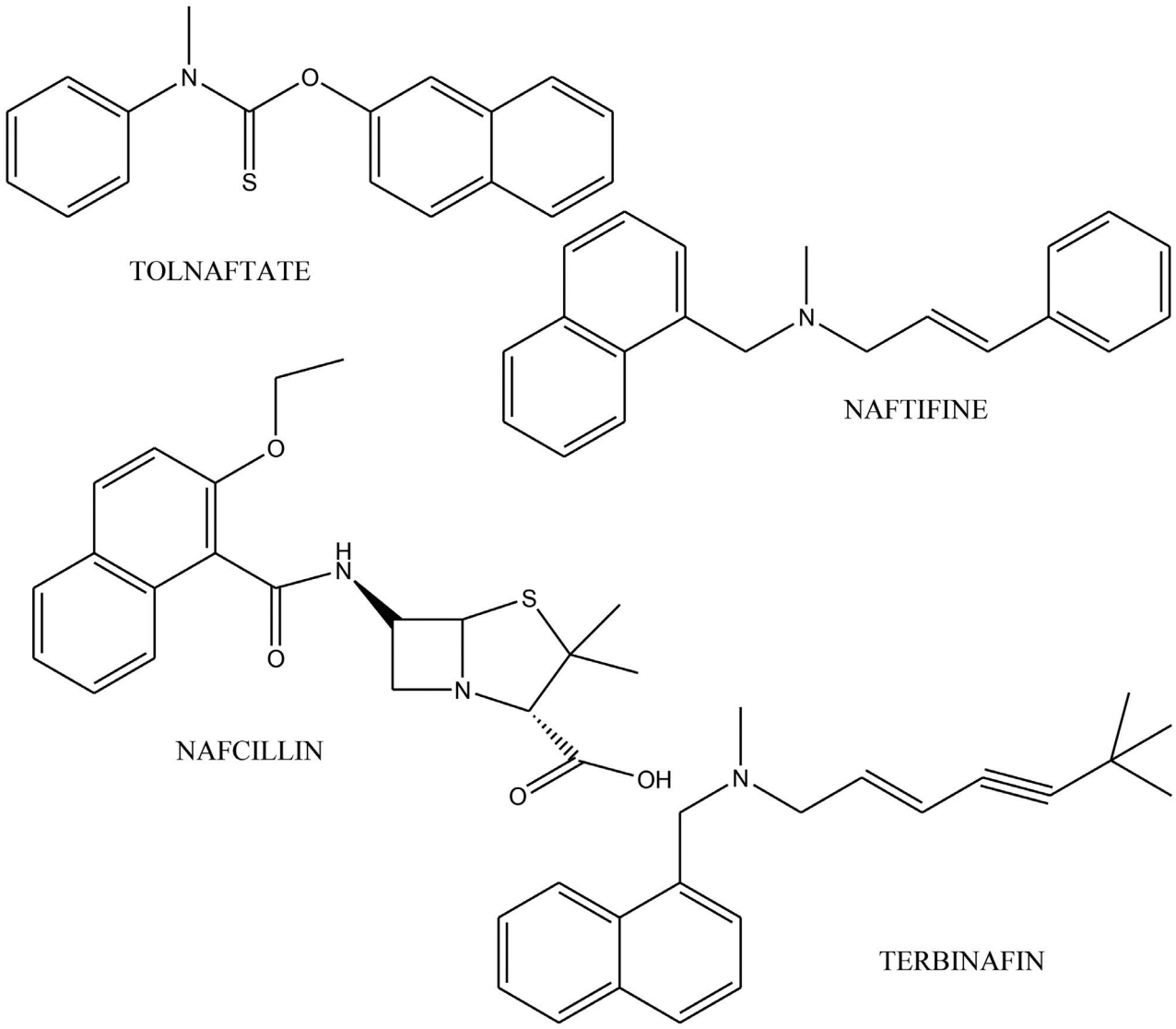


Fig. 1. Structure of clinically used naphthalene nucleus-containing antimicrobial drugs.

Moreover, numerous analogs of azetidinone andthiazolidinone moieties have also been well documented.[19–21] Various reports of studies of naphthalene and its based analogs bearing the azetidine and thiazolidone nucleus possess pharmacological potential.[22,23] However, the biological activity of this class of compounds deserves further investigation. The purpose of this present study was to evaluate the antimicrobial potential of azetidinone and thiazolidinone analogs of napthylamine.

Material and methods

Chemistry

All the chemicals used were of synthetic grade and commercially procured from Qualigen (Mumbai, India) and CDH (New Delhi, India). Melting points were determined by open capillary tube method and are uncorrected. Fourier-transform infrared spectroscopy (FTIR) spectra (KBr pellet, neat) were recorded on a Perkin Elmer RX1 spectrophotometer and ^{1}H–nuclear magnetic resonance (NMR) and ^{13}C-NMR spectra were recorded on a Brucker 300 MHz spectrometer in ($CDCl_3$) using tetramethylsilane (TMS) as an internal reference and the chemical shifts are expressed in δ ppm. Progress of the reaction and purity of the compound was monitored by thin layer chromatography using a 0.2 mm thick aluminium sheet precoated with silica gel (60F 254; Merck, United States). Spots were visualized under UV (254 nm) and iodine chamber. The solvent was removed under reduced pressure, using a rotary evaporator (Buchi, United States). All other organic solvents used were of laboratory reagent grade, dried over anhydrous sodium sulfate and used as received.

Synthesis of Schiff bases (3a–g)

The appropriate aryl aldehydes (0.01 mol) were added to a solution of β-napthylamine (1.43 g, 0.01 mol) in ethanol (20 mL), followed by dropwise addition of concentrated sulphuric acid. The reaction

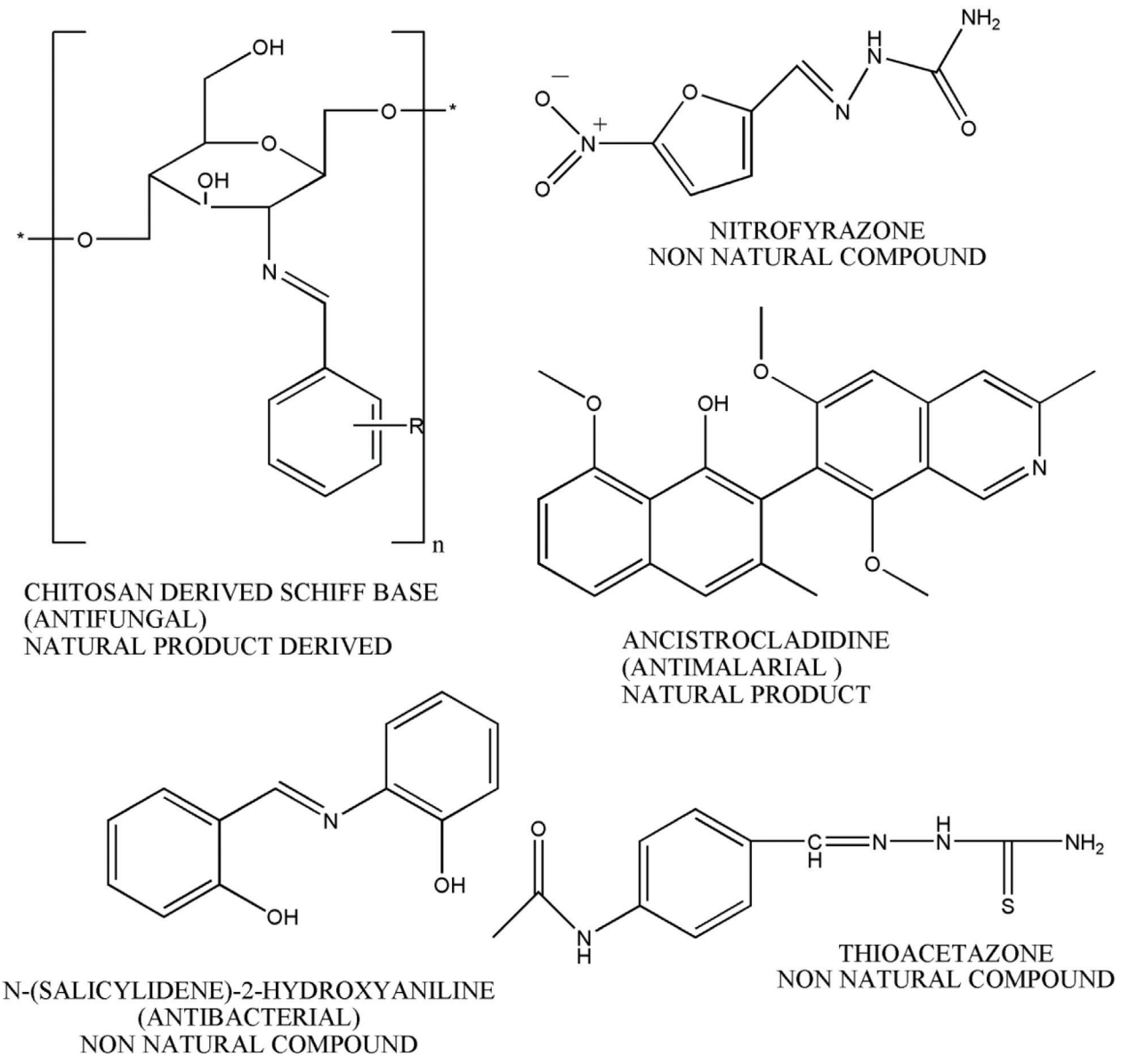


Fig. 2. Structure of clinically used imine group-containing drugs.

mixture was then refluxed for 6–8 h and cooled. After cooling, the solid obtained was filtered, washed thoroughly with water, and dried. The pure product was crystallized from ethanol/water (1/1 *v*/*v*).

Synthesis of 3-chloro-4-(substituted phenyl)-1-(naphthalen-6-yl) azetidin-2-one (4a–g)

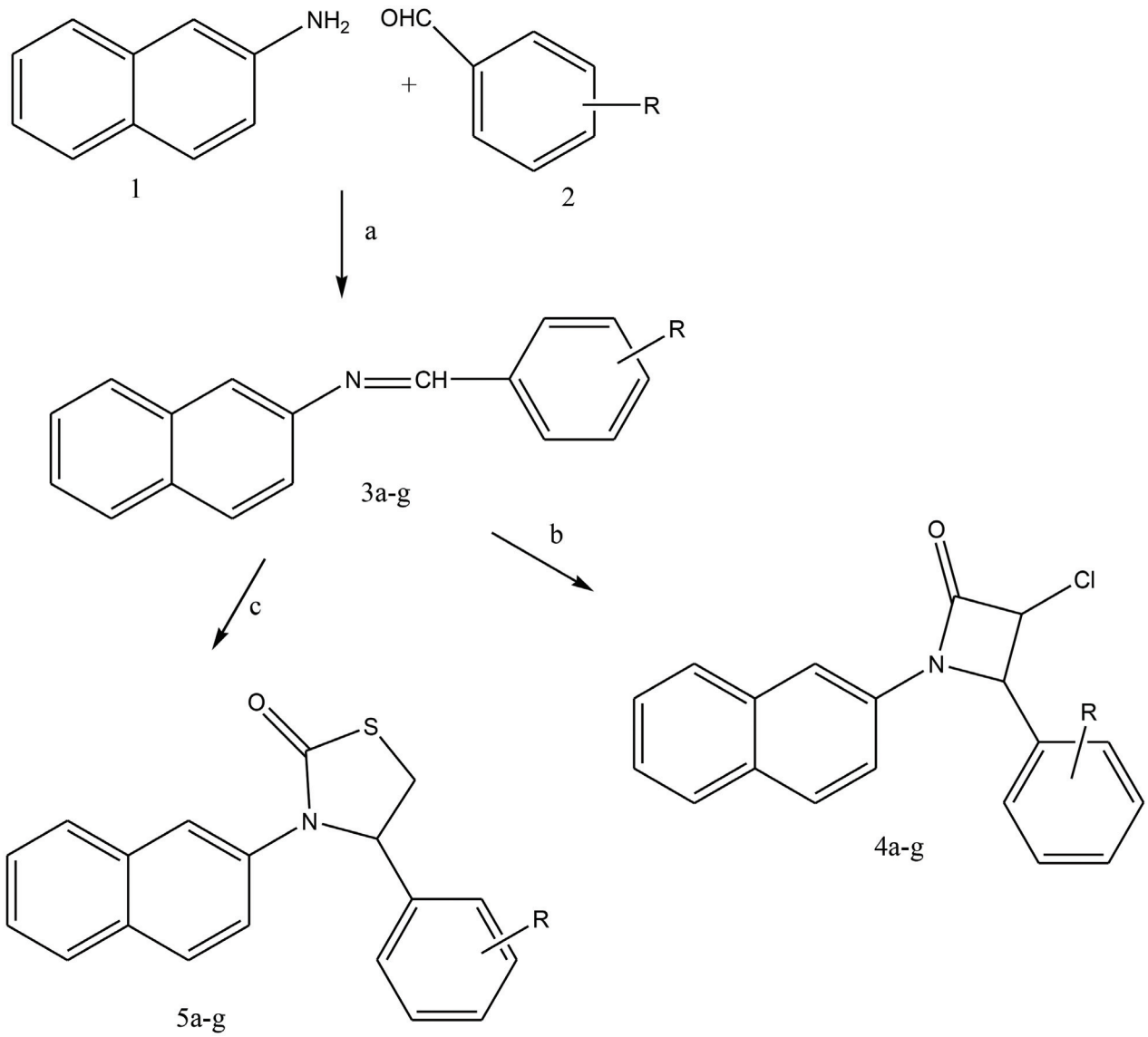
A solution of compound (3a–g, 0.01 mol) in dioxane (20 mL) and triethylamine (0.01 mol) was mixed with continuous stirring. The total mixture was then cooled at 0–5 °C and a few drops of chloroacetyl chloride were added. After addition, the whole mixture was stirred for 5–6 h and then filtered. The filtrate was then refluxed for another 5–6 h and allowed to cool at room temperature. On cooling, a solid crude product separated out, which was filtered, dried and re-crystalized with ethanol.

Synthesis of N-2-(substituted phenyl)-3-(naphthalen-6-yl) thiazolidin-4-one (5a–g)

A mixture of compound (3a–g, 0.01 mol) and thioglycollic acid (0.01 mol) was refluxed on a heating mantle at 120–125 °C for approximately 12 h. The reaction mixture was cooled and treated with 10% sodium bicarbonate solution. The product was isolated and re-crystallized from methanol–dioxane (4:1). The overall reaction scheme followed is depicted in Scheme 1.

4-(naphthalen-3-ylimino methyl) phenol 3a

Molecular formula $C_{17}H_{13}NO$; melting point 116–117 °C; yield 60%. Infrared (IR) (KBr, cm^{-1}) 3,045.0 (CH), 1,440–1,514 (–H–C=N). ^{1}H–NMR (300 MHz, $CDCl_3$, TMS = 0) δ: 8.2 (s, 1H, CH),



Scheme 1. Reagents and conditions. a. sulphuric acid, ethanol, 5–6 h reflux.; b. Triethylamine, dioxane, chloroacetyl chloride, stirring followed by 5–6 h reflux, ethanol.; c. Thioglycollic acid, 12h reflux, 10% sodium bicarbonate solution.

4.9 (s, 1H, OH), 6.7–7.4 (m, 11H, Ar–H). ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 160.6, 150.4, 135.2, 132.4, 130, 129.4, 128.2, 126.4, 120.4, 119.2, 116.

3,4,5-trimethoxybenzylidenenaphthalen-2-amine 3b

Molecular formula $C_{20}H_{19}NO_3$; melting point 131–132 °C; yield 60%. ^{1}H–NMR (300 MHz, $CDCl_3$, TMS = 0) δ: 3.7 (s, 9H, OCH_3), 8.3 (s, 1H, CH), 6.6–7.4 (m, 9H, Ar–H). ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 160.4, 150.6, 141.5, 135, 132.2, 129.4, 128.2, 126.2, 120.6, 119.2, 106.2, 56.2.

3,4-dimethoxybenzylidene naphthalen-2-amine 3c

Molecular formula $C_{19}H_{17}NO_2$; melting point 128–130 °C; yield 60%. ^{1}H–NMR (300 MHz, $CDCl_3$, TMS = 0) δ: 3.6 (s, 6H, OCH_3), 8.1 (s, 1H, CH), 6.7–7.6 (m, 10H, Ar–H).

2-methoxy-4-(naphthalen-3-ylimino methyl) phenol 3d

Molecular formula $C_{18}H_{15}NO_2$; melting point 114–115 °C; yield 60%. ^{1}H–NMR (300 MHz, $CDCl_3$, TMS = 0) δ: 3.7 (s, 3H, OCH_3), 5.0 (s, 1H, OH), 8.2 (s, 1H, CH), 6.7–7.4 (m, 10H, Ar–H). ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 160.1, 151.4, 150.2, 148, 135.2, 132.2, 129.4, 128, 127.4, 123, 120.4, 119.2, 117, 114.8, 56.

Benzylidenenaphthalen-2-amine 3e

Molecular formula $C_{17}H_{13}N$; Melting point 106–107 °C; Yield 60%; ^{1}HNMR (300 MHz, $CDCl_3$, TMS = 0) δ: 8.1 (s, 1H, CH),

7.2–7.6 (m, 12H, Ar–H).

3-nitrobenzylidenenaphthalen-2-amine 3f

Molecular formula $C_{17}H_{12}N_2O_2$; melting point 122–123 °C; yield 70%. ^{1}H–NMR (300 MHz, $CDCl_3$, TMS = 0) δ: 8.5 (s, 1H, Ar–H), 8.3 (s, 1H, CH), 8.1–8.2 (d, 2H, Ar–H), 7.3–7.6 (m, 8H, Ar–H).

4-chlorobenzylidenenaphthalen-2-amine 3g

Molecular formula $C_{17}H_{12}C_lN$; melting point 124–125 °C; yield 65%. ^{1}H–NMR (300 MHz, $CDCl_3$, TMS = 0) δ: 8.1 (s, 1H, CH), 7.3–7.6 (m, 11H, Ar–H).

3-chloro-4-(4-hydroxyphenyl)-1-(naphthalen-3-yl)azetidin-2-one 4a

Molecular formula $C_{19}H_{14}ClNO_2$; melting point 146–147 °C; yield 60%; IR (KBr, cm^{-1}) 3,450.5 (NH), 3,047.0 (CH), 1,754.1 (C=O), 1,624.9 (CO–NH), 1,448.7 (CN), 896.5, 750.5 and 677.8(C=C), 679.8 (C–Cl). ^{1}H–NMR (300 MHz, $CDCl_3$, TMS = 0) δ: 5.0 (s, 1H, OH), 5.2 (d, 1H, CH), 5.4 (d, 1H, CH), 6.8–7.4 (m, 11H, Ar–H). ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 162.1, 156.4, 141.2, 136.4, 133.2, 128, 127.4, 126.1, 125.4, 124, 121.4, 118.2, 115, 108.6, 63, 62.2.

3-chloro-4-(3,4,5-trimethoxyphenyl)-1-(naphthalen-3-yl)azetidin-2-one 4b

Molecular formula $C_{22}H_{20}ClNO_4$; melting point 134–135 °C; yield 60%; ^{1}H–NMR (300 MHz, $CDCl_3$, TMS = 0) δ: 3.5 (s, 9H, OCH_3), 5.1 (d, 1H, CH), 5.4 (d, 1H, CH), 6.1 (s, 2H, Ar–H), 6.7–7.5 (m, 7H, Ar–H). ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 162.2, 150.3, 141.2, 137.2, 133.2, 127.4, 126.5, 125.3, 124.2, 121.4, 118.1, 108.2, 104, 63, 62.2, 56.

3-chloro-4-(3,4-dimethoxyphenyl)-1-(naphthalen-3-yl)azetidin-2-one 4c

Molecular formula $C_{21}H_{18}ClNO_3$; melting point 128–130 °C; yield 60%.; IR (KBr, cm^{-1}): 3,228.0 (N–H), 3,045.0 (C–H), 1,749.4 (C=O), 1,672.2 (CO–NH), 1,420.0 (C–N), 832.8 and 779.8 (C–C), 689.2 (C–Cl). ^{1}H–NMR (300 MHz, $CDCl_3$, TMS = 0) δ: 3.6 (s, 6H, OCH_3), 5.2 (d, 1H, CH), 5.3 (d, 1H, CH), 6.6–7.6 (m, 10H, Ar–H).

3-chloro-4-(4-hydroxy-3-methoxyphenyl)-1-(naphthalen-3-yl) azetidin-2-one 4d [22]

Molecular formula $C_{20}H_{16}ClNO_3$; melting point 134–135 °C; yield 60%. ^{1}H–NMR (300 MHz, $CDCl_3$, TMS = 0) δ: 3.7 (s, 3H, OCH_3), 4.9 (s, 1H, OH), 5.1 (d, 1H, CH), 5.4 (d, 1H, CH), 6.6–7.4 (m, 10H, Ar–H). ^{13}C–NMR (300 MHz, $CDCl_3$) δ: 162.1, 151.2, 143.2, 141.4, 137.2, 133.2, 127.4, 126.5, 125.3, 124.3, 121.4, 120.6, 118.1, 116, 112.2, 108.2, 63, 62.2, 56.2.

3-chloro-1-(naphthalen-3-yl)-4-phenylazetidin-2-one 4e

Molecular formula $C_{19}H_{14}ClNO$; melting point 118–119 °C; yield 60%. IR (KBr, cm^{-1}): 3,469.6 (NH), 3,054.0 (CH), 1,756.8 (C=O), 1,670.8 (CO–NH), 1,444.4 (C–N), 854.5, 679.2(C=C), 689.2 (C–Cl). ^{1}H–NMR (300 MHz, $CDCl_3$, TMS = 0) δ: 5.1 (d, 1H, CH), 5.4 (d, 1H, CH), 6.8–7.4 (m, 12H, Ar–H).

3-chloro-1-(naphthalen-3-yl)-4-(3-nitrophenyl)azetidin-2-one 4f

Molecular formula $C_{19}H_{13}ClN_2O_3$; melting point 122–124 °C; yield 70%. IR (KBr, cm^{-1}): 3,449.5 (NH), 3,045.0 (CH); 1,757.1 (C=O), 1,622.9 (CO–NH), 1,446.7(CN), 894.5, 750.5 and 677.8 (C=C), 677.8 (C–Cl). ^{1}H–NMR (300 MHz, $CDCl_3$, TMS = 0) δ: 5.4 (d, 1H, CH), 5.2 (d, 1H, CH), 6.8–7.5 (m, 9H, Ar–H), 8.0–8.1(m, 2H, Ar–H).

3-chloro-4-(4-chlorophenyl)-1-(naphthalen-3-yl)azetidin-2-one 4g

Molecular formula $C_{19}H_{13}Cl_2NO$; melting point 128–129 °C; yield 65%; IR (KBr, cm^{-1}): 3,238.0 (N–H), 3,049.0 (C–H), 1,750.4 (C=O), 1,673.2 (CO–NH), 1,422.0 (C–N), 834.5 and 779.8 (C–C), 619.9 (C–Cl). ^{1}H–NMR (300 MHz, $CDCl_3$, TMS = 0) δ: 5.4 (d, 1H, CH), 5.1 (d, 1H, CH), 6.8–7.4 (m, 11H, Ar–H).

4-(4-hydroxyphenyl)-3-(naphthalen-3-yl)thiazolidin-2-one 5a

Molecular formula $C_{19}H_{15}NO_2S$; melting point 126–127 °C; yield 60%. ^{1}H–NMR (300 MHz, $CDCl_3$, TMS = 0) δ: 5.0 (s, 1H, OH), 4.8 (t, 1H, CH), 3.25 (dd, 2H, J = 5.6 Hz, CH_2), 6.8–7.4 (m, 11H, Ar–H). ^{13}C–NMR (300 MHz, $CDCl_3$) δ: 170.1, 156.4, 141.2, 136.4, 133.2, 128, 127.4, 126.1, 125.4, 124, 121.4, 118.2, 115, 108.6, 55, 35.2.

4-(3,4,5-trimethoxyphenyl)-3-(naphthalen-3-yl)thiazolidin-2-one 5b

Molecular formula $C_{22}H_{21}NO_4S$; melting point 128–130 °C; yield 65%. ^{1}H–NMR (300 MHz, $CDCl_3$, TMS = 0) δ: 3.25(dd, 2H, J = 5.6 Hz, CH_2), 3.7 (s, 9H, OCH_3), 5.2 (t, 1H, CH), 6.2–7.4 (m, 9H, Ar–H).

4-(3,4-dimethoxyphenyl)-3-(naphthalen-3-yl)thiazolidin-2-one 5c

Molecular formula $C_{21}H_{19}NO_3S$; melting point 133–134 °C; yield 58%. ^{1}H–NMR (300 MHz, $CDCl_3$, TMS = 0) δ: 3. 27 (dd, 2H, J = 5.7 Hz, CH_2), 3.7 (s, 6H, OCH_3), 5.2 (t, 1H, CH), 6.6–7.4 (m, 10H, Ar–H).

4-(4-hydroxy-3-methoxyphenyl)-3-(naphthalen-3-yl)thiazolidin-2-one 5d [22]

Molecular formula $C_{20}H_{17}NO_3S$; melting point 137–138 °C; yield 55%. ^{1}H–NMR (300 MHz, $CDCl_3$, TMS = 0) δ: 3.32 (dd, 2H, J = 5.6 Hz, CH_2), 3.6 (s, 3H, OCH_3), 4.9 (s, 1H, OH), 5.1 (t, 1H, CH), 6.6–7.4 (m, 10H, Ar–H).

3-(naphthalen-3-yl)-4-phenylthiazolidin-2-one 5e

Molecular formula $C_{19}H_{15}NOS$; melting point 134–135 °C; yield

Table 1. Molecular properties of the 3a–g, 4a–g and 5a–g compounds

Compound	Ar	LogP	TPSA	Natom	nON	nOHNH
3a	–4OHC$_6$H$_4$	4.17	32.59	19	2	1
3b	–3,4,5–triOCH$_3$C$_6$H$_2$	4.29	40.07	24	4	0
3c	–3,4–diOCH$_3$C$_6$H$_3$	4.30	30.83	22	3	0
3d	–4OH,3–OCH$_3$C$_6$H$_3$	3.99	41.83	21	3	1
3e	–C$_6$H$_5$	4.65	12.36	18	1	0
3f	–3NO$_2$C$_6$H$_4$	4.59	58.19	21	4	0
3g	–4ClC$_6$H$_4$	5.33	12.36	19	1	0
4a	–4OHC$_6$H$_4$	4.10	40.54	23	3	1
4b	–3,4,5–triOCH$_3$C$_6$H$_2$	4.21	48.01	28	5	0
4c	–3,4–diOCH$_3$C$_6$H$_3$	4.23	38.78	26	4	0
4d	–4OH,3–OCH$_3$C$_6$H$_3$	3.92	49.77	25	4	1
4e	–C$_6$H$_5$	4.58	20.31	22	2	0
4f	–3NO$_2$C$_6$H$_4$	4.51	66.13	25	5	0
4g	–4ClC$_6$H$_4$	5.26	20.31	23	2	0
5a	–4OHC$_6$H$_4$	4.58	40.54	23	3	1
5b	–3,4,5–triOCH$_3$C$_6$H$_2$	4.69	48.01	28	5	0
5c	–3,4–diOCH$_3$C$_6$H$_3$	4.70	38.78	26	4	0
5d	–4OH,3–OCH$_3$C$_6$H$_3$	4.40	49.77	25	4	1
5e	–C$_6$H$_5$	5.06	20.31	22	2	0
5f	–3NO$_2$C$_6$H$_4$	4.99	66.13	25	5	0
5g	–4ClC$_6$H$_4$	5.74	20.31	23	2	0

68%. ^{1}H–NMR (300 MHz, CDCl$_3$, TMS = 0) δ: 3.34 (dd, 2H, J = 5.8 Hz, CH$_2$), 5.1 (t, 1H, CH), 6.8–7.5 (m, 12H, Ar–H).

3-(naphthalen-3-yl)-4-(3-nitrophenyl)thiazolidin-2-one 5f

Molecular formula $C_{19}H_{14}N_2O_3S$; melting point 121–122 °C; yield 60%. ^{1}H–NMR (300 MHz, CDCl$_3$, TMS = 0) δ: 3.35 (dd, 2H, J = 5.74 Hz, CH$_2$), 5.2 (t, 1H, CH), 6.8–7.6 (m, 9H, Ar–H), 8.1–8.2 (m, 2H, Ar–H).

4-(4-chlorophenyl)-3-(naphthalen-3-yl)thiazolidin-2-one 5g

Molecular formula $C_{19}H_{14}ClNOS$; melting point 136–137 °C; yield 70%. ^{1}H–NMR (300 MHz, CDCl$_3$, TMS = 0) δ: 3.36 (dd, 2H, J = 5.75, CH$_2$), 5.0 (t, 1H, CH), 6.8–7.6 (m, 11H, Ar–H).

In vitro antimicrobial activity test

The *in vitro* antimicrobial potential of all newly prepared analogs was tested at Guru Gobind Singh College of Pharmacy, (Yamuna Nagar, India) using the Agar plate diffusion antimicrobial bioassay. Antimicrobial activity of all the synthesized analogs (3a–g, 4a–g and 5a–g) were tested against four standard bacterial cultures (*i.e. Bacillus subtilis* MTCC 121, *Staphylococcus aureus* MTCC 96, *Escherichia coli* MTCC 739 and *Pseudomonas aeruginosa* MTCC 2453) and one fungal strain (*Candida albicans* MTCC 3017) according to the literature as described.[24] The stock solutions for all new prepared compounds (3a–g, 4a–g and 5a–g; 5,000 µg/mL each) were prepared in DMSO (50 µg per well, *i.e.* 250 µg) and the activity was determined by measuring the zone of inhibition. The strength (*i.e.* 50 µg/mL) was used as positive control for the bioassay. The antibacterial and antifungal potentials of the prepared analogs were compared with the standard drugs ampicillin (200 µg/mL) and amphotericin B (500 µg/mL), respectively. Activity was determined by measuring the diameter of zones showing complete inhibition (mm). Growth inhibition was calculated with reference to the positive control.

Results and discussion

Chemistry

All of the new azetidinone and thiazolidione analogs of napthylamine were synthesized successfully, with the subsequent aim of finding new compounds with promising antibacterial activities. The synthetic methodology is shown in Scheme 1. The purity and structures of all the synthesized compounds were elucidated on the basis of their spectral data (*i.e.* IR, ^{1}H–NMR and ^{13}C–NMR). The IR spectra of 3a–g compounds displayed the characteristic peaks in the region of 1,440–1,514 cm^{-1} indicating the formation of a Schiff base (–H–C=N). The appearance of peaks in the region of 1,550–1,687 cm^{-1} confirmed the presence of C=O in 4a–g and 5a–g. The structural assignments were further supported by their ^{1}H–NMR

Table 2. Antibacterial and antifungal potential of all the synthesized analogs

Compound	*B. subtilis* MTCC 121		*S. aureus* MTCC 96		*E. coli* MTCC 739		*P. aeruginosa* MTCC 2453		*C. albicans* MTCC 3017	
	24h	48h	24h	48h	24h	48h	24h	48h	24h	48h
3a	10mm	–	–	–	–	–	–	–	–	–
3b	–	–	–	–	–	–	–	–	7mm	–
3c	–	–	–	–	–	–	–	–	–	–
3d	–	–	–	–	–	–	–	–	–	–
3e	12mm	–	–	–	–	–	–	–	–	–
3f	–	–	–	–	–	–	–	–	–	–
3g	–	–	–	–	–	–	–	–	–	–
4a	9mm	9mm	12mm	10mm	–	–	10mm	10mm	–	–
4b	–	–	–	–	–	–	–	–	–	–
4c	–	–	–	–	–	–	–	–	–	–
4d	12mm	–	15mm	–	–	–	–	–	–	–
4e	10mm	10mm	–	–	19mm	–	9mm	–	–	–
4f	16mm	15mm	15mm	15mm	–	–	19mm	–	13mm	–
4g	12mm	15mm	–	–	–	–	14mm	–	–	–
5a	–	–	12mm	–	–	–	–	–	–	–
5b	–	–	–	–	–	–	–	–	9mm	–
5c	–	–	–	–	–	–	–	–	–	–
5d	–	–	–	–	20mm	20mm	–	–	–	–
5e	13mm	–	–	–	–	–	–	–	13mm	–
5f	–	–	–	–	–	–	–	–	–	–
5g	13mm	–	–	–	11mm	–	–	–	–	–
Positive control	27mm	22mm	44mm	45mm	15mm	17mm	–	–	16mm	15mm
	(ampicillin 200µg/mL)		(ampicillin 200µg/mL)		(ampicillin 200µg/mL)				(amphotericin B, 500µg/mL)	
DMSO (control)	–	–	–	–	–	–	–	–	–	–

spectra, and all the synthesized compounds were found to be in conformity with the structures envisaged. The molecular properties of the title compounds, such as log P, topological polar surface area (TPSA), number of atoms other than hydrogen (Natom), number of hydrogen bond donor (nON) and number of H– bond acceptor (n OHNH), were calculated by the online Molinspiration software and the data recorded are given in Table 1.[25]

Antibacterial activity

The antibacterial potential of prepared analogs was compared with the standard drug ampicillin, whereas the antifungal potential was compared with the standard drug amphotericin B (Table 2). The observation was made over 2 days and the "–" sign signifies no zone of inhibition (ZOI). In many cases, on the first day, ZOI was observed but had disappeared on the next day.

Schiff base analogs in this series (**3**a–g) showed no activity against any of the bacteria tested. Three compounds, 4a, 4e and 4g, were found to exhibit broad spectrum activity. Compound 4d showed good activity against *B. subtilis* MTCC 121 (12 mm) and moderate activity against *S.aureus* MTCC 96 (15 mm). However, compound 4f showed a wide spectrum of antimicrobial activity, but it may be cytotoxic. Compounds 3b, 5b and 5e were found to be active against *C. albicans* MTCC 3017, with ZOIs at 24 h 7 mm, 9 mm and 13mm, respectively. Although ampicillin is a broad spectrum antibiotic, it is inactive against *Pseudomonas* species at the tested concentration, which may be due to some mutation.

Future research directions

N-heterocyclic nucleus and its analogues have attracted the interest of many medicinal chemists, and because of this many modifications have been carried out in last decade. Keeping this in view, the work in this study was carried out with different approaches to develop better analogs of napthylamine analogs having azetidin-2-one and thiazolidin-4-one moiety with comparable antimicrobial activity. The promising activity of these compounds, along with the other activity data obtained during the study, can also be useful in establishing the structure activity relationships and for the development of newer and more potent antimicrobial compounds

which will able to act against multidrug resistance.

Conclusions

In summary, the present investigation describes the synthesis and biological evaluation of naphthylamine analogs having azetidin-2-one and thiazolidin-4-one heterocyclic nucleus/moiety. All the prepared analogs were characterized by suitable methods, such as IR and ^{1}H–NMR. All spectral data were in accordance with assumed structures. The three compounds 4a, 4e, 4g and 4f exhibited broad spectrum activity.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Overall experimental work (BC), preparation of manuscript (BC), Analysis (AK), revision of analysis (RPK), research guidance (DNP).

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