RECENT DEVELOPMENTS AND MULTIPLE BIOLOGICAL ACTIVITIES AVAILABLE WITH 1, 8-NAPHTHYRIDINE DERIVATIVES: A REVIEW

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ABSTRACT

Within the wide range of nitrogen-containing heterocyclic compounds, the derivatives of 1,8-naphthyridine (NPTR) have gained a rising interest due to their reported versatile biological activities. The derivatives of NPTR scaffold are found to invite special interest from researchers nowadays on the significance of their manifestations of multiple attractive pharmacological activities which establish them as an effective and versatile tool in pharmaceutical chemistry and drug discovery. The diverse biological activities mainly include anti-inflammatory, antimicrobial, antitumor, antiepileptic, antihypertensive, etc. Many 1,8-naphthyridine analogs are found to exhibit significant biological activities and have been established as valuable agents in drug research.

Keywords: 1,8-Naphthyridine (NPTR), Quinolone, Antimicrobial activity, Anticancer activity, Antitumor, Anti-inflammatory activity, Antimalarial activity, αvβ3 antagonist.

INTRODUCTION

Nowadays, researchers are concentrating interests towards the introduction of novel and safe therapeutic agents for getting medical significance [1]. The nitrogen-containing heterocycles are the major class of chemical compounds in therapeutic uses. Naphthyridine is one of such heterocycle. The name naphthyridine is often known to the fused-ring system, which is formed by the fusion of two pyridine rings with two neighboring carbon atoms, and every ring system having only a single nitrogen atom. This name was first recommended by A. Reissert, who prepared the first series of naphthyridines in 1893. However, 1,8-naphthyridine is known as the naphthalene analog of pyridine [2]; these ring systems have given different names, like “benzodiazepines”, “pyridinopyridines” etc. depending on the arrangement of the nitrogen atom(s). Six different naphthyridine systems (Fig. 1), namely 1,5-Naphthyridine (1), 1,6-Naphthyridine (2), 1,7-Naphthyridine (3), 1,8-Naphthyridine (4), 2,6-Naphthyridine (5) and 2,7-Naphthyridine (6) are existing at the present time and amongst them, 1,8-Naphthyridine is the novel class of heterocycle [3-8].

The naphthyridine ring systems are generally prepared from 2-aminopyridines by using various types of cyclization reactions, very similar to those processes employed in quinoline chemistry. A large quantity of 1,8-naphthyridine have been synthesized and few of them have reached the clinical stages. These derivatives carry versatile biological activities such as anticancer, cytotoxic, anti-inflammatory, antimicrobial, analgesic, antidepressant, antiepileptic, antihypertensive, etc. Many 1,8-naphthyridine analogs are found to exhibit significant biological activities and have been established as valuable agents in drug research.

1, 8-Naphthyridine (NPTR)

Amongst the six isomeric pyridopyridines, the derivative having 1,8-naphthyridine (NPTR) ring gained the importance in the last 25 y. This group of derivatives has drawn interests mainly owing to the NPTR ring system which is abundant in lots of active derivatives including inherent substances and possesses different biological behavior. The quantity of publications and patents related to the chemical and biological activities of 1,8-naphthyridines derivatives which were issued and published during this era is more than the number of research on other pyridopyridines in the previous more than 90 y. In the few years, more than 900 publications have been published on the relevant topic, amongst which about 200 were patents [10]. A large number of these topics are focused on specific prospects of biological activities and assays. Clinically, the derivatives are more acceptable because of its potent efficacy and minimal side effect. So, by looking at its clinical output and safety margin, 1,8-naphthyridine nucleus is becoming the prime choice for the researchers for further investigations [11, 12]. Patent of some 1,8-naphthyridine derivatives are summarized in the table. Currently, 1,8-naphthyridine represents an extensively used scaffold with a number of attractive uses in the different pharmacological areas. Thus, a variety of pharmacological activities have been described and reported until now [13, 14]. Some
of the modern drugs of naphthyridine moieties (Fig. 2) include nalidixic acid (7), tosufloxacin (8), trovafloxacin mesylate (9), enoxacin (10), alatrofloxacin mesylate (11), gemifloxacin (12), and voreloxin (13), which already exist in the market.

### Table 1: Patents of 1,8-naphthyridine derivatives

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Publication number</th>
<th>Publication date</th>
<th>Title of publication</th>
<th>Inventors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>US 6,331,548</td>
<td>Dec. 18, 2001</td>
<td>1-Cycloalkyl-1,8-naphthyridine-4-one Derivative as type iv phosphodiesterase inhibitor</td>
<td>Shimamoto et al. [132]</td>
</tr>
<tr>
<td>2</td>
<td>US 6,340,690</td>
<td>Jan. 22, 2002</td>
<td>Antiviral methods using [1,8] naphthyridine derivatives</td>
<td>Bachand et al. [133]</td>
</tr>
<tr>
<td>3</td>
<td>US 6,451,811</td>
<td>Sep. 17, 2002</td>
<td>4-Oxo-1,4 dihydro[1,8]naphthyridine 3-carboxamides as antiviral agents</td>
<td>Vaillancourt et al. [134]</td>
</tr>
<tr>
<td>4</td>
<td>WO 03/027112</td>
<td>Apr. 3, 2003</td>
<td>1, 8-Naphthyridine derivatives as antidiabetics</td>
<td>Yamin et al. [135]</td>
</tr>
<tr>
<td>5</td>
<td>US 6,605,614</td>
<td>Aug. 12, 2003</td>
<td>[1,8] naphthyridine derivatives having antiviral activity</td>
<td>Bachand et al. [136]</td>
</tr>
<tr>
<td>6</td>
<td>US, 20040014751A1</td>
<td>Sep. 26, 2001</td>
<td>1,8-Naphthyridine derivatives and their use to treat diabetes and related disorders</td>
<td>Yamin et al. [137]</td>
</tr>
<tr>
<td>7</td>
<td>US 7,067,528 B2</td>
<td>Jun. 27, 2006</td>
<td>1, 2-Dihydro-2-oxo-1, s-naphthyridine derivative</td>
<td>Muraoka et al. [138]</td>
</tr>
<tr>
<td>8</td>
<td>US 7,109,196 B2</td>
<td>Sep. 19, 2006</td>
<td>1,8-Naphthyridine derivatives and their use to treat diabetes and related disorders</td>
<td>Yamin et al. [139]</td>
</tr>
<tr>
<td>9</td>
<td>US 7,163,948 B2</td>
<td>Jan. 16, 2007</td>
<td>Heterocyclic substituted 1,4-dihydro-4ox9-1,s-naphthyridine analogs</td>
<td>Whitten et al. [140]</td>
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<tr>
<td>10</td>
<td>US, 20100056563A1</td>
<td>Mar. 4, 2010</td>
<td>Novel 1,8-naphthyridine compounds</td>
<td>Deodalsingh et al. [141]</td>
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<tr>
<td>11</td>
<td>EP1695974B1</td>
<td>Mar. 17, 2010</td>
<td>1,8-Naphthyridines as CRF antagonists</td>
<td>Fabio et al. [142]</td>
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<td>12</td>
<td>US 7,790,716 B2</td>
<td>Sep. 7, 2010</td>
<td>Fab I inhibitors</td>
<td>Miller et al. [143]</td>
</tr>
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<td>13</td>
<td>WO2005091857A3</td>
<td>Oct. 5, 2006</td>
<td>1,6-Naphthyridine and 1,8-naphthyridine derivatives and their use to treat diabetes and related disorders</td>
<td>Rainer Heurich [144]</td>
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<td>14</td>
<td>US, 8124773B2</td>
<td>Feb. 28, 2012</td>
<td>1,8-Naphthyridine compounds for the treatment of cancer</td>
<td>Adelman et al. [145]</td>
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<td>15</td>
<td>US, 20120316166A1</td>
<td>Dec. 13, 2012</td>
<td>Hetarylaminonaphthyridines</td>
<td>Jonczyk et al. [146]</td>
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<td>17</td>
<td>US 7,675,954B2</td>
<td>Jul. 1, 2014</td>
<td>1,8-Naphthyridine compounds for the treatment of cancer</td>
<td>Adelman et al. [148]</td>
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<td>18</td>
<td>US, 8,912,216</td>
<td>Dec. 16, 2014</td>
<td>Hetaryl-[1,8]naphthyridine derivatives</td>
<td>Jonczyk et al. [149]</td>
</tr>
<tr>
<td>19</td>
<td>US, 8,952,164B2</td>
<td>Feb. 10, 2015</td>
<td>R-7-{[3-aminoethyl-4-methoxyimino-3-methyl-pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-o-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid and 1-aspartic acid salt, process for the preparation thereof and pharmaceutical composition comprising the same for antimicrobial</td>
<td>Choi, et al. [150]</td>
</tr>
<tr>
<td>20</td>
<td>US 20150250775</td>
<td>Sep. 10, 2015</td>
<td>Methods of using (+)-1,4-dihydro-7-[(3s,4s)-3-methoxy-4-(methylamino)-1-pyrroldinyl]-4-oxo-o-2-thiazolyl]-1,8-naphthyridine-3-carboxylic acid for treatment of antecedent hematologic disorders</td>
<td>Glenn Michelson [151]</td>
</tr>
</tbody>
</table>

![Fig. 2: Marketed antibiotics having a 1,8-naphthyridine nucleus](image-url)
Nalidixic acid (7) is useful in the management of various urinary tract infections (UTIs) where the gram-negative bacteria are responsible for the disease [15, 16]. Tosufloxacin, a fluoroquinolone (8) has potent broad-spectrum activity and its greater activity is found against clinically important gram-positive organisms comparable to that of other fluoroquinolones such as ciprofloxacin and ofloxacin [17]. Trovafloxacin (9) is an important drug active against Gram-negative species. It exhibits 8 to 16 time greater activity than that of either ofloxacin or ciprofloxacin [18]. Enoxacin, a quinolone (10) has a broad-spectrum antibacterial activity and is used mainly in the treatment of UTIs and STDs [19]. Alatrofloxacin, a fluoroquinolones antibacterial compound (11) has outstanding activity against bacteria [20]. Gemifloxacin mesylate (12), a synthetic chromeno [4,3-f] [1,8] naphthyridines analogs [14a-d] by a multi-component reaction and evaluate for their antimicrobial activity. The compounds with 4-fluorophenyl (14a),3-trifluoromethyl (14b), 6-Amino-8-(4-fluorophenyl) (14c) and 6-Amino-12-methoxy-8-(3-(trifluoro-methyl)phenyl) (14d) shows excellent antimicrobial activity against both type of bacterial strains with MIC value 50 mg/ml, and also the compounds (14a) and (14c) exhibit excellent antifungal activity with MIC value 250 mg/ml. The activities might be attributed due to the substitution of electron withdrawing group (F, CF3). Furthermore, derivatives having methyl group exhibit a reasonable activity, In addition, triazole substituted derivatives exhibit the excellent antifungal activity with MIC value 250 μg/ml.

Structure-activity studies indicate that 1, 4-dihydro-4-oxo-3-pyridine-carboxylic acid moiety is necessary for antimicrobial activity. The pyridone scaffold has to be annotated by an aryl ring. Isosteric replacements of nitrogen atom for carbon atoms at positions 8 are reliable with the protection of antimicrobial activity. The addition of substituents at position 2 significantly decline activity; positions 5, 6, 7 and 8 of the annulled rings could be substituted with excellent activity. For example, piperazinyl and 3-aminopyrrolidinyl substitutions at position 7 show better activity with compounds of the quinolone class against the gram-negative strain of *P. aeruginosa*. Substitution of fluorine atom also significantly enhances antibacterial activity [21]. Substitution of alkyl at the 1-position is necessary for antibacterial activity, small alkyl derivatives normally having better efficacy. Addition of aryl at the 1-position is also steady with antimicrobial activity, with a 2, 4-difluorophenyl group provides the best efficacy. Ring condensations at the 1, 8 positions also produce active compounds. Arayne et al. [33] synthesize different enoxacin analogs via nucleophilic substitution at the C3 position of the drug by primary aromatic amines. The free carboxylic acid group is used as a target for the synthesis of amide derivatives, and the result of functional group substitution on various biological activities of the parent compounds was studied. The derivative (15-19) exhibits antimicrobial activity against both the strains of bacteria through better activity, is found in the case of gram-negative strains.
Lv et al. [34] synthesize new naphthyridone analogous having mono/difluoro-methyloxime pyrrolidine ring system with remarkable improvement in lipophilicity (20 and 21). In in vivo experiments, a compound with 7-(3-aminomethyl group) (21) shows more activity than that of its parent drug against the test bacterial strains, and particularly its activity is 5.2-6.1 times more active than ciprofloxacin and gemifloxacin against gram-negative bacteria *P. aeruginosa* with ED₅₀ value 21.27 mg/kg.

Feng et al. [35] synthesize new gemifloxacin analogs having substituted benzyloxime group with significant enhancement in the lipophilic property. Most of the compounds show significant potency against tested strains including methicillin-resistant *S. epidermidis* and *S. aureus* (MIC: <0.008-8 µg/ml). Compound (22) a 2, 5-Dimethoxy derivative show 2-128 and 8-2048 times more activity than that of gemifloxacin and levofloxacin, respectively with MIC: <0.008-4 µg/ml.

Aggarwal et al. [36] synthesize new nalidixic acid based 1, 3, 4-thia/oxadiazo/azoles, their bis mercapto, sulfones, thioethers, and Mannich bases derivatives (23-25). These compounds show a moderate to excellent antibacterial activity against the tested bacterial strain. The compounds having thiadiazole moiety show better antimicrobial activity as compared to compounds having oxadiazoles moiety. Compound (23) a thiadiazole derivative show good activity against *K. pneumoniae*, *B. subtilis*, and *P. aeruginosa* with a MIC value from 6.25–125 µg/ml.

Fadla et al. [37] synthesize a new series of Schiff bases and evaluate their antimycobacterial activity. The lead Schiff base N'-(1-benzyl-2-oxoindolin-3-ylidene) substituted 1, 8-naphthyridine-3-carboxylic acid (26) exhibits remarkable inhibitory activity against four Mycobacterium strains: *M. cheloneo*, *M. intercellulari*, *M. xenopi*, and *M. smegmatis*. The para substitution, of a benzyl moiety with electron withdrawing groups, in *N*-benzylisatins is seven-times more active as shown by N'-(1-(4-chlorobenzyl)-2-oxoindolin-3-ylidene) substituted 1, 8-naphthyridine-3-carboxylic acid (27) (Z)-1-ethyl-N'-(1-(4-fluorobenzyl)-2-oxoindolin-3-ylidene) substituted 1, 8-naphthyridine-3-carboxylic acid (28a) and (Z)-1-ethyl-7-methyl-N'-(1-(4-nitrobenzyl)-2-oxoindolin-3-ylidene) substituted 1, 8-naphthyridine-3-carboxylic acid (28b) with fluoro, p-chloro and nitro substituent respectively.
Jalal et al. [38] synthesize various modified 4-morpholino-methyl-1.8-naphthyridine derivatives and evaluate their antitubercular activities against \(M. \text{tuberculosis}\) strain H37Rv in \textit{vitro}.

The compound 1,8-naphthyridine analog (29) with a 6-amino-2-(4'-methoxybenzylamine-4-morpholinomethyl-7-morpholinosubstituent shows good activity with a MIC of 0.25 μg/ml and offers a promising new lead for further development.

The field of coordination chemistry of metal complexes is growing rapidly because of its versatile and broad utilization in medical and biomedical fields [39]. The biological effectiveness of metal ions draws great interest to many researchers for the development and application of inorganic compounds with possible biologically active ligands. Quinolones are having 4-oxo-3-carboxylic-1, 4-dihydroquinoline frame is a bioligand, having bactericidal properties, good oral absorption, outstanding bioavailability, and high penetration power into tissues. Nalidixic acid (Nal) is the first member of quinolones [40]. It effectively inhibits the growth of gram-negative bacteria and is used for the treatment of different infectious diseases like UTIs, typhoid fever, bone-joint infections, respiratory infections, soft tissue infections, community-acquired pneumonia, and sexually transmitted diseases.

Zakya et al. [41] synthesize various complexes of nalidixic acid with addition of Zn (II), Fe (III), Ca (II), Mg (II), and VO (II) ions and evaluate their antibacterial potentialities. The antibacterial activities of the synthesized compounds were tested against gram-negative and gram-positive bacteria, \textit{i.e.} \textit{E. coli}, \textit{S. albus} as well as fungi, such as \textit{A. flavus} and \textit{A. niger}. The ligand coordinates in a bidentate manner via one carboxylate oxygen atom and the oxygen atom of the pyridine carbonyl group. The Zn (II) complex (30) exhibits the best activity among all. The biological activities, find out in the following order: Zn (II)-Ndx>VO (II)-Ndx>Fe (III)-Ndx>Mg (II)-Ndx>Ca (II)-Ndx.

Debnath et al. [42] synthesize a new binuclear square planar complex of nalidixic acid with silver (Ag) metal ion (fig. 3) having the molecular formula as [Ag(Nal)]\textsubscript{2}. The ligand is bonded to Ag (I) ion via the carboxylate oxygen and pyridone. The synthesized metal ion complex exhibits excellent antifungal activity as compared to that of nalidixic acid when tested against four fungal strains, \textit{S. rolfsii}, \textit{R. solani} \textit{P. aphanidermatum}, and \textit{R. bataticola}. Saleh et al. [43] report an easy and regioselective synthesis of 2-chloro-3-formyl-1, 8-naphthyridine, through Vilsmeier-Haack cyclization of \(N\)-(pyridine-2-y1) acetamide. The 1,2,4-triazole, 1,3,4-thiadiazol and 1,3,4-oxadiazole derivative, 5-(2-chloro-1, 8-naphthyridine-3-yl)-4H-1,2,4-triazole-3-thiol (31), 5-(2-chloro-1, 8-naphthyridine-3-yl)-1,3,4-thiadiazol-2-amine (32) and 5-(2-chloro-1, 8-naphthyridine-3-yl)-1,3,4-oxadiazole-2(3H)-thione (33) demonstrate good antibacterial activities against \textit{S. epidermidis} and \textit{S. aureus}.

![Figure 3: Crystal structure of [Ag(Nal)]\textsubscript{2} Complex [Source: Debnath et al. Rus J Gen Chem 2013;83:2488–2501]](image)
Pal et al.


Gao et al. [44] synthesize new tricyclic fluoroquinolones, (34a-h) containing an efficient Mannich-base moiety at the C-8 position. The compounds (34e-g) with a piperazine side chain show similar antibacterial activity than that of ciprofloxacin. In addition, the compounds also show broad-spectrum antibacterial activity, including both gram-positive and gram-negative microorganisms.

Acosta et al. [45] synthesize various 1, 8-naphthyridine derivatives by microwave-assisted synthesis with heterocyclic o-aminonitriles and cyclic ketenes catalyzed by ZnCl2 and produce a series of pyrazolo[3,4-b] [1, 8] naphthyridine-5-amines. The derivatives with a 4-p-tolyl substituent at naphthyridine skeleton (35a, 35b and 35c) are most active against C. albicans, which appear to be linked with their corresponding hydrophobicity. Amongst these compounds, 3-methyl-1-phenyl-4-p-tolyl substituted, 1, 8-naphthyridine-5-amine (35a), having a cyclohexyl fused ring, exhibits excellent activity.

Donaliso et al. [46] study the effects of 1, 8-naphthyridine derivatives (36) that effectively inhibit the transcription, regulated by the long control region of human papillomavirus (HPV) genome. They investigate with a sequence of analogs to get more effective derivatives like quinoline and thiazol substituted piperazine at 7 positions (37) and (38). These compounds have the ability to down-regulate E6 and E7 transcripts in human papillomavirus (HPV-16) positive cervical cancer CaSkI cells. The 1,8-naphthyridines appear as a satisfactory beginning mark for the development of novel compounds effective for the management of HPV-induced cervical cancer.

Sakram et al. [47] Synthesize substituted 1,8-naphthyridines based on 2-aminonicotinaldehyde and evaluate their antimicrobial property against various bacterial strains like S. aureus, B. subtilis, E. coli, and K. pneumonia and anti-fungal activity toward A. flavus and F. oxysporum. Compounds 2-Butyl-3-iodo-1,8-naphthyridine (39a), 2-Hexyl-3-iodo-1,8-naphthyridine (39b) and 3-Iodo-2-phenyl-1,8-naphthyridine (39c) show maximal zone of inhibition against the test microorganisms as compared to that of standards drug.
Valadbeigi and Ghodsi [48] synthesize a series of N-[2-(8-methoxy-2H-chromen-2-one)ethyl] piperazinyl quinolones having a carbonyl linked functional groups on the ethyl spacer of coumarin and piperazine rings and observe their antimicrobial activities against both gram-positive and gram-negative strain, *B. subtilis* PTCC 1207, *E. coli* PTCC 1047 and a fungus strain, *C. kefyr* ATCC 38296 respectively. Amongst these, the compound with 7 substituted piperazine and chromen moiety (40) shows the most potent *in vitro* antimicrobial activity.

Gençer *et al.* [49] synthesize a new series of 7-substituted fluoroquinolones and evaluate their antimicrobial activity against both gram-positive and gram-negative bacteria strain. Compound bearing a 4-dimethylaminopropylpiperazin-1-yl substituent (41) show good antibacterial activity and DNA gyrase inhibition similar to that of ciprofloxacin, mexitoxacin, and trovafloxacin with the MIC90 value 1.95 μg/ml against *S. aureus*, and *E. coli*.

Antihistaminic activity

Sherlock *et al.* [50] describe a new class of antiallergic compounds, the substituted 1, 8-naphthyridine-2 (1H)-ones which associate in the prohibition of the discharge of the leukotrienes and sulfidopeptide. Structure-activity relationship studies of the lead scaffold in this series, 1-phenyl-3-n-butyl 4-hydroxynaphthyridine-2 (1H)-one identify three derivatives of importance, 1, 8-naphthyridine substituted with 1-phenyl (42a) 8-naphthyridine substituted with 1-(3-chlorophenyl) (42b) and 1, 8-naphthyridine substituted with 1-(3-methoxyphenyl) (42c). Compound (42a) is chosen as the lead for preclinical development as an antiallergic compound.

Nishikawa *et al.* [51] synthesize oxo-pyridine carboxamide derivatives and evaluate their antiallergic activities. The 1, 8-naphthyridine-3-carboxamides (43a and 43b) is found potent antiallergic agent in the rat passive cutaneous anaphylaxis (PCA) test and also exhibit excellent inhibitory activity *in vitro* than that of caffeic acid against 5-Lipoxygenase.

As Antihypertensive agents

Different cardiovascular diseases like ischemia, hypertension, and arrhythmias are treated by β-adrenoreceptor antagonists. Though β-adrenergic inhibitors are incredibly uniform in their chemical structures, only a few β-blockers related to 1, 8-naphthyridine derivatives have been described till date [52]. Badawneh *et al.* [53] synthesize various substituted 1, 8-naphthyridine analogs, and study their antihypertensive activity. The 4-[N-methylecyclo-alkylamino]-1, 8-naphthyridine derivatives with various substitutions in positions 2 and 7 show satisfactory levels of potency (pIC50 value of W where as the compound (44) N-ethoxycarbonylpiperazin-1-yl derivative reached a really interesting value (pIC50 value of 6.92). The β-antagonist activity of (R, S)-(E)-oxime ethers of 2, 3-dihydro-1, 8-naphthyridine and of 2, 3-dihydropyrazylo [2, 3-b] pyridine (45) has β-blocking properties, It is notable that these compounds, have bulky substituents at position 7 and with these 4-t-butylphenoxy or 4-chloro-phenoxy groups show an impressive downturn in both β1- and β2-antagonist activities.
Jalal et al. [54] synthesize new derivatives of 1, 8-naphthyridine from 7-amino-2-hydroxy-4-morpholinomethyl-1,8-naphthyridine. The analogs of either 7-hydroxy-2-N-ethoxycarbonylpiperazine or a 7-hydroxy-2-piperazine substituent (46a and 46b) show a higher affinity towards β1 receptors.

Anticancer and antitumor activity

Cancer or malignancy is a most important burden of disease of worldwide, it is a group of diseases characterized by uncontrolled growth of cells and has potential to occupy or spread to other parts of the body [55-57]. A number of anticancer agents are at present in clinical use. To find new anticancer agents, the discovery of a number of 1, 8-naphthyridine (NPTR) derivatives is the new addition. Recently, NPTR and quinolines well-known heterocyclic compounds are being introduced in cancer chemotherapy and in this circumstances, 'Voreloxin' is already in clinical use [58]. The entire NPTR derivatives exhibit limited cytotoxic activity against murine P388 leukemia cells. Eweas et al. [59] synthesize new 2, 7-Dimethyl-1, 8-naphthyridine derivatives substituted with Schiff's bases, Mannich bases N-β-glycosides, pyrazolone, and S-alkylated. Furane derivative (47) 1, 8-naphthyridine hydrazide exhibit cytotoxic activity against the HepG2 cell line (IC50 equals 3.2 µg/ml). The results are comparable with 5-Fluorouracil and doxorubicin as standard drugs (IC50 5 and 3.56 µg/ml) respectively.

Elansary et al. [62] report synthesis of various 2, 4, 5, 7-tetrasubstituted pyrido [2, 3-d] pyrimidines and their allied isosteres substituted 1, 8-naphthyridines and study their anticancer activity. Compound, 7-(4-chlorophenyl)-5-(3-nitrophenyl)-2-phenyl-1, 8-naphthyridine-4-amine (51) shows potent to moderate growth inhibitory activity. Fu et al. [63] develop a proficient synthesis of new functional 1, 8-naphthyridine and chromeno [2, 3-b] quinoline derivatives (52) via cascade reaction of 2-chlorquinoline-3-carbaldehyde and enaminoes or cyclic 1, 3-dicarbonyl compounds. All the derivatives are evaluated for their cytotoxic activity in vitro against various cancer cells and a number of derivatives are established to have higher activities.

Acosta et al. [45] synthesize pyrazolo [3,4-b] [1, 8] naphthyridine-5-amines by microwave assisted organic reaction involving cyclic ketones and heterocyclic o-aminonitrites and the reaction is catalyzed by ZnCl2 leading to the new procedure. These compounds are evaluated for their antitumor activity against 60 different cell lines. Compounds, (53a) NPTR fused with cyclopentane and (53b) NPTR fused with cyclohexane show notable anticancer activity against tumor cell lines, with significant GI50 values 0.62-2.18 µM/ml.
Graf et al. [64] investigate the reaction of cyclometallated rhodium and iridium complexes with 2-methyl-1,8-naphthyridine and 4-chloro-2-methyl-1,8-naphthyridine and evaluate their cytotoxic activity towards the HT-29 and MCF-7 cancer cell lines. Rhodium complexes (54a and c), and iridium complexes (54b and d) show significant cytotoxic activity against both the cancer cell lines in the subordinate micromolar range. Amongst these complexes, maximum activity is calculated for (54d) with IC\textsubscript{50} values of 1.67 μM for MCF-7 and 2.83 μM for HT-29. In addition, it is found that the complexes (54b) and (54d) attribute a somewhat more anticancer activity towards both the cell lines in comparison to the rhodium analogous (54a) and (54c), respectively. Jia et al. [65] develop a series of naphthyridinone derivatives analogous to Voreloxin (13) and evaluate their in vitro anticancer activity against HL60 cell line. Compound (E)-7-(3-aminomethyl)-4-(benzyloxyimino)-3-methylpyrrolidine-1-yl)-4-oxo-1-(thiazol-2-yl)-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (55) shows wide range of activity with IC\textsubscript{50} value ranging from 0.5–6.25 mmol/l against all the tested cancer cell lines.

Behalo et al. [66] synthesize a series of pyrido [2,3-d]pyrimidine and 1,8-naphthyridine derivatives and evaluate their anticancer activity against MCF-7, and PC-3 cancer cell lines using MTT assay. The compound, 1,8-naphthyridinocarbonitrile (56) is found to be a most effective anticancer agent against PC-3 cell line with IC\textsubscript{50} values ranging from 9.47, 10.34, and 8.13 μg/ml respectively. The compound also shows strong anticancer activity against MCF-7 cell line. Tang et al. [67] synthesized a sequence of pyrrolo [2,3-b]pyridine containing the 1,8-naphthyridine-2-one group and studied their anticancer activity against HT-29, H460, A549, and U87MG cell line and six tyrosine kinases (c-Met, VEGFR-2, EGFR, Flt-3, PDGFR-β, and c-Kit inhibition activities. Maximum compounds show good to outstanding activity and pyrrolo pyridine substituted 1,8-naphthyridine-3-carboxamide compound (57) shows Kinase inhibition activity for Flt-3/c-Met with an IC50 value of 1.16/1.92 nM.

Melha [68] synthesizes a series of pyrazolo pyridine substituted 1,8-naphthyridine derivatives and evaluate their cytotoxic activity against Ehrlich ascites carcinoma (EAC). Compound (58) pyrazolo pyridine substituted 1,8-naphthyridine shows the best cytotoxicity and antioxidant activity against EAC.

**5-HT\textsubscript{3} receptor antagonists**

Amongst the serotonin family, 5-HT\textsubscript{3} receptor draws much more interest due to the therapeutic use of 5-HT\textsubscript{3} receptor antagonists in the management vomiting, nausea induced by cancer chemotherapy, postoperative nausea vomiting (PONV) and other clinical uses. In addition, several preclinical studies recommend that 5-HT\textsubscript{3} receptor antagonist may use the management of different CNS diseases [69, 70].

Gautam et al. [71] studies various piperazine substituted 8-naphthyridine-3-carboxylic acid derivatives for their 5-HT\textsubscript{3} receptor inhibition and anxiolytic-like activity in rodent behavioral models. Compound (2-(4-phenylpiperazine-1-yl)-1, 8-naphthyridine 3-carboxylic acid) (59) has good log P (3.35) and pA\textsubscript{2} value (7.6) greater than that of standard drug, ondansetron (pA\textsubscript{2}-6.6).

Compound (60) (2-methoxy-1, 8-naphthyridine-3-yl) (2-methoxyphenylpiperazine-1-yl) methanone and (61) is selected as the lead compounds which show a pA\textsubscript{2} value of 7.67. The naphthyridine-3-carboxamide (2-(thiophen-3-yl)-8-naphthyridine-3-yl) [4-(3-methoxyphenyl)piperazin-1-yl] methanone) (62) exhibit outstanding 5-HT\textsubscript{3} receptor antagonistic activity with pA\textsubscript{2} values of 7.5. [72-75].
CB1 receptor inverse agonists

The cannabinoid-1 receptor (CB1) is present mostly in the CNS which is stimulated by the endocannabinoids (ECs) which are endogenous lipid-based retrograde neurotransmitters. A contrary agonist/antagonist action of the CB-1 receptor have the capacity to overcome food intake in both humans and other animals. Inhibition of CB1 receptor can be used effectively in the treatment of obesity [76, 77]. Duggan et al. [78] synthesize and study SAR of the CB1 receptor adverse agonists derived from dihydro-pyrano [2, 3-b] pyridine and tetrahydro-1, 8-naphthyridine scaffolds. Rat food intake and pharmacokinetic study of compound (63) shows that tetrahydro-1, 8-naphthyridine bicyclic core structures, are orally useful in regulation of food intake and body weight in a rodent model.

CB2 receptor agonists with anticancer and immunomodulatory activity

Manera et al. [79] design and synthesize 1, 8-naphthyridine-4 (1H)-on-3-carboxamide and quinoline-4 (1H)-on-3-carboxamide derivatives. Compound (64) (p-fluorobenzyl and carboxycycloheptyl amide) substituents present at 1 and 3 positions of the 1, 8-naphthyridine-4-one nucleus, show greater affinity toward CB2 with a Ki of 1.0 nM. The 1-morpholino substituted compounds (65-68) show good CB2 affinity and CB2 versus CB1 selectivity.

Furthermore, they find that their efficiency is restricted due to the presence of the substituents at C-6 of the naphthyridine ring and 4-hydroxy-2-oxo-1, 2-dihydro-1, 8-naphthyridine derivatives characterize by a 4 methyl cyclohexyl amido substituted in position 3 of the heterocyclic nucleus with higher CB2 receptor efficacy and preference [80]. The p-fluorobenzyl quinoline-2-one derivative (69) and the morpholino ethyl derivative (70) show the excellent affinity and selectivity and act as a full agonist and a partial agonist at the CB2 receptor and induce a concentration-dependent decline of cell capability on lymph node carcinoma of the prostate (LNCaP), cell line expressing the CB2 receptor [81]. Regarding CB2R affinity, the compounds (69 and 70) prove as compounds of interest to have a maximum affinity, with Ki values of 0.7 µM and 1.5 µM and 4.5 µM respectively [82].

Saccomanni et al. [83] study the synthesis of novel aryl iodonium salts used as precursors for single-stage nucleophilic [18] F radio fluorination. The radiolabeled compound [18] F 1, 8-naphthyridine-3-carboxamide (71) is effectively synthesized for in vivo administration, and its pre-bio-distribution is assessed with micro-PET/CT. The results indicate that [18] F CB1 is a potential candidate marker for distribution of CB2 receptor. Manera et al. [84] synthesize derivatives of quinoline and NPTR and evaluate affinity and selectivity for the CB2 receptor. Compounds (72 and 73) show the excellent affinity and selectivity profile for the CB2 receptor. Componds (72 and 73) show the excellent affinity and selectivity profile for the CB2 receptor.

Malfitano et al. [85] study 1, 8-naphthyridine derivatives effects and the defensive role of the CB receptor in various neurological disorders. In this case study, the immunomodulatory and anti-inflammatory property of the designed compounds along with their possible intestinal absorption and blood-brain barrier (BBB) permeability have been found out. The test compounds, (74-76) show inhibition of the peripheral blood cells proliferation of the tested cell. The anti-proliferative effects of compound 1-benzyl, N-cyclohexyl substituted 1,8-naphthyridine-3-carboxamide (75) and 1-(4-fluorobenzyl), N-(4-methylcyclohexyl) substituted 1,8-naphthyridine-3-carboxamide (76) are moderately intervened by the CB2 receptor. These derivatives block the cell cycle and CB91 decline T cell activation. Compounds downregulate the expression of phosphorylated proteins like NF-κB, extracellular receptor kinase, Akt and COX-2 enzyme, CB91 inhibits the function of the CB2 receptor and its activity is regulated by CB2 receptor.
He also studies the potential immunomodulatory activity of 1, 8-naphthyridine and quinoline derivatives in activated lymphocytes isolated from multiple sclerosis patients. Compounds are found to block cell explosion by a mechanism that partially attributed to the CB2 receptor, down-regulated TNF-α production and does not provoke cell decrease. They also down-regulate ERK, Akt, and NF-kB phosphorylation. NPTR and quinoline derivatives inhibit cell activation markers. In multiple sclerosis patient isolated lymphocytes more effective than in that cell isolated from healthy control. In fact, 1, 8-naphthyridine-2-one derivative reduces the levels of the Cox-2 enzyme in lymphocytes. [86]. He also develops cycloheptyl substituted derivative VL15 (78) as a selective CB2 receptor agent with high selectivity and affinity at the CB2 receptor and having excellent protective role of this receptor in various neurological diseases with an autoimmune constituent like multiple sclerosis with immunomodulatory activity [87].

Anti-HIV activity

Human immunodeficiency virus type 1 (HIV-1) integrase is a viral enzyme that catalyzes the incorporation of the viral DNA into the host cell DNA, an essential step for virus replication. This process is completed via successive strand transfer, involving elimination of the terminal dinucleotide from each 30-terminal of the target viral DNA followed by successive joining of the 30-terminal of the target viral DNA of the host DNA. This virus-encoded enzyme is required for the completion of the viral replication cycle and thus illustrates a very attractive target for designing antiretroviral drugs [88, 89]. Nagasawa et al. [90] develop an HIV-1 integrase inhibitor (79a and b) which shows much-improved human microsome stability up to 75–97%. The halogenated phenyl derivatives of 1,8-naphthyridine-3-carboxylic acid (79a) and (79b) may be selected for further development.

Zhao et al. [91, 92] synthesize bicyclic inhibitors having a hydroxyl group at position 1 and 4 in 1, 8-naphthyridine-3-carboxamide scaffolds and evaluate their HIV1 integrase inhibitory activity. Amongst these amides, N-(2,4-difluorophenyl)-1-hydroxyl substituted 1, 8-naphthyridine-3-carboxamide (80a) and N-(2,4-difluorophenyl)-1,4-dihydroxyl substituted 1, 8-naphthyridine-3-carboxamide (80b) show antiviral activity in nanomolar range potencies against HIV-1 integrase. Most of the derivatives show selectivity index more than 20,000, and several compounds have better antiviral potencies than raltegravir against a group of integrase mutants consist of N155H, Y143R, G140R, and the double mutants G140S/Q148H and E138K/Q138K. He also studies substituted 1, 8-naphthyridine-3-carboxamides integrase inhibitors (81a and b) to search the agents that have better potential against recombinant integrase in biochemical assays. Amongst the new inhibitors, compound 2-(3-(2,4-difluorobenzylcarbamoyl)-1-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-4-ylamino)ethyl acetate (81a) shows a profile against the panel while substituted 4-amino 1, 8-naphthyridine-3-carboxamide (81b) exhibits the best overall absolute performance approximately five to 10 fold enhancement.

Massari et al. [93] describe that 1,8-naphthyridine (82), has a promising anti-HIV activity, which has the capability to block the HIV-1 Tat-mediated transcription. This lead to the discovery of naphthyridine derivative NM13 as the most promising compound,
gained from MT-4 cells. The introduction of an amino group at the C6 position of 1, 8-naphthyridine nucleus characterizes many of the potent 6-desfluoroquinolones. Benzothiazolyl derivative of 1,8-naphthyridine-3-carboxylic acid (83) show better anti-HIV activity, whereas 6-amino derivative of 1,8-naphthyridine-3-carboxylic acid (84) bearing the pyridinyl piperazine as a C7 substituent, show reasonable activity along with little cytotoxic activity along with positive SI values [94].

### Anti-Inflammatory activity

Non-steroidal anti-inflammatory drugs (NSAIDs) are much more useful drugs in the management of moderately and chronic inflammation, fever, and pain. However, unvarying clinical usage of well-known NSAIDs is associated with a wide range of unwanted side effects including bleeding gastrointestinal lesions, and nephrotoxicity. Thus, the discoveries of the novel and therapeutically safe and anti-inflammatory drugs represent an additional challenge to the researcher [95, 96]. Due to the development of resistance against anti-inflammatory drugs, there is an increasing demand for the discovery of novel, potent and less toxic anti-inflammatory drugs [97, 98]. Madaan et al. [99] synthesize a series of 1, 8-naphthyridine-3-carboxamide derivatives (85a-c) and evaluate their anti-cancer and anti-inflammatory activity. The derivatives of 1, 8-naphthyridine-3-carboxamide substituted with 7-chloro-N-(3-(cyclopentylamino) (85a), 7-chloro-N-(2-hydroxy-3-oxo-1-phenyl-3-(phenylamino) (85b) and 7-chloro-6-fluoro-N-(2-hydroxy-3-oxo-1-phenyl-3-(phenylamino) (85c) show considerable activities. Amongst these, compound (85c) shows effective anti-inflammatory activity on inflammatory markers in dendritic cell model at 0.2 and 2 \( \mu \text{M} \). It also very much declines the secretion of IL-6, TNF-\( \alpha \), and IL-1-\( \beta \) by murine splenocytes and Tamm-Horsfall Protein 1 (THP-1) cells against lipopolysaccharides induced levels.

Braccio et al. [100] synthesize 5-(alkylamino)-9-isopropyl [1, 2, 4] triazole derivatives of 1, 8-naphthyridines containing a CONHR moiety at 6 positions and evaluate their anti-inflammatory behavioral patterns. The compound exhibits good anti-inflammatory activity in rats. The most active compound (86) shows significant anti-inflammatory activity with percentage oedema inhibition values of 80% (\( P<0.01 \)) and 72% (\( P<0.01 \)) at the doses of 100 mg/kg 50 mg/kg, respectively [100].

As new ligand of A2A adenosine receptor

Adenosine is perhaps more important neuromodulator in the CNS and peripheral nervous systems, its formation generally rises under metabolically favorable conditions. This nucleoside controls its effects throughout the activation of four subtype adenosine receptors located on the cell surface and recognized as the A1, A2A, A2B, and A3. In the peripheral system, the A2AAR is located in different tissues, and then A2AAR agonists can be used to decrease platelet aggregation in thrombosis, ischemia for determining the strength of anti-inflammatory and immunosuppressive properties. In view of all the above, much effort and contribution of A2AAR have been focused in the
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In recent years, there has been a focus on the discovery and development of selective A2A AR ligands [101]. Manera et al. [102] synthesized 1, 8-naphthyridine derivatives containing different substituents (87a-d) at position 3, 4, and 7 of the heterocyclic nucleus. The synthesized compounds do not have any affinity towards A1AR, while several of them have the capacity to gain an interesting activity and selectivity for the A2A AR. All the synthesized compounds demonstrate a significant efficacy for A2A AR, with Ki values ranging from 30.0-67.0 µM.

Ferrarini et al. [103] synthesize derivatives of NPTR containing a phenyl group at position 2 and different substituents at 4 and 7 positions. The substitution at position 7 significantly alter the affinity, and the most attractive substitutes at this place seem to be electronegative groups; as in the 7-chloro-2-phenyl-1, 8-naphthyridine-4-ol (88) where an excellent selectivity linked with a good A1 affinity (KIC 0.15 µM) was found.

Selective AChE inhibitor

Alzheimer’s disease (AD) is a chronic neurodegenerative, irreversible disorder that is clinically characterized by a successive loss of various cognitive and functional abilities [104]. It is the most general form of dementia in Western countries, which has caused intense economic and social impact as the aging population elevates. Though a lot of factors have been concerned in the AD, its etiology and pathogenesis remain indefinite. The ‘cholinergic hypothesis’ describes the most useful approaches associated with the design of new drugs for the management of AD. This approach is based on the development of drugs with an acetylcholinesterase inhibition profile in order to restore the deficiency of cerebral acetylcholine [105]. Klenc et al. [106] invent the first radiotracer targeting the GPR91, which is a cell surface-bound receptor that controls the cellular effect to hypoxia and hyperglycemia; they design and prepare a series of NPTR derivatives (89a and b) with excellent affinity to GPR91. Pharmacological assays confirm the lead compounds for 99mTc and 18F GPR91 radiotracers within the series.

Other activities

Potent gastric antisecretory properties

Gastric endoscopic submucosal dissection (ESD) can cause artificial gastric ulcers, and there is no compromise regarding the possible perioperative management in conditions of anticipation of intra- or postoperative bleeding and support of healing. The gastric antisecretory effects of various naphthyridine derivatives have attempted to enter as a therapeutic drug for the healing of peptic ulcer [107-109]. Santilli et al. [110] and they describe the syntheses of 2-oxo-1,8-naphthyridine-3-carboxylic acid derivatives (90a and b) containing efficient gastric antisecretory activity. The ethyl ester 4-amino-1-ethyl-2-dihydro-2-oxo 1,8-naphthyridine-3-carboxylic acid (90a) and ester of substituted 4-(4-methyl-l-piperazinyl) l, 8-naphthyridine-3 carboxylic acid (90b) show good gastric antisecretory property and are chosen for further exhaustive assessment.

Atypical antipsychotic agents

Sekhar et al. [111] provide a series of 2,5-disubstituted thiazolyl-phenethyl-piperazine derivatives of 1, 8-naphthyridine scaffold in search of a novel, atypical antipsychotic drugs. Compound 2-(4-(4-(2-amino-5-methylthiazol-4-yl) phenethyl) piperazine-1-yl)-1, 8-naphthyridine-3-carbonitrile (91) exhibits good antipsychotic activity amongst the synthesized derivatives with 5-HT2A/D2 ratio of 1.1286.
Antiplatelet activity
Ferrarini et al. [112, 113] synthesize 1, 8-naphthyridine derivatives, containing 2-cycloalkylamino-3-phenyl as substituents at position 6- and 7 [92 and 93] and 2, 7-di (N-cycloamino)-3-phenyl substituted compound (94) and assess their antiplatelet activity. All the synthesized derivatives demonstrate a significant antiplatelet action in the test with arachidonate and collagen comparable to that of standard drug indomethacin. In the test with ADP, compound (94) exhibits a considerable activity. The presence of morpholinyl or a piperidinyl like moiety at position 2 and a halogen group like chlorine or a methoxy group at position 7 of the NPTR nuclei appear to favor a good activity.

DNA stabilizing agents
Naik et al. [114] describe the synthesis and molecular docking studies of new benzo [b] [1, 8] naphthyridines. The docking results reveal that the synthesized compounds favor the binding with AT-rich region of ds-DNA. The highest binding energy was found for benzo [b] [1, 8] naphthyridine-5-thiol (95) and it is -7.16 (kcal/mol). It offers a promising agent as an enantioselective binder with ds-DNA than the other compounds of benzo [b] [1, 8] naphthyridines. Photo irradiated at 365 nm, to benzo [1, 8]-naphthyridines find to support the photocleavage of plasmid pUC19 DNA. Dhamodharan et al. [115] observe the synthesis of bispyridinium and bisquinolinium derivatives of NPTR and report their relations between the human telomeric DNA and promoter G-quadruplex building DNAs. The bisquinolinium ligands bind strongly and selectively to quadruplex DNAs at low ligand concentration. The fluorescent intercalator displacement (FID) assay is estimating that naphthyridine bisquinolinium ligands (96a and b) create good binding affinity and also have selectivity for quadruplex DNAs over duplex DNA.

Acyl-CoA: cholesterol acyltransferase inhibitor
Ban et al. [116] synthesize 4-Aryl-1, 8-naphthyridine-2 (1H)-one-3-yl urea derivatives with hydrophilic groups for the purpose of getting better aqueous solubility and pharmacokinetics property. Compound SMP-797, 1-(4-amino-2, 6-dipropylphenyl)-3-(1-butyl-4-(3-(3-hydroxypropoxy) phenyl)-2-oxo-1, 2-dihydro-1, 8-naphthyridine-3-yl) urea (97) having (4-aminophenyl) ureido and 3-(hydroxypropoxyphenyl) moieties shows effective Acyl-CoA: cholesterol acyltransferase (ACAT) inhibitory properties with excellent oral efficiency.
MEK (mitogen-activated protein kinase) inhibitors

Kanouni et al [117] synthesize and develop 1, 8-naphthyridine-2,5-dione (98a-d) and evaluate MEK kinase inhibitory activity. Most of the compounds show activity against MEK1 kinase. All analogs show activity in sub-micromolar range against MEK through assays in cellular and enzymatic levels.

Phosphodiesterase (PDE 4) inhibitors

Takayama et al [118] prepare new and phosphodiesterase (PDE4) inhibitor. The compounds show selective inhibitory activities against PDE4 obtained from human peripheral blood cells and are inactively applicable to other PDE types (1, 2, 3, 5). The compound 4, 5, 7-Trimethyl-1-phenyl-1, 8-naphthyridine-2 (1H)-one (99)-YM-10335) having 1, 8-naphthyridine-2 (1H)-one skeleton completely differ structurally from rolipram and is selected as a lead compound. The derivatives also produce good inhibitory activities against TNF-α release (in vitro) and carrageenan-induced pleurisy (in vivo) assay.

Inhibitors of αβ3

The progress of effective and safe medication for the management of osteoporosis there still remains a growing field of developing research. Osteoporosis occurs due to the difference between the natural processes of bone resorption and bone growth. The first step in bone resorption is the unique function of the osteoclast cells which is regulated by glycoprotein, α3β3 integrin. An unusual way to interrupt this mechanism is the minimization of osteoclast cells activity by introducing α3β3 integrin inhibitors [119]. Hartner et al. [120] synthesize 3-[4-(6-Methoxy pyridin-3-yl)-3-(2-oxo-3-[5-(5, 6, 7, 8-tetrahydro-1, 8-naphthyridine-2-yl) propyl]-imidazolidin-1-yl) propionic acid (100) and identify it as an effective and selective α3β3 receptor antagonist. It has an outstanding in vitro profile with an IC50 value of 0.08 µM which is an important unbound part in human plasma and serves as a remarkable pharmacokinetics profile for the dog, rats, and rhesus monkey. Nagarajan et al. [121] describe the synthesis and αβ3 inhibitory activity of numerous small molecules like 2-(2-(4-(2-(5, 6, 7, 8-tetrahydro-1, 8-naphthyridine-2-yl)ethoxy)phenyl) cyclopropyl)acetic acid (101). Most of the compounds show remarkable selectivity over αβ6.

Anticonvulsant and CNS activity

Despite the wide and increasing range of antiepileptic drugs available for treatment, around 30% of epileptic patients experience faulty seizure control. Again, further 25% of patients fell serious adverse effects. Thus, there is a need to develop more efficient antiepileptic drugs that would be endowed with an improved safety profile. Recently, a lot of fused pyrimidine compounds are developed as effective drug molecules. Such an important family of the compounds is quinazolinones which are the constituents of about 150 naturally existing alkaloids and drugs. Some NPTR derivatives also show remarkably good anticonvulsant and CNS depressant activity [122]. Stuk et al. [123] study the NPTR derivatives having different moieties (102) for anxiolytic activity which may be due to the partial agonist action of benzodiazepine at the site of the GABA_A receptor. Lorrio et al. [124] investigate the neuroprotective profile of ethyl 5-amino-2-methyl-6, 7, 8, 9-tetrahydro benzo [b] [1, 8] naphthyridine-3-carboxylic acid ester (103-ITH12246) through in vitro models for Alzheimer’s disease. They also find the pharmacological activities of ITH12246 and evaluate its capacity to counter the memory mutilation elicited by scopolamine, a muscarinic antagonist characterized to approve memory loss. They also succeed to moderate the infarct amount in mice suffering from photothrombosis.
Wang et al. [125] synthesize the derivatives containing an imidazo[1,2-a] [1, 8] naphthyridine core and a side chain connected with amide bond (104a-RO8191 and b) and evaluate the HCV entry inhibitory activity in hepatitis C virus cell culture system. Among these compounds, a few compounds exhibit outstanding anti-HCV activity with EC₅₀ value ranges from 0.017-0.159 µM and low toxicity (CC₅₀>25 µM). These novel anti-HCV compounds exhibit antiviral activity by a different mechanism of action as that of RO8191 by targeting the viral entrance route.

**Antioxidants activity**

The finding of simple organic compounds endowed with good antimicrobial and antioxidant properties is of growing concern in the food industries. Preservation and protection of industrial food containing polyunsaturated fatty acids (eicosapentaenoic (20:5 ω-3) acid) have become a hot subject and growing interest because of their importance in human nutrition. For example, Omega-3-

Polyunsaturated fatty acids provide a number of health benefits related to cardiovascular disease, immune disorders, inflammation condition, allergic manifestations and the occurrence of diabetes. Several compounds having antioxidant activity have been used to slow down the radicals associated with oxidative reactions. However, some of them are known to produce toxic and carcinogenic side effects in animal models [126,127]. The discovery of compounds that can demonstrate both antimicrobial and antioxidant activities having no or zero side effects are most welcome. Nam et al. [128] demonstrate that the C7 unsubstituted tetrahydro-1,8-naphthyridine-3-ol (105a-d) have greater trapping activity than α tocopherol in inhibiting autoxidations in benzene. The C7-mono and dialkyl analogs exhibit higher antioxidant activity in benzene, as found out by a recently developed peroxyl radical clock. The closest α-TOH analogs (naphthyridineol-based tocopherol, N-TOH) show outstanding inhibition of the oxidation of cholesteryl esters in human LDL and secure endogenous α-TOH.

Yu et al. [129] study the effect of a peripheral disulfide bridge substituent on the phenolic hydroxyl bond dissociation energy (BDE) and the ionization potential (IP) of 1,8-naphthyridine diol for antioxidant properties of derivatives (106 a-b and107 a-d). Comparing with naphthalene diol, the substituent of a peripheral disulfide bridge group is very proficient in dropping the BDE, while the additions of nitrogen atoms into the naphthalenic ring only slight changes the BDE of O-H bond but considerably increase the IP. It is comparable also on consideration of the stereoelectronic behavior of the heterocyclic ring for the α-tocopherol, a distinguished antioxidant.

**Antilipolytic activity**

Aljamal and Badawneh [130] investigate the antilipolytic activity of the new NPTR derivatives (108a and b) on lipolysis induced rat fat cell β-adrenoceptors by isoprenaline and alprenolol. The NPTR derivatives substituted with 7-hydroxy-2-(4'-methoxybenzylamine)-6-nitro-3-phenyl (108a) and 7-methoxy-N2-(4-methoxybenzyl)-3-phenyl-1,8-naphthyridine-2,6-diamine (108b) show the maximum antilipolytic effect.
Review articles related to 1, 8-naphthyridine

Recently, there are significant numbers of reviews which have been published related to the chemistry, synthesis and biological activity of 1, 8-naphthyridine metal complexes and multiple activities of 1, 8-naphthyridine [131].

CONCLUSION

The 1,8-naphthyridine ring is an important pharmacophore in modern drug discovery. Attention has been gradually more given to the synthesis of 1,8-naphthyridine derivatives as a source of new biological agents. The 1,8-naphthyridine derivatives are a resource for further medicinal research. The information gained by various researchers has recommended that substituted 1,8-naphthyridines and heterocycles, which are the structural isosteres of nucleotides, allocate them to interact simply with the biopolymers, have pharmacological activity with lower toxicities. Changes in the 1,8-naphthyridine structures have offered high biological activities that have established a start point for the development of novel therapeutic drugs with improved potency and low toxicity. The present review highlights the various synthesized 1,8-naphthyridines (NPTR) and their derivatives showing multiple activities such as analgesic, anti-inflammatory, anticancer, antioxidant, antibacterial, antiviral, antipolyic antiplatelets, Anticonvulsant and CNS antiplatelet, acetyl cholinesterase inhibitory, and diuretic activity.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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