INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD)
© 2026 IJNRD | Volume 11, Issue 7, July 2026 | ISSN: 2456-4184 | IJNRD.ORG

A REVIEW ON DIAZANAPHTHALENES DERIVATIVES: A REVIEW OF MULTIPLE BIOLOGICAL ACTIVITIES

Mrs.DL.Narayanamma Degala , Sushma. Samsani , Devi Harshitha. Rudraraju , Varshitha. Satti , Vyshnavi. Puritigadda , Satya sai. Puppala , Dr.N.V.V.Jagan Mohan Reddy , Dr.D.Narendra.

ABSTRACT:

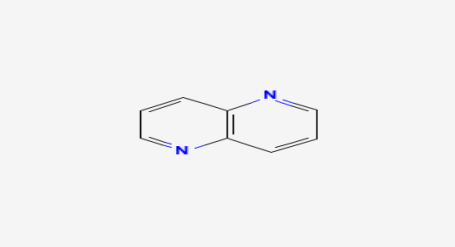
Naphthyridine is a nitrogen-containing heterocyclic compound that has gained significant attention in medicinal chemistry because of its broad spectrum of biological activities, particularly its antiviral potential. The presence of two nitrogen atoms in the fused aromatic ring system enhances its chemical reactivity and allows strong interactions with various viral targets. Naphthyridine derivatives have demonstrated promising activity against several viruses, including the Human Immunodeficiency Virus (HIV), Hepatitis C, Influenza, and COVID-19. These compounds exert antiviral effects through multiple mechanisms, such as inhibition of viral enzymes, interference with viral genome replication, and prevention of viral entry into host cells. Structural modifications of the naphthyridine scaffold have further improved antiviral potency, selectivity, and pharmacokinetic properties while reducing toxicity. Ongoing research focuses on designing novel naphthyridine derivatives with enhanced efficacy against emerging viral pathogens and drug-resistant viral strains. This review highlights the chemistry, mechanisms of action, and recent advances in the development of naphthyridine-based antiviral agents, emphasizing their potential as promising candidates for future antiviral drug discovery.

KEYWORDS:

1,8-Napthyridine, Antibacterial, Anticancer, Anti-inflammatory, Neurological.

1.INTRODUCTION:

Since 1893, a number of naphthyridine derivatives have been synthesized and explored for various biological activities in novel drug development. A broad spectrum of multiple biological activities has been associated with functional derivatives of naphthyridines. Identified as pyridine-like analog to naphthalene, the first naphthyridine derivative was synthesized and named by Arnold Reissert [1, 2] .The name “naphthyridine” was exclusively designated to the fused-ring system resulting from the fusion of two pyridine rings through two adjacent carbon atoms, with each ring containing only one nitrogen atom. Though also called diazanaphthalenes or pyridopyridines, "naphthyridine" is the most commonly used name for this class of compounds. Various review articles summarize the synthesis, structure, physicochemical properties, and pharmacological role of naphthyridines [3,4,5] .Six different isomeric forms of naphthyridines are described based on the position of the nitrogens in the bicyclic system



1,5-naphthyridine

Among these six isomeric sub-classes, 1,8-naphthyridine derivatives have attracted significant attention of researchers. This special group has been specifically investigated in the field of medicinal chemistry to a great extent and biological properties with applications in numerous therapeutic areas are reported. The reason for extensive research conducted with this isomeric form particularly is the skeleton; 1,8- naphthyridine is found to be comprising many compounds isolated from natural substances with biological activities. The discovery of nalidixic acid (1-ethyl-7-methyl-4-oxo-[1,8]-naphthyridine-3-carboxylic acid) and its antibacterial properties by George Lesher and coworkers in 1962 for the treatment of gram-negative urinary tract infections is considered to be pathbreaking in the field of 1,8-naphthyridines [6]. This invention prompted further extensive research in the field of designing derivatives possessing 1,8-naphthyridine moiety and investigation of other possible biological activities. Subsequently, various research groups have synthesized substituted 1,8-naphthyridines as target structures and demonstrated promising activities in multiple therapeutic areas. Over the past, this class of compounds has scored an exclusive position in the field of medicinal chemistry on account of various pharmacological properties. However, only limited review articles are available in literature, which summarize the biological properties of this special class of synthetic compounds. Reviews by Brown and Litvinov [7, 8] cover the synthesis and chemistry of 1,8-naphthyridine derivatives, with brief discussion of their biological activities.Another review by Srivastava et al. [9] It discusses the synthesis and structure–activity relationships of quinoline and naphthyridine derivatives with potential antitumor properties. A recent review by Fadda et al. [10] A recent review by Fadda et al. summarizes the chemistry and synthetic procedures of various 1,8- naphthyridine derivatives.

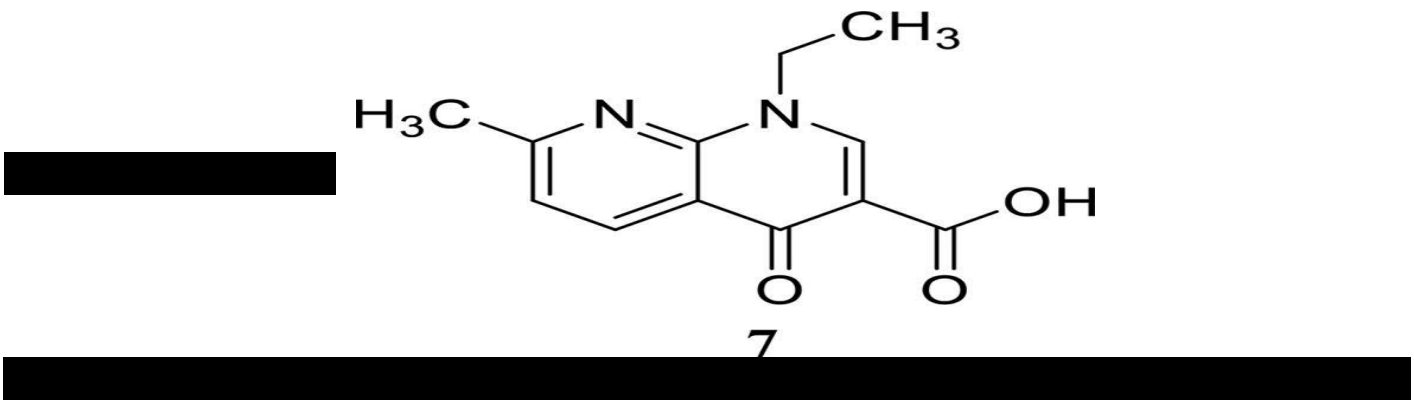
To promote future research with 1,8-naphthyridine derivatives, it will be beneficial to review the information available for these compounds till date. Therefore, in the present review, we intend to comprehensively summarize and discuss multiple biological activities of 1,8-naphthyridine derivatives reported till date, ranging from antimicrobial, antiviral, antituberculosis, anticancer, immunomodulatory, anti-inflammatory, analgesic, neurological, anti-osteoporotic, antiallergic, antimalarial, gastric antisecretory, bronchodilators, anticonvulsant, antihypertensive activity. Other biological activities of these compounds include platelet aggregation inhibition, antioxidant activity, EGFR and protein kinase inhibition, ionotropic effects, β-3 antagonism, MDR modulation, and adenosine and adrenoceptor agonism/antagonism and pesticides.The objective of this review is to summarize recent advances in the biological properties of 1,8-naphthyridine derivatives, and to elucidate the mechanisms of action and functional roles associated with this scaffold. On the basis of chemical class and functional groups, we have categorically segregated the diverse set of biological activities for these compounds reported in the literature to the best of our knowledge. The strategic compilation of reported literature relevant to biological activities and therapeutic areas might be helpful in exploring the further scope of 1,8-naphthyridine derivatives in new drug discovery for other therapeutic indications as well.

2.BIOLOGICAL PROPERTIES OF 1,8-NAPHTHYRIDINE DERIVATIVES:

ANTIMICROBIAL ACTIVITY:

Among all the biological activities explored till date for 1,8- naphthyridine group, antimicrobial potential has been most widely reported in the literature. The biological activity of 1,8-naphthyridines was first reported

with nalidixic acid in 1962. Nalidixic acid (1-ethyl-7-methyl-4-oxo-[1,8]naphthyridine-3-carboxylic acid) is the synthetic quinolone antibiotic, which was discovered by Lesher and coworkers as an antimalarial by-product in a distillate during chloroquine synthesis. Although nalidixic acid was initially used only for gram-negative urinary tract infections in humans, it paved the way for developing other antibacterial and antifungal agents based on the 1,8-naphthyridine scaffold.[11]



7

(nitrofurylvinyl-1,8-naphthyridine)

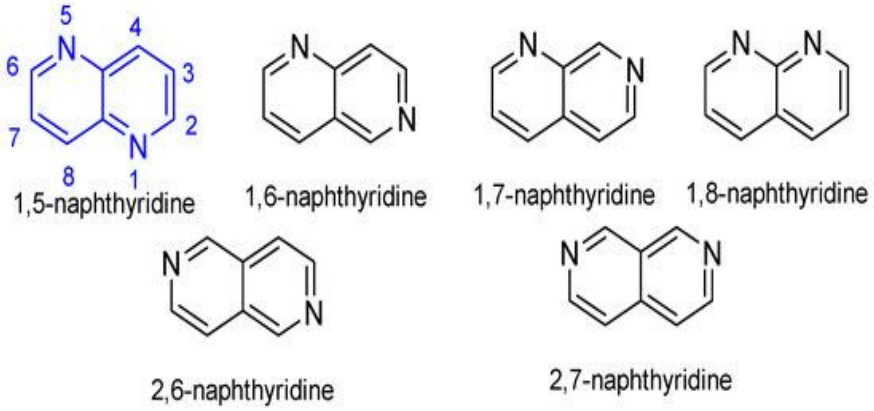
Subsequent to nalidixic acid, nitrofurylvinyl derivatives of 1,8-naphthyridine (nitrofurylvinyl-1,8-naphthyridine and 1-substituted 1,4-dihydro-7-(2-(5-nitro-2-furyl)vinyl)-4-oxo 1,8-naphthyridine derivatives) were shown to possess antibacterial activity by Nishigaki et al. [12] and Nagasaki et al. [13]. In addition, furo[3,2-b][1,8]naphthyridine deriva tives and imidazo[4,5-b][1,8]naphthyridine derivatives were also reported with antimicrobial activities [14–16]. 1-Alkyl-1,4-dihydro-4-oxo-1,8- and-1,6-naphthyridine-3 carboxylic acids have been explored as antibacterial agents [17]. Biologically active halogenated compounds (7-fluoromethyl-1,8-naphthyridine derivatives) were studied for antibacterial activity [18].

Antimicrobial properties of 1,8-naphthyridines variously substituted with functional groups at different positions are categorically summarized as follows.

3.CARBOXILIC ACIDS:

Carboxylic acids with 1,8-naphthyridine moiety are well reported as antibacterial agents. 7-Substituted 1-ethyl-1,4 dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids and 1,2,3,4-tetrahydro-4-oxo-1,8-naphthyridine-3-carboxylic acid esters , carbonitriles, and carboxamides have displayed in vivo antibacterial activity [19, 20]. 1-Vinyl-1,4-dihydro-4-oxo 1,8- have been studied as antibacterial agents [21]. Novel arylfluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids were assessed by Chuetal. [22] for antibacterial activity. The compounds showed potential in vitro and in vivo antibacterial efficacy. Best in vitro antibacterial potency was shown when the 1-substituent is either p-fluorophenyl or o,p-difluorophenyl and the 7-substituent is a 3-amino-1 pyrrolidinyl group. A series of 7,8-disubstituted 1-cyclopropyl 6-fluoroquinoline-3-carboxylic acids, 7-substituted 1-cyclo propyl-6-fluoro-1,8-naphthyridine-3-carboxylic acids , and 10-substituted 9-fluoropyridobenzoxazine-6-carboxylic acids have demonstrated potential antibacterial activity against gram-negative organisms. Stimulation of in vitro activities by the side chains on the 8-hydrogen quinolone and 1,8-naphthyridine against gram-negative organisms was as follows: 3-aminopyrrolidinyl>3-(aminomethyl)pyrrolidinyl> piperazinyl>alkylated 3-(aminomethyl)pyrrolidinyl [23]. Var ious 7-substituted-1-tert-butyl-6-fluoro-1,8-naphthyridine-3 carboxylic acids have been explored for antibacterial activities. Based on in vitro and in vivo antimicrobial activity, toxicity and pharmacokinetic profile, compound 7-diazabicyclo naphthyridine was selected for clinical evaluation [24]. 5 Substituted-6-fluoro-7-(cycloalkylamino)-1,4-dihydro-4-oxo 1,8-naphthyridine-3-carboxylic acids have been prepared and tested for their in vitro and in vivo activities. These derivatives also demonstrated antibacterial properties. It was found that better in vitro activity was shown by the 5-methyl group with the 1-cyclopropyl appendage, but poorer activity with the 1 tert-butyl moiety. Also, the in vitro and in vivo activities of the 5-methyl derivative were found to be increased

by (3S)-3 amino-pyrrolidine [25]. Gemifloxacin (7-[(4Z)-3-(amino methyl)-4-(methoxyimino)-1-pyrrolidinyl]-1-cyclopropyl-6 fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid) emerged as another 1,8-naphthyridine-derived antimicrobial and antibacterial agent for treatment of respiratory tract infections. Gemifloxacin showed the most potent antimicrobial activity tested against S. pneumoniae and M. catarrhalis [26]. DW286, 7-[3-(aminomethyl)-4 (methoxyimino)-3-methyltetrahydro-1H-1-pyrrolyl]-1-cyclo propyl-6-fluoro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid , is reported as a fluoronaphthyridone-based antibacterial agent [27]. As studied by Yun et al. [28], DW286 demonstrated stronger activities against gram-positive bacteria, such as Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, and Enterococcus faecalis when compared to other drugs such as ciprofloxacin, gemifloxacin,sparfloxacin,andtrovafloxacin.DW286showed similar trend of activity against gram-negative bacteria, such as Staphylococcus aureus, Staphylococcus epidermidis, Strep tococcus pneumoniae, and Enterococcus faecalis, as compared to those of trovafloxacin and gemifloxacin but was weaker than that of ciprofloxacin.DW286alsoshowedinvivo potency in a mouse systemic infection model against three S. aureus strains, including methicillin-resistant S. aureus (MRSA) andquinolone-

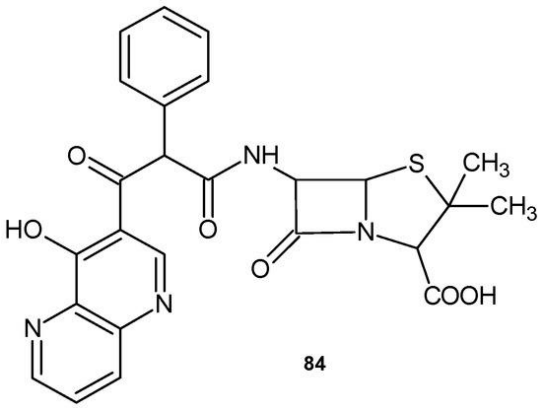


resistant S. aureus (QRSA). 7-Chloro-1 cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3 carboxylic acids were tested for antibacterial activity. In another study by Huang,sulfur-containing quinolone, 7-(2 thia-5-azabicyclo[2.2.1]heptan-5-yl)-1-cyclopropyl-6-fluoro-4 oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid exhibited a superior antibacterial activity against quino lone-susceptible and multidrug-resistant strains in comparison with the clinically used fluoroquinolones ciprofloxacin and vancomycin, especially against Streptococcus pneumonia and multidrug-resistant S. pneumoniaclinical isolates [29, 30]

4.PYRIDONE-CARBOXILIC ACIDS:

Enoxacin is an antimicrobial fluoroquinolone with a 7-piperazinyl-1,8-naphthyridine skeleton. AT-2266 (enoxacin) 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1,8 naphthyridine-3-carboxylic acid emerged as a new agent with broad spectrum and potent antibacterial activity against gram-positive and gram-negative microorganisms, even stronger than pipemidic acid, nalidixic acid, and similar to that of norfloxacin. AT-2266 showed no cross-resistance with antibiotics and inhibited most highly resistant bacteria to nalidixic acid at concentrations ranging from 1.56 to 3.13mg/ mL[31, 32]. AT-2266 also showed in vivo antibacterial activity in mice with pulmonary, dermal, or urinary tract infections. This effect was higher than norfloxacin, pipemidic acid, and nalidixic acid against all of the infections. AT-2266 was able to demonstrate good activity against infections induced by gentamicin-resistant and nalidixic acid-resistant organ isms [33]. Structure–activity relationships of pyridonecarbox ylic acids with substitutions at C-1, C-6, and C-7 positions as antibacterial agents were described by Matsumoto and coworkers [34]. Enoxacin, originally AT-2266, showed

the most broad and potent in vitro antibacterial activity, an excellent in vivo efficacy on systemic infections and a weak acute toxicity. Enoxacin exerted inhibitory effects on cyto chrome P-450-mediated theophylline metabolism. Seven enoxacin derivatives were designed and investigated for theophylline metabolism [35]. However, many adverse effects are reported to be associated with enoxacin.



84

Another group of pyridine carboxylic acids comprising 7-(3 amino-1-pyrrolidinyl)-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8 naphthyridine-3-carboxylic acid and its analogs are reported by Egawa et al. [36] to possess antibacterial activity. Based on the in vitro and in vivo antibacterial screening, three compounds, 1-ethyl- and 1-vinyl-7-(3-amino-1-pyrrolidinyl)-6 fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids and 1-vinyl-7-[3-(methylamino)-1-pyrrolidinyl] analog were found to be more active than enoxacin. Pyridone carboxylic acid derivatives including enoxacin were examined against gram-negative bacilli in the presence and absence of ethylenediaminetetraacetic acid (EDTA) or gentamicin. The minimal inhibitory concentrations (MICs) of nalidixic acid, cinoxacin, and piromidic acid were reduced by the addition of EDTA or gentamicin. However, the MICs of enoxacin, pipemidic acid, and ofloxacin remained unaffected [37]. 6-Fluoro-1,4-dihydro-4-oxo-7-(4-pyridyl)-1,8-naphthyridine-3 carboxylic acid derivatives with ethyl, 2-fluoroethyl, 2-hydroxyethyl, vinyl, or cyclopropyl substitutions at C-1 position were investigated for potential antibacterial activity. 1-Cyclopropyl derivative was found to be most active with comparable activity to that of enoxacin against experimental infections due to S. aureus [38, 39]. Enantiomers of 7-(3 aminopyrrolidin-1-yl)-1-(2,4-difluorophenyl)-1,4-dihydro-6 fluoro-4-oxo-1,8-naphthyridine-3-carboxylic acid , a potent member of the quinolone carboxylic acid class of antibacterial agents were synthesized and have shown promising antibacterial activity [40]. Another pyridine carboxylic acid T-3262 [p-toluene sulfonic acid salt of DL-7-(3 amino-1-pyrrolidinyl)-1-(2,4-difluorophenyl)-6-fluoro-1,4 dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid monohydrate] has also shown broad spectrum of antibacterial activity against gram-positive and gram-negative bacteria. The activity of T-3262 against most Enterobacteriaceae was found to be comparable with that of ciprofloxacin except against Proteus spp. and Providenciarettgeri and more potent than that of ofloxacin and norfloxacin. In an in vivo mice model of systemicinfection,T-3262demonstratedbetter efficacy than norfloxacin and comparable effect with that of ofloxacin and ciprofloxacin [41]. In another study, T-3262 demonstrated better activity than ofloxacin against Enter obacteriaceae, ciprofloxacin, and ofloxacin against Pseudomonas cepacia and Pseudomonas maltophilia, which are resistant to imipenemand gentamicin[42].Chemically modified fluoro pyridine carboxylic acid with a 1,8-naphthyridine ring, such as enoxacin and to sufloxacin, to their 2-aza derivatives were studied. However, the compounds did not demonstrate better activities than those of enoxacin and to sufloxacin [43].

A series of amino acid prodrugs of racemic and chiral 7-(3 amino-1-pyrrolidinyl)-6-fluoro-1,8-naphthyridine-3-carboxylic acids were evaluated by Sanchez and coworkers [44] for antibacterial activity. The amino acid analogs were less active in vitro, but had equal or increased efficacy in vivo when compared with the parent compounds. The most active compound of the series was [S-(R,R)]-7-[3-[(2-amino-1-oxo propyl)-amino]-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihy dro-4-oxo-1,8-naphthyridine-3-carboxylicacid(PD131112).

PD 131628 ((S)-7-(3-amino-1-pyrrolidinyl)-1-cyclopropyl-6-flu oro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid) , another amino pyrrolidine-substituted fluorocyclopropyl naphthyridine quinolone is a potent anti-infective agent which possesses high in vitro activity against a wide spectrum of bacterialspecies.Whencomparedwithciprofloxacin,PD131628 was found to exhibit higher activity against gram-positive organisms, almost equivalent activity against gram-negative organisms and relatively inactive against gram-negative anae robes.InvitroactivityofPD131628wasfoundtobehigherthan ciprofloxacin, imipenem, ampicillin, penicillin G, oxacillin, cefazolin, ceftazidime, cefoxitin, cefsulodin, aztreonam, piper acillin, amikacin, spectinomycin, doxycycline, erythromycin, metronidazole, and vancomycin [45]. In another set of studies, PD 131628 demonstrated better activity than ciprofloxacin or ofloxacin against Escherichia coli [46].

To study the effects of 7-[3-(1-aminoethyl)-1-pyrrolidinyl] moiety on potency and in vivo antibacterial efficacy, a series of stereo chemically pure 7-[3-(1-aminoethyl)-1-pyrrolidinyl] 1,4-dihydro-4-oxoquinoline and 1,8-naphthyridine-3-carbox ylic acid derivatives with varied substituents at the 1-, 5-, and 8-positions were synthesized. When compared with their 7-[3-(aminomethyl)-1-pyrrolidinyl] analogs, the (3R,1S)-3-(1 aminoethyl) pyrrolidines resulted in two- to fourfold increase in antibacterial activity against gram-positive bacteria in vitro and an average of 10-fold increase in oral efficacy. Active compounds were identified with outstanding antibacterial activity and low degrees of phototoxicity and mammalian cell cytotoxicity [47]. In yet another attempt to investigate pyridine carboxylic acids as antibacterial agents, 7-(1-amino cyclopropyl)-4-oxo-1,8-naphthyridine-3-carboxylic acid derivatives showed in vitro antibacterial activities against both gram-positive and gram-negative bacteria, which were found to be comparable to those of ciprofloxacin(CPFX)and ofloxacin (OFLX) [48]. To study the effect of two methyl groups adjacent to the distal nitrogen in the pyrrolidinyl moiety on antibacterial activity, a series of the R- and S-isomers of 7-[3-(1-amino-1 methylethyl)-1-pyrrolidinyl]-1,4-dihydro-4-oxoquinoline- and 1,8-naphthyridine-3-carboxylic acids were prepared. As com paredtotheS-isomer,theR-isomerdisplayeda2–20-foldbetter in vitro antibacterial activity against gram-negative and gram positive organisms and a 2–15-fold better in vivo activity in a mouse infection model. R-Isomers also showed better safety profile by a reduced risk of phototoxicity and cytotoxicity when examined in a phototoxicity mouse model and an in vitro mammalian cell cytotoxicity protocol [49]. Pyrrolidine derivatives, bearing an alkyloxime substituent at the 4-position and an amino methyl substituent in the 3-positionofthepyrrolidine ring were synthesized and coupled with various quinolone carboxylic acids to produce a series of new fluoroquinolone antibacterials. These fluoroquinolones were found to possess potent antimicrobial activity against both gram-negative and gram-positive organisms, including methicillin resistant Staphylococcus aureus (MRSA).Further, addition of the moiety resulted in an improvement of the pharmacokinetic parameters of the novel quinolones. The shortlisted compound, 7-(4 (aminomethyl)-3-(methoxyimino) pyrrolidin-1-yl)-1-cyclo propyl-6-fluoro-4-oxo-1,4-dihydro[1,8]naphthyridine-3carboxylicacid(LB20304),showed the best in vivo efficacy and pharmacokinetic profile in animals, as well as good physical properties [50].

5.THIAZOLE DERIVATIVES:

Thiazolo derivatives are known to possess potential antibac terial activity. Based on this, oxazolo- and imidazolo[3,2-a] [1,8]naphthyridine derivatives were evaluated by Kondo et al. [51] for in vitro antibacterial activity and inhibitory effects on DNA gyrase of Escherichia coli K-12 C600. Thiazolo[3,2-a][1,8]naphthyridine derivatives demon strated better antibacterial activity against gram-positive and gram-negative bacteria and inhibition of DNA gyrase than oxazolo and imidazolo analogs. However, the resultant effect was comparable with ofloxacin and enoxacin. In another set of studies, thiazoloquinolone and thiazetoqui nolone derivatives with 1,8-naphthyridine moiety were explored for antibacterial activity. These derivatives were shown to possess antibacterial activities and cytotoxicity comparable with those of norfloxacin, ofloxacin, enoxacin, and ciprofloxacin and even higher activity than dihyrothia zoloquinolone

derivatives. Most of the thiazoloquinolone derivatives were more cytotoxic than thiazetoquinolone derivatives against mammalian cells. 6-Fluoro-1-methyl-4 oxo-7-(1-piperazinyl)-4H-[1,3]thiazeto[3,2-a]quinoline-3-carboxylic acid showed the most potent antibacterial activity of all compounds tested, as well as a very low cytotoxicity. This compound showed antibacterial activity and cytotoxicity comparable to that of ciprofloxacin [52]. 2-Cyclopropyl[1,8] naphthyridine-3-carboxylic acid (4-phenyl-2-thioxo-thiazol-3 yl)-amides also demonstrated moderate antibacterial activity against S. aureus and E. coli [53].

6.AZETIDINYLQUINOLONES:

1,8-Naphthyridine derivatives with azetidine group have also been studied for antibacterial activity. The effects of the azetidine moiety at position 2 on antibacterial activity was studied by Frigola et al. [54, 55] with a series of 7-(2,3 disubstituted-1-azetidinyl)-1,4-dihydro-6-fluoro-4-oxoquino line- and 1,8-naphthyridine-3-carboxylic acids , with varied substituents at the 1-, 5-, and 8-positions. Antibacterial potential against gram-positive and gram-negative bacteria and pharmacokinetic and physicochemical properties of selected derivatives were compared to the relevant 7-(3 amino-1-azetidinyl) and 7-(3-amino-3-methyl-1-azetidinyl) analogs. It was concluded that combination of a cyclopropyl or a substituted phenyl group at N-1 and a trans-3-amino-2 methyl-1-azetidinyl group at C-7 position resulted in the best antibacterial, pharmacokinetic, and physicochemical proper ties of these sets of compounds. A series of stereo chemically pure 7-(3-amino-2-methyl-1-azetidinyl)-1,4-dihydro-6-fluoro 4-oxoquinoline- and 1,8-naphthyridine-3-carboxylic acids, with varied substituents at the 1-, 5-, and 8-positions were synthesized to investigate the possible effects of chirality on the potency and in vivo efficacy relative to the corresponding racemic mixtures. Several chiral 9-fluoro-2,3-dihydro-3-meth yl-7-oxo-10-(substituted-1-azetidinyl)-7H-pyrido[1,2,3-de] 1,4-benzoxazine-6-carboxylic acids were synthesized. It was suggested by structure–activity relationship studies that the absolute stereochemistry at the asymmetric centers of both the azetidine and the oxazine rings was critical to stimulate in vitro activity and oral efficacy. The best antibacterial activity was displayed by the 3S configuration in the pyridobenzoxazine series and the (2S,3R) configuration of the 3-amino-2 methylazetidine moiety [56]. A new fluorinated naphthyridine with an azetidine moiety, E-4695 ( )-7-[3-(R)-amino-2 (S)-methyl-1-azetidinyl]-1-cyclopropyl-1,4-dihydro-6-fluoro-4 oxo-1,8-naphthyridine-3-carboxylic acid was explored for activity against gram-positive and anaerobic pathogens. This compound was found to exhibit strong antibacterial proper ties against gram-positive cocci, including species of the genera Staphylococcus, Streptococcus, and Enterococcus. The response was found to be even higher than that of ciprofloxacin and ofloxacin. Also, good activity was shown against gram-negative pathogens such as members of the family Enterobacteriaceae (with the exception of Providencia spp. and Pseudomonas aeruginosa). E-4695 also showed higher degree of potency than ciprofloxacin against C. perfringens and B. fragilis isolates, respectively. Also, in an in vivo model, E-4695 was able to demonstrate better activity against infection with Streptococcus pneumoniae 29206 (ED50, 41.2mg/kg) as compared with ciprofloxacin (ED50, 200mg/kg) [57].

7.OTHER GROUPS:

A series of quinolone and naphthyridine antibacterial agents possessing the C7-heterocycle bicyclic 2,5-diazabicyclo[n.2.m] alkanes and a series including 4-aminopiperidine and 3 amino-8-azabicyclo[3.2.1]octanes have been evaluated in vitro and in vivo for antibacterial activity against a variety of gram-negative and gram-positive organisms and also against the target enzyme bacterial DNA gyrase. All the derivatives showed similar potency as compared with the parent 7-piperazinyl analogs. The best activity was found to be associated with endo-7-(3-amino-8-azabicyclo[3.2.1]oct-8yl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid, which displayed activity surpassing that of the piperazine parent compound [58]. Esters of 2-methyl-1,8 naphthyridine-3-carbamic acid have exhibited antifungal properties against Alternaria alternata, Fusarium oxysporum, and Curvularia lunata [59]. Organotin(IV) derivatives of 1 ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-car boxylic acid (nalidixic acid) have demonstrated antifungal as well as antibacterial activities [60]. 2-Chloro-1,8-naphthyr idine-3-carbaldehyde derivatives showed in vitro anti fungal

properties against Alternaria alternate, Fusarium oxysporum, and Curvularia lunata [61]. 2-[(3-Methyl-1H indazol-1-yl)-3-substituted phenyl-1,8-naphthyridine deriva tives also exhibited moderate antibacterial activity, when tested against Staphylococcus aureus, Bacillus subtilis, Escher ichia coli and Pseudomonas aeruginosa and good antifungal activity against Candida albicans and Asperigillus niger [62]. Various 1,8-naphthyridines with novel DNA ligase inhibitory activity were designed and studied for antibacterial potential. A series of 2-amino-[1,8]-naphthyridine-3-carboxamides (ANCs) with potent inhibition of bacterial NAD(þ)-dependent DNA ligases were discovered. The design of these compounds was specifically guided by highly resolved X-ray structures of inhibitors in complex with either Streptococcus pneumoniae or Escherichia coli LigA. Out of these candidates, 2-amino-6 bromo-7-(trifluoromethyl)-[1,8]-naphthyridine-3-carboxa mide demonstrated promising in vitro (MIC Staphylococ cus aureus 1mg/L) and in vivo antistaphylococcal activity [63]. QSAR with a correlation of the antitubercular and antibacte rial (Staphylococcus aureus and Escherichia coli) activities of substituted 3- or 4-phenyl-1,8-naphthyridine derivatives is discussed by Sivakumar et al. [64].

8.ANTIVIRAL ACTIVITY (HIV/HCV):

1,8-Naphthyridine derivatives have also been examined for anti-HIV/HCV potential. Pyridone carboxylic acid derivatives with 1- or 2-naphthyl substituents at N-1 position showed potent in vitro anti-HIV activities with some compounds possessing even better activity than that of atevirdine [65]. BMS-A78277,5,10dihydrobenzo[beta][1,8] naphthyridine-N oxide , belongs to the class of novel non-nucleoside reverse transcriptase inhibitors (NNRTIs) which demonstrated improved activity profile against mutants of HIV-1 with pharmacokinetic profiles amenable to once-daily dosing. Biotransformation of this NNRTI candidate was studied by Daniels et al. [66] in cynomolgus monkey model. 1-Hydroxy 1,8-naphthyridin-2(1H)-one derivatives are also reported as potent and selective HIV-1 ribonuclease H inhibitors [67]. An SAR study on 6-benzylamino-4-oxo-1,4-dihydro-1,8-naph thyridines and 4-oxo-1,4-dihydroquinolines as HIV integrase inhibitors is reported by Nagasawa et al. [68]. A series of 1,8-dihydroxy-2-oxo-1,2-dihydroquinoline-3-carbox amides, 1,4-dihydroxy-2-oxo-1,2-dihydro-1,8-naphthyri dine-3-carboxamides , and 1-hydroxy-2-oxo-1,2-dihydro 1,8-naphthyridine-3-carboxamides were synthesized and were found as potent HIV-1 integrase inhibitors. These candidates possessed high antiviral potency against cells harboring resistant integrase mutants to raltegravir (inte grase strand transfer inhibitor). In cell-based assays, active compounds exhibited inhibitory potential with EC50 values in nanomolar range against HIV-1 vectors harboring wild-type HIV integrase (IN) [69]. Further substituted derivatives of these 1-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-car boxamides were synthesized as IN inhibitors with enhanced activity against recombinant IN. 4-Amino-1-hydroxy-2-oxo 1,8-naphthyridines demonstrated antiviral potencies against HIV vectors that carry wild-type (WT) with single digit nanomolar EC50values. These compounds also possessed high selectivity indices as reflected by low toxicity in cultured cells [70]. Two series of imidazo[1,2-a][1,8]naphthyridine derivatives have been explored by Huang et al. [71] as anti-HCV agents with direct C–H arylation. Promising anti HCV activities were demonstrated by synthesized compounds. Recently, 1,8-naphthyridine derivatives of newly discovered small-molecule IFN-like agent were synthesized by Wang et al. [72] with potent anti-HCV activity (EC50¼0.017 0.159mM) and low toxicity (CC50> 25mM). The mechanistic action of these compounds involves inhibition of HCV entry.

9.ANTI TUBERCULOSIS ACTIVITY:

1,8-Naphthyridines have also been investigated for anti tuberculosis potential. 4-Phenyl-1,8-naphthyridine derivatives showed potential activity against Mycobacterium tuberculosis H37Rv [73]. To evaluate the antimycobacterial activity, a series of 1,8-naphthyridine derivatives with substitutions at the 2, 3, 4, and 7 positions were synthesized and assessed in vitro in accordance with an international program with the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF). These compounds demonstrated consider able activity against Mycobacterium tuberculosis H37Rv [74]. A series of 4-phenyl-1,8-naphthyridine derivatives substituted in the positions 2, 6, and 7 were synthesized and tested for in vitro antimycobacterial

activity as part of a TAACF TB screening program. Ninety-one to ninety-nine percent inhibition against Mycobacterium tuberculosis H(37) Rv was demonstrated by active compounds [75].

Aseriesof1-(cyclopropyl/tert-butyl/4-fluorophenyl)-1,4-dihydro-6-nitro-4-oxo-7-(substituted secondary amino)-1,8-naph thyridine-3-carboxylic acid derivatives were synthesized by Sriram et al. [76] and assessed for in vitro and in vivo activity against Mycobacterium tuberculosis H37Rv (MTB), multi-drug resistant Mycobacterium tuberculosis (MDR-TB) and Mycobacterium smegmatis (MC2). Compounds were also tested for inhibition of supercoiling activity of DNA gyrase from M. smegmatis. The shortlisted active compound, 1-tert-butyl-1,4 dihydro-7-(4,4-dimethyloxazolidin-3-yl)-6-nitro-4-oxo-1,8 naphthyridine-3-carboxylicacid,demonstrated potential in vitro activity against MTB and MDR-TB (3 and 455 times more potent than isoniazid against MTB and MDR-TB, respectively). This compound also showed remarkable in vivo activity in animal model by decreasing the bacterial load in lung and spleen tissues.

Various 3-nitro-2-(sub)-5,12-dihydro-5-oxobenzothiazolo [3,2-a]-1,8-naphthyridine-6-carboxylic acids were synthesized and tested by Dinakaranetal.[77]for their in vitro and in vivo activity against Mycobacterium tuberculosis H(37) Rv (MTB) and multi-drug resistant M. tuberculosis (MDR-TB). 2-(1,4 Dioxa-8-azaspiro[4.5]dec-8-yl)-3-nitro-5,12-dihydro-5 oxobenzothiazolo[3,2-a]-1,8-naphthyridine-6-carboxylic acid was identified as the most active compound against MTB and MTR-TB, respectively, in vitro. This activity was more potent than that of gatifloxacin and isoniazid. This compound simultaneously showed in vivo activity by decreasing the mycobacterial load in lung and spleen tissues.

10.ANTICANCER POTENTIAL:

1,8-Naphthyridine derivatives have gained special attention by researchers on account of possessing anticancer properties. A number of different substituted 1,8-naphthyridines have been explored for anticancer potential. Are view by Sri vastava et al. summarizes the synthesis and SAR of potent antitumor active quinoline and naphthyridine derivatives, including 1,8-derivatives of naphthyridines. It was concluded that amino pyrrolidine functionality at C-7, 20-thiazolyl at N-1 and carboxy group at C-3 in 1,8-naphthyridine ring was necessary for demonstration of in vitro cytotoxicity.

The most important and most explored 1,8-naphthyridine derivative for anticancer potential is voreloxin, SNS-595 (þ)-1,4-dihydro-7-(trans-3-methoxy-4-methylamino-1-pyrrolidinyl)-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid. SNS-595, a naphthyridine cell cycle inhibitor and stimulator of apoptosis for the treatment of cancers was originally developed by Sunesis Pharmaceuticals Inc. under license from Dainippon Sumitomo Pharma Co., Ltd. [78–80]. Voreloxin, formerly known as SNS-595, has demonstrated potential in vitro activity against a broad panel of cancer cell lines and in vivo tumor models. It is under phase III clinical trial investigation for acute myelogenous leukemia (AML) and ovarian cancer. The mechanism of action of vorelox in includes DNA intercalation and inhibition of topoisomerase II that results in selective DNA damage. Initial studies by Hoch and coworkers [81] demonstrated in vitro anti proliferative activity in 11 tumor cell lines. Similar trend in activity was observed in vitro in drug-resistant cell lines, including P-glycoprotein overexpressing lines and with reduced topoisomerase levels. Voreloxin demonstrated strong dose-dependent tumor growth inhibition (63–88%) in 10 of 11 solid tumor xenograft models (breast, ovarian, colon, lung, gastric, and melanoma), two hematologic tumor xenograft models, three multidrug resistant tumor models, and three murine syngeneic tumor models (Colon 26, Lewis lung carcinoma, M5076 ovarian sarcoma).These data demonstrated that voreloxin is a broadly active antitumor agent in vitro and in vivo, with potent activity in aggressive and drug-resistant tumor models. A detailed study for elucidating anticancer mechanism of action for voreloxin was conducted by Hawtin RE in 2010. Biochemical and cell-based studies established that voreloxin intercalates into DNA and poisons topoisomerase II, causing breaks in DNA double-strand, G2 arrest, and apoptosis [82]. A study by Hawtinetal. [83] shows that the mechanism of action for this drug involves induction of a cell cycle specific pattern of DNA damage and repair that is distinct from the

anthracycline, doxorubicin. Vosaroxin induces less extent of overall DNA fragmentation. Subsequently, in vitro synergistic cytotoxic effects of voreloxin with cytarabine were studied in three cancer cell lines: HL-60 (acute promyelocytic leukemia), MV4-11 (acute myelocytic leukemia), and CCRF-CEM (acute lymphoblastic leukemia). This was followed with a mouse model of bone marrow ablation by examining the effects of voreloxin on peripheral white blood cell and platelet counts to assess the marrow impact and recovery. An additive or synergistic activity of these two drugs was observed in vitro and supra-additive activity in vivo [84]. The synergistic effect of voreloxin with cytarabine was also studied for cell cycle arrest and apoptosis in myeloid leukemia cells [85]. These results prompted an efficient usage of combination therapy of voreloxin with cytarabine.

Clinically, voreloxin showed complete remissions inpatients with solid and hematologic malignancies, specifically cancers which were resistant to anthracyclines. Phase-I clinical studies for ovarian cancer and acute myeloid leukemia were performed with voreloxin. A good anticancer activity with acceptable safety profile was observed [86]. Phase Ib study of vosaroxin was performed in patients with relapsed or refractory acute leukemia. Results showed that voreloxin had an acceptable safety profile, linear PK, and encouraging clinical activity in relapsed/refractory leukemia [87]. Based on the preclinical activity of voreloxin in chemoresistant tumors, early phase I clinical activity and mechanism of action similar to other topoisomerase II inhibitors such as the anthracyclines and etoposide, a phase II clinical trial was conducted as a second-line treatment of small cell lung cancer (SCLC) [88].

ANTI INFLAMMATORY AND ANTI ANALGESIC ACTIVITY:

1,8-Naphthyridine derivatives have been exclusively reported to display anti-inflammatory activities in a variety of in vitro and in vivo models. Early instances of anti-inflammatory activity were shown by derivatives belonging to 2,4-disubsti tuted N,N-dialkyl-1,8-naphthyridine-3-carboxamides synthe sized by Di Braccio and coworkers [89]. Subsequently, derivatives of the same group were also tested for anti inflammatory activity in the carrageenan-induced edema assay in rat and antiaggressive activities, along with their gross behavioral effects and acute toxicity [90].

As shown by Kuroda et al. [100], derivatives of 4-hydroxy-2 (1H)-oxo-1-phenyl-1,8-naphthyridine-3-carboxamides were found to be particularly active against carrageenan-, zymosan-, and arachidonic acid-induced rat paw edemas and also potently inhibited the reversed passive Arthus reaction in rats. Hence, these compounds were shown to possess a broader spectrum of anti-inflammatory activity than the classical non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin and piroxicam. 5-Phenyl-3H-imidazo[4,5-c] [1,8]naphthyridin-4(5H)-ones were reoprted by Suzuki et al. [101] as a new class of non-steroidal anti-inflammatory agents with potent activity similar to glucocorticoids. Com pounds of this series have shown potent oral antiinflammatory activities in carrageenan-, zymosan-,and reversedpassive Arthus reaction-induced rat paw edema models.

Another series of 1,8-naphthyridines, N,N-dialkyl-5-chloro [1,2,4]-triazolo[4,3-a][1,8]naphthyridine-6-carboxamides were reported to possess anti-inflammatory activity [102]. Similarly, derivatives of 9-substituted N,N-dialkyl-5-(alkyl amino or cycloalkylamino)[1,2,4]triazolo[4,3-a][1,8]naphthyr idine-6-carboxamides exhibited potential anti inflammatory activity in carrageenan-induced paw edema assay in rat and also anti-aggressive properties (isolation induced aggressiveness test in mice) [103]. N-Substituted 5-amino-N,N-diethyl-9-isopropyl[1,2,4]triazolo[4,3-a][1,8] naphthyridine-6-carboxamides were tested for potential anti-inflammatory, analgesic, antipyretic properties, for their effect on spontaneous mice locomotor activity and acute gastrolesivity in rats. It was observed that several compounds showed potent anti-inflammatory and/or analgesic activities. All the compounds tested were completely lacking in acute gastrolesivity. The N-monosubstituted 5-aminoderivatives seemed to be more potent anti-inflammatory agents than the corresponding N,N-disubstituted derivatives, whereas the latter compounds exhibited higher analgesic activity

[104]. The in vitro anti-inflammatory activity of shortlisted 1,8 derivatives belonging to [1,2,4]triazolo[4,3-a][1,8]naphthyr idine class was studied by Dianzani and coworkers [105] in 2006 using human stimulated human polymorphonuclear cells (PMN) and endothelial cells. The effect on prostaglandin E2 (PGE2) and prostacyclin production by human umbilical vascular endothelial cells (HUVEC), production of reactive oxygen species (ROS) by PMNs and PMN adhesion to HUVEC were investigated. Results showed no effect of these compounds on the production of PGE2 or PGI2. However these compounds inhibited O2 production and myeloperoxidase release from stimulated PMNs in a dose- but not time-dependent manner. Inhibition of cell adhesion evoked by pro-inflammatory stimuli was also observed in a concentration-dependent manner. The results obtained on PG production suggested a cyclooxygenase (COX)-independent mechanism. Another set of analogs of triazolo-1,8-naphthyr idines; 5-(alkylamino)-N,N-diethyl[1,2,4]triazolo[4,3-a][1,8] naphthyridine-6-carboxamides were assessed for anti inflammatory activity by inhibition of carrageenan-induced paw edema in the rat [106]. Also, amino derivatives of same group at 5-position, 5-amino[1,2,4]triazolo[4,3-a][1,8]naphthyridine-carboxamides,werefoundtoexhibitconsiderable in vivo anti-inflammatory and/or analgesic activities, but no acute gastrolesivity in a rat model [107,108]. Recently, a new group of 5-(alkylamino)-9-isopropyl[1,2,4]triazolo[4,3-a][1,8] naphthyridine derivatives with a CONHR group at the 6-position were tested as analgesic and/or anti-inflammatory agents [109].

APPLICATIONS IN NEUROLOGICAL DISORDERS:

1,8-Naphthyridine derivatives also find a great application as therapeutic agents for various neurological disorders.

ACHE INHIBITORS IN ALZHEMER'S DIEASES:

1,8-Naphthyridine derivatives have been investigated as inhibitors of acetyl cholinesterase (AChE) and butyryl cholinesterase(BuChE) activities. These compounds represent a new family of molecules with multitarget-directed ligand strategy for the treatment of Alzheimer's disease. A new family of tacrine analogs (tetra hydro amino acridine/THA) containing the azaheterocyclic pyrazolo[4,3-d]pyridine or pyrazolo[3,4 b][1,8]naphthyridine groups as isosteres of the quinoline ring of THA were synthesized by Barreiro et al. [110]. These derivatives exhibited inhibitory effect on rat brain cholinesterase using Ellman's method. Active compounds demon strated no significant neurotoxic effects on cultured rat cortical cells. A novel tacrine derivative, ITH4012 (ethyl 5-amino-6,7,8,9-tetrahydro-2-methyl-4-phenylbenzol[1,8] naphthyridine-3-carboxylate), is reported as a novel acetylcholinesterase inhibitor with calcium promotor and neuroprotective properties. It can reduce cell death induced by various damaging agents such as thapsigargin (reticular stress), H2O2 (free radicals), and veratridine (calcium overload) in bovine chromaffin cell. This compound also reduced amyloid b-25–35-induced apoptosis in the human neuroblas toma cell line SH-SY5Y stressed with rotenone/oligomycin A. Its mechanism of action involved a slight elevation in the cytosolic concentration of Ca2þ in Fura-2-loaded bovine chromaffin cells. In addition, exposure of bovine chromaffin cells to neuroprotective concentrations of this compound enhanced the expression of the anti-apoptotic protein Bcl 2 [111]. In another study, this compound also imparted protection to cells stressed with okadaic acid (OA) or amyloid b-1–42 peptide (Abeta(1–42)). Additionally, it prevented the OA-induced protein phosphatase 2A(PP2A)inhibition, one of the enzymes involved in tau dephosphorylation. This was accompanied with neuroprotection against neurotoxicity elicited by oxygen and glucose deprivation in hippocampal slices [112]. ITH12246, ethyl 5-amino-2-methyl-6,7,8,9 tetrahydrobenzo[b][1,8]naphthyridine-3-carboxylate was found to be acetylcholinesterase inhibitor. These studies were based on the in silico analysis which predicted that this molecule should be successfully docked in the peripheral anionic site (PAS) and easily accommodated in the catalytic anionic site (CAS) of AChE [113]. ITH12246 (ethyl 5-amino-2 methyl-6,7,8,9-tetrahydrobenzo[b][1,8]naphthyridine-3-car boxylate) is reported as 1,8-naphthyridine derivative with an interesting neuroprotective profile shown in in vitro models of Alzheimer's disease. This activity was based on a regulatory action on inhibition of enzyme PP2A, which prevented binding of its inhibitor okadaic acid.

This compound demonstrated in vitro neuroprotective activity against both oxidative stress and Ca2þ overload-derived excitotoxicity in SH-SY5Y neuroblastoma cells and rat hippocampal slices. The compound showed potency to counteract the memory impairment evoked by scopolamine in a mice model by improving the memory index and also reduced the photo thrombosis-triggered infarct volume [114].

ANTIPSYCHOTIC DRUGS:

A series of 2-{4-[4-(2,5-disubstitutedthiazolyl)phenyl ethyl]piperazin-1-yl}-1,8-naphthyridine-3-carbonitriles were examined as atypical antipsychotic agents by spectral data (IR, 1H NMR, and MS) and the purity was ascertained by microanalysis. The compounds were investigated for the D2 and 5-HT2A binding affinity in vitro by radio ligand displacement assays on membrane homogenates isolated from rat striatum and rat cortex, respectively. Also, in vivo pharmacological activity in Swiss albino mice was assessed. In addition, the D2 antagonism studies were conducted using climbing mouse assay model and 5-HT2A antagonism studies were performed using quipazine-induced head twitches in mice. Results showed that none of the compounds exhibited catalepsy. Only one compound was found to be the most active among the synthesized compounds with 5-HT2A/D2 ratio of 1.1286 although the standard drug risperidone exhibited 5-HT2A/D2 ratio of 1.0989 [115].

ANTI-OSTEOPOROTIC AGENTS/a(v)b(3) ANTAGONISTS:

The vitronectin receptor a(v)b(3) has been identified as a promising potential target for the treatment of osteoporosis. Several 1,8-naphthyridine derivatives have demonstrated by Duggan et al. [116] for potential application as anti-osteoporotic agents by targeting a(v)b(3) receptor.5,6,7,8-Tetrahydro [1,8]naphthyridine moiety (THN) is reported as a lipophilic and moderately basic N-terminus that imparts molecules with high potency and selectivity for the integrin receptor a(v)b(3). The THN-containing derivatives are well reported as potent inhibitors of bone resorption in vitro and in vivo.

3(S)(6Methoxypyridin3yl)3[2oxo3[3(5,6,7,8tetrahydro[1,8]naphthyridinyl)propyl]imidazolidin-1-yl] propionic acid is reported by Hutchinson et al. [117] as a strong and selective antagonist of the a(v)b(3) receptor. With a good in vitro efficacy and pharmacokinetics in rat, dog, and rhesus monkey, this compound also showed potency in the in vivo models of bone turnover and was further selected for clinical development. 5,6,7,8-Tetrahydro-1,8-naphthyridin-2 yl-propan-1-amine and 3-[(7R)-7-methyl-5,6,7,8-tetrahy dro-1,8-naphthyridin-2-yl]propan-1-amine are reported as key intermediates in the synthesis of a(v)b(3)antagonists[118]. A series of 3-substituted tetrahydro-[1,8]naphthyridine containing a(v)b(3) antagonists were synthesized. These com pounds showed potent a(v)b(3) inhibiting activity [119].

As demonstrated by Breslin et al. [120], 7-methyl substituted tetrahydro-[1,8]naphthyridine, a non-peptide a(v)b(3) antagonist, has shown potent activity and was selected for clinical development based on its improved pharmacokietics profile and efficacy in an in vivo model of bone turnover. Subtle modifications were incorporated into the structure of clinical candidate in order to maintain potency and selectivity. 3-(S)-Pyrimidin-5-yl-9-(5,6,7,8-tetrahydro-[1,8]naphthyridine2-yl)-non-anoic acid and 3-(S)-(methylpyrimidin-5-yl)-9 (5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-non-anoic acid are reported as potent and selective antagonists of the a(v)b(3) receptor. These two compounds have been able to display good activity in vitro along with good pharmacokinetic profile in rat, dog, and rhesus monkey. These can didates also possessed potential activity in an in vivo model of bone turnover following once-daily oral administration and were further selected for clinical development for the treatment of osteoporosis [121].

ANTI-ALLERGIC ACTIVITY:

Early reports of anti-allergic activity of 1-phenyl-3-n-butyl-4 hydroxynaphthyridin-2(1H)-one derivatives are cited in 1988. The study identified three compounds of interest, 1-phenyl-3 (2-propenyl)-4-acetoxy-1,8-naphthyridin-2(1H)-one,1-(30 chloro phenyl)-3-(2-propenyl)-4-acetoxy-1,8-naphthyridin 2(1H)-one and 1-(30-methoxyphenyl)-3-(2-propenyl)-4 acetoxy-1,8-naphthyridin-2(1H)-one. The possible mechanism of anti-allergic action was suggested as inhibition of the release of the sulfidopeptide leukotrienes [122]. Furo[2,3-b] [1,8]naphthyridine-3,4(2H,9H)-diones and 4H-furo[2,3-d] pyrido[1,2-alpha]-pyrimidine-3,4(2H)-diones have also demonstrated anti-allergic activity [123]. Another compound, leuketriene inhibitor. This compound was able to inhibit leukotriene LTD4 and thromboxaneB2 release by anaphylactic guinea pig lung [124]. 1,4-Dihydro-7-methyl-4-oxo-1,8-naph thyridine-3-carboxamide derivatives showed potent anti-allergic activity in the rat passive cutaneous anaphylaxis (PCA) test. These compounds were also able to inhibit the enzyme 5-lipoxygenase (5-LO), much better than caffeic acid [125].Sch 37224, 1-(1,2-dihydro-4-hydroxy-2-oxo-1-phenyl-1,8-naph thyridin-3-yl)pyrrolidinium has been reported as leuketriene inhibitor. This compound was able to inhibit leukotriene LTD4 and thromboxaneB2 release by anaphylactic guinea pig lung (126) 1,4-Dihydro-7-methyl-4-oxo-1,8-naph thyridine-3-carboxamide derivatives showed potent anti-allergic activity in the rat passive cutaneous anaphylaxis (PCA) test. These compounds were also able to inhibit the enzyme 5-lipoxygenase (5-LO), much better than caffeic acid [127].

ANTIMALARIAL PROPERTIES:

Initial research on 1,8-naphthyridines is reported for the investigation of antimalarial potential by Adams etal.[128] in 1946. Various 1,8-naphthyridines including 8-aza analogs of chloroquine and amodiaquine, and other 1,8-naphthyridines with2-and7-methylgroupshaveshownminimalantimalarial activity in a preliminary in vivo screen against Plasmodium vinckei vinckei [129]. 2-Oxo-tetrahydro-1,8-naphthyridines are described as antimalarials and selective inhibitors (in low nanomolar range) of malarial protein farnesyltrans ferase. Much less activity was observed on mammalian protein prenyl transferases [130].

BRONCHODILATORS:

A number of novel derivatives of imidazol[4,5-c][1,8]naphthyridin-4(5H)-ones were synthesized as new bronchodilators. Active compounds with phenyl and n-butyl substitution at 5-position demonstrated more potent bronchodilator activity in vitro and in vivo than theophylline. Selected compound 5-phenyl-1H-imidazo[4,5-c][1,8]naphthyridin-4(5H)-one (KF17625) was assessed by Suzuki et al. [131] in antigen inhalation-induced bronchospasm model and antigen-induced contraction of trachea. This compound was able to inhibit carbachol-, histamine-, or leukotriene D4-induced contraction and relaxed spontaneous tone in guinea pig isolated tracheal preparations. This effect was found to be even more potent than aminophylline, which implies direct relaxing of the airway smooth muscle. No influence on adenosine binding was observed, but inhibitory potential was observed in canine tracheal phosphor diesterase (PDE)IV assay and concanavalin-A induced histamine release from rat mast cell.

ANTICONVULSANTS:

As demonstrtaed by Leonard and coworkers [132], 2-substituted-4-methyl-7-amino/4,7-dimethyl-1,8-naphthyri dine derivatives possessed potential anticonvulsant activity. Active compounds, 2-(3-morpholino-20-hydroxypropyloxy)-4 methyl-7-amino-1,8-naphthyridine, 2-(30-diphenyla mino-20-hydroxypropyloxy)-4-methyl-7-amino-1,8-naphthyri dine, and 2-(30-diethanolamino-propyloxy)-4,7 dimethyl-1,8-naphthyridine, at the dose of 250mg/kg were able to show similar potency as compared to diazepam (5mg/kg).

CONCLUSION:

Based on the extensive research conducted by numerous researchers, it can be concluded that 1,8-naphthyridine derivatives possess a versatile portfolio of pharmacological properties in many therapeutic areas. This comprehensive review has demonstrated an array of multiple biological activities reported for 1,8-naphthyridine derivatives in a systematic manner. Certainly, 1,8-naphthyridine emerges out as an interesting scaffold with its functional derivatives displaying multidirectional biological properties. A good preclinical activity profile of these compounds is reported when screened in specific cell-based assays and animal disease models. Also, seleted candidates have demonstrated potent activity in clinical development, which suggests that this group of compounds may be further developed and improved with the aim of designing better drugs.

The primary application of drugs containing 1,8-naphthyridine scaffold has been established as antibacterial agents, such as gemifloxacin, ciprofloxacin, ofloxacin. Anticancer potential of voreloxin (SNS-595) based on DNA intercalation and inhibition of topoisomerase-II is also remarkable. Voreloxin has specifically emerged as the most noticed candidate from this chemical class and, hence, highlights the immense scope of exploring this chemical class in cancer. Other interesting properties are anti-inflammatory and neuroprotective, which can be further explored to develop drug candidates. Currently, active research is being carried out by various groups with new 1,8-naphthyridine derivatives being synthesized and investigated for additional biological properties. We hope that this review is helpful for researchers as a resourceful tool to comprehend the spectrum of biological potencies of 1,8-naphthyridines and may further enrich the field of new drug discovery and medicinal research by investigating this group of compounds into much more depth.

REFERENCES:

1. A. Reissert, Berichte 1893, 26, 2137.
2. C. F. H. Allen, Chem. Rev. 1950, 47, 275–305.
3. W. Czuba, Chem. Heterocycl. Compd. 1979, 15,1–13.
4. A. S. Noravyan, E. G. Paronikyan, S. A. Vartanyan, Pharm. Chem. J. 1985, 19, 439–448.
5. V. P. Litvinov, S. V. Roman, V. D. Dyachenko, Russ. Chem. Rev. 2000, 69, 201–220.
6. G. Y. Lesher, E. J. Froelich, M. D. Gruett, J. H. Bailey, R. P. Brundage, J. Med. Pharm. Chem. 1962, 5, 1063–1065.
7. E. V. Brown, J. Org. Chem. 1965, 30, 1607–1610.
8. V. P. Litvinov, Russ. Chem. Rev. 2004, 73, 637–670.
9. S. K. Srivastava, A. Jha, S. K. Agarwal, R. Mukherjee, A. C. Burman, Anticancer Agents Med. Chem. 2007, 7, 685–709.
10. A. A. Fadda, S. A. El-Hadidy, K. M. Elattar, Synth. Commun. 2015, 1–37, 00397911.2015.1089577.
11. R. E. Thompson, J. Rae, Br. J. Urol. 1964, 36,42–47.
12. S. Nishigaki, N. Mizushima, F. Yoneda, J. Med. Chem. 1971, 14, 638–640.
13. S. Nagasaki, N. Nakazawa, Y. Osada, T. Hashizume, Y. Oshima, Chem. Pharm. Bull. (Tokyo) 1972, 20, 639–649.
14. N. Suzuki, Y. Tanaka, R. Dohmori, Chem. Pharm. Bull. (Tokyo) 1980, 28, 235–244.
15. N. Suzuki, Chem. Pharm. Bull. (Tokyo) 1980, 28, 761–768.
16. I. Hayakawa, N. Suzuki, K. Suzuki, Y. Tanaka, Chem. Pharm. Bull. (Tokyo) 1984, 32, 4914–4922.
17. T. Hirose, S. Mishio, J. Matsumoto, S. Minami, Chem. Pharm. Bull. (Tokyo) 1982, 30, 2399–2409.
18. J. Tani, Y. Mushika, T. Yamaguchi, Chem. Pharm. Bull. (Tokyo) 1982, 30, 3517–3529.
19. S. Nishigaki, M. Ichiba, S. Fukazawa, M. Kanahori, K. Shinomura, Chem. Pharm. Bull. (Tokyo) 1975, 23, 3170–3177.
20. A. A. Santilli, A. C. Scotese, J. A. Yurchenco, J. Med. Chem. 1975, 18, 1038–1041.
21. S. Mishio, T. Hirose, A. Minamida, J. Matsumoto, S. Minami, Chem. Pharm. Bull. (Tokyo) 1985, 33, 4402–4408.

22. D. T. Chu, P. B. Fernandes, A. K. Claiborne, E. H. Gracey, A. G. Pernet, J. Med. Chem. 1986, 29, 2363–2369.
23. J. P. Sanchez, J. M. Domagala, S. E. Hagen, C. L. Heifetz, M. P. Hutt, J. B. Nichols, A. K. Trehan, J. Med. Chem. 1988, 31, 983–991.
24. D. Bouzard, P. Di Cesare, M. Essiz, J. P. Jacquet, J. R. Kiechel, P. Remuzon, A. Weber, T. Oki, M. Masuyoshi, R. E. Kessler, J. Fung-Tomc, J. Desiderio, J. Med. Chem. 1990, 33, 1344–1352.
25. D. Bouzard, P. Di Cesare, M. Essiz, J. P. Jacquet, B. Ledoussal, P. Remuzon, R. E. Kessler, J. Fung-Tomc, J. Med. Chem. 1992, 35, 518–525.
26. A. Marchese, E. A. Debbia, G. C. Schito, J. Antimicrob. Chemother. 2000, 46,11–15.
27. E. J. Kim, W. H. Shin, Biol. Pharm. Bull. 2004, 27, 641–646.
28. H. J. Yun, Y. H. Min, J. A. Lim, J. W. Kang, S. Y. Kim, M. J. Kim, J. H. Jeong, Y. J. Choi, H. J. Kwon, Y. H. Jung, M. J. Shim, E. C. Choi, Antimicrob. Agents Chemother. 2002, 46, 3071–3074.
29. X.Huang,D.Chen,N.Wu,A.Zhang,Z.Jia,X.Li,Bioorg. Med. Chem. Lett. 2009, 19, 4130–4133.
30. X. Huang, A. Zhang, D. Chen, Z. Jia, X. Li, Bioorg. Med. Chem. Lett. 2010, 20, 2859–2863.
31. S. Nakamura, A. Minami, H. Katae, S. Inoue, J. Yamagishi, Y. Takase, M. Shimizu, Antimicrob. Agents Chemother. 1983, 23, 641–648.
32. K. Kouno, M. Inoue, S. Mitsuhashi, Antimicrob. Agents Chemother. 1983, 24,78–84.
33. S. Nakamura, K. Nakata, H. Katae, A. Minami, S. Kashimoto, J. Yamagishi, Y. Takase, M. Shimizu, Antimicrob. Agents Ch. 1983, 23(5), 742–749.
34. J. Matsumoto, T. Miyamoto, A. Minamida, Y. Nishimura, H. Egawa, H. Nishimura, J. Med. Chem. 1984, 27, 292–301.
35. Y. Mizuki, I. Fujiwara, T. Yamaguchi, Y. Sekine, Anti microb. Agents Ch. 1996, 40, 1875–1880.
36. H. Egawa, T. Miyamoto, A. Minamida, Y. Nishimura, H. Okada, H. Uno, J. Matsumoto, J. Med. Chem. 1984, 27, 1543–1548.
37. Y. Miyake, K. Mitsui, H. Suginaka, J. Antimicrob. Ch. 1986, 17, 327–332.
38. Y. Nishimura, J. Matsumoto, J. Med. Chem. 1987, 30, 1622–1626.
39. Y. Nishimura, A. Minamida, J. Matsumoto, Chem. Pharm. Bull. (Tokyo) 1988, 36, 1223–1228.
40. T. Rosen, D. T. Chu, I. M. Lico, P. B. Fernandes, L. Shen, S. Borodkin, A. G. Pernet, J. Med. Chem. 1988, 31, 1586–1590.
41. M. Takahata, M. Otsuki, T. Nishino, J. Antimicrob. Ch. 1988, 22, 143–154.
42. A. M. Espinoza, N. X. Chin, A. Novelli, H. C. Neu, Antimicrob. Agents Ch. 1988, 32, 663–670.
43. T.Miyamoto,J.Matsumoto,Chem.Pharm.Bull.(Tokyo) 1990, 38, 3359–3365.
44. J. P. Sanchez, J. M. Domagala, C. L. Heifetz, S. R. Priebe, J. A. Sesnie, A. K. Trehan, J. Med. Chem. 1992, 35, 1764–1773.
45. M. A. Cohen, M. D.Huband, G. B. Mailloux, S. L. Yoder, G. E. Roland, J. M. Domagala, C. L. Heifetz, Antimicrob. Agents Ch. 1991, 35, 141–146
46. C. S. Lewin, J. Med. Microbiol. 1992, 36, 353–357.
47. J. M. Domagala, S. E. Hagen, T. Joannides, J. S. Kiely, E. Laborde, M. C. Schroeder, J. A. Sesnie, M. A. Shapiro, M. J. Suto, S. Vanderroest, J. Med. Chem. 1993, 36, 871–882.
48. Y. Todo, J. Nitta, M. Miyajima, Y. Fukuoka, Y. Yamashiro, N. Nishida, I. Saikawa, H. Narita, Chem. Pharm. Bull. (Tokyo) 1994, 42, 2063–2070.
49. S. E. Hagen, J. M. Domagala, S. J. Gracheck, J. A. Sesnie, M. A. Stier, M. J. Suto, J. Med. Chem. 1994, 37, 733 738.
50. C. Y. Hong, Y. K. Kim, J. H. Chang, S. H. Kim, H. Choi, D.H.Nam,Y.Z.Kim,J.H.Kwak,J.Med.Chem.1997,40, 3584–3593.
51. H. Kondo, M. Taguchi, Y. Inoue, F. Sakamoto, G. Tsukamoto, J. Med. Chem. 1990, 33, 2012–2015.
52. M. Ozaki, J. Segawa, M. Kitano, Y. Tomii, T. Honmura, M.Matsuda,M.Kise,T.Nishino,Biol. Pharm. Bull. 1996, 19, 1457–1462.

53. A. Narender, M. T. Chary, E. Laxminarayana, V. Haripriya, Indian J. Chem. 2013, 52, 440–447.
54. J. Frigola, J. Pares, J. Corbera, D. Va~ no, R. Merce, A. Torrens, J. Mas, E. Valentı, J. Med. Chem. 1993, 36, 801–810.
55. J. Frigola, A. Torrens, J. A. Castrillo, J. Mas, D. Va~ no, J. M. Berrocal, C. Calvet, L. Salgado, J. Redondo, S. Garcıa-Granda, E. Valenti, J. Med. Chem. 1994, 37, 4195–4210.
56. J. Frigola, D. Va~ no, A. Torrens, A. Gomez-Gomar, E. Ortega, S. Garcıa-Granda, J. Med. Chem. 1995, 38, 1203–1215.
57. J. Guinea, D. Gargallo-Viola, M. Robert, E. Tudela, M. A. Xicota, J. Garcia, M. Esteve, R. Coll, M. Pares, R. Roser, Antimicrob. Agents Ch. 1995, 39, 413–421.
58. J. S. Kiely, M. P. Hutt, T. P. Culbertson, R. A. Bucsh, D. F. Worth, L. E. Lesheski, R. D. Gogliotti, J. C. Sesnie, M. Solomon, T. F. Mich, J. Med. Chem. 1991, 34, 656–663.
59. D. Ramesh, B. Sreenivasulu, Indian J. Chem. 2004, 43B, 897–900.
60. S. Ahmed, M. H. Bhatti, S. Ali, F. Ahmed, Turk. J. Chem. 2006, 30, 193–202.
61. M. R. Kumar, E. Laxminarayana, D. Ramesh, B. Sreenivasulu, M. T. Chary, Int. J. Chem. Sci. 2010, 8, 2025–2036.
62. U.Sahoo,A.K.Seth,A.K.Sen,B.Dhanya,S.P.Chauhan, G. U. Sailor, T. K. Ghelani, R. Chawla, Int. J. ChemTech Res. 2010, 2, 1051–1056.
63. J. P. Surivet, R. Lange, C. Hubschwerlen, W. Keck, J. L. Specklin, D. Ritz, D. Bur, H. Locher, P. Seiler, D. S. Strasser, L. Prade, C. Kohl, C. Schmitt, G. Chapoux, E. Ilhan, N. Ekambaram, A. Athanasiou, A. Knezevic, D. Sabato, A. Chambovey, M. Gaertner, M. Enderlin, M.Boehme,V.Sippel,P.Wyss,Bioorg.Med.Chem.Lett. 2012, 22, 6705–6711.
64. P. M. Sivakumar, G. Iyer, M. Doble, Med. Chem. Res. 2012, 21, 788–795.
65. Y.S.Oh,S.H.Cho,J.Heterocycl. Chem. 1998, 35,17–23.
66. J. S. Daniels, R. Espina, K. Cao, H. Yuan, J. Lin, S. Diamond, B. Johnson, J. Rodgers, S. Prakash, S. Unger, D. Christ, G. Miwa, L. S. Gan, A. Mutlib, Chem. Res. Toxicol. 2007, 20, 1709–1717.
67. P. D. Williams, D. D. Staas, S. Venkatraman, H. M. Loughran, R. D. Ruzek, T. M. Booth, T. A. Lyle, J. S. Wai, J. P. Vacca, B. P. Feuston, L. T. Ecto, J. A. Flynn, D. J. DiStefano, D. J. Hazuda, C. M. Bahnck, A. L. Himmelberger, G. Dornadula, R. C. Hrin, K. A. Stillmock, M. V. Witmer, M. D. Miller, J. A. Grobler, Bioorg. Med. Chem. Lett. 2010, 20, 6754–6757.
68. J. Y. Nagasawa, J. Song, H. Chen, H. W. Kim, J. Blazel, S. Ouk, B. Groschel, V. Borges, V. Ong, L. T. Yeh, J. L. Girardet, J. M. Vernier, A. K. Raney, A. B. Pinkerton, Bioorg. Med. Chem. Lett. 2011, 21, 760–763.
69. X. Z. Zhao, S. J. Smith, M. Metifiot, B. C. Johnson, C. Marchand, Y. Pommier, S. H. Hughes, T. R. Burke, J. Med. Chem. 2014, 57, 1573–1582.
70. X. Z. Zhao, S. J. Smith, M. Metifiot, C. Marchand, P. L. Boyer, J. Med. Chem. 2014, 57, 5190–5202.
71. S. Huang, J. Qing, S. Wang, H.Wang,L.Zhang,Y.Tang, Org. Biomol. Chem. 2014, 12, 2344–2348.
72. H. Wang, S. Wang, L. Cheng, L. Chen, Y Wang, J. Qing, S. Huang, Y. Wang, X. Lei, Y. Wu, Z. Ma, L. Zhang, Y. Tang, ACS Med. Chem. Lett. 2015, 6, 977–981.
73. P. L. Ferrarini, C. Manera, C. Mori, M. Badawneh, G. Saccomanni, Farmaco 1998, 53, 741–746.
74. M. Badawneh, C. Manera, C. Mori, G. Saccomanni, P. L. Ferrarini, Farmaco 2002, 57, 631–639.
75. M. Badawneh, L. Bellini, T. Cavallini, J. Al Jamal, C. Manera,G.Saccomanni,P.L.Ferrarini,Farmaco2003, 58, 859–866.
76. D. Sriram, P. Senthilkumar, M. Dinakaran, P. Yogeeswari, A. China, V. Nagaraja, J. Med. Chem. 2007, 50, 6232–6239.
77. M. Dinakaran, P. Senthilkumar, P. Yogeeswari, D. Sriram, Biomed. Pharmacother. 2009, 63,11–18.
78. D. A. Mills, H. M. Fekrazad, C. F. Verschraegen, Curr. Opin. Investig. Drugs 2008, 9, 647–657.
79. J. A. Abbas, R. K. Stuart, Expert Opin. Investig. Drugs 2012, 21, 1223–1233.
80. C. Freeman, N. Keane, R. Swords, F. Giles, Expert Opin. Pharmacother. 2013, 14, 1417–1427.

81. U. Hoch, J. Lynch, Y. Sato, S. Kashimoto, F. Kajikawa, Y. Furutani, J. A. Silverman, Cancer Chemoth. Pharm. 2009, 64,53–65.
82. R. E. Hawtin, D. E. Stockett, J. A. Byl, R. S. McDowell, T. Nguyen, M. R. Arkin, A. Conroy, W. Yang, N. Osheroff, J. A. Fox, PLoS ONE 2010, 5, e10186.
83. R. E. Hawtin, D. E. Stockett, O. K. Wong, C. Lundin, T. Helleday, J. A. Fox, Oncotarget 2010, 1, 606–619.
84. C.D.Scatena, J. L. Kumer, J. P. Arbitrario, A. R. Howlett, R. E. Hawtin, J. A. Fox, J. A. Silverman, Cancer Chemoth. Pharm. 2010, 66, 881–888.
85. E. J. Walsby, S. J. Coles, S. Knapper, A. K. Burnett, Haematologica 2011, 96, 393–399.
86. R. H. Advani, H. Hurwitz, M. S. Gordon, S. W. Ebbinghaus, D. S. Mendelson, H. A. Wakelee, U. Hoch, J. A. Silverman, N. A. Havrilla, C. J. Berman, J. A. Fox, R. S. Allen, D. C. Adelman, Clin. Cancer Res. 2010, 16, 2167–2175.
87. J. E. Lancet, F. Ravandi, R. M. Ricklis, L. D. Cripe, H.M.Kantarjian,F.J.Giles, A.F.List,T. Chen,R.S.Allen, J. A. Fox, G. C. Michelson, J. E. Karp, Leukemia 2011, 25, 1808–1814.
88. L. M. Krug, J. Crawford, D. S. Ettinger, G. I. Shapiro, D. Spigel, T. Reiman, J. S. Temel, G. C. Michelson, D. Y. Young, U. Hoch, D. C. Adelman, J. Thorac. Oncol. 2011, 6, 384–386.