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SYNTHESIS, *MT* –QSAR STUDIES FOR PREDICATION OF ANTIMICROBIAL ACTIVITY OF SCHIFF BASES, CARBOHYDRAZIDE AND ANILIDES/AMIDES DERIVATIVES OF NALIDIXIC ACID

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ABSTRACT

In the present investigation, a series of schiff base (1-20), carbohydrazide (31-43) and amides/anilides (21-30/44-56) of nalidixic acid was synthesized in appreciable yield and characterized by physicochemical as well as spectral means. The synthesized compounds were evaluated *in vitro* for their antimicrobial activity against Gram-positive bacteria *S. aureus, B. subtilis,* Gram negative bacteria *E. coli* & fungal strains *C. albicans* & *A. niger* by tube dilution method. Antimicrobial activity results indicated that compounds 16, 24, 36, 53 (MIC = 6.25 µg/mL) were the most potent antimicrobial agents. The results of antimicrobial screening also indicated that compounds having NO_2, Br, F, Cl, OCH_3 substituents were the most active one. *mt*-QSAR investigation used Hansch analysis was applied to find out correlation between antimicrobial activities with physicochemical properties of synthesized compounds. The *mt*-QSAR revealed that the antibacterial and antifungal activity of these synthesized derivatives against microorganisms under test was mainly governed by second order molecular connectivity index ($^2\chi$)and zero order molecular connectivity index ($^0\chi^{\varpi}$). It also indicated the importance of zero order molecular connectivity index ($^0\chi^{\varpi}$)in describing the antimicrobial activity of synthesized compounds.

KEYWORDS: **Nalidixic acid, Schiff bases, Antimicrobial and QSAR.**

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INTRODUCTION

The urinary tract infections were articularly common in women. The most common infecting pathogen found is *Escherichia coli*. *Staphylococcus saprophyticus*, a coagulase-negative staphylococcus, is a common cause of infection in young women. Among the other infecting microorganisms involved are *Staphylococcus epidermidis,* enterococci and *Pseudomonas* species. In men, the urinary tract infections are less common and often occur during abnormalities of genitourinary tract such as prostatic hypertrophy. One of the common causes in infective urethritis in man is the pathogen *Neisseria gonorrhoeae* and nongonococcal urethritis may be due to *Chlamydia trachomatis* and *Ureaplasma urealyticum*. Epididymitis is often associated with urethritis. Different antibiotics and sulphonamides are widely used in the treatment of infections of the urinary tract. Nalidixic acid is one such drug. It is an 8-aza-4-quinolone; a derivative of 1,8- naphthyridine. Nalidixic acid was introduced as a chemotherapeutic agent in 1962 [1]. It failed to achieve adequate concentrations in the plasma or tissues for the treatment of systemic infections following oral or potential administration but got concentrated in the urine, where it could be effective for eradicating urinary tract infections [2].The emergence of resistance in most of the pathogenic bacteria to the currently available antibacterial agents is the major problem in the treatment of serious bacterial infections caused by these organisms. These resistant strains curtail the life span of the drug [3]. The resistance to the nalidixic acid appears to be the result of one of three mechanisms: alterations in the quinolone enzymatic targets (DNA gyrase), decreased outer membrane permeability or the development of efflux mechanisms [4]. The accumulation of several bacterial mutations (DNA gyrase and bacterial permeability) has been associated with the development of very high minimum inhibitory concentrations to ciprofloxacin in isolates of *Staphylococcus aureus*, Enterobacteriaceae species and *P. aeruginosa*. Resistance to quinolones can also develop because of the alterations in bacterial permeability and the development of efflux pumps. During the past years an increasing interest has been devoted to the study of new and more selective antimicrobial agents. Due to this, not only have new synthetic methods been developed, but a greater amount of interest has been devoted to comprehension of their mechanism of action and structure activity relationships[5]. Structure activity relationships (SAR) of compounds based on nalidixic acid have led to a large group of synthetic antibacterial agents collectively known as the quinolones [6]. Resistance was found to emerge rapidly, even while on therapy. These agents inhibit DNA synthesis by promotes cleavage of bacterial DNA in the DNA-enzyme complexes of DNA gyrase, resulting in rapid bacterial death [7]. Nalidixic acid is known to be effective against indole positive *Proteus* in urinary tract infections. Failure observed in patients may be due to reinfection from the prostate gland. Nalidixic acid is particularly active against the majority of gram-negative organisms that infect urinary tract especially *E. coli.* It is often effective against other coliform bacteria such as *Klebsiella* and *Enterobacter aerogenosa*. *Brucella* species and some strains of *Salmonella* and *Shigella* are also sensitive. However, most *Pseudomonas* species are resistant to nalidixic acid. This drug is ineffective against gram-positive bacteria including *Staphylococcus* and *Enterococcus fecalis* (formerly, *Staphylococcus fecalis).* Studies have indicated that nalidixic acid is effective against 99% strains of *E coli*, 98% of *P. Mirabilis*, 92% of *Klebsiella* and *Enterobacter* and 80% of other coliform species [8].Biological activities of the molecules are a function of their chemical and physical properties. A structure-activity relationship was a quantitative association between a chemical substructure and the potential of a chemical to exhibit a certain biological effect. A quantitative structure-activity relationship (QSAR) is a mathematical model that relates a quantitative measure of chemical structure to a biological effect. Thus, the structure-activity relationship of the molecules could be explained quantitatively [9]. Quantitative structure-activity relationships (QSARs) represent an attempt to correlate structural properties of the compounds with biological activities and chemical reactivity. These chemical descriptors, which include parameters to account for hydrophobicity,

electronic, inductive, or polar properties, and steric effects, were determined empirically or by calculations [10].The significant *in vitro* antimicrobial activity (using Agar dilution and Punch well diffusion method) of synthesized quinazolone derivatives bearing nalidixic acid moiety on randomLy collected microbial strains has been reported by Grover et. al [2]. We have previously reported the synthesis, antimicrobial evaluation and QSAR studies of some simple organic acid derivatives as possible antimicrobial agents [11-16] as a part of our composite programme on rational drug design [11-23]. Antimicrobial activity associated with nalidixic acid moieties prompted us to synthesize some nalidixic acid derivatives carrying the biodynamic heterocyclic systems at positions-3 with an objective to obtain schiff base, hydrazones and anilides / amides of enhanced biological activities. Further, we have decided to carry out the QSAR studies to perceive the importance of molecular properties, which are critical in accentuating the antimicrobial activity of nalidixic acid derivatives. Schiff bases are considered to be among the most important group of compounds in medicinal chemistry due to their preparative accessibility, structural variety and wide biological profile [24]. Keep this observation in mind and in continuation of our study in the field of antimicrobial evaluation and QSAR studies [25-29], we hereby report the synthesis, antimicrobial evaluation and QSAR studies of nalidixic acid derivatives.

MATERIALS AND METHODS

Nalidixic acid was purchased from sigma aldrich, USA. Chemicals and all solvents used in this study were procured from Merck AG (Mumbai, India), SD Fines (Mumbai, India), Sigma Aldrich (Bangalore,India) and Qualigens (Navi Mumbai, India). The melting points of synthesized compounds were determined in open capillary using Elico melting point apparatus and recorded in ^{o} C without correction. Reaction progress was monitored by thin layer chromatography on precoated silica gel G plates used iodine vapour as detecting agent and the purity of the compounds was ascertained by single spot on TLC sheet. The spots were detected by exposure to iodine vapors. Nuclear magnetic resonance (^{1}H NMR & ^{13}C NMR) spectra were recorded in Bruker Avance II 400 NMR spectrophotometer using DMSO as a solvent and are expressed in parts per million (δ, ppm) downfield from tetramethylsilane (internal standard) NMR data are given as multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet) and number of protons. Infrared (IR) spectra were recorded on a Brucker Alpha ECO-ATR spectrophotometer. Elemental analysis was performed on a Perkin–Elmer 2400 C, H, and N analyzer. Mass spectra were taken on Waters Micromass Q-ToF Micro instrument.

1. Chemistry

Procedure of synthesis of ethyl ester of nalidixic acid

The mixture of nalidixic acid (0.08 mol) and ethanol (0.74 mol) was refluxed with sulphuric acid (1-2 mL) till the completion of reaction monitored by TLC on silica gel G plates. Then the reaction mixture was added to 200 mL ice cold water and excess of acid was neutralized by a solution of sodium bicarbonate. The crude ester was extracted with ether (50 mL). The ether layer was separated and ester was obtained on evaporation of ether layer.

Procedure of synthesis of nalidixic acid hydrazide

The ethanolic solution of ester (0.01 mol) and hydrazine-hydrate (0.015 mol) was refluxed for appropriate time. The reaction mixture was then cooled and the precipitated solid was washed with water, dried and recrystallized from ethanol.

General procedure of synthesis of schiff bases of nalidixic acid (1-20)

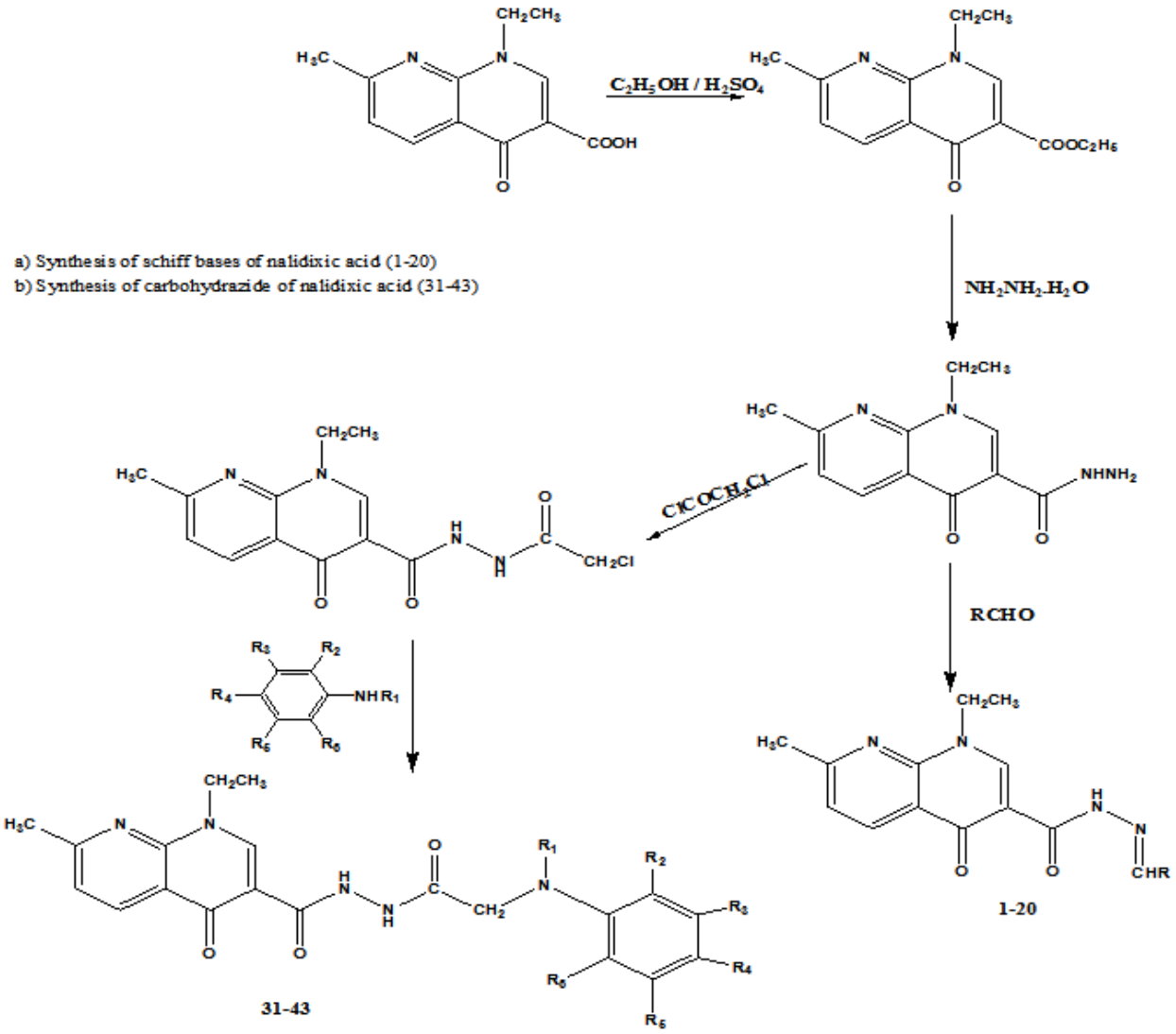
A solution of different aldehydes (0.05 mol) in ethanol was added to a solution of nalidixic acid hydrazide (synthesized above, 0.05 mol) in 50 mL ethanol and refluxed for 5 h. Then the reaction mixture was allowed to cool at room temperature and the precipitated schiff base was filtered, dried and recrystallized from ethanol.

General procedure of synthesis of carbohydrazide of nalidixic acid (31-43)

The nalidixic acid hydrazide (0.01 mol) was refluxed for 8-10 hr with chloroacetyl chloride (0.01 mol) in the presence of few dropes of glacial acetic acid formed chlorinated

acetylated derivative of nalidixic acid. In the last step chlorinated acetyl derivative of nalidixic acid (0.01 mol) was refluxed for 10-15 hr with different aniline (0.01 mol) in the presence of few drops of glacial acetic acid furnished carbohydrazide derivatives of nalidixic acid. The novel derivatives were achieved through the versatile and efficient synthetic route outlined in Scheme 1.

SCHEME I



1 = R= H; 2 = R = C_6H_5O;
3 = R = C_4H_3O; 4 = R = C_8H_7;
5 = R = C_6H_5; 6 = R = CH_3;
7 = R = $C_8H_{10}N$; 8 = R= $C_6H_4NO_2$;
9 = R = C_7H_7O; 10 = R = $C_8H_9O_2$;
11 = R = $C_6H_4NO_2$; 12 = R = C_7H_7O;
13 = R = C_6H_4Cl; 14 = R = C_6H_4F;
15 = R = $C_{10}H_7O$; 16 = R = C_6H_3BrF;
17 = R = C_6H_4Cl; 18 = R = C_6H_5O;
19 = R = $C_8H_9O_2$; 20 = R = C_7H_4N

31 = R_1, R_2, R_3, R_5, R_6=H,R_4=CH_3;
32 = R_1, R_2, R_3, R_5, R_6=H, R_4=OCH_3;
33 = R_1, R_2, R_3, R_5, R_6=H, R_4=NO_2;
34 = R_1, R_2, R_3, R_4, R_5, R_6=H;
35 = R_1, R_2, R_3, R_5, R_6=H, R_4=Cl;
36 = R_1, R_2, R_3, R_5, R_6=H, R_4=Br;
37 = R_1, R_2, R_4, R_5, R_6=H, R_3= NO_2;
38 = R_1, R_3, R_5, R_6=H, R_2= NO_2, R_4=Cl;
39 = R_1, R_3, R_4, R_5, R_6=H, R_2= Cl;
40 = R_1, R_3, R_5, R_6=H, R_2, R_4 = CH_3;
41 = R_1, R_2, R_4, R_5, R_6=H, R_3= Cl;
42 = R_1, R_3, R_4, R_5, R_6=H, R_2= NO_2;
43 = R_1, R_2, R_4, R_5, R_6=H, R_3 = CH_3;

1-ethyl-1,4-dihydro-7-methyl-N'-methylene-4-oxo-1,8-naphthyridine-3-carbohydrazide (1). Yield 75.2%; m.p. 252-258 ˚C; IR (cm^{-1}): 2858.64 (Aliphatic C-H *str*), 1441.96 (C-H bend), 3020.52 (Aromatic C-H *str*), 1493.19 (C=C *str*, Phenyl nucleus), 753.52 (Aromatic C-C out of plan bonding), 913.22 (Aromatic C-H out of plan bending), 792.68 (C-H deformation, aromatic), 1605.11 (C=O, ketone), 3394.95 (N-H *str*, 2^0amine), 1677.58 (N-H in plane bending, 2^0 amine), 3112.43 (N-H *str*, 2^0 amide), 1677.58 (C=O , 2^0 amide), 1327.39 (C–N *str*, 3^0), 1642.11 (–C=N *str*); ^{1}H NMR (DMSO-d_6) δ ppm: 1.387-1.427 (t, 3H, CH_3 of CH_2CH_3), 4.583-4.672 (q, 2H, CH_2 of CH_2CH_3), 2.682 (s, 3H, CH_3 of naphthyridine ring), 7.462-7.489 (q, 1H, CH of N=CH-CH_3), 8.548 (d, 1H of naphthyridine ring), 7.409 (d, 1H of naphthyridine ring), 9.142 (s, 1H of naphthyridine ring); ^{13}C NMR (DMSO-d_6) δ ppm: 13.6 (CH_3, NCH_2CH_3), 48.2 (CH_2, NCH_2CH_3), 145.6 (C, C-2), 111.8 (C,C-3), 177.5 (C, C-4), 135.8 (C,C-5), 114.2 (C,C-6), 161.9 (C,C-7), 24.8 (CH_3, C-7), 153.8 (C, C-4'); Elemental analysis: Calculated for $C_{13}H_{14}N_4O_2$: C, 60.45; H, 5.46; N, 21.69; Found: C, 60.51; H, 5.41; N, 21.66; MS ES+ (ToF): *m/z* 259 [M^+ + 1]. *1-ethyl-1,4-dihydro-7-methyl-4-oxo-N'-(phenoxymethylene)-1,8-naphthyridine-3-carbohydrazide* (2). Yield 75.92%; m.p. 241-244˚C; IR (cm^{-1}): 2865.65 (Aliphatic C-H *str* of alkyl gp.), 1483.46 (C-H bending vibration of alkyl gp.), 3018.69 (Aromatic C-H *str*), 1442.21 (C=C *str*, Phenyl nucleus), 655.72 (Aromatic C-C out of plan bonding), 868.26 (Aromatic C-H out of plan bending), 779.98 (C-H deformation, aromatic), 1604.50 (C=O, ketone), 3320.11 (N-H *str*, 2^0amine), 1658.98 (N-H in plane bending, 2^0 amine), 3104.64 (N-H *str*, 2^0 amide), 1680.98 (C=O , 2^0 amide), 1365.97 (C–N *str*, 3^0), 1690.50 (–C=N); ^{1}H NMR (DMSO-d_6) δ ppm: 1.39-1.42 (t, 3H, CH_3 of CH_2CH_3), 4.52-4.65 (q, 2H, CH_2 of CH_2CH_3), 2.55 (s, 3H, CH_3 of naphthyridine ring), 7.26-7.28 (q, 1H, CH of N=CH-CH_3), 8.15 (d, 1H of naphthyridine ring), 7.11 (d, 1H of naphthyridine ring), 9.05 (s, 1H of naphthyridine ring); ^{13}C NMR (DMSO-d_6) δ ppm: 14.1 (CH_3,NCH_2CH_3), 51.2 (CH_2,NCH_2CH_3), 148.7 (C, C-2), 109.9 (C,C-3), 182.0 (C, C-4), 139.9 (C,C-5), 118.2 (C,C-6), 168.6 (C,C-7), 24.8 (CH_3, C-7), 143.3 (C, C-4'),126.1 (C, C-1"), 130.5 (C,C-2",C-6"), 114.4 (C,C-3",C-5"), 163.0 (C,C-4"), 55.9 (C, C-4"-OCH_3); Elemental analysis: Calculated for $C_{19}H_{18}N_4O_3$: C, 65.13; H, 5.18; N, 15.99; Found: C, 65.10; H, 5.47; N, 15.93; MS ES+ (ToF): *m/z* 351 [M^+ + 1]. *1-ethyl-N'-(furan-2-yl)methylene-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (3). Yield 50.37%; m.p. 262-265˚C; IR (cm^{-1}): 2871.65 (Aliphatic C-H *str* of alkyl gp.), 1461.39 (C-H bending vibration of alkyl gp.), 3028.69 (Aromatic C-H *str*), 1441.23 (C=C *str*, Phenyl nucleus), 669.72 (Aromatic C-C out of plan bonding), 867.26 (Aromatic C-H out of plan bending), 778.18 (C-H deformation, aromatic), 1609.80 (C=O, ketone), 3326.13 (N-H *str*, 2^0amine), 1657.98 (N-H in plane bending, 2^0 amine), 3108.64 (N-H *str*, 2^0 amide), 1693.98 (C=O , 2^0 amide), 1362.47 (C–N *str*, 3^0), 1690.20 (–C=N); ^{1}H NMR (DMSO-d_6) δ ppm: 1.23 1.328-1.360 (t, 3H, CH_3 of CH_2CH_3), 3.272-3.413 (q, 2H, CH_2 of CH_2CH_3), 2.527 (s, 3H, CH_3 of naphthyridine ring), 7.164 (d, 1H of naphthyridine ring), 7.826 (d, 1H of naphthyridine ring), 8.052 (s, 1H of naphthyridine ring), 7.157 (s, 1H, NH of CONH); ^{13}C NMR (DMSO-d_6) δ ppm: 11.9 (CH_3,NCH_2CH_3), 46.5 (CH_2,NCH_2CH_3), 152.8 (C, C-2), 113.5 (C,C-3), 171.2 (C, C-4), 131.4 (C,C-5), 109.9 (C,C-6), 158.0 (C,C-7), 24.8 (CH_3, C-7), 137.3 (C, C-4'),149.1 (C, C-1"), 109.5 (C,C-2"), 109.9 (C,C-3"), 143.9 (C,C-4"); Elemental analysis: Calculated for $C_{17}H_{16}N_4O_3$: C, 62.95; H, 4.97; N, 17.27; Found: C, 62.93; H, 4.99; N, 15.93; MS ES+ (ToF): *m/z* 325 [M^+ + 1]. *1-ethyl-1,4-dihydro-7-methyl-4-oxo-N'-((E)-3-(phenylallylidene)-1,8-naphthyridine-3-carbohydrazide* (4). Yield 63.13%; m.p. 252-255˚C; IR (cm^{-1}): 2854.20 (Aliphatic C-H *str* of alkyl gp.), 1461.84 (C-H bending vibration of alkyl gp.), 3027.72 (Aromatic C-H *str*), 1493.20 (C=C *str*, Phenyl nucleus), 690.49 (Aromatic C-C out of plan bonding), 845.41 (Aromatic C-H out of plan bending), 744.48 (C-H deformation, aromatic), 1659.05 (C=O, ketone), 3343.99 (N-H *str*, 2^0amine), 1551.89 (N-H in plane bending, 2^0 amine), 3112.37 (N-H *str*, 2^0 amide), 1659.05 (C=O , 2^0 amide), 1366.02 (C–N *str*, 3^0), 1686.52 (–C=N); ^{1}H NMR (DMSO-d_6) δ ppm: 1.328-1.380 (t, 3H, CH_3 of CH_2CH_3), 3.452-3.523 (q, 2H, CH_2 of CH_2CH_3), 2.647 (s, 3H, CH_3 of naphthyridine ring), 7.264 (d, 1H of naphthyridine ring), 7.406 (d, 1H of naphthyridine ring), 9.022 (s,

1H of naphthyridine ring), 8.423-8.462 (m, 5H of Ar-H), 8.247 (s, 1H, NH of CONH); ^{13}C NMR (DMSO-*d_6*) δ ppm: 14.5 (CH_3,NCH_2CH_3), 45.9 (CH_2,NCH_2CH_3), 150.4 (C, C-2), 115.8 (C,C-3), 180.2 (C, C-4), 139.6 (C,C-5), 116.3 (C,C-6), 163.8 (C,C-7), 24.8 (CH_3, C-7), 137.3 (C, C-4'),126.3 (C,C-5'), 139.0 (C,C-6') 135.2 (C, C-1"), 126.4 (C,C-2",C-6"), 128.7 (C,C-3",C-5"), 128.0 (C,C-4"); Elemental analysis: Calculated for $C_{21}H_{20}N_4O_2$: C, 69.98; H, 5.59; N, 15.55; Found: C, 69.95; H, 5.57; N, 15.93; MS ES+ (ToF): *m/z* 361 [M^+ + 1]. *N'-benzylidene-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (5). Yield 74.45%; m.p. 265-268˚C; IR (cm^{-1}): 2864.90 (Aliphatic C-H *str* of alkyl gp.), 1478.89 (C-H bending vibration of alkyl gp.), 3020.83 (Aromatic C-H *str*), 1478.89 (C=C *str*, Phenyl nucleus), 750.57 (Aromatic C-C out of plan bonding), 864.55 (Aromatic C-H out of plan bending), 803.86 (C-H deformation, aromatic), 1659.05 (C=O, ketone), 3319.43 (N-H *str*, 2^0amine), 1592.53 (N-H in plane bending, 2^0 amine), 3222.18 (N-H *str*, 2^0 amide), 1691.87 (C=O , 2^0 amide), 1366.17 (C–N *str*, 3^0), 1668.87 (–C=N); ^{1}H NMR (DMSO-*d_6*) δ ppm: 1.14 1.367-1.384 (t, 3H, CH_3 of CH_2CH_3), 3.492-3.524 (q, 2H, CH_2 of CH_2CH_3), 2.647 (s, 3H, CH_3 of naphthyridine ring), 7.374 (d, 1H of naphthyridine ring), 7.206 (d, 1H of naphthyridine ring), 7.062 (s, 1H of naphthyridine ring), 8.241-8.361 (m, 4H of Ar-H), 8.057 (s, 1H, NH of CONH); ^{13}C NMR (DMSO-*d_6*) δ ppm: 13.1 (CH_3,NCH_2CH_3), 49.1 (CH_2,NCH_2CH_3), 151.2 (C, C-2), 119.0 (C,C-3), 174.2 (C, C-4), 135.6 (C,C-5), 119.1 (C,C-6), 159.8 (C,C-7), 24.8 (CH_3, C-7), 143.0 (C, C-4'), 133.8 (C, C-1"), 129.2 (C,C-2",C-6"), 128.9 (C,C-3",C-5"), 131.7 (C,C-4"); Elemental analysis: Calculated for $C_{19}H_{18}N_4O_2$: C, 68.25; H, 5.43; N, 16.76; Found: C, 68.23; H, 5.47; N, 16.73; MS ES+ (ToF): *m/z* 335 [M^+ + 1]. *1-ethyl-N'-ethylidene-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (6). Yield 82.78%; m.p. 232-235˚C; IR (cm^{-1}): 2925.91 (Aliphatic C-H *str* of alkyl gp.), 1352.24 (C-H bending vibration of alkyl gp.), 3021.86 (Aromatic C-H *str*), 1449.63 (C=C *str*, Phenyl nucleus), 655.55 (Aromatic C-C out of plan bonding), 804.03 (Aromatic C-H out of plan bending), 904.31 (C-H deformation, aromatic), 1649.83(C=O, ketone), 3498.28 (N-H *str*, 2^0amine), 1566.62 (N-H in plane bending, 2^0 amine), 3180.78 (N-H *str*, 2^0 amide), 1708.96 (C=O , 2^0 amide), 1377.06 (C–N *str*, 3^0), 1649.75 (–C=N); ^{1}H NMR (DMSO-*d_6*) δ ppm:1.390-1.437 (t, 3H, CH_3 of CH_2CH_3), 4.593-4.662 (q, 2H, CH_2 of CH_2CH_3), 2.652 (s, 3H, CH_3 of naphthyridine ring), 7.562-7.589 (q, 1H, CH of N=CH-CH_3), 8.558 (d, 1H of naphthyridine ring), 7.309 (d, 1H of naphthyridine ring), 9.151 (s, 1H of naphthyridine ring); ^{13}C NMR (DMSO-*d_6*) δ ppm: 13.7 (CH_3, NCH2CH3), 51.0 (CH_2, NCH2CH3), 148.7 (C, C-2), 115.0 (C,C-3), 175.2 (C, C-4), 135.7 (C,C-5), 112.8 (C,C-6), 160.9 (C,C-7), 24.8 (CH_3,C-7), 143.0 (C, C-4'), 131.1 (C, C5"); Elemental analysis: Calculated for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.58; Found: C, 61.72; H, 5.94; N, 20.61; MS ES+ (ToF): *m/z* 273 [M^+ + 1]. *N'-(4-(dimethylamino)benzylidene-1-ethyl1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (7). Yield 61.78%; m.p. 212-215˚C; IR (cm^{-1}): 2925.37 (Aliphatic C-H *str* of alkyl gp.), 1443.04 (C-H bending vibration of alkyl gp.), 3155.95 (Aromatic C-H *str*), 1513.50(C=C *str*, Phenyl nucleus), 667.91 (Aromatic C-C out of plan bonding), 880.31(Aromatic C-H out of plan bending), 813.20 (C-H deformation, aromatic), 1726.01(C=O, ketone), 3329.57 (N-H *str*, 2^0amine), 1547.49 (N-H in plane bending, 2^0 amine), 3248.38 (N-H *str*, 2^0 amide), 1674.49 (C=O , 2^0 amide), 1352.04 (C–N *str*, 3^0); ^{1}H NMR (DMSO-*d_6*) δ ppm: 1.35 1.237-1.280 (t, 3H, CH_3 of CH_2CH_3), 3.172-3.213 (q, 2H, CH_2 of CH_2CH_3), 2.527 (s, 3H, CH_3 of naphthyridine ring), 7.264 (d, 1H of naphthyridine ring), 7.816 (d, 1H of naphthyridine ring), 9.012(s, 1H of naphthyridine ring), 8.241-8.257 (m, 4H of Ar-H), 8.047 (s, 1H, NH of CONH), 3.412 (s, 3H of $N(CH_3)_2$; ^{13}C NMR (DMSO-*d_6*) δ ppm: 12.7 (CH_3,NCH_2CH_3), 48.9 (CH_2,NCH_2CH_3), 148.7 (C, C-2), 113.9 (C,C-3), 180.2 (C, C-4), 138.9 (C,C-5), 116.1 (C,C-6), 161.2 (C,C-7), 24.8 (CH_3, C-7), 143.0 (C, C-4'), 123.3 (C, C-1"), 130.1 (C,C-2",C-6"), 114.4 (C,C-3",C-5"), 151.7 (C,C-4"), 40.3 (C,C-4"-$N(CH_3)_2$); Elemental analysis: Calculated for $C_{21}H_{23}N_5O_2$: C, 66.83; H, 6.14; N, 18.55; Found: C, 66.79; H, 6.17; N, 18.57; MS ES+ (ToF): *m/z* 378 [M^+ + 1]. *N'-(4-(nitrobenzylidene)-1-ethyl1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (8). Yield 67.72%; m.p. 222-225˚C; IR (cm^{-1}): 2881.52 (Aliphatic C-H *str* of

alkyl gp.), 1463.02 (C-H bending vibration of alkyl gp.), 3043.63 (Aromatic C-H *str*), 1519.47 (C=C *str*, Phenyl nucleus), 744.91 (Aromatic C-C out of plan bonding), 802.82 (Aromatic C-H out of plan bending), 776.33 (C-H deformation, aromatic), 1720.61(C=O, ketone), 3319.56 (N-H *str*, 2^0amine), 1599.92 (N-H in plane bending, 2^0 amine), 3161.72 (N-H *str*, 2^0 amide), 1720.61 (C=O , 2^0 amide), 1384.44 (C–N *str*, 3^0), 1689.92 (–C=N), 1384.44 (-NO_2); ^{1}H NMR (DMSO-d_6) δ ppm: 1.337-1.380 (t, 3H, CH_3 of CH_2CH_3), 3.472-3.513 (q, 2H, CH_2 of CH_2CH_3), 2.627 (s, 3H, CH_3 of naphthyridine ring), 7.464 (d, 1H of naphthyridine ring), 7.606 (d, 1H of naphthyridine ring), 9.052(s, 1H of naphthyridine ring), 8.441-8.467 (m, 4H of Ar-H), 8.157 (s, 1H, NH of CONH); ^{13}C NMR (DMSO-d_6) δ ppm: 13.0 (CH_3,NCH_2CH_3), 49.1 (CH_2,NCH_2CH_3), 148.0 (C, C-2), 112.9 (C,C-3), 179.2 (C, C-4), 135.9 (C,C-5), 114.1 (C,C-6), 162.6 (C,C-7), 24.8 (CH_3,C-7), 143.0 (C, C-4'), 139.5 (C, C-1"), 130.5 (C,C-2",C-6"), 121.4 (C,C-3",C-5"), 150.7 (C,C-4"; Elemental analysis: Calculated for $C_{19}H_{17}N_5O_2$: C, 60.15; H, 4.52; N, 18.46; Found: C, 60.18; H, 4.51; N, 18.44; MS ES+ (ToF): *m/z* 380 [M^+ + 1]. *N'-(2-methoxybenzylidene)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (9). Yield 70.32%; m.p. 196-199˚C; IR (cm^{-1}):): 2863.80 (Aliphatic C-H *str* of alkyl gp.), 1461.84 (C-H bending vibration of alkyl gp.), 3061.06 (Aromatic C-H *str*), 1530.04 (C=C *str*, Phenyl nucleus), 668.04 (Aromatic C-C out of plan bonding), 875.13 (Aromatic C-H out of plan bending), 779.89 (C-H deformation, aromatic), 1692.13(C=O, ketone), 3357.98 (N-H *str*, 2^0amine), 1551.85 (N-H in plane bending, 2^0 amine), 3129.31 (N-H *str*, 2^0 amide), 1692.13 (C=O , 2^0 amide), 1402.23 (C–N *str*, 3^0), 1641.47 (–C=N), 2933.37 (-CH *str*, OCH_3); ^{1}H NMR (DMSO-d_6) δ ppm: 1.342-1.361 (t, 3H, CH_3 of CH_2CH_3), 3.252-3.413 (q, 2H, CH_2 of CH_2CH_3), 2.642 (s, 3H, CH_3 of naphthyridine ring), 7.012 (d, 1H of naphthyridine ring), 7.816 (d, 1H of naphthyridine ring), 9.022(s, 1H of naphthyridine ring), 7.641-7.667 (m, 4H of Ar-H), 8.127 (s, 1H, NH of CONH), 3.821 (s, 3H of Ar-OCH_3); ^{13}C NMR (DMSO-d_6) δ ppm: 12.6 (CH_3,NCH_2CH_3), 47.9 (CH_2,NCH_2CH_3), 151.0 (C, C-2), 111.9 (C,C-3), 180.2 (C, C-4), 140.0 (C,C-5), 117.0 (C,C-6), 165.9 (C,C-7), 24.8 (CH_3,C-7), 143.0 (C, C-4'), 116.9 (C, C-1"), 160.5 (C,C-2"), 55.9 (C, C-2"-OCH_3) 114.4 (C,C-3"), 132.1 (C,C-4"), 121.2 (C,C-5"), 130.2(C,C-6"); Elemental analysis: Calculated for $C_{20}H_{20}N_4O_3$: C, 65.92; H, 5.53; N, 15.38; Found: C, 65.89; H, 5.57; N, 15.42; MS ES+ (ToF): *m/z* 365 [M^+ + 1]. *N'-(3,4-dimethoxybenzylidene)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (10). Yield 70.6%; m.p. 206-209˚C; IR (cm^{-1}): 2865.88 (Aliphatic C-H *str* of alkyl gp.), 1433.92 (C-H bending vibration of alkyl gp.), 3027.46 (Aromatic C-H *str*), 1551.92(C=C *str*, Phenyl nucleus), 656.05 (Aromatic C-C out of plan bonding), 874.14 (Aromatic C-H out of plan bending), 802.14 (C-H deformation, aromatic), 1703.16 (C=O, ketone), 3357.76 (N-H *str*, 2^0amine), 1551.92 (N-H in plane bending, 2^0 amine), 3128.91 (N-H *str*, 2^0 amide), 1703.16 (C=O , 2^0 amide), 1352.23 (C–N *str*, 3^0), 1640.31 (–C=N), 2898.93 (-CH Str.,OCH_3); ^{1}H NMR (DMSO-d_6) δ ppm: 1.124-1.136 (t, 3H, CH_3 of CH_2CH_3), 3.152-3.213 (q, 2H, CH_2 of CH_2CH_3), 2.572 (s, 3H, CH_3 of naphthyridine ring), 6.692 (d, 1H of naphthyridine ring), 7.876 (d, 1H of naphthyridine ring), 8.052(s, 1H of naphthyridine ring), 7.141-7.267 (m, 3H of Ar-H), 8.019 (s, 1H, NH of CONH), 3.741 (s, 6H of Ar-OCH_3); ^{13}C NMR (DMSO-d_6) δ ppm: 13.1 (CH_3,NCH_2CH_3), 48.4 (CH_2,NCH_2CH_3), 146.7 (C, C-2), 113.8 (C,C-3), 173.2 (C, C-4), 138.4 (C,C-5), 112.9 (C,C-6), 159.9 (C,C-7), 24.8 (CH_3,C-7), 143.0 (C, C-4'), 127.1 (C, C-1"), 114.4 (C,C-2"), 149.9 (C,C-3"), 56.2 (C,C-3",4"-OCH_3), 115.4 (C,C-5"), 122.5 (C,C-6"); Elemental analysis: Calculated for $C_{21}H_{22}N_4O_4$: C, 63.95; H, 5.62; N, 14.20; Found: C, 63.93; H, 5.65; N, 14.23; MS ES+ (ToF): *m/z* 395 [M^+ + 1]. *N'-(2-nitrobenzylidene)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (11). Yield 64.9%; m.p. 183-186˚C; IR (cm^{-1}): 2857.13 (Aliphatic C-H *str* of alkyl gp.), 1483.17 (C-H bending vibration of alkyl gp.), 3072.27 (Aromatic C-H *str*), 1443.67 (C=C *str*, Phenyl nucleus), 748.78 (Aromatic C-C out of plan bonding), 874.91 (Aromatic C-H out of plan bending), 805.00 (C-H deformation, aromatic), 1737.03 (C=O, ketone), 3311.09 (N-H *str*, 2^0amine), 1572.37 (N-H in plane bending, 2^0 amine), 3129.16 (N-H *str*, 2^0 amide), 1705.02 (C=O , 2^0 amide), 1327.14 (C–N *str*, 3^0), 1650.02 (–C=N), 1327.14 (-NO_2); ^{1}H NMR (DMSO-d_6) δ ppm:

1.147-1.296 (t, 3H, CH_3 of CH_2CH_3), 3.261-3.363 (q, 2H, CH_2 of CH_2CH_3), 2.627 (s, 3H, CH_3 of naphthyridine ring), 6.679 (d, 1H of naphthyridine ring), 7.881 (d, 1H of naphthyridine ring), 8.086(s, 1H of naphthyridine ring), 8.241-8.376 (m, 4H of Ar-H), 8.025 (s, 1H, NH of CONH); ^{13}C NMR (DMSO-*d_6*) δ ppm: 12.9 (CH_3,NCH_2CH_3), 49.1 (CH_2,NCH_2CH_3), 148.1 (C, C-2), 111.8 (C,C-3), 179.0 (C, C-4), 136.2 (C,C-5), 114.0 (C,C-6), 162.6 (C,C-7), 24.8 (CH_3,C-7), 143.0 (C, C-4'), 126.3 (C, C-1"), 148.2 (C,C-2"), 121.2 (C,C-3"), 132.0 (C,C-4"), 135.0 (C,C-5"), 130.1 (C,C-6"); Elemental analysis: Calculated for $C_{19}H_{17}N_5O_4$: C, 60.15; H, 4.52; N, 18.46; Found: C, 60.13; H, 4.54; N, 18.42; MS ES+ (ToF): *m/z* 380 [M^+ + 1]. *N'-(3-methoxybenzylidene)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (12). Yield 59%; m.p. 244-247˚C; IR (cm^{-1}): 2836.79 (Aliphatic C-H *str* of alkyl gp.), 1478.80 (C-H bending vibration of alkyl gp.), 3023.05 (Aromatic C-H *str*), 1518.63 (C=C *str*, Phenyl nucleus), 706.32 (Aromatic C-C out of plan bonding), 874.52 (Aromatic C-H out of plan bending), 803.91 (C-H deformation, aromatic), 1698.27 (C=O, ketone), 3331.05 (N-H *str*, 2^0amine), 1619.69 (N-H in plane bending, 2^0 amine), 3124.77 (N-H *str*, 2^0 amide), 1720.87 (C=O , 2^0 amide), 1366.61 (C–N *str*, 3^0), 1679.69 (–C=N), 2930.05 (-CH Str.,OCH_3); ^{1}H NMR (DMSO-*d_6*) δ ppm: 1.174-1.269 (t, 3H, CH_3 of CH_2CH_3), 3.126-3.146 (q, 2H, CH_2 of CH_2CH_3), 2.679 (s, 3H, CH_3 of naphthyridine ring), 6.697 (d, 1H of naphthyridine ring), 7.878 (d, 1H of naphthyridine ring), 8.168 (s, 1H of naphthyridine ring), 7.241-7.276 (m, 4H of Ar-H), 8.057 (s, 1H, NH of CONH). ^{13}C NMR (DMSO-*d_6*) δ ppm: 13.0 (CH_3,NCH_2CH_3), 47.4 (CH_2,NCH_2CH_3), 150.7 (C, C-2), 113.8 (C,C-3), 176.2 (C, C-4), 137.2 (C,C-5), 116.1 (C,C-6), 164.1 (C,C-7), 24.8 (CH_3,C-7), 143.0 (C, C-4'), 134.8 (C, C-1"), 113.4 (C,C-2"), 160.8 (C,C-3"), 55.9 (C,C-3"-OCH_3), 116.6 (C,C-4"), 129.9 (C,C-5"), 121.5 (C,C-6"); Elemental analysis: Calculated for $C_{20}H_{20}N_4O_3$: C, 65.92; H, 5.53; N, 15.38; Found: C, 65.94; H, 5.51; N, 15.36; MS ES+ (ToF): *m/z* 365 [M^+ + 1]. *N'-(2-chlorobenzylidene)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (13). Yield 65.76%; m.p. 182-185˚C; IR (cm^{-1}): 2834.78 (Aliphatic C-H *str* of alkyl gp.), 1433.80 (C-H bending vibration of alkyl gp.), 3027.44 (Aromatic C-H *str*), 1493.14 (C=C *str*, Phenyl nucleus), 749.23 (Aromatic C-C out of plan bonding), 875.12 (Aromatic C-H out of plan bending), 804.93 (C-H deformation, aromatic), 1711.42 (C=O, ketone), 3357.90 (N-H *str*, 2^0amine), 1630.63 (N-H in plane bending, 2^0 amine), 3139.43 (N-H *str*, 2^0 amide), 1720.63 (C=O , 2^0 amide), 1366.17 (C–N *str*, 3^0), 1680.63 (–C=N), 656.37 (C-Cl); ^{1}H NMR (DMSO-*d_6*) δ ppm: 1.274-1.298 (t, 3H, CH_3 of CH_2CH_3), 3.162-3.198 (q, 2H, CH_2 of CH_2CH_3), 2.682 (s, 3H, CH_3 of naphthyridine ring), 6.679 (d, 1H of naphthyridine ring), 7.864 (d, 1H of naphthyridine ring), 8.268 (s, 1H of naphthyridine ring), 7.614-7.727 (m, 4H of Ar-H), 8.127 (s, 1H, NH of CONH); ^{13}C NMR (DMSO-*d_6*) δ ppm: 13.8 (CH_3,NCH_2CH_3), 49.4 (CH_2,NCH_2CH_3), 146.7 (C, C-2), 114.0 (C,C-3), 177.5 (C, C-4), 138.2 (C,C-5), 114.2 (C,C-6), 162.6 (C,C-7), 24.8 (CH_3, C-7), 143.0 (C, C-4'), 133.4 (C, C-1"), 134.0 (C,C-2"), 129.0 (C,C-3"), 132.5 (C,C-4"), 127.0 (C,C-5"), 130.6 (C,C-6"); Elemental analysis: Calculated for $C_{20}H_{20}N_4O_3$: C, 61.87; H, 4.65; N, 15.19; Found: C, 61.84; H, 4.67; N, 15.21; MS ES+ (ToF): *m/z* 369 [M^+ + 1]. *N'-(4-fluorobenzylidene)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (14). Yield 98.12%; m.p. 203-206˚C; IR (cm^{-1}): 2898.18 (Aliphatic C-H *str* of alkyl gp.), 1462.08 (C-H bending vibration of alkyl gp.), 3007.59 (Aromatic C-H *str*), 1462.08 (C=C *str*, Phenyl nucleus), 707.82 (Aromatic C-C out of plan bonding), 870.74 (Aromatic C-H out of plan bending), 827.70 (C-H deformation, aromatic), 1711.52 (C=O, ketone), 3358.43 (N-H *str*, 2^0amine), 1639.62 (N-H in plane bending, 2^0 amine), 3139.04 (N-H *str*, 2^0 amide), 1689.62 (C=O , 2^0 amide), 1370.93 (C–N *str*, 3^0), 1649.19 (–C=N), 1228.82 (C-F); ^{1}H NMR (DMSO-*d_6*) δ ppm: 1.174-1.218 (t, 3H, CH_3 of CH_2CH_3), 3.026-3.089 (q, 2H, CH_2 of CH_2CH_3), 2.528 (s, 3H, CH_3 of naphthyridine ring), 6.719 (d, 1H of naphthyridine ring), 7.872 (d, 1H of naphthyridine ring), 8.098 (s, 1H of naphthyridine ring), 7.694-8.127 (m, 4H of Ar-H), 8.072 (s, 1H, NH of CONH); ^{13}C NMR (DMSO-*d_6*) δ ppm: 12.9 (CH_3,NCH_2CH_3), 50.0 (CH_2,NCH_2CH_3), 149.0 (C, C-2), 113.2 (C,C-3), 175.2 (C, C-4), 139.2 (C,C-5), 112.0 (C,C-6), 163.2 (C,C-7), 24.8 (CH_3,C-7), 143.0 (C, C-4'), 129.4 (C, C-1"), 130.8 (C,C-2", C-6"),

115.8 (C,C-3",5"), 165.2 (C,C-4"); Elemental analysis: Calculated for $C_{19}H_{17}FN_4O_2$: C, 64.76; H, 4.86; N, 15.90; Found: C, 64.73; H, 4.89; N, 15.87; MS ES+ (ToF): *m/z* 353 [M^+ + 1]. *1-ethyl-1,4-dihydro-N'-((2-hydroxynaphthalen-1-yl)methylene)-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (15). Yield 56%; m.p. 226-229˚C; IR (cm^{-1}): 2843.83 (Aliphatic C-H *str* of alkyl gp.), 1483.51 (C-H bending vibration of alkyl gp.), 3000.23 (Aromatic C-H *str*), 1461.88 (C=C *str*, Phenyl nucleus), 742.93 (Aromatic C-C out of plan bonding), 870.59 (Aromatic C-H out of plan bending), 815.04 (C-H deformation, aromatic), 1649.88 (C=O, ketone), 3331.38 (N-H *str*, 2^0amine), 1530.04 (N-H in plane bending, 2^0 amine), 3104.93 (N-H *str*, 2^0 amide), 1682.07 (C=O , 2^0 amide), 1365.97 (C–N *str*, 3^0), 1645.07 (–C=N), 1127.86 (3^0 OH); ^{1}H NMR (DMSO-d_6) δ ppm: 1.247-1.281 (t, 3H, CH_3 of CH_2CH_3), 3.162-3.198 (q, 2H, CH_2 of CH_2CH_3), 2.617 (s, 3H, CH_3 of naphthyridine ring), 6.627 (d, 1H of naphthyridine ring), 7.891 (d, 1H of naphthyridine ring), 8.178 (s, 1H of naphthyridine ring), 8.194-8.227 (m, 6H of Ar-H), 8.127 (s, 1H, NH of CONH); ^{13}C NMR (DMSO-d_6) δ ppm: 13.0 (CH_3,NCH_2CH_3), 49.2 (CH_2,NCH_2CH_3), 148.7 (C, C-2), 114.6 (C,C-3), 175.2 (C, C-4), 139.4 (C,C-5), 114.1 (C,C-6), 163.0 (C,C-7), 24.8 (CH_3,C-7), 154.7 (C, C-4'), 99.5 (C, C-1"), 168.3 (C,C-2"), 128.0 (C,C-3",C-5"), 128.7(C,C-6"),130.8 (C,C-7"),126.4 (C,C-8"); Elemental analysis: Calculated for $C_{23}H_{20}N_4O_3$: C, 68.99; H, 5.03; N, 13.99; Found: C, 69.00; H, 5.07; N, 13.97; MS ES+ (ToF): *m/z* 401 [M^+ + 1]. *N'-(5-bromo-2-fluorobenzylidene)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (16). Yield 71.35%; m.p. 226-229˚C; IR (cm^{-1}): 2876.14 (Aliphatic C-H *str* of alkyl gp.), 1327.58 (C-H bending vibration of alkyl gp.), 3043.37 (Aromatic C-H *str*), 1407.78 (C=C *str*, Phenyl nucleus), 744.91 (Aromatic C-C out of plan bonding), 706.66 (Aromatic C-H out of plan bending), 803.85 (C-H deformation, aromatic), 1625.41(C=O, ketone), 3343.82 (N-H *str*, 2^0amine), 1551.93 (N-H in plane bending, 2^0 amine), 3174.30 (N-H *str*, 2^0 amide), 1625.41 (C=O , 2^0 amide), 1327.58 (C–N *str*, 3^0), 1668.78 (–C=N), 1051.59 (-C-F, monofluorinated compound), 611.30 (C-Br, monobrominated compound); ^{1}H NMR (DMSO-d_6) δ ppm: 1.406-1453 (t, 3H, CH_3 of CH_2CH_3), 4.603-4.672 (q, 2H, CH_2 of CH_2CH_3), 7.329 (s, 3H, CH_3 of naphthyridinring), 8.093 (d, 1H of naphthyridine ring), 8.705 (d, 1H of naphthyridine ring), 8.705 (s, 1H of naphthyridine ring), 7.750-7.778 (m, 3H of Ar-H); ^{13}C NMR (DMSO-d_6) δ ppm: 13.1 (CH_3,NCH_2CH_3), 49.4 (CH_2,NCH_2CH_3), 149.2 (C, C-2), 112.8 (C,C-3), 178.2 (C, C-4), 138.2 (C,C-5), 114.2 (C,C-6), 161.6 (C,C-7), 24.8 (CH_3,C-7), 142.9 (C, C-4'), 120.4 (C, C-1"), 158.7 (C,C-2"), 117.8 (C,C-3"), 135.6 (C,C-4"),118.8 (C,C-5"), 134.3 (C,C-6"); Elemental analysis: Calculated for $C_{19}H_{16}BrFN_4O_2$: C, 52.92; H, 3.74; N, 12.99; Found: C, 52.95; H, 3.71; N, 12.97; MS ES+ (ToF): *m/z* 432 [M^+ + 1]. *N'-(4-chlorobenzylidene)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (17). Yield 74.68%; m.p. 226-229˚C; IR (cm^{-1}): 2851.66 (Aliphatic C-H *str* of alkyl gp.), 1483.52 (C-H bending vibration of alkyl gp.), 3007.77 (Aromatic C-H *str*), 1443.35 (C=C *str*, Phenyl nucleus), 668.03 (Aromatic C-C out of plan bonding), 874.26 (Aromatic C-H out of plan bending), 805.01 (C-H deformation, aromatic), 1692.13 (C=O, ketone), 3302.61 (N-H *str*, 2^0amine), 1566.84 (N-H in plane bending, 2^0 amine), 3138.46 (N-H *str*, 2^0 amide), 1692.13 (C=O , 2^0 amide), 1383.34 (C–N *str*, 3^0), 1662.16 (–C=N), 702.70 (C-Cl); ^{1}H NMR (DMSO-d_6) δ ppm: 1.153-2.018 (t, 3H, CH_3 of CH_2CH_3), 3.132-3.265 (q, 2H, CH_2 of CH_2CH_3), 2.557 (s, 3H, CH_3 of naphthyridine ring), 7.857 (d, 1H of naphthyridine ring), 8.035 (d, 1H of naphthyridine ring); ^{13}C NMR (DMSO-d_6) δ ppm: 13.5 (CH_3,NCH_2CH_3), 49.1 (CH_2,NCH_2CH_3), 147.1 (C, C-2), 113.8 (C,C-3), 176.2 (C, C-4), 140.2 (C,C-5), 116.2 (C,C-6), 162.6 (C,C-7), 24.8 (CH_3, C-7), 143.0 (C, C-4'), 129.5 (C, C-1"), 130.6 (C,C-2", C-6"), 128.9 (C,C-3",C5"), 136.6 (C,C-4"); Calculated for $C_{19}H_{17}ClN_4O_2$: C, 61.87; H, 4.65; N, 15.19; Found: C, 61.84; H, 4.67; N, 15.17; MS ES+ (ToF): *m/z* 369 [M^+ + 1]. *N'-(2-hydroxybenzylidene)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (18). Yield 56%; m.p. 226-229˚C; IR (cm^{-1}): 2843.42 (Aliphatic C-H *str* of alkyl gp.), 1483.52 (C-H bending vibration of alkyl gp.), 3037.40 (Aromatic C-H *str*), 1518.66 (C=C *str*, Phenyl nucleus), 668.08 (Aromatic C-C out of plan bonding), 824.53 (Aromatic C-H out of plan bending), 748.91

(C-H deformation, aromatic), 1698.25 (C=O, ketone), 3342.62 (N-H *str*, 2^0amine), 1612.17 (N-H in plane bending, 2^0 amine), 3150.67 (N-H *str*, 2^0 amide), 1698.25 (C=O , 2^0 amide), 1346.38 (C–N *str*, 3^0), 1640.02 (–C=N), 1150 (3^0 OH); ^{1}H NMR (DMSO-d_6) δ ppm: 1.231-1.281 (t, 3H, CH_3 of CH_2CH_3), 3.273-4.165 (q, 2H, CH_2 of CH_2CH_3), 2.675 (s, 3H, CH_3 of naphthyridine ring), 7.975 (d, 1H of naphthyridine ring), 8.153 (d, 1H of naphthyridine ring); ^{13}C NMR (DMSO-d_6) δ ppm: 12.9 (CH_3,NCH_2CH_3), 49.4 (CH_2,NCH_2CH_3), 148.7 (C, C-2), 114.6 (C,C-3), 177.5 (C, C-4), 139.2 (C,C-5), 115.1 (C,C-6), 160.6 (C,C-7), 24.5 (CH_3,C-7), 143.1 (C, C-4'), 118.5 (C, C-1"), 160.1 (C,C-2"), 116.0 (C,C-3"), 132.5 (C,C-4"), 121.5 (C,C-5"), 130.2 (C,C-6"); Elemental analysis: Calculated for $C_{19}H_{18}N_4O_3$: C, 65.13; H, 5.18; N, 15.99; Found: C, 65.11; H, 5.15; N, 16.01; MS ES+ (ToF): *m/z* 351 [M^+ + 1]. *N'-(2,4-dimethoxybenzylidene)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (19). Yield 86.78%; m.p. 226-229˚C; IR (cm^{-1}): 2955.13 (Aliphatic C-H *str* of alkyl gp.), 1461.78 (C-H bending vibration of alkyl gp.), 3061.09 (Aromatic C-H *str*), 1493.25 (C=C *str*, Phenyl nucleus), 668.14 (Aromatic C-C out of plan bonding), 819.83 (Aromatic C-H out of plan bending), 765.58 (C-H deformation, aromatic), 1611.73(C=O, ketone), 3376.28 (N-H *str*, 2^0amine), 1630.80 (N-H in plane bending, 2^0 amine), 3194.16 (N-H *str*, 2^0 amide), 1692.04 (C=O , 2^0 amide), 1383.39 (C–N *str*, 3^0), 1690.04 (–C=N), 2903.1 (-CH Str., OCH_3); ^{1}H NMR (DMSO-d_6) δ ppm: 1.053-1.418 (t, 3H, CH_3 of CH_2CH_3), 2.932-2.965 (q, 2H, CH_2 of CH_2CH_3), 3.857 (s, 6H, CH_3 of $-OCH_3$), 3.354 (s, 3H, -CH_3), 7.905 (d, 1H of naphthyridine ring), 8.053 (d, 1H of naphthyridine ring); ^{13}C NMR (DMSO-d_6) δ ppm: 13.1 (CH_3,NCH_2CH_3), 48.2 (CH_2,NCH_2CH_3), 147.2 (C, C-2), 112.6 (C,C-3), 175.5 (C, C-4), 137.2 (C,C-5), 113.1 (C,C-6), 162.6 (C,C-7), 24.8 (CH_3,C-7), 142.0 (C, C-4'), 55.6 (C,C-2",4"-OCH_3), 109.2 (C, C-1"), 161.2 (C,C-2"), 100.5 (C,C-3"), 164.0 (C,C-4"), 106.7 (C,C-5"), 131.2 (C,C-6"); Elemental analysis: Calculated for $C_{21}H_{22}N_4O_4$: C, 63.95; H, 5.62; N, 14.20; Found: C, 63.97; H, 5.60; N, 14.22; MS ES+ (ToF): *m/z* 395 [M^+ + 1]. *N'-(3-cyanobenzylidene)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (20). Yield 42.86%; m.p. 226-229˚C; IR (cm^{-1}): 2859.06 (Aliphatic C-H *str* of alkyl gp.), 1461.79 (C-H bending vibration of alkyl gp.), 3027.22 (Aromatic C-H *str*), 1461.79 (C=C *str*, Phenyl nucleus), 667.98 (Aromatic C-C out of plan bonding), 814.63 (Aromatic C-H out of plan bending), 788.67 (C-H deformation, aromatic), 1726.16 (C=O, ketone), 3399.97 (N-H *str*, 2^0amine), 1536.23 (N-H in plane bending, 2^0 amine), 3149.95 (N-H *str*, 2^0 amide), 1391.00 (C–N *str*, 3^0), 1640.23 (–C=N), 1346.35 (-CN 3^0); ^{1}H NMR (DMSO-d_6) δ ppm: 1.353-1.418 (t, 3H, CH_3 of CH_2CH_3), 3.247-3.956 (q, 2H, CH_2 of CH_2CH_3), 2.645 (s, 3H, -CH_3 of naphthyridine ring), 6.685 (d, 1H of naphthyridine ring), 7.935 (d, 1H of naphthyridine ring); ^{13}C NMR (DMSO-d_6) δ ppm: 12.1 (CH_3,NCH_2CH_3), 47.4 (CH_2,NCH_2CH_3), 148.7 (C, C-2), 113.8 (C,C-3), 177.5 (C, C-4), 138.2 (C,C-5), 114.1 (C,C-6), 162.6 (C,C-7), 24.8 (CH_3,C-7), 143.0 (C, C-4'), 134.5 (C, C-1",C-4"), 132.5 (C,C-2",C-6"), 114.2 (C, C-3"CN). Elemental analysis: Calculated for $C_{20}H_{17}N_5O_2$: C, 66.84; H, 4.77; N, 19.49; Found: C, 66.80; H, 4.75; N, 19.46; MS ES+ (ToF): *m/z* 360 [M^+ + 1]. *N'-(2-(p-tolylamino)acetyl)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (31). Yield 59.84%; m.p. 226-229˚C; IR (cm^{-1}): 2933.59 (Aliphatic C-H *str* of alkyl gp.), 1436.17 (C-H bending vibration of alkyl gp.), 3031.28 (Aromatic C-H *str*), 1516.51 (C=C *str*, Phenyl nucleus), 676.30 (Aromatic C-C out of plan bonding), 803.11 (Aromatic C-H out of plan bending), 780.74 (C-H deformation, aromatic), 1646.74 (C=O, ketone), 3366.06 (N-H *str*, 2^0amine), 1540.03 (N-H in plane bending, 2^0 amine), 3158.86 (N-H *str*, 2^0 amide), 1720.38 (C=O , 2^0 amide), 1354.09 (C–N *str*, 3^0); ^{1}H NMR (DMSO-d_6) δ ppm: 1.348-1.397 (t, 3H, CH_3 of CH_2CH_3), 2.586-2.965 (q, 2H, CH_2 of CH_2CH_3), 2.561 (s, 3H, CH_3 of naphthyridine ring), 6.659 (d, 1H of naphthyridine ring), 7.869 (d, 1H of naphthyridine ring), 9.178 (s, 1H of naphthyridine ring), 4.563 (d, 2H, CH_2 of CH_2NH), 6.936-7.491 (m, 4H, Ar-H); ^{13}C NMR (DMSO-d_6) δ ppm: 13.0 (CH_3, NCH_2CH_3), 49.1 (CH_2, NCH_2CH_3), 141.9 (C, C-2), 109.4 (C, C-3), 173.9 (C, C-4), 138.2 (C, C-5), 116.1 (C,C-6), 157.9 (C,C-7), 24.8 (C_3,C-7), 165.9 (C, C-1'), 170.3 (C, C-4'), 57.3 (C, C-5'), 144.6 (C, C-1"), 113.4 (C, C-2", C-6"), 129.9 (C, C-3", C-5"), 126.8 (C, C-4"), 24.3 (C, C-4" CH_3); Elemental analysis: Calculated for

$C_{21}H_{23}N_5O_3$: C, 64.11; H, 5.89; N, 17.80; Found: C, 64.13; H, 5.87; N, 17.76; MS ES+ (ToF): *m/z* 394 [M^+ + 1].*N'-(2-(4-methoxyphenylamino)acetyl)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (32). Yield 66.94%; m.p. 226-229˚C; IR (cm^{-1}): 2933.75 (Aliphatic C-H *str* of alkyl gp.), 1472.43 (C-H bending vibration of alkyl gp.), 3064.53 (Aromatic C-H *str*), 1496.48 (C=C *str*, Phenyl nucleus), 668.15 (Aromatic C-C out of plan bonding), 874.70 (Aromatic C-H out of plan bending), 80326 (C-H deformation, aromatic), 1688.37 (C=O, ketone), 3325.81 (N-H *str*, 2^0amine), 1558.64 (N-H in plane bending, 2^0 amine), 3177.84 (N-H *str*, 2^0 amide), 1716.09 (C=O , 2^0 amide), 1339.42 (C–N *str*, 3^0) 2980.90 (-CH Str., OCH_3); ^{1}H NMR (DMSO-d_6) δ ppm: 1.327-1.367 (t, 3H, CH_3 of CH_2CH_3), 3.186-3.265 (q, 2H, CH_2 of CH_2CH_3), 2.591 (s, 3H, CH_3 of naphthyridine ring), 6.798 (d, 1H of naphthyridine ring), 7.894 (d, 1H of naphthyridine ring), 9.132 (s, 1H of naphthyridine ring), 3.963 (d, 2H, CH_2 of CH_2NH), 6.742-7.237 (m, 4H, Ar-H); ^{13}C NMR (DMSO-d_6) δ ppm: 12.1 (CH_3, NCH_2CH_3), 49.4 (CH_2, NCH_2CH_3), 148.7 (C, C-2), 113.8 (C, C-3), 172.6 (C, C-4), 130.4 (C, C-5), 114.2 (C,C-6), 167.2 (C,C-7), 24.8 (C_3,C-7), 165.9 (C, C-1'), 170.3 (C, C-4'), 57.3 (C, C-5'), 139.9 (C, C-1"), 114.5 (C, C-2", C-6"), 115.1 (C, C-3", C-5"), 149.1 (C, C-4"), 55.9 (C, C-4" OCH_3); Elemental analysis: Calculated for $C_{21}H_{23}N_5O_4$: C, 61.60; H, 5.66; N, 17.10; Found: C, 61.62; H, 5.67; N, 17.13; MS ES+ (ToF): *m/z* 410 [M^+ + 1]. *N'-(2-(4-nitrophenylamino)acetyl)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (33). Yield 67.76%; m.p. 226-229˚C; IR (cm^{-1}): 2934.66 (Aliphatic C-H *str* of alkyl gp.), 1339.40 (C-H bending vibration of alkyl gp.), 3031.27 (Aromatic C-H *str*), 1558.72 (C=C *str*, Phenyl nucleus), 657.06 (Aromatic C-C out of plan bonding), 894.97 (Aromatic C-H out of plan bending), 803.29 (C-H deformation, aromatic), 1622.38 (C=O, ketone), 3392.45 (N-H *str*, 2^0amine), 1558.66 (N-H in plane bending, 2^0 amine), 3184.75 (N-H *str*, 2^0 amide), 1646.71 (C=O , 2^0 amide), 1368.76 (C–N *str*, 3^0), 1516.51 (-NO_2); ^{1}H NMR (DMSO-d_6) δ ppm: 1.350-1.392 (t, 3H, CH_3 of CH_2CH_3), 2.574-2.655 (q, 2H, CH_2 of CH_2CH_3), 2.461 (s, 3H, CH_3 of naphthyridine ring), 6.529 (d, 1H of naphthyridine ring), 7.519 (d, 1H of naphthyridine ring), 9.108 (s, 1H of naphthyridine ring), 8.521 (d, 1H, NH of –CONH), 4.575 (d, 2H, CH_2 of CH_2NH), 7.863-7.891 (m, 4H, Ar-H); ^{13}C NMR (DMSO-d_6) δ ppm: 13.1 (CH_3, NCH_2CH_3), 44.1 (CH_2, NCH_2CH_3), 138.9 (C, C-2), 107.9 (C, C-3), 177.6 (C, C-4), 139.6 (C, C-5), 114.1 (C,C-6), 162.4 (C,C-7), 24.8 (C_3,C-7), 162.5 (C, C-1'), 169.1 (C, C-4'), 56.1 (C, C-5'), 153.7 (C, C-1"), 114.4 (C, C-2", C-6"), 121.9 (C, C-3", C-5"), 136.8 (C, C-4"); Elemental analysis: Calculated for $C_{20}H_{20}N_6O_5$: C, 56.60; H, 4.75; N, 19.80; Found: C, 56.62; H, 4.71; N, 19.83; MS ES+ (ToF): *m/z* 425 [M^+ + 1]. *1-ethyl-1,4-dihydro-7-methyl-4-oxo-N'-(2-phenylamino)acetyl)-1,8-naphthyridine-3-carbohydrazide* (34). Yield 37.46%; m.p. 226-229˚C; IR (cm^{-1}): 2831.31 (Aliphatic C-H *str* of alkyl gp.), 1457.07 (C-H bending vibration of alkyl gp.), 3031.37 (Aromatic C-H *str*), 1521.17 (C=C *str*, Phenyl nucleus), 708.06 (Aromatic C-C out of plan bonding), 874.90 (Aromatic C-H out of plan bending), 802.71 (C-H deformation, aromatic), 1705.53 (C=O, ketone), 3317.79 (N-H *str*, 2^0amine), 1575.96 (N-H in plane bending, 2^0 amine), 3184.79 (N-H *str*, 2^0 amide), 1716.29 (C=O , 2^0 amide), 1386.92 (C–N *str*, 3^0); ^{1}H NMR (DMSO-d_6) δ ppm: 1.179-1.218 (t, 3H, CH_3 of CH_2CH_3), 3.567-4.143 (q, 2H, CH_2 of CH_2CH_3), 2.575 (s, 3H, CH_3 of naphthyridine ring), 6.640 (d, 1H of naphthyridine ring), 7.984 (d, 1H of naphthyridine ring), 8.036 (s, 1H of naphthyridine ring), 4.042 (d, 2H, CH_2 of CH_2NH), 7.261-7.321 (m, 5H, AR-H); ^{13}C NMR (DMSO-d_6) δ ppm: 11.9 (CH_3, NCH_2CH_3), 42.9 (CH_2, NCH_2CH_3), 148.1 (C, C-2), 113.1 (C, C-3), 172.1 (C, C-4), 131.3 (C, C-5), 104.1 (C,C-6), 162.6 (C,C-7), 24.8 (C_3,C-7), 165.9 (C, C-1'), 170.3 (C, C-4'), 57.1 (C, C-5'), 147.6 (C, C-1"), 113.5 (C, C-2", C-6"), 129.6 (C, C-3", C-5"), 117.2 (C, C-4"); Elemental analysis: Calculated for $C_{20}H_{21}N_5O_3$: C, 63.31; H, 5.58; N, 18.46; Found: C, 63.29; H, 5.59; N, 18.49; MS ES+ (ToF): *m/z* 380 [M^+ + 1]. *N'-(2-(4-chlorophenylamino) acetyl)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (35). Yield 86.27%; m.p. 226-229˚C; IR (cm^{-1}2933.99 (Aliphatic C-H *str* of alkyl gp.), 1436.15 (C-H bending vibration of alkyl gp.), 3003.61 (Aromatic C-H *str*), 1439.93 (C=C *str*, Phenyl nucleus), 668.21 (Aromatic C-C out of plan bonding), 802.59

(Aromatic C-H out of plan bending), 780.45 (C-H deformation, aromatic), 1716.99 (C=O, ketone), 3308.66 (N-H *str*, 2^0amine), 1569.11 (N-H in plane bending, 2^0 amine), 3142.96 (N-H *str*, 2^0 amide), 1686.70 (C=O , 2^0 amide), 1339.40 (C–N *str*, 3^0), 780.45 (-C-Cl, monochlorinated compound); ^{1}H NMR (DMSO-d_6) δ ppm: 1.352-1.386 (t, 3H, CH_3 of CH_2CH_3), 3.176-3.213 (q, 2H, CH_2 of CH_2CH_3), 2.718 (s, 3H, CH_3 of naphthyridine ring), 6.781 (d, 1H of naphthyridine ring), 7.894 (d, 1H of naphthyridine ring), 8.136 (s, 1H of naphthyridine ring), 3.981 (d, 2H, CH_2 of CH_2NH), 7.016-7.138 (m, 4H, AR-H); ^{13}C NMR (DMSO-d_6) δ ppm: 13.2 (CH_3, NCH_2CH_3), 49.1 (CH_2, NCH_2CH_3), 146.2 (C, C-2), 113.8 (C, C-3), 177.6 (C, C-4), 138.2 (C, C-5), 114.0 (C,C-6), 162.3 (C,C-7), 24.8 (C_3,C-7), 165.9 (C, C-1'), 170.3 (C, C-4'), 57.3 (C, C-5'), 145.7 (C, C-1"), 114.9 (C, C-2", C-6"), 129.7 (C, C-3", C-5"), 122.7 (C, C-4"); Elemental analysis: Calculated for $C_{20}H_{20}ClN_5O_3$: C, 58.04; H, 4.87; N, 16.92; Found: C, 58.03; H, 4.89; N, 16.94; MS ES+ (ToF): *m/z* 414 [M^+ + 1]. *N'-(2-(4-bromophenylamino)acetyl)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (36). Yield 73.39%; m.p. 226-229˚C; IR (cm^{-1}): 2912.26 (Aliphatic C-H *str* of alkyl gp.), 1352.19 (C-H bending vibration of alkyl gp.), 3058.42 (Aromatic C-H *str*), 1439.93 (C=C *str*, Phenyl nucleus), 656.38 (Aromatic C-C out of plan bonding), 874.04 (Aromatic C-H out of plan bending), 707.24 (C-H deformation, aromatic), 1615.51 (C=O, ketone), 3349.76 (N-H *str*, 2^0amine), 1615.51 (N-H in plane bending, 2^0 amine), 3127.84 (N-H *str*, 2^0 amide), 1716.49 (C=O , 2^0 amide), 1352.19 (C–N *str*, 3^0), 634.96 (-C-Br, monobrominated compound); ^{1}H NMR (DMSO-d_6) δ ppm: 1.379-1.425 (t, 3H, CH_3 of CH_2CH_3), 4.577-4.643 (q, 2H, CH_2 of CH_2CH_3), 2.685 (s, 3H, CH_3 of naphthyridine ring), 7.540 (d, 1H of naphthyridine ring), 8.524 (d, 1H of naphthyridine ring), 9.133 (s, 1H of naphthyridine ring), 3.383 (d, 2H, CH_2 of CH_2NH); ^{13}C NMR (DMSO-d_6) δ ppm: 13.9 (CH_3, NCH_2CH_3), 49.4 (CH_2, NCH_2CH_3), 148.7 (C, C-2), 113.1 (C, C-3), 175.7 (C, C-4), 137.1 (C, C-5), 114.1 (C,C-6), 162.6 (C,C-7), 24.8 (C_3,C-7), 165.9 (C, C-1'), 170.3 (C, C-4'), 57.3 (C, C-5'), 146.6 (C, C-1"), 115.7 (C, C-2", C-6"), 132.5 (C, C-3", C-5"), 111.5 (C, C-4"); Elemental analysis: Calculated for $C_{20}H_{20}BrN_5O_3$: C, 52.41; H, 4.40; N, 16.28; Found: C, 52.39; H, 4.42; N, 16.26; MS ES+ (ToF): *m/z* 459 [M^+ + 1]. *N'-(2-(3-nitrophenylamino)acetyl)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (37). Yield 68.32%; m.p. 226-229˚C; IR (cm^{-1}):): 2867.64 (Aliphatic C-H *str* of alkyl gp.), 1445.25 (C-H bending vibration of alkyl gp.), 3051.96 (Aromatic C-H *str*), 1513.69 (C=C *str*, Phenyl nucleus), 668.28 (Aromatic C-C out of plan bonding), 802.71 (Aromatic C-H out of plan bending), 735.41 (C-H deformation, aromatic), 1692.43 (C=O, ketone), 3329.93 (N-H *str*, 2^0amine), 1552.14 (N-H in plane bending, 2^0 amine), 3051.96 (N-H *str*, 2^0 amide), 1685.32 (C=O , 2^0 amide), 1351.31 (C–N *str*, 3^0), 1492.80 (-NO_2); ^{1}H NMR (DMSO-d_6) δ ppm: 1.297-1.352 (t, 3H, CH_3 of CH_2CH_3), 3.177-3.634 (q, 2H, CH_2 of CH_2CH_3), 2.585 (s, 3H, CH_3 of naphthyridine ring), 6.840 (d, 1H of naphthyridine ring), 7.824 (d, 1H of naphthyridine ring), 9.037 (s, 1H of naphthyridine ring), 4.381 (d, 2H, CH_2 of CH_2NH), 7.481-7.986 (m 4H, Ar-H); ^{13}C NMR (DMSO-d_6) δ ppm: 12.8 (CH_3, NCH_2CH_3), 48.9 (CH_2, NCH_2CH_3), 146.3 (C, C-2), 113.8 (C, C-3), 177.5 (C, C-4), 138.2 (C, C-5), 113.9 (C,C-6), 161.9 (C,C-7), 24.8 (C_3,C-7), 164.3 (C, C-1'), 169.3 (C, C-4'), 57.2 (C, C-5'), 148.5 (C, C-1"), 107.4 (C, C-2", C-6"), 149.2 (C, C-3", C-5"), 109.5 (C, C-4"); Elemental analysis: Calculated for $C_{20}H_{20}N_6O_5$: C, 56.60; H, 4.75; N, 19.80; Found: C, 56.63; H, 4.72; N, 19.78; MS ES+ (ToF): *m/z* 425 [M^+ + 1]. *N'-(2-(4-chloro-2-nitrophenylamino)acetyl)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (38). Yield 80.28%; m.p. 226-229˚C; IR (cm^{-1}): 2855.65 (Aliphatic C-H *str* of alkyl gp.), 1484.45 (C-H bending vibration of alkyl gp.), 3032.02 (Aromatic C-H *str*), 1446.06 (C=C *str*, Phenyl nucleus), 720.19 (Aromatic C-C out of plan bonding), 829.22 (Aromatic C-H out of plan bending), 804.58 (C-H deformation, aromatic), 1698.43 (C=O, ketone), 3321.45 (N-H *str*, 2^0amine), 1572.78 (N-H in plane bending, 2^0 amine), 3032.02 (N-H *str*, 2^0 amide), 1680.32 (C=O , 2^0 amide), 1337.35 (C–N *str*, 3^0), 1407.89 (-NO_2), 804.58 (C-Cl); ^{1}H NMR (DMSO-d_6) δ ppm: 1.267-1.284 (t, 3H, CH_3 of CH_2CH_3), 3.212-3.269 (q, 2H, CH_2 of CH_2CH_3), 2.816 (s, 3H, CH_3 of naphthyridine ring), 7.019 (d, 1H of naphthyridine ring), 7.917 (d, 1H of naphthyridine ring), 7.982-8.018 (m, 3H, Ar-

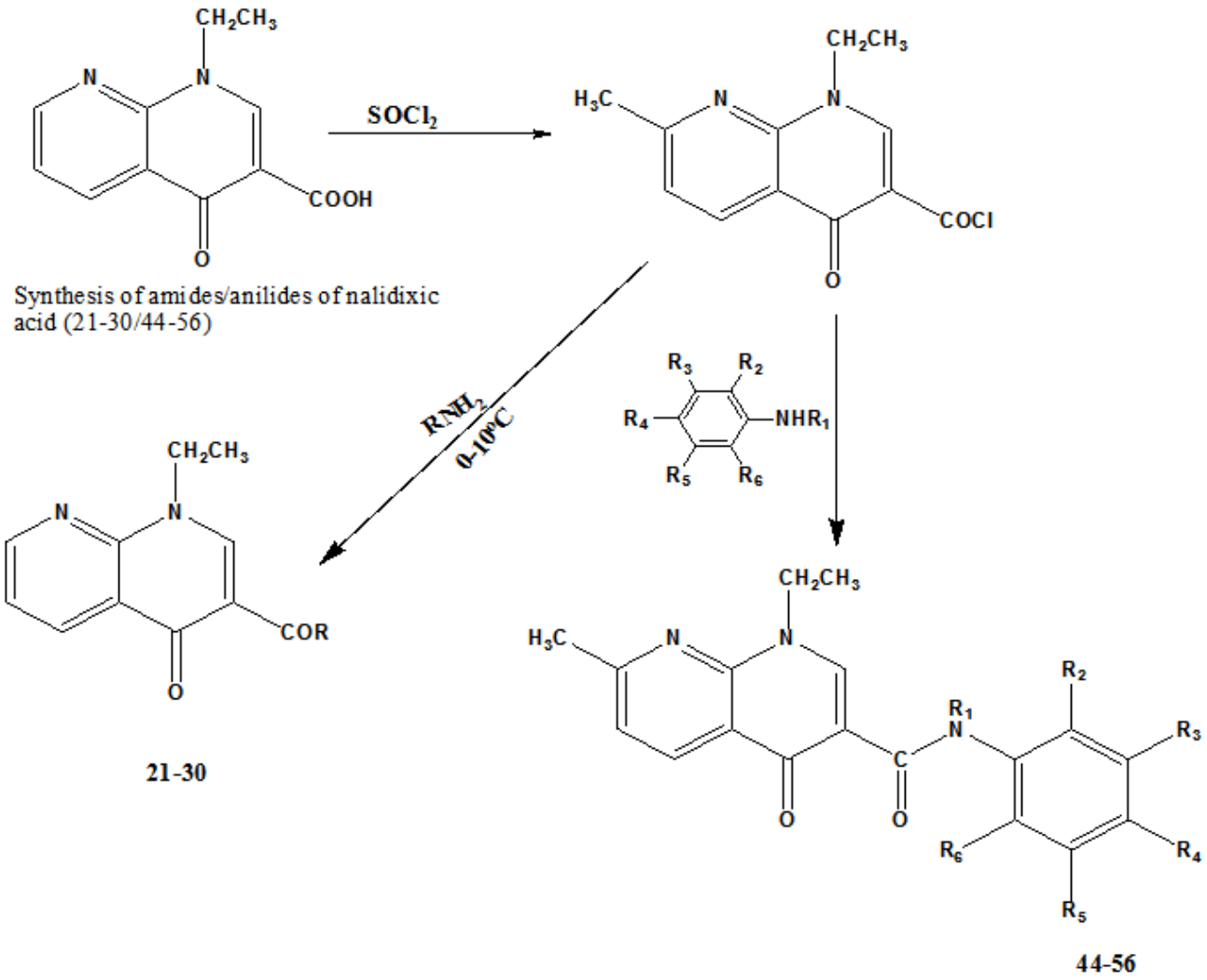
H), 8.081 (s, 1H of naphthyridine ring); ^{13}C NMR (DMSO-*d_6*) δ ppm: 13.0 (CH_3, NCH_2CH_3), 49.1 (CH_2, NCH_2CH_3), 148.0 (C, C-2), 111.3 (C, C-3), 171.8 (C, C-4), 138.1 (C, C-5), 109.4 (C,C-6), 162.4 (C,C-7), 24.8 (C_3,C-7), 165.1 (C, C-1'), 170.1 (C, C-4'), 56.1 (C, C-5'), 136.7 (C, C-1"), 115.8 (C, C-2", C-6"), 139.2 (C, C-3", C-5"), 123.6 (C, C-4"); Elemental analysis: Calculated for $C_{20}H_{19}ClN_6O_5$: C, 52.35;H, 4.17; N, 18.32; Found: C, 52.37; H, 4.15; N, 18.30; MS ES+ (ToF): *m/z* 459 [M^+ + 1]. *N'-(2-(2-chlorophenylamino)acetyl)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (39). Yield 69.53%; m.p. 226-229˚C; IR (cm^{-1}): 2898.25 (Aliphatic C-H *str* of alkyl gp.), 1445.27 (C-H bending vibration of alkyl gp.), 3015.13 (Aromatic C-H *str*), 1518.90 (C=C *str*, Phenyl nucleus), 668.26 (Aromatic C-C out of plan bonding), 802.62 (Aromatic C-H out of plan bending), 708.02 (C-H deformation, aromatic), 1673.13 (C=O, ketone), 3315.34 (N-H *str*, 2^0amine), 1551.99 (N-H in plane bending, 2^0 amine), 3015.13 (N-H *str*, 2^0 amide), 1672.31 (C=O , 2^0 amide), 1352.79 (C–N *str*, 3^0), 623.89 (-C-Cl); ^{1}H NMR (DMSO-*d_6*) δ ppm: 1.417-1.484 (t, 3H, CH_3 of CH_2CH_3), 3.312-3.369 (q, 2H, CH_2 of CH_2CH_3), 2.681 (s, 3H, CH_3 of naphthyridine ring), 7.126 (d, 1H of naphthyridine ring), 7.872 (d, 1H of naphthyridine ring), 7.149-7.194 (m, 3H, Ar-H), 8.061 (s, 1H of naphthyridine ring); ^{13}C NMR (DMSO-*d_6*) δ ppm: 13.6 (CH_3, NCH_2CH_3), 49.2 (CH_2, NCH_2CH_3), 148.4 (C, C-2), 113.4 (C, C-3), 177.4 (C, C-4), 138.6 (C, C-5), 114.2 (C,C-6), 162.6 (C,C-7), 24.8 (C_3,C-7), 165.9 (C, C-1'), 170.6 (C, C-4'), 56.8 (C, C-5'), 143.5 (C, C-1"), 122.8 (C, C-2"), 129.7 (C, C-3"), 118.6 (C, C-4"), 127.7 (C, C-5"), 114.9 (C, C-6"); Elemental analysis: Calculated for $C_{20}H_{20}ClN_5O_3$: C, 58.04;H, 4.87; N, 16.92; Found: C, 58.07; H, 4.85; N, 16.90; MS ES+ (ToF): *m/z* 414 [M^+ + 1]. *N'-(2-(2, 4-dimethylphenylamino) acetyl)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (40). Yield 58.82%; m.p. 226-229˚C; IR (cm^{-1}): 2859.81 (Aliphatic C-H *str* of alkyl gp.), 1444.81 (C-H bending vibration of alkyl gp.), 3042.92 (Aromatic C-H *str*), 1572.61 (C=C *str*, Phenyl nucleus), 657.12 (Aromatic C-C out of plan bonding), 802.62 (Aromatic C-H out of plan bending), 708.23 (C-H deformation, aromatic), 1678.06 (C=O, ketone), 3383.95 (N-H *str*, 2^0amine), 3042.92 (N-H *str*, 2^0 amide), 1560.21 (C=O , 2^0 amide), 1365.17 (C–N *str*, 3^0); ^{1}H NMR (DMSO-*d_6*) δ ppm: 1.146-1.168 (t, 3H, CH_3 of CH_2CH_3), 3.142-3.165 (q, 2H, CH_2 of CH_2CH_3), 2.754 (s, 3H, CH_3 of naphthyridine ring), 6.618 (d, 1H of naphthyridine ring), 7.920 (d, 1H of naphthyridine ring), 7.113-7.208 (m, 3H, Ar-H), 8.281 (s, 1H of naphthyridine ring), 3.960 (d, 2H CH_2 of -NHCOCH$_2$NH); ^{13}C NMR (DMSO-*d_6*) δ ppm: 13.4 (CH_3, NCH_2CH_3), 49.6 (CH_2, NCH_2CH_3), 148.7 (C, C-2), 113.8 (C, C-3), 176.9 (C, C-4), 139.6 (C, C-5), 115.9 (C,C-6), 168.1 (C,C-7), 24.8 (C_3,C-7), 162.1 (C, C-1'), 170.3 (C, C-4'), 55.9 (C, C-5'),123.8 (C, C-1"), 122.5 (C, C-2"), 114.5 (C, C-3"), 156.7 (C, C-4"), 116.7 (C, C-5"), 122.3 (C, C-6"), 55.8 (C, C-2" CH_3); Elemental analysis: Calculated for $C_{22}H_{25}N_5O_3$: C,64.85;H,6.18; N,17.19; Found: C,64.83; H,6.20; N, 17.21; MS ES+ (ToF): *m/z* 408 [M^+ + 1]. *N'-(2-(3-chlorophenylamino) acetyl)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (41). Yield 75.62%; m.p. 226-229˚C; IR (cm^{-1}): 2912.24 (Aliphatic C-H *str* of alkyl gp.), 1466.98 (C-H bending vibration of alkyl gp.), 3076.89 (Aromatic C-H *str*), 1492.97 (C=C *str*, Phenyl nucleus), 668.11 (Aromatic C-C out of plan bonding), 802.69 (Aromatic C-H out of plan bending), 708.04 (C-H deformation, aromatic), 1711.81 (C=O, ketone), 3305.51 (N-H *str*, 2^0amine), 1566.48 (N-H in plane bending, 2^0 amine), 3144.57 (N-H *str*, 2^0 amide), 1715.09 (C=O , 2^0 amide), 635.40 (-C-Cl); ^{1}H NMR (DMSO-*d_6*) δ ppm: 1.164-1.181 (t, 3H, CH_3 of CH_2CH_3), 3.104-3.152 (q, 2H, CH_2 of CH_2CH_3), 2.645 (s, 3H, CH_3 of naphthyridine ring), 6.818 (d, 1H of naphthyridine ring), 8.120 (d, 1H of naphthyridine ring), 7.013-7.108 (m, 4H, Ar-H), 8.081 (s, 1H of naphthyridine ring), 3.980 (d, 2H CH_2 of -NHCOCH$_2$NH); ^{13}C NMR (DMSO-*d_6*) δ ppm: 13.6 (CH_3, NCH_2CH_3), 49.4 (CH_2, NCH_2CH_3), 147.9 (C, C-2), 112.3 (C, C-3), 177.3 (C, C-4), 138.6 (C, C-5), 114.3 (C,C-6), 164.1 (C,C-7), 24.8 (C_3,C-7), 163.8 (C, C-1'), 168.3 (C, C-4'), 57.3 (C, C-5'), 149.0 (C, C-1"), 113.9 (C, C-2"), 135.1 (C, C-3"), 117.3 (C, C-4"), 131.0 (C, C-5"), 111.6 (C, C-6"); Elemental analysis: Calculated for $C_{20}H_{20}ClN_5O_3$: C, 58.04;H, 4.87; N, 16.92; Found: C, 58.06; H, 4.83; N, 16.90; MS ES+ (ToF): *m/z* 414 [M^+ + 1]. *N'-(2-(2-nitrophenylamino) acetyl)-1-ethyl-1,4-dihydro-*

7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide (42). Yield 80.80%; m.p. 226-229˚C; IR (cm^{-1}): 2923.46 (Aliphatic C-H *str* of alkyl gp.), 1445.37 (C-H bending vibration of alkyl gp.), 3045.24 (Aromatic C-H *str*), 1502.76 (C=C *str*, Phenyl nucleus), 679.30 (Aromatic C-C out of plan bonding), 882.03 (Aromatic C-H out of plan bending), 707.94 (C-H deformation, aromatic), 3319.16 (N-H *str*, 2^0amine), 1583.18 (N-H in plane bending, 2^0 amine), 3045.24 (N-H *str*, 2^0 amide), 1680.09 (C=O, 2^0 amide), 1328.74 (C–N *str*, 3^0), 1407.49 (-C-NO_2); ^{1}H NMR (DMSO-d_6) δ ppm: 1.264-1.281 (t, 3H, CH_3 of CH_2CH_3), 3.204-3.252 (q, 2H, CH_2 of CH_2CH_3), 2.554 (s, 3H, CH_3 of naphthyridine ring), 7.881 (d, 1H of naphthyridine ring), 8.021 (d, 1H of naphthyridine ring), 7.413-7.608 (m, 4H, Ar-H), 8.078 (s, 1H of naphthyridine ring), 4.096 (d, 2H CH_2 of -$NHCOCH_2NH$); ^{13}C NMR (DMSO-d_6) δ ppm: 13.0 (CH_3, NCH_2CH_3), 47.9 (CH_2, NCH_2CH_3), 148.1 (C, C-2), 113.5 (C, C-3), 176.9 (C, C-4), 138.2 (C, C-5), 114.9 (C,C-6), 164.9 (C,C-7), 24.8 (C_3,C-7), 165.4 (C, C-1'), 168.3 (C, C-4'), 56.9 (C, C-5'), 138.6 (C, C-1"), 132.9 (C, C-2"), 121.9 (C, C-3"), 118.1 (C, C-4"), 135.7 (C, C-5"), 114.6 (C, C-6"); Elemental analysis: Calculated for $C_{20}H_{20}N_6O_5$: C, 56.60;H, 4.75; N, 19.80; Found: C, 56.62; H, 4.73; N, 19.78; MS ES+ (ToF): *m/z* 425 [M^+ + 1]. *N'-(2-(m-tolylamino)acetyl)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (43). Yield 79.02%; m.p. 226-229˚C; IR (cm^{-1}): 2923.77 (Aliphatic C-H *str* of alkyl gp.), 1445.45 (C-H bending vibration of alkyl gp.), 3015.24 (Aromatic C-H *str*), 1445.45 (C=C *str*, Phenyl nucleus), 668.15 (Aromatic C-C out of plan bonding), 802.80 (Aromatic C-H out of plan bending), 726.77 (C-H deformation, aromatic), 1625.30 (C=O, ketone), 3315.24 (N-H *str*, 2^0amine), 1583.96 (N-H in plane bending, 2^0 amine), 3045.80 (N-H *str*, 2^0 amide), 1670.96 (C=O, 2^0 amide), 1330.32 (C–N *str*, 3^0); ^{1}H NMR (DMSO-d_6) δ ppm: 1.464-1.481 (t, 3H, CH_3 of CH_2CH_3), 3.114-3.452 (q, 2H, CH_2 of CH_2CH_3), 2.654 (s, 3H, CH_3 of naphthyridine ring), 8.281 (d, 1H of naphthyridine ring), 7.821 (d, 1H of naphthyridine ring), 6.913-7.208 (m, 4H, Ar-H), 8.178 (s, 1H of naphthyridine ring), 2.396 (s, 3H of Ar-CH_3); ^{13}C NMR (DMSO-d_6) δ ppm: 13.4 (CH_3, NCH_2CH_3), 46.8 (CH_2, NCH_2CH_3), 149.0 (C, C-2), 115.0 (C, C-3), 173.5 (C, C-4), 137.9 (C, C-5), 115.0 (C,C-6), 163.1 (C,C-7), 24.7 (C_3,C-7), 163.3 (C, C-1'), 170.3 (C, C-4'), 57.6 (C, C-5'), 147.5 (C, C-1"), 113.2 (C, C-2"), 139.2 (C, C-3"), 115.7 (C, C-4"), 125.9 (C, C-5"), 110.9 (C, C-6"); Elemental analysis: Calculated for $C_{21}H_{23}N_5O_3$: C, 64.11;H, 5.89; N, 17. 80; Found: C, 64.09; H, 5.86; N, 17.78; MS ES+ (ToF): *m/z* 394 [M^+ + 1].

General procedure for synthesis of amides/anilides of nalidixic acid (21-30/44-56)

The acid chloride of nalidixic acid was prepared by reaction of nalidixic acid with thionyl chloride. The solution of corresponding amine (0.1 mol)/aniline (0.1 mol) in ether (50 mL) was added drop-wise to a solution of acid chloride (0.1 mol) in ether (50 mL) maintained at 0-10 ^{0}C/ room temperature. The solution was stirred for 30 minutes and the precipitated amide was separated by filtration. The crude amide was recrystallized from alcohol. In case of anilide, the precipitated crude anilide was treated with water and the ether layer was separated, washed successively with 5% hydrochloric acid, 4% sodium carbonate and water to remove residual aniline. Evaporation of ether layer yielded crude anilide which was then recrystallized from alcohol.

SCHEME 2



21 = R = NH_2; 22 = R = $NHCH_3$;
23 = R = $N(CH_3)_2$; 24 = R = C_7H_8N;
25 = R = $N(C_2H_5OH)_2$; 26 = R = $NHCH(CH_3)_2$;
27 = R = $NHCH_2CH_2CH_3$; 28 = R = $N(C_2H_5)_2$;
29 = R = $C_{12}H_{10}N$; 30 = R = $NHCH_2CH_2OH$

44 = R_1, R_2, R_3, R_5, R_6=H, R_4=CH_3;
45 = R_1, R_2, R_3, R_5, R_6=H, R_4=OCH_3;
46 = R_1, R_2, R_3, R_5, R_6=H, R_4=NO_2;
47 = R_1, R_2, R_3, R_4, R_5, R_6=H;
48 = R_1, R_2, R_3, R_5, R_6=H, R_4=Cl;
49 = R_1, R_2, R_3, R_5, R_6=H, R_4=Br;
50 = R_1, R_2, R_4, R_5, R_6=H, R_3= NO_2;
51 = R_1, R_3, R_5, R_6=H, R_2= NO_2, R_4=Cl;
52 = R_1, R_3, R_4, R_5, R_6=H, R_2= Cl;
53 = R_1, R_3, R_5, R_6=H, R_2, R_4 = CH_3;
54 = R_1, R_2, R_4, R_5, R_6=H, R_3= Cl;
55 = R_1, R_3, R_4, R_5, R_6=H, R_2= NO_2;
56 = R_1, R_2, R_4, R_5, R_6=H, R_3 = CH_3;

1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxamide (21). Yield 71.42%; m.p. 226-229˚C; IR (cm^{-1}): 2913.72 (Aliphatic C-H *str* of alkyl gp.), 1472.33 (C-H bending vibration of alkyl gp.), 3004.92 (Aromatic C-H *str*), 1435.83 (C=C *str*, Phenyl nucleus), 674.80 (Aromatic C-C out of plan bonding), 814.05 (Aromatic C-H out of plan bending), 754.84 (C-H deformation, aromatic), 1652.98 (C=O, ketone), 3367.78 (N-H *str*, 2^0 amide), 1715.86 (C=O , 2^0 amide); ^{1}H NMR (DMSO-d_6) δ ppm: 1.214-1.261 (t, 3H, CH_3 of

CH_2CH_3), 3.561-3.626 (q, 2H, CH_2 of CH_2CH_3), 7.149 (d, 1H of naphthyridine ring), 8.215 (d, 1H of naphthyridine ring), 9.138 (s, 1H of naphthyridine ring); ^{13}C NMR (DMSO-d_6) δ ppm: 14.2 (CH_3, NCH_2CH_3), 49.0 (CH_2, NCH_2CH_3), 151.4 (C, C-2), 119.3 (C, C-3), 182.8 (C, C-4), 136.1 (C,C-5), 119.0 (C,C-6), 169.4 (C,C-7), 24.8 (CH_3,C-7), 172.6 (C, C-3 $CONH_2$); Calculated for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67; N, 18.17; Found: C, 62.33; H, 5.63; N, 18.19; MS ES+ (ToF): *m/z* 232 [M^+ + 1]. *1-ethyl-1,4-dihydro-N,7-dimethyl-4-oxo-1,8-naphthyridine-3-carboxamide* (22). Yield 92.02%; m.p. 226-229˚C; IR (cm^{-1}): 2964.23 (Aliphatic C-H *str* of alkyl gp.), 1339.39 (C-H bending vibration of alkyl gp.), 3064.98 (Aromatic C-H *str*), 1457.17 (C=C *str*, Phenyl nucleus), 675.01 (Aromatic C-C out of plan bonding), 892.19 (Aromatic C-H out of plan bending), 706.66 (C-H deformation, aromatic), 1622.85 (C=O, ketone), 3325.78 (N-H *str*, 2^0 amide), 1685.72 (C=O , 2^0 amide); ^{1}H NMR (DMSO-d_6) δ ppm: 1.114-1.161 (t, 3H, CH_3 of CH_2CH_3), 3.156-3.726 (q, 2H, CH_2 of CH_2CH_3), 7.249 (d, 1H of naphthyridine ring), 8.251 (d, 1H of naphthyridine ring), 9.183 (s, 1H of naphthyridine ring), 2.802 (d, 3H, CH_3 of -NH CH_3); ^{13}C NMR (DMSO-d_6) δ ppm: 13.1 (CH_3, NCH_2CH_3), 50.1 (CH_2, NCH_2CH_3), 146.9 (C, C-2), 118.8 (C, C-3), 172.8 (C, C-4), 133.9 (C, C-5), 114.8 (C,C-6), 170.6 (C,C-7), 24.8 (CH_3,C-7), 159.8 (C=O, $CONH_2$), 26.3 (C, $CONHCH_3$); Calculated for $C_{13}H_{15}N_3O_2$: C,63.66; H,6.16; N,17.13; Found: C, 63.63; H, 6.19; N, 17.11; MS ES+ (ToF): *m/z* 246 [M^+ + 1]. *1-ethyl-1,4-dihydro-N,N,7-trimethyl-4-oxo-1,8-naphthyridine-3-carboxamide* (23). Yield 59.8%; m.p. 226-229˚C; IR (cm^{-1}): 2905.03 (Aliphatic C-H *str* of alkyl gp.), 1472.48 (C-H bending vibration of alkyl gp.), 3003.44 (Aromatic C-H *str*), 1533.25 (C=C *str*, Phenyl nucleus), 667.89 (Aromatic C-C out of plan bonding), 891.91 (Aromatic C-H out of plan bending), 813.53 (C-H deformation, aromatic), 1669.26 (C=O, ketone), 3336.35 (N-H *str*, 2^0 amide), 1690.12 (C=O, 2^0 amide); ^{1}H NMR (DMSO-d_6) δ ppm: 1.420-1.461 (t, 3H, CH_3 of CH_2CH_3), 4.165-4.762 (q, 2H, CH_2 of CH_2CH_3), 7.441 (d, 1H of naphthyridine ring), 8.415 (d, 1H of naphthyridine ring), 9.281 (s, 1H of naphthyridine ring), 3.162 (d, 6H, $2CH_3$ of $-N(CH_3)_2$); ^{13}C NMR (DMSO-d_6) δ ppm: 12.9 (CH_3, NCH_2CH_3), 48.4 (CH_2, NCH_2CH_3), 143.2 (C, C-2), 114.2 (C, C-3), 165.8 (C, C-4), 123.9 (C, C-5), 118.0 (C,C-6), 160.9 (C,C-7), 24.8 (CH_3,C-7), 160.5 (C=O, $CONH_2$), 37.1(C, $CON(CH_3)_2$; Elemental analysis: Calculated for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.20; Found: C, 64.87; H, 6.59; N, 16.19; MS ES+ (ToF): *m/z* 260 [M^+ + 1]. *N-benzyl-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxamide* (24). Yield 69.53%; m.p. 226-229˚C; IR (cm^{-1}): 2945.57 (Aliphatic C-H *str* of alkyl gp.), 1339.34 (C-H bending vibration of alkyl gp.), 3026.18 (Aromatic C-H *str*), 1558.66 (C=C *str*, Phenyl nucleus), 684.15 (Aromatic C-C out of plan bonding), 811.51 (Aromatic C-H out of plan bending), 735.18 (C-H deformation, aromatic), 1609.03 (C=O, ketone), 3336.05 (N-H *str*, 2^0 amide), 1699.55 (C=O , 2^0 amide); ^{1}H NMR (DMSO-d_6) δ ppm: 1.121-1.253 (t, 3H, CH_3 of CH_2CH_3), 3.417-3.508 (q, 2H, CH_2 of CH_2CH_3), 7.460 (d, 1H of naphthyridine ring), 7.881 (d, 1H of naphthyridine ring), 8.023 (s, 1H of naphthyridine ring), 7.241-7.436(m, 5H, Ar-H); ^{13}C NMR (DMSO-d_6) δ ppm: 14.2 (CH_3, NCH_2CH_3), 45.9 (CH_2, NCH_2CH_3), 153.8 (C, C-2), 116.8 (C, C-3), 175.9 (C, C-4), 132.8 (C, C-5), 116.9 (C,C-6), 169.1 (C,C-7), 24.8 (CH_3,C-7), 159.8 (C, C-1'), 44.1(C, C-3'), 141.7 (C, C-1"), 127.0 (C,C-2",C-6"), 128.6 (C, C-3", C-5"), 126.8 (C, C-4"); Elemental analysis: Calculated for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.08; Found: C, 71.03; H, 5.98; N, 13.11; MS ES+ (ToF): *m/z* 322 [M^+ + 1]. *1-ethyl-1,4-dihydro-N,N-bis(2-hyroxyethyl)7-trimethyl-4-oxo-1,8-naphthyridine-3-carboxamide* (25). Yield 52.68%; m.p. 226-229˚C; IR (cm^{-1}): 2900.89 (Aliphatic C-H *str* of alkyl gp.), 1472.49 (C-H bending vibration of alkyl gp.), 2979.99 (Aromatic C-H *str*), 1533.30 (C=C *str*, Phenyl nucleus), 668.26 (Aromatic C-C out of plan bonding), 811.88 (Aromatic C-H out of plan bending), 779.94 (C-H deformation, aromatic), 1646.77 (C=O, ketone), 3355.20 (N-H *str*, 2^0 amide), 1681.09 (C=O , 2^0 amide); ^{1}H NMR (DMSO-d_6) δ ppm: 1.140-1.193 (t, 3H, CH_3 of CH_2CH_3), 3.497-3.508 (q, 2H, CH_2 of CH_2CH_3), 6.670 (d, 1H of naphthyridine ring), 8.081 (d, 1H of naphthyridine ring), 8.123 (s, 1H of naphthyridine ring), 3.157-3.246 (t, 2H, CH_2 of $N(CH_2CH_2OH)_2$; ^{13}C NMR (DMSO-d_6) δ ppm: 13.9 (CH_3, NCH_2CH_3), 49.0 (CH_2, NCH_2CH_3), 149.7 (C, C-2), 114.8 (C, C-3), 177.9 (C, C-4), 138.2 (C, C-5), 114.1 (C,C-6), 162.6 (C,C-7), 24.8 (CH_3,C-7), 59.9 (C=O, $CON(C_2H_5OH)_2$);

Elemental analysis: Calculated for $C_{16}H_{21}N_3O_4$: C, 60.17; H, 6.63; N, 13.16; Found: C, 60.19; H, 6.61; N, 13.13; MS ES+ (ToF): *m/z* 320 [M^+ + 1]. *1-ethyl-1,4-dihydro-N-isopropyl-7-methyl-4-oxo-1,8-naphthyridine-3-carboxamide* (26). Yield 65.09%; m.p. 226-229˚C; IR (cm^{-1}): 2933.58 (Aliphatic C-H *str* of alkyl gp.), 1489.54 (C-H bending vibration of alkyl gp.), 2986.90 (Aromatic C-H *str*), 1569.12 (C=C *str*, Phenyl nucleus), 688.62 (Aromatic C-C out of plan bonding), 812.90 (Aromatic C-H out of plan bending), 780.14 (C-H deformation, aromatic), 1683.91 (C=O, ketone), 3384.36 (N-H *str*, 2^0 amide), 1685.72 (C=O, 2^0 amide); ^{1}H NMR (DMSO-d_6) δ ppm: 1.137-1.169 (t, 3H, CH_3 of CH_2CH_3), 3.179-3.280 (q, 2H, CH_2 of CH_2CH_3), 3.218 (s, 3H, CH_3 of naphthyridine ring), 6.810 (d, 1H of naphthyridine ring), 8.181 (d, 1H of naphthyridine ring), 8.723 (s, 1H of naphthyridine ring), 4.372-4.527 (m, 1H of CH of –$NHCH(CH_3)_2$), 1.256 (d, 3H, CH_3 of –$NHCH(CH_3)_2$); ^{13}C NMR (DMSO-d_6) δ ppm: 13.1 (CH_3, NCH_2CH_3), 47.9 (CH_2, NCH_2CH_3), 143.8 (C, C-2), 110.8 (C, C-3), 171.9 (C, C-4), 129.8 (C, C-5), 109.9 (C,C-6), 152.8 (C,C-7), 24.8 (CH_3,C-7), 159.2 (C=O, $CONHCH(CH)_3$),23.3 (CH_3, $CONHCH(CH)_3$); Elemental analysis: Calculated for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37; Found: C, 65.90; H,7.04; N, 15.40; MS ES+ (ToF): *m/z* 274 [M^+ + 1]. *1-ethyl-1,4-dihydro-7-methyl-4-oxo-N-propyl-1,8-naphthyridine-3-carboxamide* (27). Yield 81.32%; m.p. 226-229˚C; IR (cm^{-1}): 2925.57 (Aliphatic C-H *str* of alkyl gp.), 1479.34 (C-H bending vibration of alkyl gp.), 3029.18 (Aromatic C-H *str*), 1658.66 (C=C *str*, Phenyl nucleus), 674.15 (Aromatic C-C out of plan bonding), 821.51 (Aromatic C-H out of plan bending), 785.18 (C-H deformation, aromatic), 1639.03 (C=O, ketone), 3386.05 (N-H *str*, 2^0 amide), 1669.55 (C=O , 2^0 amide); ^{1}H NMR (DMSO-d_6) δ ppm: 1.140-1.213 (t, 3H, CH_3 of CH_2CH_3), 3.297-3.308 (q, 2H, CH_2 of CH_2CH_3), 7.710 (d, 1H of naphthyridine ring), 8.081 (d, 1H of naphthyridine ring), 8.123 (s, 1H of naphthyridine ring), 3.172-3.227 (t, 2H, terminal CH_2 of $CH_2CH_2CH_3$); ^{13}C NMR (DMSO-d_6) δ ppm: 12.9 (CH_3, NCH_2CH_3), 39.9 (CH_2, NCH_2CH_3), 156.8 (C, C-2), 113.8 (C, C-3), 177.9 (C, C-4), 138.8 (C, C-5), 114.1 (C,C-6), 148.9 (C,C-7), 24.8 (CH_3,C-7), 159.5 (C=O, $CONHCH_2CH_2CH_3$, 23.3 (CH_2, $CONHCH_2CH_2CH_3$), 11.2 (CH_3, $CONHCH_2CH_2CH_3$); Elemental analysis: Calculated for $C_{15}H_{19}N_3O_2$: C, 65.91; H,7.01; N, 15.37; Found: C,65.89; H, 7.05; N, 15.39; MS ES+ (ToF): *m/z* 274 [M^+ + 1]. *N,N,1-triethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxamide acid* (28). Yield 67.88%; m.p. 226-229˚C; IR (cm^{-1}): 2856.76 (Aliphatic C-H *str* of alkyl gp.), 1457.15 (C-H bending vibration of alkyl gp.), 3025.54 (Aromatic C-H *str*), 1506.89 (C=C *str*, Phenyl nucleus), 688.77 (Aromatic C-C out of plan bonding), 831.49 (Aromatic C-H out of plan bending), 780.19 (C-H deformation, aromatic), 1688.41 (C=O, ketone), 3397.03 (N-H *str*, 2^0 amide), 1682.52 (C=O, 2^0 amide); ^{1}H NMR (DMSO-d_6) δ ppm: 1.164-1.181 (t, 3H, CH_3 of CH_2CH_3), 3.314-3.352 (q, 2H, CH_2 of CH_2CH_3), 2.665 (s, 3H, CH_3 of naphthyridine ring), 8.181 (d, 1H of naphthyridine ring), 6.671 (d, 1H of naphthyridine ring), 8.178 (s, 1H of naphthyridine ring); ^{13}C NMR (DMSO-d_6) δ ppm: 14.1 (CH_3, NCH_2CH_3), 38.8 (CH_2, NCH_2CH_3), 148.3 (C, C-2), 108.3 (C, C-3), 171.3 (C, C-4), 128.1 (C, C-5), 114.1 (C,C-6), 163.1 (C,C-7), 24.8 (CH_3,C-7), 159.9 (C=O, $CON(CH_2CH_3)_2$), 41.0 (CH_2,$CON(CH_2CH_3)_2$), 12.9 (CH_3, $CON(CH_2CH_3)_2$); Elemental analysis: Calculated for $C_{16}H_{21}N_3O_2$: C, 66.88;H, 7.37;N, 14.62; Found: C,66.90; H,7.34; N, 14.60; MS ES+ (ToF): *m/z* 288 [M^+ + 1]. *1-ethyl-1,4-dihydro-7-methyl-4-oxo-N,N-diphenyl-1,8-naphthyridine-3-carboxamide* (29). Yield 72.35%; m.p. 226-229˚C; IR (cm^{-1}): 2872.40 (Aliphatic C-H *str* of alkyl gp.), 1435.51 (C-H bending vibration of alkyl gp.), 3041.19 (Aromatic C-H *str*), 1506.86 (C=C *str*, Phenyl nucleus), 688.20 (Aromatic C-C out of plan bonding), 810.39 (Aromatic C-H out of plan bending), 743.10 (C-H deformation, aromatic), 1653.01 (C=O, ketone), 3354.26 (N-H *str*, 2^0 amide), 1690.21 (C=O, 2^0 amide); ^{1}H NMR (DMSO-d_6) δ ppm: 1.264-1.281 (t, 3H, CH_3 of CH_2CH_3), 3.114-3.252 (q, 2H, CH_2 of CH_2CH_3), 2.565 (s, 3H, CH_3 of naphthyridine ring), 7.881 (d, 1H of naphthyridine ring), 7.221 (d, 1H of naphthyridine ring), 8.078 (s, 1H of naphthyridine ring), 7.986-8.126 (m, 9H, Ar-H); ^{13}C NMR (DMSO-d_6) δ ppm: 12.1 (CH_3, NCH_2CH_3), 40.9 (CH_2, NCH_2CH_3), 147.4 (C, C-2), 114.8 (C, C-3), 179.5 (C, C-4), 118.6 (C, C-5), 106.9 (C,C-6), 159.9 (C,C-7), 24.8 (C_3,C-7), 159.3 (C=O, $CON(C_6H_4)_2$);

Elemental analysis: Calculated for $C_{24}H_{21}N_3O_2$: C, 75.18;H, 5.52; N, 10.96; Found: C, 75.20; H, 5.55; N, 10.94; MS ES+ (ToF): *m/z* 384 [M^+ + 1]. *1-ethyl-1,4-dihydro-N-(2-hydroxyethyl)-7-methyl-4-oxo-1,8-naphthyridine-3-carboxamide* (30). Yield 78.67%; m.p. 226-229˚C; IR (cm^{-1}): 2941.04 (Aliphatic C-H *str* of alkyl gp.), 1472.48 (C-H bending vibration of alkyl gp.), 3048.85 (Aromatic C-H *str*), 1533.29 (C=C *str*, Phenyl nucleus), 676.97 (Aromatic C-C out of plan bonding), 813.25 (Aromatic C-H out of plan bending), 768.56 (C-H deformation, aromatic), 1616.06 (C=O, ketone), 3308.59 (N-H *str*, 2^0 amide), 1685.66 (C=O, 2^0 amide); ^{1}H NMR (DMSO-d_6) δ ppm: 1.164-1.181 (t, 3H, CH_3 of CH_2CH_3), 3.214-3.352 (q, 2H, CH_2 of CH_2CH_3), 2.745 (s, 3H, CH_3 of naphthyridine ring), 8.381 (d, 1H of naphthyridine ring), 6.821 (d, 1H of naphthyridine ring), 8.078 (s, 1H of naphthyridine ring), 4.236 (d, 2H, CH_2 of CH_2OH); ^{13}C NMR (DMSO-d_6) δ ppm: 13.4 (CH_3, NCH_2CH_3), 49.2 (CH_2, NCH_2CH_3), 148.6 (C, C-2), 102.8 (C, C-3), 170.9 (C, C-4), 109.9 (C, C-5), 114.6 (C,C-6), 169.1 (C,C-7), 24.8 (C_3,C-7), 159.5 (C=O, $CONHCH_2CH_2OH$), 41.6 (CH_2, $CONHCH_2CH_2OH$), 61.1 (CH_2OH, $CONHCH_2CH_2OH$); Elemental analysis: Calculated for $C_{14}H_{17}N_3O_3$: C, 61.08;H, 6.22; N, 15.26; Found: C, 61.04; H, 6.25; N, 15.23; MS ES+ (ToF): *m/z* 276 [M^+ + 1]. *1-ethyl-1,4-dihydro-7-methyl-4-oxo-N-p-tolyl-1,8-naphthyridine-3-carboxamide* (44). Yield 70.13%; m.p. 226-229˚C; IR (cm^{-1}): 2880.16 (Aliphatic C-H *str* of alkyl gp.), 1438.56 (C-H bending vibration of alkyl gp.), 3007.04 (Aromatic C-H *str*), 1510.91 (C=C *str*, Phenyl nucleus), 674.90 (Aromatic C-C out of plan bonding), 822.49 (Aromatic C-H out of plan bending), 780.96 (C-H deformation, aromatic), 1678.27 (C=O, ketone), 3100.99 (N-H *str*, 2^0 amide), 1712.45 (C=O, 2^0 amide), 1367.51 (C–N *str*, 3^0); ^{1}H NMR (DMSO-d_6) δ ppm: 1.264-1.281 (t, 3H, CH_3 of CH_2CH_3), 3.241-3.552 (q, 2H, CH_2 of CH_2CH_3), 3.154 (s, 3H, CH_3 of naphthyridine ring), 8.161 (d, 1H of naphthyridine ring), 6.921 (d, 1H of naphthyridine ring), 7.931-8.028 (m, 4H, Ar-H), 8.087 (s, 1H of naphthyridine ring), 1.196 (s, 3H of Ar-CH_3); ^{13}C NMR (DMSO-d_6) δ ppm: 13.1 (CH_3, NCH_2CH_3), 49.3 (CH_2, NCH_2CH_3), 147.9 (C, C-2), 114.6 (C, C-3), 177.1 (C, C-4), 138.1 (C, C-5), 114.6 (C,C-6), 165.0 (C,C-7), 239 (C_3,C-7), 163.9 (C, C-1'), 132.9 (C, C-1"), 121.2 (C, C-2"), 129.3 (C, C-3"), 135.0 (C, C-4"), 129.3 (C, C-5"), 121.5 (C, C-6"); Calculated for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.08; Found: C, 71.04; H, 5.93; N, 13.04; MS ES+ (ToF): *m/z* 322 [M^+ + 1]. *1-ethyl-1,4-dihydro-N-(4-methoxyphenyl)-7-methyl-4-oxo-1,8-naphthyridine-3-carboxamide* (45). Yield 65.09%; m.p. 226-229˚C; IR (cm^{-1}): 2863.55 (Aliphatic C-H *str* of alkyl gp.), 1438.20 (C-H bending vibration of alkyl gp.), 2982.41 (Aromatic C-H *str*), 1503.20 (C=C *str*, Phenyl nucleus), 700.29 (Aromatic C-C out of plan bonding), 809.41 (Aromatic C-H out of plan bending), 797.95 (C-H deformation, aromatic), 1599.61 (C=O, ketone), 3145.96 (N-H *str*, 2^0 amide), 1692.97 (C=O , 2^0 amide), 1380.17 (C–N *str*, 3^0), 2922.76 (-OCH_3); ^{1}H NMR (DMSO-d_6) δ ppm: 1.173-1.228 (t, 3H, CH_3 of CH_2CH_3), 3.914-4.125 (q, 2H, CH_2 of CH_2CH_3), 2.654 (s, 3H, CH_3 of naphthyridine ring), 8.961 (d, 1H of naphthyridine ring), 7.421 (d, 1H of naphthyridine ring), 8.219-8.358 (m, 4H, Ar-H), 8.187 (s, 1H of naphthyridine ring), 4.056 (s, 3H of Ar-OCH_3); ^{13}C NMR (DMSO-d_6) δ ppm: 13.4 (CH_3, NCH_2CH_3), 49.6 (CH_2, NCH_2CH_3), 148.7 (C, C-2), 113.8 (C, C-3), 176.9 (C, C-4), 139.6 (C, C-5), 115.9 (C,C-6), 168.1 (C,C-7), 24.8 (C_3,C-7), 162.1 (C, C-1'), 123.8 (C, C-1"), 122.5 (C, C-2"), 114.5 (C, C-3"), 156.7 (C, C-4"), 116.7 (C, C-5"), 122.3 (C, C-6"), 55.8 (C, C-3" OCH_3); Elemental analysis: Calculated for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46; Found: C, 67.61; H, 5.67; N, 12.43; MS ES+ (ToF): *m/z* 338 [M^+ + 1]. *1-ethyl-1,4-dihydro-7-methyl-N-(4-nitrophenyl)-4-oxo-1,8-naphthyridine-3-carboxamide* (46). Yield 81.32%; m.p. 226-229˚C; IR (cm^{-1}): 2916.06 (Aliphatic C-H *str* of alkyl gp.), 1467.67 (C-H bending vibration of alkyl gp.), 3020.58 (Aromatic C-H *str*), 1504.39 (C=C *str*, Phenyl nucleus), 695.06 (Aromatic C-C out of plan bonding), 836.66 (Aromatic C-H out of plan bending), 782.42 (C-H deformation, aromatic), 1698.75 (C=O, ketone), 3120.75 (N-H *str*, 2^0 amide), 1701.45 (C=O, 2^0 amide), 1367.87 (C–N *str*, 3^0), 1367.87 (-NO_2); ^{1}H NMR (DMSO-d_6) δ ppm: 1.273-1.328 (t, 3H, CH_3 of CH_2CH_3), 3.134-3.265 (q, 2H, CH_2 of CH_2CH_3), 2.514 (s, 3H, CH_3 of naphthyridine ring), 8. 169 (d, 1H of naphthyridine ring), 7. 120 (d, 1H of naphthyridine ring), 8.169-8.268 (m, 4H, Ar-H), 8.047 (s, 1H of naphthyridine ring); ^{13}C NMR (DMSO-d_6) δ ppm: 13.0 (CH_3,

NCH_2CH_3), 47.4 (CH_2, NCH_2CH_3), 146.9 (C, C-2), 114.0 (C, C-3), 177.1 (C, C-4), 137.9 (C, C-5), 114.1 (C,C-6), 162.5 (C,C-7), 24.5 (C_3,C-7), 163.0 (C, C-1'), 143.0 (C, C-1"), 122.5 (C, C-2"), 121.5 (C, C-3"), 144.0 (C, C-4"), 121.7 (C, C-5"), 122.5 (C, C-6"); Elemental analysis: Calculated for $C_{18}H_{16}N_4O_4$: C, 61.36; H, 4.58; N, 15.90; Found: C, 61.33; H, 4.56; N, 15.64; MS ES+ (ToF): *m/z* 353 [M^+ + 1]. *1-ethyl-1,4-dihydro-7-methyl-4-oxo-N-phenyl-1,8-naphthyridine-3-carboxamide* (47). Yield 67.88%; m.p. 226-229˚C; IR (cm^{-1}): 2863.83 (Aliphatic C-H *str* of alkyl gp.), 1435.07 (C-H bending vibration of alkyl gp.), 3021.53 (Aromatic C-H *str*), 1456.62 (C=C *str*, Phenyl nucleus), 694.35 (Aromatic C-C out of plan bonding), 882.57 (Aromatic C-H out of plan bending), 770.08 (C-H deformation, aromatic), 1695.17 (C=O, ketone), 3144.00 (N-H *str*, 2^0 amide), 1668.84 (C=O, 2^0 amide), 1368.44 (C–N *str*, 3^0); ^{1}H NMR (DMSO-d_6) δ ppm: 1.327-1.358 (t, 3H, CH_3 of CH_2CH_3), 3.243-3.356 (q, 2H, CH_2 of CH_2CH_3), 2.941 (s, 3H, CH_3 of naphthyridine ring), 7.916 (d, 1H of naphthyridine ring), 7.012 (d, 1H of naphthyridine ring), 7.691-7.786 (m, 5H, Ar-H), 8.274 (s, 1H of naphthyridine ring); ^{13}C NMR (DMSO-d_6) δ ppm: 12.9 (CH_3, NCH_2CH_3), 49.0 (CH_2, NCH_2CH_3), 148.2 (C, C-2), 113.6 (C, C-3), 177.9 (C, C-4), 138.3 (C, C-5), 114.1 (C,C-6), 162.6 (C,C-7), 24.8 (C_3,C-7), 163.1 (C, C-1'), 135.9 (C, C-1"), 121.6 (C, C-2"), 129.0 (C, C-3"), 124.4 (C, C-4"), 129.0 (C, C-5"), 121.5 (C, C-6"); Elemental analysis: Calculated for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67; Found: C, 70.37; H, 5.56; N, 13.64; MS ES+ (ToF): *m/z* 308 [M^+ + 1]. *N-(4-chlorophenyl)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxamide* (48). Yield 72.35%; m.p. 226-229˚C; IR (cm^{-1}): 2848.99 (Aliphatic C-H *str* of alkyl gp.), 1456.56 (C-H bending vibration of alkyl gp.), 3055.21 (Aromatic C-H *str*), 1456.56 (C=C *str*, Phenyl nucleus), 688.46 (Aromatic C-C out of plan bonding), 829.10 (Aromatic C-H out of plan bending), 780.51 (C-H deformation, aromatic), 1646.23 (C=O, ketone), 3127.35 (N-H *str*, 2^0 amide), 1692.62 (C=O, 2^0 amide), 1368.52 (C–N *str*, 3^0), 635.67 (-C-Cl, monochlorinated compound); ^{1}H NMR (DMSO-d_6) δ ppm: 1.257-1.328 (t, 3H, CH_3 of CH_2CH_3), 3.134-3.265 (q, 2H, CH_2 of CH_2CH_3), 3.141 (s, 3H, CH_3 of naphthyridine ring), 7.826 (d, 1H of naphthyridine ring), 6.942 (d, 1H of naphthyridine ring), 7.791-7.868 (m, 4H, Ar-H), 8.148 (s, 1H of naphthyridine ring); ^{13}C NMR (DMSO-d_6) δ ppm: 13.9 (CH_3, NCH_2CH_3), 49.8 (CH_2, NCH_2CH_3), 144.9 (C, C-2), 114.8 (C, C-3), 174.8 (C, C-4), 135.9 (C, C-5), 114.8 (C,C-6), 164.0 (C,C-7), 24.6 (C_3,C-7), 164.1 (C, C-1'), 134.0 (C, C-1"), 123.0 (C, C-2"), 129.9 (C, C-3"), 129.1 (C, C-4"), 123.0 (C, C-5"), 126.5 (C, C-6"); Calculated for $C_{18}H_{16}ClN_3O_2$: C, 63.25; H, 4.72; N, 12.29; Found: C, 63.27; H, 4.70; N, 12.27; MS ES+ (ToF): *m/z* 342 [M^+ + 1]. *N-(4-bromophenyl)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxamide* (49). Yield 78.67%; m.p. 226-229˚C; IR (cm^{-1}): 2908.99 (Aliphatic C-H *str* of alkyl gp.), 1435.62 (C-H bending vibration of alkyl gp.), 3015.50 (Aromatic C-H *str*), 1532.25 (C=C *str*, Phenyl nucleus), 664.00 (Aromatic C-C out of plan bonding), 827.93 (Aromatic C-H out of plan bending), 766.06 (C-H deformation, aromatic), 1699.06 (C=O, ketone), 3127.77 (N-H *str*, 2^0 amide), 1674.77 (C=O, 2^0 amide), 1329.13 (C–N *str*, 3^0), 614.27 (-C-Br, monobrominated compound); ^{1}H NMR (DMSO-d_6) δ ppm: 1.175-1.280 (t, 3H, CH_3 of CH_2CH_3), 3.243-3.356 (q, 2H, CH_2 of CH_2CH_3), 3.041 (s, 3H, CH_3 of naphthyridine ring), 7.862 (d, 1H of naphthyridine ring), 7.249 (d, 1H of naphthyridine ring), 7.971-7.986 (m, 4H, Ar-H), 8.058 (s, 1H of naphthyridine ring); ^{13}C NMR (DMSO-d_6) δ ppm: 13.1 (CH_3, NCH_2CH_3), 49.0 (CH_2, NCH_2CH_3), 148.9 (C, C-2), 113.0 (C, C-3), 175.9 (C, C-4), 138.2 (C, C-5), 114.1 (C,C-6), 162.6 (C,C-7), 24.8 (C_3,C-7), 163.9 (C, C-1'), 132.8 (C, C-1"), 123.8 (C, C-2"), 131.7 (C, C-3"), 118.7 (C, C-4"), 131.9 (C, C-5"), 123.8 (C, C-6"); Elemental analysis: Calculated for $C_{18}H_{16}BrN_3O_2$: C, 55.97; H, 4.18; N, 10.88; Found: C, 55.94; H, 4.20; N, 10.89; MS ES+ (ToF): *m/z* 387 [M^+ + 1]. *1-ethyl-1,4-dihydro-7-methyl-N-(3-nitrophenyl)-4-oxo-1,8-naphthyridine-3-carboxamide* (50). Yield 54.50%; m.p. 226-229˚C; IR (cm^{-1}): 2868.78 (Aliphatic C-H *str* of alkyl gp.), 1471.53 (C-H bending vibration of alkyl gp.), 3033.84 (Aromatic C-H *str*), 1538.78 (C=C *str*, Phenyl nucleus), 664.33 (Aromatic C-C out of plan bonding), 873.96 (Aromatic C-H out of plan bending), 811.53 (C-H deformation, aromatic), 1601.86 (C=O, ketone), 3111.46 (N-H *str*, 2^0 amide), 1683.78 (C=O, 2^0 amide), 1349.77

(C–N *str*, 3^0), 1349.77 (-NO_2); ^{1}H NMR (DMSO-d_6) δ ppm: 1.275-1.308 (t, 3H, CH_3 of CH_2CH_3), 3.324-3.366 (q, 2H, CH_2 of CH_2CH_3), 3.741 (s, 3H, CH_3 of naphthyridine ring), 7.923 (d, 1H of naphthyridine ring), 9.249 (d, 1H of naphthyridine ring), 8.571-8.698 (m, 4H, Ar-H), 8.358 (s, 1H of naphthyridine ring); ^{13}C NMR (DMSO-d_6) δ ppm: 14.0 (CH_3, NCH_2CH_3), 48.4 (CH_2, NCH_2CH_3), 147.3 (C, C-2), 113.9 (C, C-3), 177.4 (C, C-4), 142.0 (C, C-5), 116.2 (C,C-6), 169.0 (C,C-7), 24.8 (C_3,C-7), 163.2 (C, C-1'), 136.8 (C, C-1"), 115.8 (C, C-2"), 148.7 (C, C-3"), 116.7 (C, C-4"), 121.9 (C, C-5"), 127.8 (C, C-6"); Elemental analysis: Calculated for $C_{18}H_{16}N_4O_4$: C, 61.36; H, 4.58; N, 15.90; Found: C, 61.39; H, 4.55; N, 15.89; MS ES+ (ToF): *m/z* 353 [M^+ + 1]. *N-(4-chloro-2-nitrophenyl)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxamide* (51). Yield 76.25%; m.p. 226-229˚C; IR (cm^{-1}): 2942.64 (Aliphatic C-H *str* of alkyl gp.), 1339.65 (C-H bending vibration of alkyl gp.), 3043.68 (Aromatic C-H *str*), 1456.62 (C=C *str*, Phenyl nucleus), 722.92 (Aromatic C-C out of plan bonding), 815.22 (Aromatic C-H out of plan bending), 751.97 (C-H deformation, aromatic), 1626.86 (C=O, ketone), 3113.27 (N-H *str*, 2^0 amide), 1680.78 (C=O , 2^0 amide), 1367.19 (C–N *str*, 3^0), 722.92 (-C-Cl, monochlorinated compound), 1367.19 (-NO_2); ^{1}H NMR (DMSO-d_6) δ ppm: 1.245-1.293 (t, 3H, CH_3 of CH_2CH_3), 3.302-3.420 (q, 2H, CH_2 of CH_2CH_3), 2.561 (s, 3H, CH_3 of naphthyridine ring), 7.864-7.982 (m, 3H, Ar-H), 8.169 (d, 1H of naphthyridine ring); ^{13}C NMR (DMSO-d_6) δ ppm: 13.9 (CH_3, NCH_2CH_3), 46.9 (CH_2, NCH_2CH_3), 148.0 (C, C-2), 114.2 (C, C-3), 179.0 (C, C-4), 138.2 (C, C-5), 114.8 (C,C-6), 164.2 (C,C-7), 24.8 (C_3,C-7), 163.1 (C, C-1'), 131.4 (C, C-1"), 145.8 (C, C-2"), 124.7 (C, C-3"), 136.7 (C, C-4"), 135.2 (C, C-5"), 123.9 (C, C-6"); Elemental analysis: Calculated for $C_{18}H_{15}ClN_4O_4$: C, 55.89; H, 3.91; N, 14.49; Found: C, 55.87; H, 3.89; N, 14.47; MS ES+ (ToF): *m/z* 387 [M^+ + 1]. *N-(2-chlorophenyl)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxamide* (52). Yield 81.0%; m.p. 226-229˚C; IR (cm^{-1}): 2903.99 (Aliphatic C-H *str* of alkyl gp.), 1460.28 (C-H bending vibration of alkyl gp.), 3045.40 (Aromatic C-H *str*), 1516.35 (C=C *str*, Phenyl nucleus), 668.35 (Aromatic C-C out of plan bonding), 889.36 (Aromatic C-H out of plan bending), 778.46 (C-H deformation, aromatic), 1609.58 (C=O, ketone), 3145.36 (N-H *str*, 2^0 amide), 1681.79 (C=O, 2^0 amide), 1368.68 (C–N *str*, 3^0), 632.89 (-C-Cl, monochlorinated compound); ^{1}H NMR (DMSO-d_6) δ ppm: 1.162-1.224 (t, 3H, CH_3 of CH_2CH_3), 3.260-3.462 (q, 2H, CH_2 of CH_2CH_3), 2.661 (s, 3H, CH_3 of naphthyridine ring), 7.642-7.982 (m, 4H, Ar-H); ^{13}C NMR (DMSO-d_6) δ ppm: 13.1 (CH_3, NCH_2CH_3), 49.1 (CH_2, NCH_2CH_3), 148.7 (C, C-2), 113.6 (C, C-3), 178.5 (C, C-4), 136.9 (C, C-5), 114.3 (C,C-6), 162.1 (C,C-7), 23.2 (C_3,C-7), 163.5 (C, C-1'), 134.9 (C, C-1"), 135.1 (C, C-2"), 125.8 (C, C-3"), 126.7 (C, C-4"), 125.2 (C, C-5"), 123.0 (C, C-6"); Elemental analysis: Calculated for $C_{18}H_{16}ClN_3O_2$: C, 63.25; H, 4.72; N, 12.29; Found: C, 63.27; H, 4.70; N, 12.27; MS ES+ (ToF): *m/z* 342 [M^+ + 1]. *1-ethyl-1,4-dihydro-7-methyl-N-(2,4-dimethylphenyl)-4-oxo-1,8-naphthyridine-3-carboxamide* (53). Yield 81.0%; m.p. 226-229˚C; IR (cm^{-1}): 2854.63 (Aliphatic C-H *str* of alkyl gp.), 1368.17 (C-H bending vibration of alkyl gp.), 3036.50 (Aromatic C-H *str*), 1435.22 (C=C *str*, Phenyl nucleus), 747.04 (Aromatic C-C out of plan bonding), 898.96 (Aromatic C-H out of plan bending), 793.78 (C-H deformation, aromatic), 1674.72 (C=O, ketone), 3127.30 (N-H *str*, 2^0 amide), 1674.72 (C=O , 2^0 amide), 1368.17 (C–N *str*, 3^0); ^{1}H NMR (DMSO-d_6) δ ppm: 1.357-1.508 (t, 3H, CH_3 of CH_2CH_3), 2.342-2.366 (q, 2H, CH_2 of CH_2CH_3), 2.471 (s, 3H, CH_3 of naphthyridine ring), 8.932 (d, 1H of naphthyridine ring), 9.294 (d, 1H of naphthyridine ring), 8.271-8.298 (m, 3H, Ar-H), 2.574 (s, 3H, CH_3 of Ar ring), 9.358 (s, 1H of naphthyridine ring); ^{13}C NMR (DMSO-d_6) δ ppm: 12.7 (CH_3, NCH_2CH_3), 51.0 (CH_2, NCH_2CH_3), 150.0 (C, C-2), 114.1 (C, C-3), 177.2 (C, C-4), 133.7 (C, C-5), 116.0 (C,C-6), 159.9 (C,C-7), 25.8 (C_3,C-7), 163.1 (C, C-1'), 131.9 (C, C-1"), 134.2 (C, C-2"), 131.1 (C, C-3"), 133.5 (C, C-4"), 126.3 (C, C-5"), 121.4 (C, C-6"), 15.5 (C, C-2"CH_3), 24.6 (C,C-4" CH_3); Elemental analysis: Calculated for $C_{20}H_{21}N_3O_2$: C, 71.62; H, 6.31; N, 12.53; Found: C, 71.65; H, 6.29; N, 12.51; MS ES+ (ToF): *m/z* 336 [M^+ + 1]. *1-ethyl-1,4-dihydro-7-methyl-N-(2,4-dimethylphenyl)-4-oxo-1,8-naphthyridine-3-carboxamide* (54). Yield 83.2%; m.p. 226-229˚C; IR (cm^{-1}): 2917.31 (Aliphatic C-H *str* of alkyl gp.), 1457.67 (C-H

bending vibration of alkyl gp.), 3045.69 (Aromatic C-H *str*), 1457.67 (C=C *str*, Phenyl nucleus), 740.70 (Aromatic C-C out of plan bonding), 811.04 (Aromatic C-H out of plan bending), 781.96 (C-H deformation, aromatic), 1615.24 (C=O, ketone), 3114.17 (N-H *str*, 2^0 amide), 1685.73 (C=O , 2^0 amide), 1369.35 (C–N *str*, 3^0); ^{1}H NMR (DMSO-d_6) δ ppm: 1.212-1.245 (t, 3H, CH_3 of CH_2CH_3), 3.026-3.260 (q, 2H, CH_2 of CH_2CH_3), 4.616 (s, 3H, CH_3 of naphthyridine ring), 7.546-7.829 (m, 3H, Ar-H), 7.969 (d, 1H of naphthyridine ring); ^{13}C NMR (DMSO-d_6) δ ppm: 13.0 (CH_3, NCH_2CH_3), 49.6 (CH_2, NCH_2CH_3), 149.0 (C, C-2), 112.9 (C, C-3), 180.0 (C, C-4), 131.2 (C, C-5), 114.2 (C,C-6), 164.4 (C,C-7), 26.3 (C_3,C-7), 163.1 (C, C-1'), 137.3 (C, C-1"), 122.0 (C, C-2"), 134.5 (C, C-3"), 123.5 (C, C-4"), 130.3 (C, C-5"), 119.7 (C, C-6"); Elemental analysis: Calculated for $C_{18}H_{16}ClN_3O_2$: C, 63.25; H, 4.72; N, 12.29; Found: C, 63.23; H, 4.75; N, 12.27; MS ES+ (ToF): *m/z* 342 [M^+ + 1].*1-ethyl-1,4-dihydro-7-methyl-N-(2-nitrophenyl)-4-oxo-1,8-naphthyridine-3-carboxamide* (55). Yield 76.77%; m.p. 226-229˚C; IR (cm^{-1}): 2854.99 (Aliphatic C-H *str* of alkyl gp.), 1435.60 (C-H bending vibration of alkyl gp.), 3034.52 (Aromatic C-H *str*), 1506.22 (C=C *str*, Phenyl nucleus), 662.80 (Aromatic C-C out of plan bonding), 813.98 (Aromatic C-H out of plan bending), 745.49 (C-H deformation, aromatic), 1615.59 (C=O, ketone), 3106.85 (N-H *str*, 2^0 amide), 1696.07 (C=O, 2^0 amide), 1435.60 (C–N *str*, 3^0), 1344.67 (-NO_2); ^{1}H NMR (DMSO-d_6) δ ppm: 1.317-1.368 (t, 3H, CH_3 of CH_2CH_3), 2.962-2.996 (q, 2H, CH_2 of CH_2CH_3), 2.576 (s, 3H, CH_3 of naphthyridine ring), 7.932 (d, 1H of naphthyridine ring), 8.249 (d, 1H of naphthyridine ring), 8.217-8.287 (m, 4H, Ar-H); ^{13}C NMR (DMSO-d_6) δ ppm: 13.7 (CH_3, NCH_2CH_3), 50.3 (CH_2, NCH_2CH_3), 148.7 (C, C-2), 113.8 (C, C-3), 177.5 (C, C-4), 138.0 (C, C-5), 112.8 (C,C-6), 160.9 (C,C-7), 24.8 (C_3,C-7), 162.6 (C, C-1'), 133.3 (C, C-1"), 140.3 (C, C-2"), 121.5 (C, C-3"), 125.3 (C, C-4"), 135.1 (C, C-5"), 122.5 (C, C-6"); Elemental analysis: Calculated for $C_{18}H_{16}N_4O_4$: C, 61.36; H, 4.58; N, 15.90; Found: C, 61.33; H, 4.60; N, 15.87; MS ES+ (ToF): *m/z* 353 [M^+ + 1]. *1-ethyl-1,4-dihydro-7-methyl-4-oxo-N-m-tolyl-1,8-naphthyridine-3-carboxamide* (56). Yield 69.87%; m.p. 226-229˚C; IR (cm^{-1}): 2920.44 (Aliphatic C-H *str* of alkyl gp.), 1456.09 (C-H bending vibration of alkyl gp.), 3004.00 (Aromatic C-H *str*), 1456.09 (C=C *str*, Phenyl nucleus), 666.71 (Aromatic C-C out of plan bonding), 821.91 (Aromatic C-H out of plan bending), 780.15 (C-H deformation, aromatic), 1687.74 (C=O, ketone), 3137.86 (N-H *str*, 2^0 amide), 1682.45 (C=O, 2^0 amide), 1362.63 (C–N *str*, 3^0); ^{1}H NMR (DMSO-d_6) δ ppm: 1.324-1.418 (t, 3H, CH_3 of CH_2CH_3), 3.142-3.356 (q, 2H, CH_2 of CH_2CH_3), 2.482 (s, 3H, CH_3 of naphthyridine ring), 8.123 (d, 1H of naphthyridine ring), 9.261 (d, 1H of naphthyridine ring), 8.210-8.286 (m, 4H, Ar-H), 2.562 (s, 3H, CH_3 of Ar ring); ^{13}C NMR (DMSO-d_6) δ ppm: 12.9 (CH_3, NCH_2CH_3), 49.9 (CH_2, NCH_2CH_3), 148.9 (C, C-2), 114.6 (C, C-3), 172.9 (C, C-4), 138.0 (C, C-5), 121.3 (C,C-6), 162.7 (C,C-7), 26.4 (C_3,C-7), 163.1 (C, C-1'), 135.8 (C, C-1"), 121.3 (C, C-2"), 138.6 (C, C-3"), 124.7 (C, C-4"), 128.9 (C, C-5"), 118.5 (C, C-6"), 24.3 (C, C-3" CH_3); Elemental analysis: Calculated for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.08; Found: C, 69.99; H, 5.93; N, 13.05; MS ES+ (ToF): *m/z* 322 [M^+ + 1].

2. Evaluation of antimicrobial activity

Determination of MIC

The antimicrobial activity of synthesized compounds were performed against Gram-positive bacteria: *Staphylococcus aureus* (MTCC 2901), *Bacillus subtilis* (MTCC 2063), Gram-negative bacterium: *Escherichia coli* (MTCC 1652) and fungal strains: *Candida albicans* (MTCC 227) and *Aspergillus niger* (MTCC 8189) using tube dilution method [30]. Dilutions of test and standard compounds were prepared in double strength nutrient broth – I.P. (bacteria) or Sabouraud dextrose broth I.P. (fungi) [31]. The samples were incubated at 37 °C for 24 h (bacteria), at 25 °C for 7 d (A. niger) and at 37 °C for 48 h (C. albicans) and the results were recorded in terms of MIC.

3. QSAR studies

The structures of 1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid derivatives were first pre-optimized with the Molecular Mechanics Force Field (MM+) procedure included in Hyperchem 6.03 [32] and the resulting geometries are further refined by means of the semi empirical method PM3 (Parametric Method-3). We chosed a gradient

norm limit of 0.01kcal/A° for the geometry optimization. The lowest energy structure was used for each nalidixic acid derivative to calculate different molecular descriptors like log of octanol–water partition coefficient (logP), molar refractivity (MR), Kier's molecular connectivity (0χ, $0\chi\varpi$, 1χ, $1\chi\varpi$, $\chi2$, $2\chi\varpi$) and shape ($\kappa1$, $\kappa\alpha1$) topological indices, Randic topological index (R), Balaban topological index (J), Wiener topological index (W), Total energy (Te), energies of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), dipole moment (μ), electronic energy (Ele.E), nuclear energy (Nu.E) and molecular surface area (SA) by used TSAR 3.3 [33] software for windows. Further, the regression analysis was performed using the SPSS software package[34].

RESULTS AND DISCUSSION

1. Chemistry

Synthesis of target compounds 1-20/31-43 and 21-30/44-56 was carried out as outlined in Scheme 1 and 2 respectively. Esters of nalidixic acid (1-20/31-43) were synthesized by its reaction with corresponded alcohol in the presence of sulphuric acid. Nalidixic acid hydrazide was synthesized by reaction of ethyl ester of nalidixic acid with hydrazine hydrate which on reaction with corresponding aldehydes yielded schiff bases of nalidixic acid. Carbohydrazide (31-43) were prepared by the reaction of nalidixic acid hydrazide with chloroacetyl chloride in the presence of few drops of glacial acetic acid which was further refluxed with different aniline in the presence of a few drops of glacial acetic acid (Scheme 1). Amides and anilides (21-30/44-56) were prepared by the reaction of nalidixoyl chloride with corresponding amines/anilines (Scheme 2). The purity of compounds was checked by single-spot thin layer chromatography on silica gel G. All the compounds were obtained in appreciable yield and their physicochemical characteristics are presented in Table 1. The formation of target compounds was ascertained on the basis of results of elemental analysis in addition to their consistent IR and NMR spectral characteristics.

Table1
The physicochemical characteristics of synthesized nalidixic acid derivatives

Comp.	Molecular formula	M.Wt	M.Pt.(^{0}C)	R_f* value	%Yield
1	$C_{13}H_{14}N_4O_2$	258.28	238-240	0.51	75.19
2	$C_{19}H_{18}N_4O_3$	350.37	137-140	0.55	75.92
3	$C_{17}H_{16}N_4O_3$	324.33	188-190	0.54	50.37
4	$C_{21}H_{20}N_4O_2$	360.41	140-142	0.48	63.23
5	$C_{19}H_{18}N_4O_2$	334.37	213-215	0.66	74.45
6	$C_{14}H_{16}N_4O_2$	272.3	211-213	0.54	82.78
7	$C_{21}H_{23}N_5O_2$	377.44	183-185	0.52	61.68
8	$C_{19}H_{17}N_5O_4$	379.37	148-150	0.61	67.72
9	$C_{20}H_{20}N_4O_3$	364.4	193-195	0.57	70.32
10	$C_{21}H_{22}N_4O_4$	394.42	194-197	0.60	70.60
11	$C_{19}H_{17}N_5O_4$	379.37	198-200	0.68	48.67
12	$C_{20}H_{20}N_4O_3$	364.4	196-200	0.58	50.28
13	$C_{19}H_{17}ClN_4O_2$	368.82	217-220	0.62	65.76
14	$C_{19}H_{17}FN_4O_2$	352.36	165-170	0.65	98.12

15	$C_{23}H_{20}N_4O_3$	400.43	215-219	0.55	74.65
16	$C_{19}H_{16}BrFN_4O_2$	431.26	138-140	0.51	71.35
17	$C_{19}H_{17}ClN_4O_2$	368.82	137-140	0.65	74.68
18	$C_{19}H_{18}N_4O_3$	350.37	174-178	0.62	85.21
19	$C_{21}H_{22}N_4O_4$	394.42	106-110	0.54	86.78
20	$C_{20}H_{17}N_5O_2$	359.38	218-220	0.44	42.86
21	$C_{12}H_{13}N_3O_2$	231.25	128-130	0.43	71.42
22	$C_{13}H_{15}N_3O_2$	245.28	120-123	0.25	97
23	$C_{14}H_{17}N_3O_2$	259.3	122-126	0.34	59.8
24	$C_{19}H_{19}N_3O_2$	321.37	118-120	0.55	69.53
25	$C_{16}H_{21}N_3O_4$	319.36	156-158	0.46	52.68
26	$C_{15}H_{19}N_3O_2$	273.33	158-162	0.32	65.09
27	$C_{15}H_{19}N_3O_2$	273.33	150-154	0.25	81.32
28	$C_{16}H_{21}N_3O_2$	287.36	120-122	0.27	67.88
29	$C_{24}H_{21}N_3O_2$	383.44	100-102	0.37	72.35
30	$C_{14}H_{17}N_3O_3$	275.33	138-140	0.33	78.67
31	$C_{21}H_{23}N_5O_3$	393.44	226-228	0.52	59.84
32	$C_{21}H_{23}N_5O_4$	409.44	235-237	0.57	66.94
33	$C_{20}H_{20}N_6O_5$	424.41	224-228	0.43	67.76
34	$C_{20}H_{21}N_5O_3$	379.41	230-232	0.58	37.46
35	$C_{20}H_{20}ClN_5O_3$	413.86	228-230	0.54	86.27
36	$C_{20}H_{20}BrN_5O_3$	458.31	232-235	0.47	73.39
37	$C_{20}H_{20}N_6O_5$	424.41	228-230	0.58	68.32
38	$C_{20}H_{19}ClN_6O_5$	458.86	100-104	0.43	80.28
39	$C_{20}H_{20}ClN_5O_3$	413.86	228-230	0.61	69.53
40	$C_{22}H_{25}N_5O_3$	407.47	220-224	0.42	58.82
41	$C_{20}H_{20}N_5O_3$	413.86	228-230	0.58	75.62
42	$C_{20}H_{20}N_6O_5$	424.41	232-234	0.51	80.80
43	$C_{21}H_{23}N_5O_3$	393.44	230-232	0.76	79.02
44	$C_{19}H_{19}N_3O_2$	321.37	170-173	0.41	70.13
45	$C_{19}H_{19}N_3O_3$	337.37	150-152	0.43	65.09
46	$C_{18}H_{16}N_4O_4$	352.34	164-168	0.36	81.32
47	$C_{18}H_{17}N_3O_2$	307.35	180-182	0.48	67.88

48	$C_{18}H_{16}ClN_3O_2$	341.79	170-172	0.25	72.35
49	$C_{18}H_{16}BrN_3O_2$	386.24	198-200	0.63	78.67
50	$C_{18}H_{16}N_4O_4$	352.34	160-162	0.52	54.50
51	$C_{18}H_{15}ClN_4O_4$	386.79	100-102	0.61	76.25
52	$C_{18}H_{15}ClN_3O_2$	341.79	148-150	0.48	81
53	$C_{20}H_{21}N_3O_2$	335.4	157-160	0.59	48.4
54	$C_{18}H_{16}ClN_3O_2$	341.79	158-160	0.65	83.2
55	$C_{18}H_{16}N_4O_4$	352.34	240-242	0.67	76.77
56	$C_{19}H_{19}N_3O_2$	321.37	158-160	0.58	69.87

**** TLC mobile phase: Ethanol: Dichloromethane: Ammonia (7:2:1)***

The IR stretching band (C=O) ranging from 1720-1670 cm^{-1} indicated the formation of a secondary amide linkage. Further C=N stretching band at 1690-1640 cm^{-1} indicated the formation of Schiff's base and hence confirm the formation of target compounds. Presence of phenyl nucleus in the synthesized compounds was indicated by the presence of skeletal stretching band of phenyl nucleus at 1558-1407 cm^{-1}. IR stretching band ranging from 780-623 cm^{-1} in compounds 13, 35, 38, 39, 48, 51, 52 and 54 indicated the presence of chloro group, whereas, IR stretching band at 1228-1051 cm^{-1} indicated the presence of the fluoro group in compounds 14 and 16 respectively. Presence of nitro group in compounds 8, 11, 33, 37, 38, 42, 50, 51 and 55 was indicated by an IR stretching band ranging from 1516-1327 cm^{-1}. Presence of methoxy group in compounds 9, 10, 12, 19, 32 and 45 was indicated by IR stretching band ranging from 2980-2898 cm^{-1}. Presence of bromo group in compounds 16 and 36 was indicated by an IR stretching band from 634-611 cm^{-1}. Further C-C out of plane bending in aromatic compounds are ranging from 753-665 cm^{-1}. The formation of Schiff bases was confirmed by the appearance of singlet signal around δ 7.262-7.589 ppm. The appearance of multiplet signal around δ 6.742-8.698 ppm depicted the presence of aromatic protons. The appearance of triplet signal in the range of δ 1.124-1.484 ppm in all compounds confirmed the presence of methyl group on naphthyridine ring, whereas the presence of methylene group on naphthyridine ring was indicated by NMR signals at δ 2.574-4.672.

2. Antimicrobial activity

The synthesized compounds were screened for their *in vitro* antibacterial activity against *S. aureus, B. subtilis, E. coli* and antifungal activity against *C. albicans* and *A. niger* by tube dilution method [30] using ciprofloxacin and fluconazole as reference standards for antibacterial and antifungal activity, respectively. Compounds Among all the synthesized compounds, compound *N'-(5-bromo-2-fluorobenzylidene)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (16) was emerged as promising antimicrobial agent against five test species (MIC=6.25µg/mL). *N-benzyl-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxamide* (24) showed significant antibacterial and antifungal activity against Gram positive (*Staphylococcus aureus*, *Bacillus subtilis)* and Gram negative bacteria (*E. coli)* and fungal strain (*Candida albicans*). *N'-(2,4-dimethoxybenzylidene)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (19), *1-ethyl-1,4-dihydro-N,7-dimethyl-4-oxo-1,8-naphthyridine-3-carboxamide* (22)**,** *N'-(2-(4-bromophenylamino)acetyl)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide* (36) and *1-ethyl-1,4-dihydro-7-methyl-4-oxo-N-m-tolyl-1,8-naphthyridine-3-carboxamide* (56) showed marked antibacterial activity against Gram negative bacteria and antifungal activity against *Candida albicans* (MIC=6.25µg/mL). *1-ethyl-1,4-dihydro-7-methyl-N-(2,4-dimethylphenyl)-4-oxo-1,8-naphthyridine-3-carboxamide* (53) exhibited maximum antibacterial activity against Gram negative *E. coli* and antifungal activity against *Candida albicans* and

Aspergillus niger. N-(4-chloro-2-nitrophenyl)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxamide (51) only showed antibacterial activity against Gram positive bacteria *Staphylococcus aureus*, *Bacillus subtilis* not for Gram negative bacterial and fungal strains.The results of antimicrobial evaluation revealed that the nature of the substituents has a considerable impact on the biological activities of the target nalidixic acid and the following structure activity relationship (SAR) can be deduced: Results of antimicrobial screening indicated that the presence of electron withdrawing 4-chloro-3-nitro substituents on phenylimino portion of the synthesized compounds (33 and 51) increase antimicrobial activity against *S. aureus* with MIC= 6.25µg/mL, whereas presence of electron withdrawing chloro group on phenylimino portion (compound 38) increase antifungal activity against *C. albicans.* The role of electron withdrawing group improving antimicrobial activities is supported by the studies of Sharma et al. [35]. Presence of electron withdrawing 2-floro-5-bromo substituent on phenyl portion (16) increases the antimicrobial activity against bacterial and fungal species. Change in position of bromo susbstituent from 5th to 4th or from meta to para in the phenyl portion (36) increases the antimicrobial activity against Gram negative bacteria *E. coli* and fungi *C. albicans.* In contrast with Tripathi et al. [36] who stated that the OH group at ortho position leads to a measurable change in activity of the compounds, the presence of the OH group at ortho position of naphthyl portion of compound 15 does not improve antimicrobial activity of the compound. Among the different electron withdrawing groups, halo (chloro and bromo) group is most effective in conferring the antimicrobial activity to potential. Presence of electron releasing group on phenyl portion (9, 10, 12 and 19) on phenylimino portion of the synthesized compounds (22, 23, 26, 27, 28, 32 and 45) does not improve antimicrobial potential. The aforementioned results indicated the fact that different structural requirements are essential for a compound to be selected as antibacterial or antifungal agent. This is similar to the results obtained by Sortino et al. [37].

3. QSAR Studies

Quantitative structure activity relationship (QSAR) was a predictive tool for preliminary evaluation of the activity of chemical compounds by using computer-aided models. In order to identify the substituent effect on the antimicrobial activity, quantitative structure activity relationship (QSAR) studies were undertaken, using the linear free energy relationship (LFER) model described by Hansch and Fujita [38]. Biological activity data determined as MIC values were first transformed into pMIC values (*i.e.* –log MIC) and used as dependent variables in QSAR study (Table 2)

Table 2
Antimicrobial activities (pMIC in µmol/ml) of synthesized compounds

S. No.	$pMIC_{sa}$	$pMIC_{ec}$	$pMIC_{bs}$	$pMIC_{ca}$	$pMIC_{an}$	$pMIC_{ab}$	$pMIC_{af}$	$pMIC_{am}$
1	1.32	1.32	1.32	1.32	1.32	1.32	1.32	1.32
2	1.45	1.45	1.45	1.45	1.45	1.45	1.45	1.45
3	1.41	1.41	1.41	1.41	1.41	1.41	1.41	1.41
4	1.46	1.46	1.46	1.46	1.46	1.46	1.46	1.46
5	1.43	1.43	1.43	1.43	1.43	1.43	1.43	1.43
6	1.34	1.04	1.64	1.34	1.34	1.34	1.34	1.34
7	1.48	1.18	1.48	1.48	1.48	1.38	1.48	1.42
8	1.48	1.48	1.48	1.48	1.48	1.48	1.48	1.48
9	1.46	1.46	1.77	1.46	1.46	1.57	1.46	1.52
10	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50
11	1.48	1.18	1.48	1.48	1.48	1.38	1.48	1.42
12	1.46	1.16	1.46	1.46	1.46	1.36	1.46	1.40
13	1.47	1.47	1.47	1.47	1.47	1.47	1.47	1.47
14	1.45	1.45	1.45	1.45	1.45	1.45	1.45	1.45
15	1.51	1.51	1.51	1.51	1.51	1.51	1.51	1.51
16	1.84	1.84	1.84	1.84	1.84	1.84	1.84	1.84
17	1.47	1.17	1.47	1.47	1.47	1.37	1.47	1.41
18	1.45	1.45	1.45	1.45	1.45	1.45	1.45	1.45
19	1.50	1.80	1.50	1.80	1.50	1.60	1.65	1.62
20	1.46	1.16	1.46	1.46	1.46	1.36	1.46	1.40
21	1.27	1.27	1.27	1.27	1.27	1.27	1.27	1.27
22	1.29	1.59	1.29	1.59	1.29	1.39	1.44	1.41
23	1.32	1.32	1.32	1.32	1.32	1.32	1.32	1.32
24	1.71	1.71	1.71	1.71	1.11	1.71	1.41	1.59
25	1.41	1.11	1.41	1.41	1.41	1.31	1.41	1.35
26	1.34	1.04	1.34	1.34	1.34	1.24	1.34	1.28
27	1.34	1.04	1.34	1.34	1.34	1.24	1.34	1.28
28	1.36	1.36	1.36	1.36	1.36	1.36	1.36	1.36
29	1.49	1.79	1.49	1.49	1.79	1.59	1.64	1.61
30	1.34	1.34	1.34	1.64	1.34	1.34	1.49	1.40
31	1.50	1.20	1.50	1.50	1.50	1.40	1.50	1.44
32	1.52	1.52	1.52	1.52	1.52	1.52	1.52	1.52
33	1.53	1.23	1.53	1.53	1.53	1.43	1.53	1.47
34	1.48	1.18	1.48	1.48	1.48	1.38	1.48	1.42
35	1.22	1.22	1.52	1.52	1.52	1.32	1.52	1.40
36	1.26	1.87	1.26	1.87	1.56	1.46	1.71	1.56
37	1.53	1.53	1.53	1.53	1.53	1.53	1.53	1.53
38	1.87	1.56	1.56	1.87	1.56	1.67	1.72	1.69
39	1.52	1.22	1.52	1.52	1.82	1.42	1.67	1.52
40	1.51	1.21	1.51	1.51	1.51	1.41	1.51	1.45
41	1.52	1.52	1.52	1.52	1.52	1.52	1.52	1.52
42	1.53	1.23	1.53	1.53	1.53	1.43	1.53	1.47
43	1.50	1.20	1.50	1.50	1.50	1.40	1.50	1.44
44	1.41	1.41	1.41	1.41	1.41	1.41	1.41	1.41
45	1.43	1.43	1.43	1.43	1.43	1.43	1.43	1.43
46	1.45	1.45	1.45	1.45	1.45	1.45	1.45	1.45
47	1.39	1.39	1.39	1.39	1.39	1.39	1.39	1.39
48	1.44	1.44	1.44	1.44	1.44	1.44	1.44	1.44
49	1.49	1.49	1.49	1.49	1.49	1.49	1.49	1.49
50	1.45	1.45	1.45	1.45	1.45	1.45	1.45	1.45
51	1.79	1.49	1.79	1.49	1.49	1.69	1.49	1.61
52	1.44	1.44	1.44	1.44	1.44	1.44	1.44	1.44
53	1.43	1.73	1.43	1.73	1.73	1.53	1.73	1.61
54	1.44	1.44	1.44	1.44	1.44	1.44	1.44	1.44
55	1.45	1.45	1.45	1.45	1.45	1.45	1.45	1.45
56	1.41	1.41	1.41	1.41	1.41	1.41	1.41	1.41
S.D.	0.12	0.20	0.11	0.13	0.12	0.11	0.11	0.10
Std.	3.33*	3.33*	3.33*	2.64**	2.64**	-	-	-

The different molecular descriptors selected for the present study are listed in (Table 3) and values of selected molecular descriptors calculated for the synthesized compounds (1-56) are presented in (Table 4).

Table 3
QSAR descriptors used in the study

S. No.	QSAR descriptor	Type
1.	log P	Lipophilic
2.	Zero order molecular connectivity index ($^{0}\chi$)	Topological
3.	First order molecular connectivity index ($^{1}\chi$)	Topological
4.	Second order molecular connectivity index ($^{2}\chi$)	Topological
5.	Valence zero order molecular connectivity index ($^{0}\chi^{v}$)	Topological
6.	Valence first order molecular connectivity index ($^{1}\chi^{v}$)	Topological
7.	Valence second order molecular connectivity index ($^{2}\chi^{v}$)	Topological
8.	Kier's alpha first order shape index ($\kappa\alpha_1$)	Topological
9.	Kier's alpha second order shape index ($\kappa\alpha_2$)	Topological
10.	Kier's first order shape index (κ_1)	Topological
11.	Randic topological index	Topological
12.	Balaban topological index	Topological
13.	Wiener's topological index	Topological
14.	Kier's second order shape index (κ_2)	Topological
15.	Ionization potential	Electronic
16.	Dipole moment (μ)	Electronic
17.	Energy of highest occupied molecular orbital (HOMO)	Electronic
18.	Energy of lowest unoccupied molecular orbital (LUMO)	Electronic
19.	Total energy (Te)	Electronic
20.	Nuclear Energy (Nu. E)	Electronic
21.	Molar refractivity (MR)	Steric

Table 4
Values of selected molecular descriptors used in QSAR study

S.No.	log P	MR	$^{0}\chi$	$^{0}\chi^{v}$	$^{2}\chi$	κ_1	J	W	LUMO	HOMO	μ
1	0.46	71.00	13.99	10.80	7.94	15.39	1.77	664.00	-0.78	-9.18	6.64
2	3.26	68.16	12.35	9.54	6.39	15.06	1.81	692.00	-0.40	-9.07	2.58
3	1.88	89.73	17.10	13.31	10.23	18.78	1.36	1418.00	-0.83	-8.38	7.05
4	3.34	107.58	19.23	15.22	11.29	21.70	1.28	2146.00	-0.81	-8.40	6.70
5	2.93	97.34	17.81	14.06	10.59	19.75	1.34	1612.00	-0.79	-8.82	7.09
6	0.63	76.41	14.70	11.67	8.29	16.37	1.76	789.00	-0.77	-9.02	6.21
7	2.73	111.05	20.26	16.43	12.11	22.68	1.32	2314.00	-0.75	-7.87	4.97
8	2.89	104.66	20.26	15.25	12.11	22.68	1.32	2314.00	-1.14	-9.12	13.57
9	2.68	103.80	19.39	15.39	11.29	21.70	1.36	1994.00	-0.76	-8.56	6.68
10	2.43	110.27	20.97	16.72	12.10	23.66	1.33	2506.00	-0.81	-8.38	7.24
11	2.89	104.66	20.26	15.25	12.03	22.68	1.38	2200.00	-0.92	-9.17	6.87
12	2.68	103.80	19.39	15.39	11.39	21.70	1.31	2032.00	-0.72	-8.82	6.58
13	3.45	102.14	18.68	15.18	11.10	20.73	1.36	1790.00	-0.83	-8.92	7.83
14	3.07	97.56	18.68	14.36	11.21	20.73	1.33	1828.00	-0.84	-8.86	6.99
15	3.65	115.48	21.25	16.59	13.01	23.17	1.15	2620.00	-0.74	-8.50	6.03
16	3.87	105.18	19.55	16.28	11.74	21.70	1.36	1992.00	-0.83	-9.01	7.72
17	3.45	102.14	18.68	15.18	11.21	20.73	1.33	1828.00	-0.84	-8.88	7.06
18	2.65	99.03	18.68	14.43	11.10	20.73	1.36	1790.00	-0.84	-8.80	7.91
19	2.43	110.27	20.97	16.72	12.10	23.66	1.36	2472.00	-0.77	-8.40	7.47
20	2.80	103.53	19.39	14.93	11.39	21.70	1.31	2032.00	-0.91	-9.11	9.49
21	0.39	64.23	12.58	9.73	7.42	13.43	1.92	470.00	-0.67	-9.09	5.06
22	0.63	69.13	13.28	10.65	7.56	14.41	1.93	558.00	-0.66	-9.06	4.94
23	0.88	74.03	14.15	11.60	8.28	15.39	1.95	648.00	-0.60	-9.01	5.21
24	2.41	93.74	17.10	13.74	10.23	18.78	1.44	1383.00	-0.66	-9.08	5.22
25	0.00	86.61	16.98	13.32	9.37	19.33	1.97	1144.00	-0.61	-9.00	6.07
26	1.39	78.30	14.86	12.23	8.78	16.37	1.92	772.00	-0.64	-9.05	4.54
27	1.45	78.40	14.70	12.06	8.29	16.37	1.89	789.00	-0.64	-9.03	4.52
28	1.57	83.52	15.57	13.01	8.61	17.36	1.97	870.00	-0.57	-8.97	5.24
29	4.24	113.58	20.38	16.37	12.41	22.20	1.40	2066.00	-0.59	-8.62	6.62
30	0.19	75.42	14.70	11.51	8.29	16.37	1.89	789.00	-0.62	-9.04	4.76
31	1.66	110.05	20.97	16.57	12.54	23.66	1.35	2582.00	-0.75	-8.45	6.55
32	0.94	111.47	21.67	16.98	12.71	24.64	1.34	2884.00	-0.75	-8.30	6.10
33	1.15	112.34	22.54	16.84	13.43	25.62	1.33	3188.00	-0.92	-9.16	13.13
34	1.19	105.01	20.10	15.65	11.91	22.68	1.36	2309.00	-0.76	-8.59	6.23
35	1.71	109.82	20.97	16.77	12.54	23.66	1.35	2582.00	-0.79	-8.63	7.50
36	1.99	112.63	20.97	17.57	12.54	23.66	1.35	2582.00	-0.80	-8.68	7.59
37	1.15	112.34	22.54	16.84	13.45	25.62	1.32	3122.00	-0.88	-9.21	9.97
38	1.67	117.14	23.41	17.96	14.00	26.60	1.39	3343.00	-0.91	-8.93	9.46
39	1.71	109.82	20.97	16.77	12.43	23.66	1.37	2538.00	-0.76	-8.64	6.11
40	2.13	115.09	21.84	17.50	13.07	24.64	1.37	2815.00	-0.76	-8.42	6.16
41	1.71	109.82	20.97	16.77	12.55	23.66	1.35	2560.00	-0.79	-8.78	7.11
42	1.15	112.34	22.54	16.84	13.36	25.62	1.38	3056.00	-0.83	-8.91	9.18
43	1.66	110.05	20.97	16.57	12.55	23.66	1.35	2560.00	-0.76	-8.54	6.00
44	2.78	93.95	17.27	13.96	10.51	18.78	1.48	1349.00	-0.75	-8.29	5.53
45	2.06	95.37	17.97	14.37	10.68	19.75	1.46	1544.00	-0.75	-8.13	6.09
46	2.27	96.23	18.84	14.22	11.41	20.73	1.45	1741.00	-1.06	-9.19	13.37
47	2.32	88.91	16.40	13.04	9.89	17.81	1.49	1178.00	-0.76	-8.45	6.03
48	2.83	93.71	17.27	14.15	10.51	18.78	1.48	1349.00	-0.83	-8.49	7.71
49	3.11	96.53	17.27	14.96	10.51	18.78	1.48	1349.00	-0.84	-8.55	7.82
50	2.27	96.23	18.84	14.22	11.42	20.73	1.44	1690.00	-0.94	-9.12	11.09
51	2.79	101.04	19.71	15.34	11.97	21.70	1.54	1824.00	-1.04	-9.12	8.03
52	2.83	93.71	17.27	14.15	10.41	18.78	1.51	1315.00	-0.75	-8.58	5.86
53	3.25	98.99	18.14	14.88	11.04	19.75	1.51	1490.00	-0.75	-8.23	5.65
54	2.83	93.71	17.27	14.15	10.52	18.78	1.47	1332.00	-0.81	-8.64	6.99
55	2.27	96.23	18.84	14.22	11.34	20.73	1.54	1639.00	-0.89	-9.11	6.86
56	2.78	93.95	17.27	13.96	10.52	18.78	1.47	1332.00	-0.75	-8.41	5.68

In the present study, we attempted to develop three different types of *mt*-QSAR models *viz. mt*-QSAR model for described antibacterial activity of synthesized compounds *against S. aureus, B. subtilis* and *E. coli*, *mt*-QSAR model for describing antifungal activity of synthesized compounds against *C. albicans* and *A. niger* as well as a common *mt*-QSAR model for describing the antimicrobial (overall antibacterial and antifungal) activity of

synthesized 1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid derivatives by calculating their average antibacterial activity, antifungal activity and antimicrobial activity values which were presented in (Table 5).

Table 5
Correlation matrix for antifungal activity of the synthesized compounds

	$pMIC_{af}$	log P	MR	$^{0}\chi^{v}$	κ_1	R	J	LUMO	HOMO	μ
$pMIC_{af}$	1.000									
log P	0.246	1.000								
MR	0.790	0.470	1.000							
$^{0}\chi^{v}$	0.822	0.380	0.986	1.000						
κ_1	0.788	0.258	0.964	0.967	1.000					
R	0.790	0.380	0.987	0.972	0.987	1.000				
J	-0.592	-0.628	-0.873	-0.812	-0.792	-0.861	1.000			
LUMO	-0.250	-0.330	-0.395	-0.353	-0.439	-0.446	0.543	1.000		
HOMO	0.205	0.330	0.367	0.365	0.218	0.283	-0.418	0.248	1.000	
μ	0.312	0.164	0.393	0.364	0.470	0.461	-0.429	-0.827	-0.380	1.000

Our previous studies in the field of QSAR [27-29, 39-40] indicated that the multi-target QSAR (*mt*-QSAR) models were better than one-target QSAR (*ot*-QSAR) models in describing the antimicrobial activity. So, in the present study we have developed multi-target QSAR models to describe the antimicrobial activity of synthesized 1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid derivatives. According to the *ot*-QSAR models, one should use five different equations with different errors to predict the activity of a new compound against five microbial species. The utilization of *ot*-QSAR models, which are almost in the whole literature however, were not practical when we had to predict each compound results for more than one target. In those cases we had to develop one *ot*-QSAR for each target. However, very recently the interest has been increased in the development of multi-target QSAR (*mt*-QSAR) models. As opposed to *ot*-QSAR, the *mt*-QSAR model was a single equation that considers the nature of molecular descriptors which are common and essential for describing the antibacterial and antifungal activity [41-44]. During the regression analysis studies it was observed that the response values of compounds 2, 16, 24 and 53 were outside the limits of response values of other synthesized 1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid derivatives. Thus these compounds were designated as outliers and were not included in the data set for QSAR model generation. In multivariate statistics, it is common to define three types of outliers [45]. X/Y relation outliers are substances for which the relationship between the descriptors (X variables) and the dependent variables (Y variables) were not the same as in the (rest of the) training data. X outliers are substances whose molecular descriptors do not lie in the same range as the (rest of the) training data. Y outliers are only defined for training or test samples. They are substances for which the reference value of response is invalid. As there was no difference in the activity (Table 2) as well as the molecular descriptor range (Table 4) of these outliers when compared to other synthesized nalidixic derivatives, which indicated the fact that these outliers belong to the category of Y outliers (substances for which the reference value of response is invalid). In order to develop mt-QSAR models, initially we calculated the average antibacterial, antifungal and antimicrobial activities values of nalidixic acid derivatives which are presented in (Table 2). These average antifungal activity values were correlated with the molecular descriptors of synthesized compounds (Table 5). In general, high colinearity ($r > 0.5$) was observed between different parameters. The high interrelationship was observed between Randic index (R) and Kier's first and second order shape indicex (κ_1) and molar referactivity (MR) ($r = 0.987$), and low interrelationship was observed for electronic parameter, dipole moment (μ) and lipophilic parameter (log P) ($r = 0.164$). Correlation of antibacterial, antifungal and antimicrobial activities of synthesized compounds with their molecular descriptors is given in (Table 6).

Table 6
Correlation of antibacterial, antifungal and antimicrobial activities of synthesized compounds with calculated molecular descriptors

Descriptors	$pMIC_{ab}$	$pMIC_{af}$	$pMIC_{am}$
Cos E	0.151	0.028	0.111
log P	0.446	0.246	0.401
MR	0.611	0.790	0.746
$^{0}\chi$	0.608	0.792	0.745
$^{0}\chi^{v}$	0.603	0.822	0.755
$^{1}\chi$	0.619	0.790	0.752
$^{1}\chi^{v}$	0.594	0.815	0.746
$^{2}\chi$	0.625	0.780	0.752
$^{2}\chi^{v}$	0.586	0.802	0.736
$^{3}\chi$	0.540	0.660	0.644
$^{3}\chi^{v}$	0.423	0.613	0.546
κ_1	0.579	0.788	0.724
κ_2	0.528	0.772	0.683
κ_3	0.465	0.746	0.631
$\kappa\alpha_1$	0.567	0.796	0.720
$\kappa\alpha_2$	0.509	0.776	0.673
$\kappa\alpha_3$	0.447	0.751	0.621
R	0.619	0.790	0.752
J	-0.547	-0.592	-0.619
W	0.553	0.779	0.703
Te	-0.617	-0.798	-0.754
Ee	-0.611	-0.804	-0.753
Ne	0.609	0.803	0.751
SA	0.528	0.788	0.691
IP	-0.171	-0.205	-0.201
LUMO	-0.449	-0.250	-0.406
HOMO	0.171	0.205	0.201
μ	0.389	0.312	0.394

Topological parameter, valence zero order molecular connectivity index ($^{0}\chi^{v}$) was found to be the dominating descriptor for antifungal activity of the synthesized compounds (Table 5, Eq. 1).

LR-mt-QSAR model for antifungal activity

$$pMIC_{af} = 0.0381\,^{0}\chi^{v} + 0.907 \quad (1)$$

$n = 52$
$r = 0.822$
$q^2 = 0.633$
$s = 0.053$
$F = 103.83$

Here and thereafter, n - number of data points, r - correlation coefficient, q^2 -cross validated r^2 obtained by leave one out method, s - standard error of the estimate and F - Fischer statistics. The developed QSAR model for antifungal activity (Eq. 1) indicated that there is a positive correlation between $^{0}\chi^{v}$ and antifungal activity of the synthesized compounds which means that antifungal activity values of synthesized compounds will increase with an increase in their $^{0}\chi^{v}$ values and vice versa. This is evidenced by low antifungal activity of compound **21** ($pMIC_{af}$ = 1.27 μM/mL, Table 2) having low $^{0}\chi^{v}$ value (9.73, Table 4). The molecular connectivity index, an adjacency based topological index proposed by Randic is denoted by χ and is defined as sum over all the edges (ij) as per following:

$$\chi = \sum_{i=1}^{n} (\varsigma_i \varsigma_\varphi)^{-1/2}$$

Where V_i and V_j are the degrees of adjacent vertices i and j and n is the number of vertices in a hydrogen suppressed molecular structure [46]. The topological index χ signifies the degree of branching, connectivity of atoms and unsaturation in the molecule which accounts for variation in activity [47]. The developed QSAR model (Eq. 1) was cross validated by q^2 value (q^2 = 0.633) obtained by leave one out (LOO) method. The value of q^2 more than 0.5 indicated that the model developed is a valid one. According to the recommendations of Golbraikh and Tropsha, the only way to estimate the true predictive power of a model is to test their ability to predict accurately the biological activities of compounds. As the observed and predicted values are close to each other (Table 7), the *mt*-QSAR model for antifungal activity (Eq. 1) is a valid one [48].

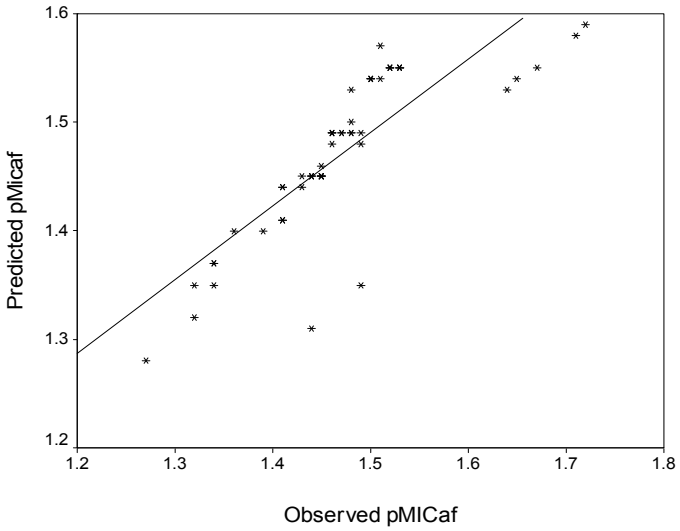
Table 7
Observed, predicted and residual antimicrobial activities of the synthesized compounds

Comp.	$pMIC_{ab}$			$pMIC_{af}$			$pMIC_{am}$		
	Obs.	Pre.	Res.	Obs.	Pre.	Res.	Obs.	Pre.	Res.
1	1.32	1.32	0.00	1.32	1.32	0.00	1.32	1.32	0.00
2	1.45	1.26	0.19	1.45	1.27	0.18	1.45	1.28	0.17
3	1.41	1.40	0.01	1.41	1.41	0.00	1.41	1.40	0.01
4	1.46	1.44	0.02	1.46	1.49	-0.03	1.46	1.46	0.00
5	1.43	1.41	0.02	1.43	1.44	-0.01	1.43	1.42	0.01
6	1.34	1.33	0.01	1.34	1.35	-0.01	1.34	1.34	0.00
7	1.38	1.46	-0.08	1.48	1.53	-0.05	1.42	1.50	-0.08
8	1.48	1.46	0.02	1.48	1.49	-0.01	1.48	1.46	0.02
9	1.57	1.44	0.13	1.46	1.49	-0.03	1.52	1.46	0.06
10	1.50	1.46	0.04	1.50	1.54	-0.04	1.50	1.51	-0.01
11	1.38	1.46	-0.08	1.48	1.49	-0.01	1.42	1.46	-0.04
12	1.36	1.44	-0.08	1.46	1.49	-0.03	1.40	1.46	-0.06
13	1.47	1.43	0.04	1.47	1.49	-0.02	1.47	1.46	0.01
14	1.45	1.43	0.02	1.45	1.45	0.00	1.45	1.43	0.02
15	1.51	1.50	0.01	1.51	1.54	-0.03	1.51	1.50	0.01
16	1.84	1.45	0.39	1.84	1.53	0.31	1.84	1.49	0.35
17	1.37	1.43	-0.06	1.47	1.49	-0.02	1.41	1.46	-0.05
18	1.45	1.43	0.02	1.45	1.46	-0.01	1.45	1.43	0.02
19	1.60	1.46	0.14	1.65	1.54	0.11	1.62	1.51	0.11
20	1.36	1.44	-0.08	1.46	1.48	-0.02	1.40	1.45	-0.05
21	1.27	1.30	-0.03	1.27	1.28	-0.01	1.27	1.28	-0.01
22	1.39	1.31	0.08	1.44	1.31	0.13	1.41	1.31	0.10
23	1.32	1.33	-0.01	1.32	1.35	-0.03	1.32	1.34	-0.02
24	1.71	1.40	0.31	1.41	1.43	-0.02	1.59	1.41	0.18
25	1.31	1.37	-0.06	1.41	1.41	0.00	1.35	1.40	-0.05
26	1.24	1.35	-0.11	1.34	1.37	-0.03	1.28	1.36	-0.08
27	1.24	1.33	-0.09	1.34	1.37	-0.03	1.28	1.36	-0.08
28	1.36	1.34	0.02	1.36	1.40	-0.04	1.36	1.39	-0.03
29	1.59	1.48	0.11	1.64	1.53	0.11	1.61	1.50	0.11
30	1.34	1.33	0.01	1.49	1.35	0.14	1.40	1.34	0.06
31	1.40	1.48	-0.08	1.50	1.54	-0.04	1.44	1.50	-0.06
32	1.52	1.49	0.03	1.52	1.55	-0.03	1.52	1.52	0.00
33	1.43	1.51	-0.08	1.53	1.55	-0.02	1.47	1.51	-0.04
34	1.38	1.46	-0.08	1.48	1.50	-0.02	1.42	1.47	-0.05
35	1.32	1.48	-0.16	1.52	1.55	-0.03	1.40	1.51	-0.11
36	1.46	1.48	-0.02	1.71	1.58	0.13	1.56	1.54	0.02
37	1.53	1.51	0.02	1.53	1.55	-0.02	1.53	1.51	0.02
38	1.67	1.53	0.14	1.72	1.59	0.13	1.69	1.55	0.14
39	1.42	1.48	-0.06	1.67	1.55	0.12	1.52	1.51	0.01
40	1.41	1.50	-0.09	1.51	1.57	-0.06	1.45	1.53	-0.08
41	1.52	1.48	0.04	1.52	1.55	-0.03	1.52	1.51	0.01
42	1.43	1.51	-0.08	1.53	1.55	-0.02	1.47	1.51	-0.04
43	1.40	1.48	-0.08	1.50	1.54	-0.04	1.44	1.50	-0.06
44	1.41	1.41	0.00	1.41	1.44	-0.03	1.41	1.42	-0.01

45	1.43	1.41	0.02	1.43	1.45	-0.02	1.43	1.43	0.00
46	1.45	1.44	0.01	1.45	1.45	0.00	1.45	1.43	0.02
47	1.39	1.39	0.00	1.39	1.40	-0.01	1.39	1.39	0.00
48	1.44	1.41	0.03	1.44	1.45	-0.01	1.44	1.42	0.02
49	1.49	1.41	0.08	1.49	1.48	0.01	1.49	1.45	0.04
50	1.45	1.44	0.01	1.45	1.45	0.00	1.45	1.43	0.02
51	1.69	1.46	0.23	1.49	1.49	0.00	1.61	1.46	0.15
52	1.44	1.41	0.03	1.44	1.45	-0.01	1.44	1.42	0.02
53	1.53	1.43	0.10	1.73	1.47	0.26	1.61	1.45	0.16
54	1.44	1.41	0.03	1.44	1.45	-0.01	1.44	1.42	0.02
55	1.45	1.44	0.01	1.45	1.45	0.00	1.45	1.43	0.02
56	1.41	1.41	0.00	1.41	1.44	-0.03	1.41	1.42	-0.01

The plot of predicted $pMIC_{af}$ against observed $pMIC_{af}$ (Fig. 1) also favours the developed model expressed by Eq. 1. Further, the plot of observed $pMIC_{af}$ *vs* residual $pMIC_{af}$ (Fig. 2) indicated that there was no systemic error in model development as the propagation of error was observed on both sides of zero [49]. In case of antibacterial activity, topological parameter, second order molecular connectivity index ($^2\chi$, Table 6) was found most dominant in expressed antibacterial activity of the synthesized compounds. So, QSAR model for antibacterial activity (Eq. 2) was developed using $^2\chi$.

Figure 1
Plot of predicted $pMIC_{af}$ against observed $pMIC_{af}$



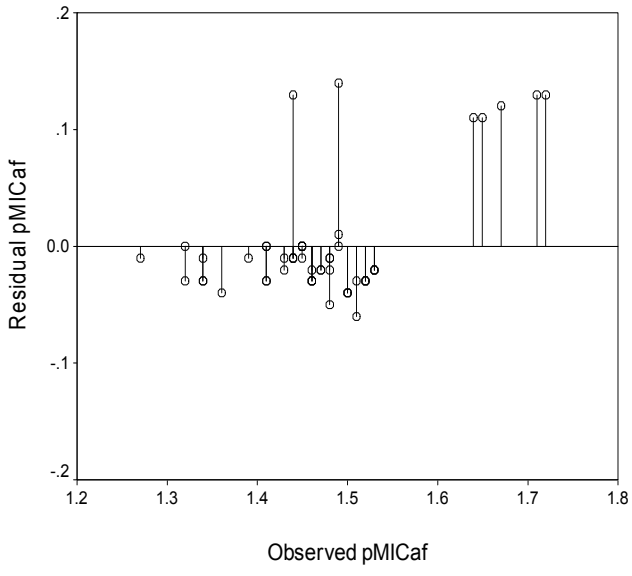
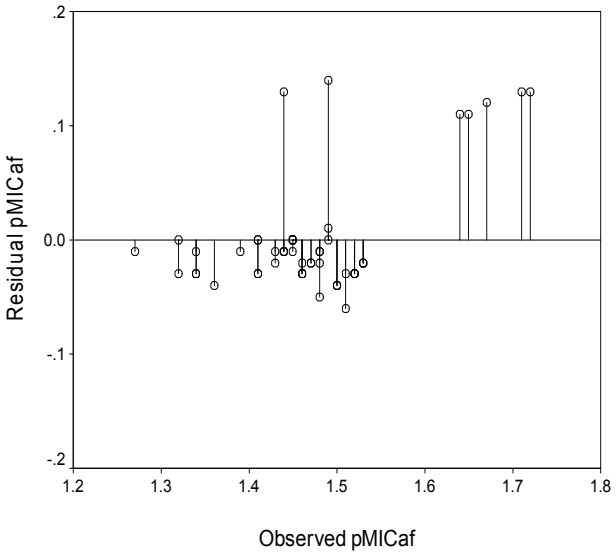


Figure 2
Plot of observed $pMIC_{af}$ vs residual $pMIC_{af}$



LR-*mt*-QSAR model for antibacterial activity

$$pMIC_{ab} = 0.0350\ {}^{2}\chi + 1.041 \qquad (2)$$

n = 52
r = 0.625
q^2 = 0.341
s = 0.074
F = 32.11

As in case of antifungal activity, antibacterial activity of the synthesized compounds is positively correlated with their $^{2}\chi$ values which means that antibacterial activity of the synthesized compounds will increase with increase in their $^{2}\chi$ values (Tables 3 and 5). The validity and predictability of the QSAR model for antibacterial activity *i.e.* Eq. 2 was cross validated by q^2 value (q^2 = 0.341) obtained by leave one out (LOO) method. The value of q^2 less than 0.5 indicated that the developed model is an invalid one. But one should not forget the recommendations of Golbraikh and Tropsha, who reported that the only way to estimate the true predictive power of a model was to test their ability to predict accurately the biological activities of compounds. As the observed and predicted values are close to each other (Table 7), the *mt*-QSAR model for antibacterial activity Eq. (2) is a valid one [48]. Topological parameter valence zero order molecular connectivity index ($^{0}\chi^{v}$) was also found to be most effective in describing antimicrobial activity of the synthesized compounds (Eq. 3, Table 6).

LR-*mt*-QSAR model for antimicrobial activity

$$pMIC_{am} = 0.0324\ {}^{0}\chi^{v} + 0.966 \qquad (3)$$

n = 52
r = 0.755
q^2 = 0.528
s = 0.056
F = 66.23

Antimicrobial activity of the synthesized compounds were positively correlated with valence zero order molecular connectivity index ($^0\chi^v$) which means that antimicrobial activity of the synthesized compounds will increase with increase in their $^0\chi^v$ values (Tables 3 and 5). The validity of QSAR model for antimicrobial activity (Eq. 3) is indicated by their high q^2 value (0.528) as well as the low residual values (Table 8). Further, plot of predicted $pMIC_{am}$ against observed $pMIC_{am}$ (Fig. 3) also favours the developed model expressed by Eq. 3. The plot of observed $pMIC_{am}$ *vs* residual $pMIC_{am}$ (Fig. 4) indicated that there was no systemic error in model development as the propagation of error was observed on both sides of zero. The high residual values observed in case of outliers (**2,** 16, 24 and 53) justify their removal while developing QSAR models.

Figure 3
Plot of predicted $pMIC_{am}$ against observed $pMIC_{am}$

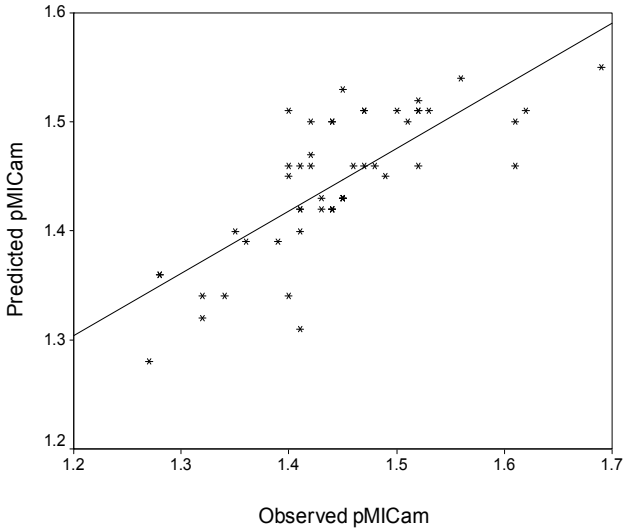
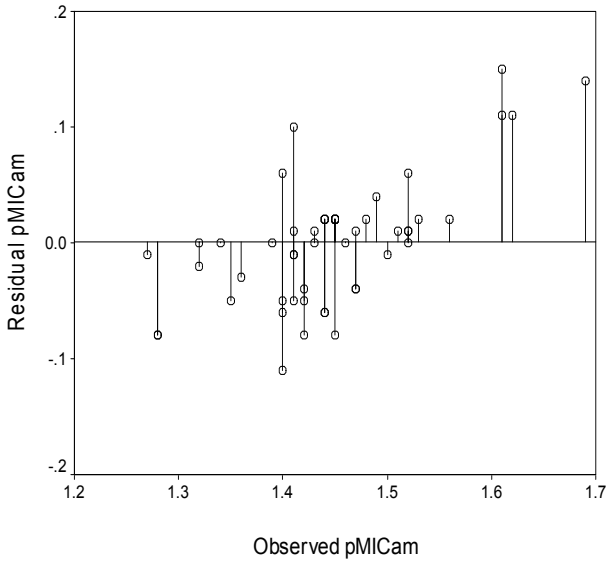


Figure 4
Plot plot of observed $pMIC_{am}$ vs residual $pMIC_{am}$



It was observed from *mt*-QSAR models [Eq. 1-3] that the antibacterial, antifungal and the overall antimicrobial activities of the synthesized nalidixic derivatives are governed by topological parameters, valence zero order molecular connectivity index ($^0\chi^v$) and second order molecular connectivity index ($^2\chi$).

CONCLUSION

A series of 1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid derivatives was synthesized and evaluated for its antimicrobial activity against Gram positive bacteria *Staphylococcus aureus*, *Bacillus subtilis*, Gram negative bacteria *Escherichia coli* and *in- vitro* antifungal activity against *Aspergillus niger* and *Candida albicans.* Antimicrobial activity results demonstrated that most of these compounds were showed better antimicrobial activity than the parent compound, nalidixic acid. Among all the screened compounds, compound 16 was emerged as promising antimicrobial agent against five test species (MIC=6.25µg/mL). Compound 24 showed significant antibacterial and antifungal activity against Gram positive (*Staphylococcus aureus*, *Bacillus subtilis)* and Gram negative bacteria (*E. coli)* and fungal strain (*Candida albicans*). Compound 19**,** 22, 36 and 56 showed marked antibacterial activity against Gram negative bacteria and antifungal activity against *Candida albicans* (MIC=6.25µg/mL). Compound 53 exhibited maximum antibacterial activity against Gram negative *E. coli* and antifungal activity against *Candida albicans* and *Aspergillus niger.* Compound 51 only showed antibacterial activity against Gram positive bacteria *Staphylococcus aureus*, *Bacillus subtilis* not for Gram negative bacterial and fungal strains. Compound 6 and 9 both enhanced antibacterial activity against *Bacillus subtilis.* Compound 29 is active against Gram negative bacteria *Escherichia coli* and Fungus *Candida albicans.* Compound 38 is most effective against *Staphylococcus aureus* and *Candida albicans.* The results of QSAR study gave rise to QSAR models with good predictive ability for antibacterial and antifungal activity of synthesized nalidixic acid derivatives. Based on the QSAR analysis it was indicative that second order molecular connectivity index($^{2}\chi$)and zero order molecular connectivity index ($^{0}\chi^{\varsigma}$) are the pre-requisites for these synthesized nalidixic acid derivatives to act as potential antimicrobial agents.

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