

The Impact of Modifying the Chemical Structure of Nalidixic Acid on the Antimicrobial Activity of Its Derivatives: A Review

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Authors' contributions

This work was carried out in collaboration between both authors. Author ŁP design the study, performed the literature searches and wrote the first draft of the manuscript. Author MGG analyzed collected literature data and helped with writing the final draft of manuscript. Both authors read and approved the final manuscript.

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ABSTRACT

Nalidixic acid was the first quinolone antibiotic introduced to the treatment of urinary tract infections. It was effective especially against Gram-positive and Gram-negative bacteria but resistance to it emerged rapidly. In this article we reviewed the newly synthesized nalidixic acid based compounds as effective antibacterial, antitubercular and antifungal agents. We mainly focused on the effect of various chemical structure modifications of nalidixic acid on the antimicrobial activity of its derivatives. These newly synthesized compounds may serve as lead structures for the design of more specific, efficacious, affordable drugs, particularly active against resistant microorganisms.

Keywords: Nalidixic acid derivatives; antibacterial activity; antitubercular activity; antifungal activity.

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1. INTRODUCTION

The molecular manipulation on the chemical structure in drug design to get an active compound with minimal side effects is constantly of interest in the field of organic and medicinal chemistry. The elimination, introduction or substitution of certain groups in a drug is a common procedure which may result in the increase of biological activity and prevent to develop the resistance to pathogenic microorganisms. The emergence of multidrug resistance is an increasingly important issue. Different infections caused by microorganisms including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis* (MRSE), vancomycin-resistant enterococci (VRE), penicillin and cephalosporin-resistant streptococci are still serious clinical problems [1]. Search for new chemotherapeutics constitutes real challenge for microbiologists, pharmacologists as well as medicinal chemists.

Nalidixic acid, introduced in the early 1960s, was the first member of quinolone family of antibacterial agents synthesized and clinically used [2]. This quinolone derivative failed to achieve adequate concentrations in the plasma or tissues but got concentrated in the urine therefore it was dedicated to treatment of urinary tract infections [3]. Synthesis of nalidixic acid promoted a series of studies leading to the development of new quinolone antibiotics with broad spectrum of bactericidal activity, excellent oral bioavailability, good tissue penetration and favourable safety and tolerability profiles [4].

Nalidixic acid inhibits DNA synthesis by promoting cleavage of bacterial DNA, what results in rapid bacterial death [5]. This drug is a highly specific inhibitor of DNA gyrase, a topoisomerase that catalyzes the introduction of negative supercoils in a closed-circular DNA using energy from the ATP hydrolysis [2,6]. It is particularly effective against Gram-negative bacteria like *Escherichia coli* (99% strains) and other coliforms of bacteria such as *Klebsiella* (92% strains) and *Enterobacter aerogenosa* but resistant to most of the *Pseudomonas* sp. [7,8]. *Brucella* species and some strains of *Salmonella* and *Shigella* are also sensitive [8]. However, it is known that antibacterial spectrum of nalidixic acid exhibits resistance towards most common pathogens that infect urinary tract like *Staphylococcus*, *Bacillus* and *Proteus* species [9].

Basing on the above facts, in this paper we would like to report an impact of modifying the chemical structure of nalidixic acid on the antimicrobial activity of its derivatives.

2. ANTIBACTERIAL ACTIVITY

Increases of the incidence of resistant bacterial infections to multiple drugs in the past several years has become a major health care problem. Therefore the search for new antimicrobial agents will remain an important and challenging task for medicinal chemists.

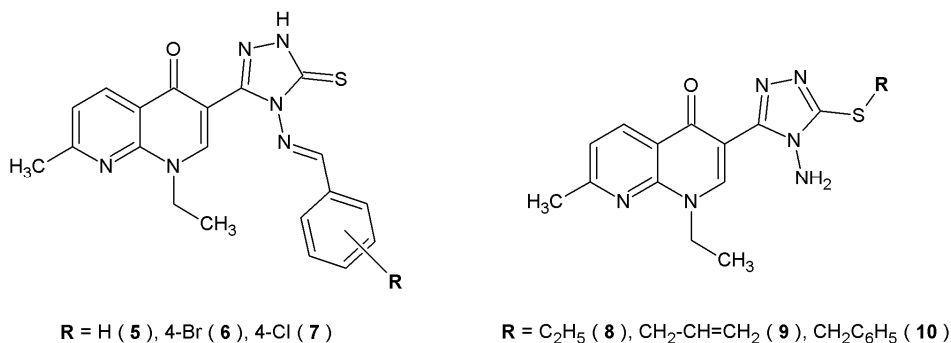
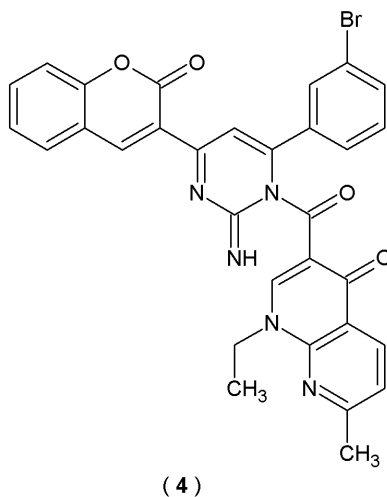
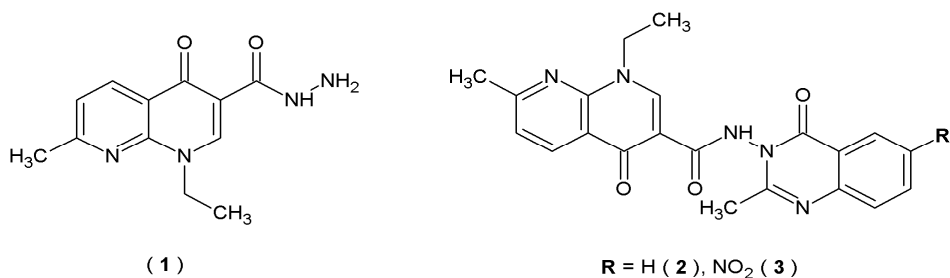
Quinazolone derivatives of nalidixic acid synthesized by Grover et al. [8] showed significant *in vitro* activity against tested bacteria. *Streptococcus pyogenes*, coagulase negative *Staphylococcus*, *Proteus vulgaris* and *Aeromonas hydrophila* were found to be susceptible. Synthesized molecules inhibited the growth of *Aeromonas hydrophila* at concentration 200 µg/ml (2, 3) or 300 µg/ml (1) with the same inhibition zone as standard antibiotic (ampicillin). The above mentioned bacteria often cause diarrhoea in both adults and children and are resistant to pure nalidixic acid. Among the respiratory tract pathogens tested, newly synthesized compound 3 showed high activity against *Streptococcus pyogenes* at 300 µg/ml, which is also resistant to nalidixic acid. While, the derivative 2 inhibited the growth of Gram-negative *P. vulgaris* at 150 µg/ml with the same inhibition zone as standard drug ampicillin but smaller than parent drug nalidixic acid. Unfortunately, the inhibition zone of 1 against nalidixic acid resistant coagulase negative *Staphylococcus* was insignificant. Summarizing the introduction of substituted quinazolone ring to nalidixic acid moiety was beneficial and synthesized derivatives showed enhanced antimicrobial activity compared with nalidixic acid.

Waheed et al. [10] synthesized new compounds using condensation reaction of guanidinyll derivatives of nalidixic acid with chalcones, which were *in vitro* tested against Gram-positive *Staphylococcus aureus* and Gram-negative *Escherichia coli*. Obtained derivatives failed to demonstrate any inhibitory potential against *S. aureus*. All the derivatives inhibited the growth of *E. coli* with the zones of inhibition comparable to standard drugs (nalidixic acid and sparfloxacin). However, they acted at concentration 100 µg/ml which was five times higher than that of standard chemotherapeutics. Among tested compounds

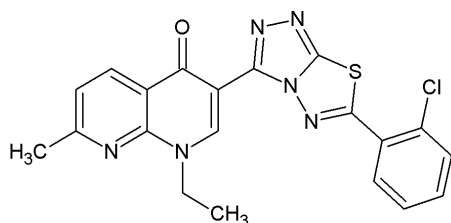
m-bromo substituted molecule (4) was the most active.

New 1,2,4-triazole derivatives of nalidixic acid synthesized by Abdelmoty et al. [1] were screened for its antibacterial activity against methicillin resistant *Staphylococcus aureus* (MRSA), *Bacillus cereus*, *Escherichia coli* and *Klebsiella pneumoniae*. The *in vitro* results revealed that among all newly synthesized molecules, three Schiff's bases (5, 6, 7) and three *S*-alkyl derivatives (8, 9, 10) were the most potent against all bacterial strains. The

compound 8 exhibited the most promising antibacterial activity with MIC values against Gram-positive representatives lower than reference drugs nalidixic acid and ampicillin. The inhibition of growth of Gram-negative strains caused by this compound was comparable to nalidixic acid and superior to that of ampicillin. In this case, the *S*-alkylation with ethyl group was the most justified. However, generally the replacement of the carboxylic group of nalidixic acid with unsubstituted 1,2,4-triazole moiety or *S*-alkyl derivatives of Schiff's bases decreases the antibacterial properties.

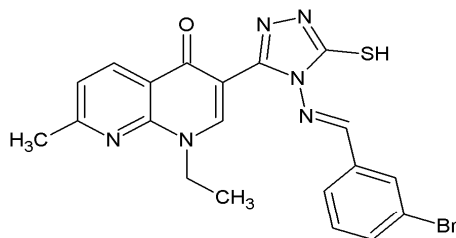


Aggarwal et al. [3] synthesized a series of nalidixic acid based 4-amino-5-mercapto-1,2,4-triazoles. Thirty three derivatives were *in vitro* tested against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. The study revealed that triazolothiadiazoles, arylideneamino-1,2,4-triazoles, acylamino-1,2,4-triazoles showed moderate to good antibacterial activity in comparison to reference drugs streptomycin and ciprofloxacin. Compound 11, triazolothiadiazole with chloro substituent at *ortho* position on aromatic ring, exhibited maximum antimicrobial potency against all tested microorganisms at a MIC value of 16 µg/ml. The inhibition of bacteria growth was comparable to standard drugs, particularly in relation to *S. aureus* and *E. coli* [3].

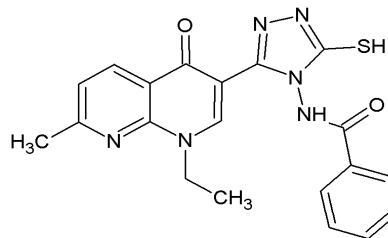


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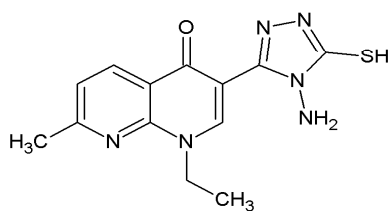
Among the arylidene amino triazoles, compound 12 was the most potent. Compound 13 was also



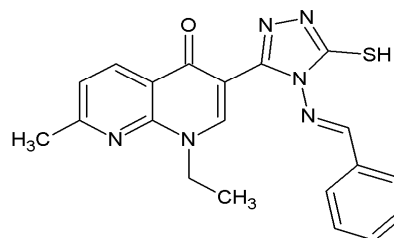
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(13)



(14)



(15)

found to be effective against all tested strains of bacteria with MIC value of 63 µg/ml. Most of derivatives showed significant inhibitory properties against *P. aeruginosa* (MIC 16-125 µg/ml). The differences in the antibacterial properties were obviously due to molecular diversity. The conversion of free amino group of compound 14 to phenylmethyleneamino moiety of compound 15 greatly increased inhibitory properties against Gram-negative bacteria but about 4 times decreased the activity against Gram-positive *S. aureus* and *B. subtilis*. The substitution in phenyl ring proved to be essential for enhancement of antimicrobial potential [3].

The same research team published the synthesis and *in vitro* evaluation of inhibition growth of above mentioned bacterial strains by novel nalidixic acid based 1,3,4-thia (oxa) diazoles and its derivatives [11]. A variety of *S*-alkylated derivatives, its corresponding sulfides, sulfones, Mannich bases of 1,3,4-thiadiazoles and oxadiazoles showed diverse inhibitory properties against Gram-positive and Gram-negative bacteria. Most of newly synthesized compounds exhibited good inhibitory properties particularly against Gram-negative strains. Synthesized compounds showed significant inhibitory activity against *P. aeruginosa* and moderate to good activity against *E. coli* and *K. pneumoniae* [11].

However, 2-thione derivatives of 1,3,4-thiadiazole and 1,3,4-oxadiazole inhibited the growth of Gram-positive strains more effectively than Gram-negative. Generally, 1,3,4-thiadiazole derivatives were found to be more effective than 1,3,4-oxadiazole. It is also known that the antimicrobial activity depends on the nature of substituents besides the basic skeleton of the molecules. Among the *bis*-(1,3,4-thia/oxadiazol-2-yl)disulfides, increase in chain length of substituent up to the hexyl was accompanied by the permanent enhancement of antibacterial activity. Compound 16 with 1,4-bis-(methylene) benzene group as a spacer between two molecules of thiadiazole showed remarkable antibacterial properties at MIC range of 31,25-125 µg/ml. The Mannich base of 1,3,4-thiadiazole with *p*-chloro substituent in phenyl ring (compound 17) showed significant enhancement in the inhibitory activity. However, in relation to Mannich bases, most derivatives with substituted phenyl ring exhibited a decrease in the activity profile. Compounds 17 with MIC 6.25-125 µg/ml and 18 with MIC 6.25-62.5 µg/ml proved to be the most effective against all the tested microorganisms [11].

Deeba et al. [9] synthesized nalidixic acid based hydrazone and its complexes with metals (Cu, Ni, Zn and Fe). Synthesized compounds were *in vitro* tested against panel of Gram-positive and Gram-negative bacteria. Unfortunately, it was observed that the hydrazone ligand had weaker antibacterial properties against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas aeruginosa* than standard nalidixic acid. Its metal complexes exhibited better activity but still lower than that of reference drug [9].

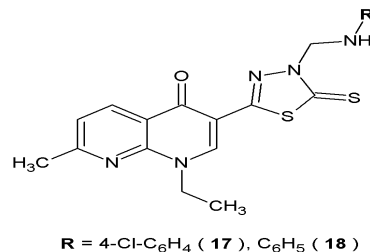
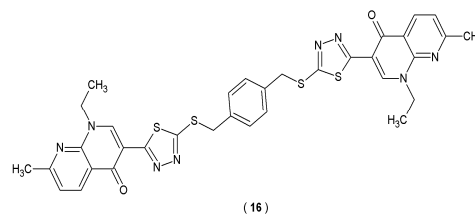
3. ANTITUBERCULAR ACTIVITY

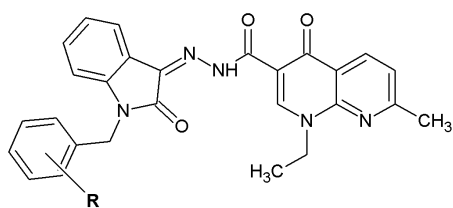
Tuberculosis is a serious health problem and still causes death of about three million people every year worldwide. Additionally, the increase of *Mycobacterium tuberculosis* strains resistant to first line antimycobacterial drugs such as rifampicin and isoniazid has further worsened that problem [12]. This situation requires more effective drugs for adequate management of tuberculosis. In response, a new series of hydrazones derived from nalidixic acid hydrazide and *N*-substituted benzylisatin were synthesized by Aboul-Fadl et al. [6] and *in vitro* investigated against four *Mycobacterium* strains: *M. intercellulari*, *M. xenopi*, *M. cheleneo* and *M. smegmatis*. Antimycobacterial activity was assessed in relation to the first line antitubercular

drug isoniazid. The most active compounds (19, 20, 21) proved to be 139 times more potent than standard drug. The MIC value determined for these molecules was 0.09 µg/ml. The derivative 22 had also excellent inhibitory properties against tested *Mycobacterium* strains with MIC value of 0.625 µg/ml. The remarkable enhancement of activity was associated with *para*-substitution of benzyl moiety in *N*-benzylisatins with electron-withdrawing group (chloro, fluoro or nitro) [6].

4. ANTIFUNGAL ACTIVITY

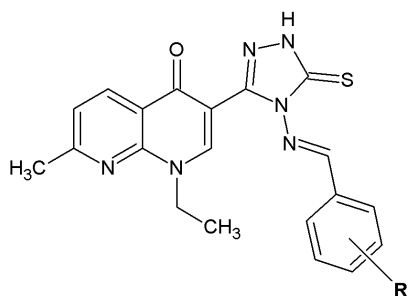
The newly synthesized quinazolone derivatives of nalidixic acid were also active against *Candida albicans* [8]. This activity was absent in the parent compound – pure nalidixic acid. The most promising compound – pure nalidixic acid. The most promising compound 1 showed at 300 µg/ml activity comparable to standard drug fluconazole. On the contrary, the 1,2,4-triazole derivatives of nalidixic acid were inactive against *Candida albicans* and plant pathogens *Fusarium oxysporum* and *Aspergillus terreus* as well as against food poisoning species *Penicillium chrysogenum* [1]. Fungi of *Fusarium* genus not only cause the damage of cultivations but are also secrete mycotoxins, hazardous to human health [13]. *A. terreus* causes opportunistic infections in humans which are resistant to amphotericin B and its incidence is increasing more rapidly than to any other *Aspergillus* [14]. However, compound 23 inhibited the growth of *Trichophyton rubrum* at 34% of inhibition in relation to standard (clotrimazole) and was more active than nalidixic acid [1]. Approximately 80-93% of chronic dermatophyte infections are thought to be caused by *T. rubrum* [15].



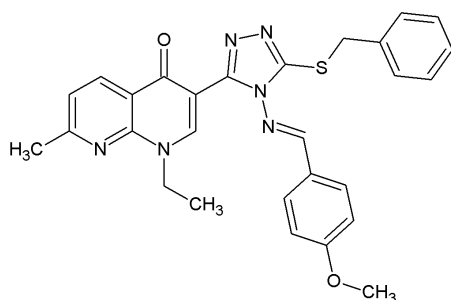


R = 4-F (19), 4-NO₂ (20), 4-Cl (21), H (22)

The *in vitro* screening results also revealed that a number of tested derivatives (5, 8, 23, 24 and 25) showed higher activity than nalidixic acid against the soil-associated dermatophyte *Microsporum gypseum*. Compound 25 with 41% of inhibition was the most potent.



R = 2-OCH₃ (23), 4-OCH₃ (24)

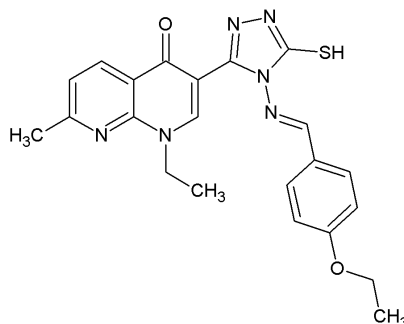


(25)

The results suggest that conversion of nalidixic acid based 1,2,4-triazoles to Schiff's bases (5, 23, 24) and some S-alkylation (8 and 25) is critical for the antifungal activity [1].

Additionally, novel 4-amino-5-mercapto-1,2,4-triazole nalidixic acid based compounds were tested against two fungal species, *Fusarium oxysporum* and *Aspergillus niger*, which are one of the most common causes of otomycosis and additionally can produce mycotoxins [3]. Most of the tested compounds showed lower fungicidal than bactericidal activity. Compound 11 was the most potent with comparable antifungal activity against both tested species.

The aryl diamino triazoles exhibited higher inhibitory activity against *F. oxysporum* than *A. niger* and compounds 15 and 26 showed the best activity properties.



(26)

In general, compounds with electron-releasing substituents showed better activity against both fungi than these with electron-withdrawing substituent [3].

Another research article describes the evaluation of the inhibitory potency of *N*'-(2-hydroxybenzylidene)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide and its complexes with metals against two selected fungi species [9]. It was found that synthesized compounds had about six times weaker activity against *Candida albicans* and *Aspergillus niger* than nalidixic acid.

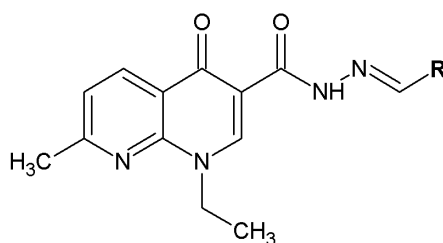
A series of newly synthesized nalidixic acid derivatives were *in vitro* screened against five fungal food-poisoning plant pathogens (*Rhizoctonia bataticola*, *Sclerotium rolfsii*, *Rhizoctonia solani*, *Fusarium oxysporum* and *Alternaria porii*) [16,17]. The evaluation of fungicidal properties of thirty one substituted hydrazones of nalidixic acid revealed that most compounds exhibited maximum inhibition of *A. porii* growth followed by *F. oxysporum* [16]. Compound 27 showed the best antifungal activity against all test species, comparable with reference hexaconazole, a commercial fungicide.

The significantly high fungicidal properties of hydrazone derivatives were due to an electron-withdrawing nitro group at *para* position and an electron-releasing methyl group at *meta* position. The increase of activity was observed when a hydroxyl group (compound 28) was placed or with a methoxy group (compound 29) in aromatic ring. The derivatives with unsaturated aliphatic and heterocyclic substitution exhibited higher antifungal properties (compounds 30 and 31).

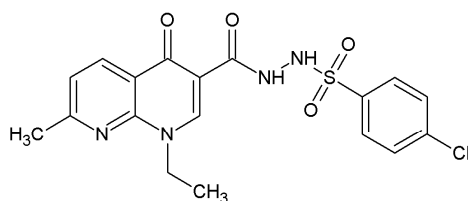
The increase in size of saturated or unsaturated rings resulted in a decrease of activity.

Most of the nalidixic acid based diacyl and sulfonyl acyl hydrazines derivatives showed moderate to good antifungal activity against *A. parii*. Among forty hydrazines derivatives tested, compound 32 (*p*-chlorophenyl substituted) was the most active against this fungi species. Compound 33 (*o*-chlorophenyl substituted) inhibited the growth of *S. roffsii* most effectively. Compound 34 (*m*-chlorophenyl substituted) exhibited maximum antifungal activity against *R. solani*.

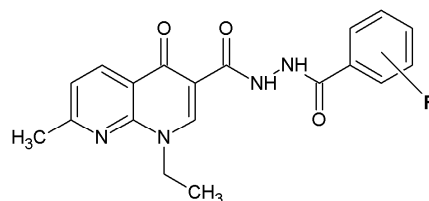
In general, aromatic compounds with halogen substituents at *meta* and *para* position were more active as compared to other substituents but mono chloro analogues were more potent than dichloro substituted compounds. The replacing one acyl group with sulfonyl group also resulted in the increase of antifungal activity against all the tested fungi. In addition, a slight but progressive increase in fungicidal properties was observed with increasing carbon chain [17]. The summary of antimicrobial activity of nalidixic acid derivatives is presented in Table 1.



R = cyclohexyl (27), 4-OH-C₆H₄ (28), 4-OCH₃-C₆H₄ (29), 2-pyridyl (30), crotonyl (31)



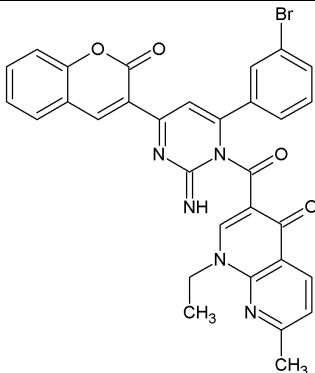
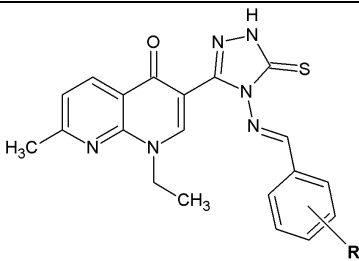
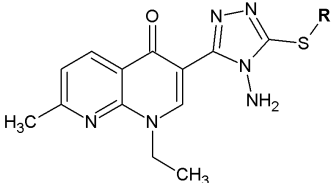
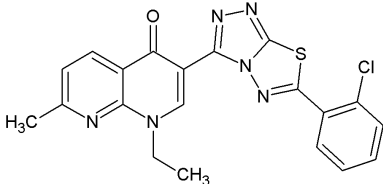
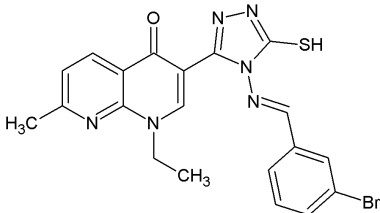
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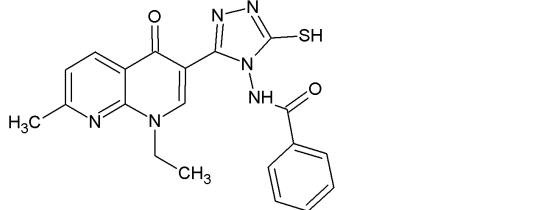
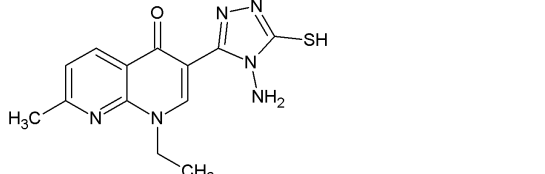
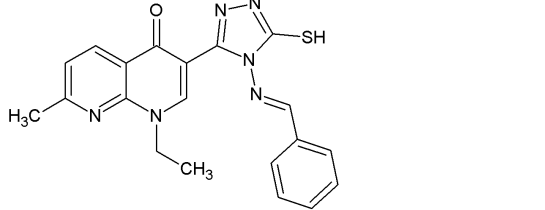
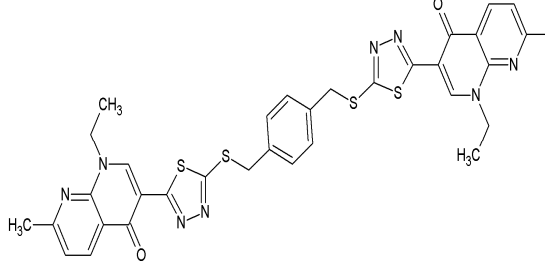
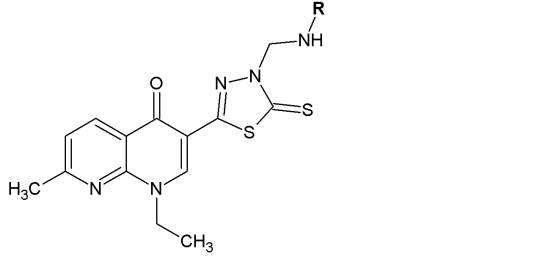


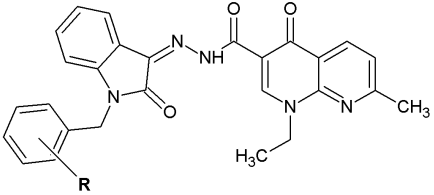
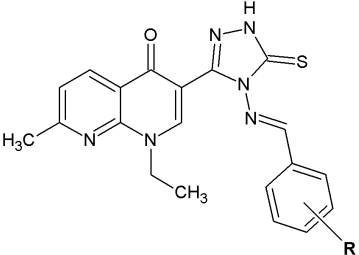
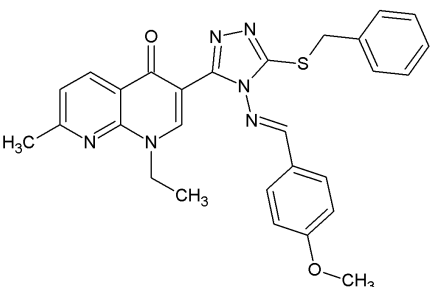
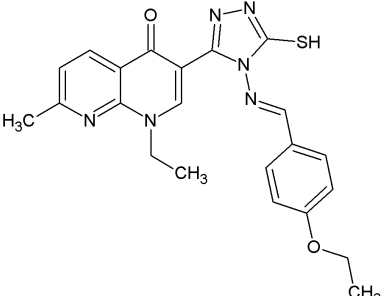
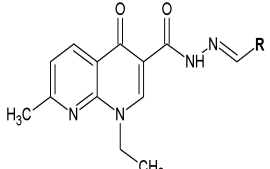
R = 2-Cl (33), 3-Cl (34)

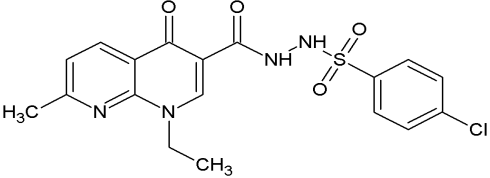
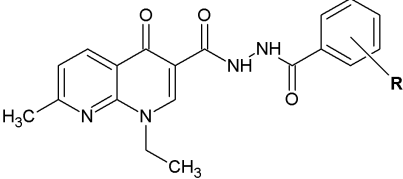
Table 1. Biological activity of nalidixic acid derivatives

Number and structure of compound	Bioactivity	Reference
<p>(1)</p>	Moderate to good antibacterial activity against <i>Aeromonas hydrophila</i> , <i>Streptococcus pyogenes</i> . Good antifungal activity against <i>Candida albicans</i> .	[8]
<p>R = H (2), NO₂ (3)</p>	Moderate to good antibacterial activity against <i>Proteus vulgaris</i> , <i>Aeromonas hydrophila</i> , <i>Streptococcus pyogenes</i> and coagulase negative <i>Staphylococcus</i> .	[8]

Number and structure of compound	Bioactivity	Reference
 <p>(4)</p>	High antibacterial activity against <i>Escherichia coli</i> .	[10]
 <p>R = H (5), 4-Br (6), 4-Cl (7)</p>	High antibacterial activity against <i>Staphylococcus aureus</i> (MRSA), <i>Bacillus cereus</i> , <i>Escherichia coli</i> and <i>Klebsiella pneumoniae</i> . High antifungal activity against soil-associated dermatophyte <i>Microsporum gypseum</i> (compound 5).	[1]
 <p>R = C₂H₅ (8), CH₂-CH=CH₂ (9), CH₂C₆H₅ (10)</p>	High antibacterial activity against <i>Staphylococcus aureus</i> (MRSA), <i>Bacillus cereus</i> , <i>Escherichia coli</i> and <i>Klebsiella pneumoniae</i> . High antifungal activity against soil-associated dermatophyte <i>Microsporum gypseum</i> (compound 8).	[1]
 <p>(11)</p>	Good antibacterial activity against <i>Staphylococcus aureus</i> , <i>Bacillus subtilis</i> , <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> and <i>Pseudomonas aeruginosa</i> . High antifungal activity against <i>Fusarium oxysporum</i> and <i>Aspergillus niger</i> .	[3]
 <p>(12)</p>	Good antibacterial activity against <i>Staphylococcus aureus</i> , <i>Bacillus subtilis</i> , <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> and <i>Pseudomonas aeruginosa</i> .	[3]

Number and structure of compound	Bioactivity	Reference
 <p>(13)</p>	<p>Good antibacterial activity against <i>Staphylococcus aureus</i>, <i>Bacillus subtilis</i>, <i>Escherichia coli</i>, <i>Klebsiella pneumoniae</i> and <i>Pseudomonas aeruginosa</i>.</p>	<p>[3]</p>
 <p>(14)</p>	<p>Good antibacterial activity against <i>Staphylococcus aureus</i>, <i>Bacillus subtilis</i>, <i>Escherichia coli</i>, <i>Klebsiella pneumoniae</i> and <i>Pseudomonas aeruginosa</i>.</p>	<p>[3]</p>
 <p>(15)</p>	<p>High antibacterial activity against <i>Staphylococcus aureus</i>, <i>Bacillus subtilis</i>, <i>Escherichia coli</i>, <i>Klebsiella pneumoniae</i> and <i>Pseudomonas aeruginosa</i>. High antifungal activity against <i>Fusarium oxysporum</i> and <i>Aspergillus niger</i>.</p>	<p>[3]</p>
 <p>(16)</p>	<p>High antibacterial activity against <i>Pseudomonas aeruginosa</i> and moderate to good activity against <i>Escherichia coli</i> and <i>Klebsiella pneumoniae</i>.</p>	<p>[11]</p>
 <p>R = 4-Cl-C₆H₄ (17), C₆H₅ (18)</p>	<p>High antibacterial activity against <i>Pseudomonas aeruginosa</i> and good activity against <i>Escherichia coli</i> and <i>Klebsiella pneumoniae</i>.</p>	<p>[11]</p>

Number and structure of compound	Bioactivity	Reference
 <p>R = 4-F (19), 4-NO₂ (20), 4-Cl (21), H (22)</p>	<p>High antitubercular activity against four <i>Mycobacterium</i> strains: <i>M. intercellulari</i>, <i>M. xenopi</i>, <i>M. cheleneo</i> and <i>M. smegmatis</i>.</p>	[6]
 <p>R = 2-OCH₃ (23), 4-OCH₃ (24)</p>	<p>Good antifungal activity against <i>Trichophyton rubrum</i> (compound 23) and high antifungal activity against soil-associated dermatophyte <i>Microsporum gypseum</i> (compound 24).</p>	[15]
 <p>(25)</p>	<p>High antifungal activity against soil-associated dermatophyte <i>Microsporum gypseum</i>.</p>	[1]
 <p>(26)</p>	<p>High antifungal activity against <i>Fusarium oxysporum</i> and <i>Aspergillus niger</i>.</p>	[3]
 <p>R = cyclohexyl (27), 4-OH-C₆H₄ (28), 4-OCH₃-C₆H₄ (29), 2-pyridyl (30), crotonyl (31)</p>	<p>Good to high antifungal activity against <i>Rhizoctonia bataticola</i>, <i>Sclerotium rolfsii</i>, <i>Rhizoctonia solani</i>, <i>Fusarium oxysporum</i> and <i>Alternaria porii</i>.</p>	[16]

Number and structure of compound	Bioactivity	Reference
 <p>(32)</p>	Moderate to good antifungal activity against <i>Alternaria porii</i> .	[17]
 <p>R = 2-Cl (33), 3-Cl (34)</p>	High antifungal activity against <i>Sclerotium rolfsii</i> (compound 33) and high antifungal activity against <i>Rhizoctonia solani</i> (compound 34).	[17]

5. CONCLUSION

In conclusion crucial for antimicrobial activity of nalidixic acid derivatives is the modification of carboxylic group of nalidixic acid. In general the substitution by moieties with electron-releasing substituents afforded with better bioactivity in contrary to substitution by moieties with electron-withdrawing substituents, which usually decreased the antimicrobial activity

A number of the above mentioned compounds represent fruitful matrix for the development of new class of antibacterial, antitubercular and antifungal agents. However, only the suitable molecular modifications can lead to the further enhancement of antimicrobial potency of these derivatives.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

- Abdelmoty SG, Heta HF. Synthesis of new 1,2,4-triazole derivatives of nalidixic acid as potential antibacterial and antifungal agents. Bull Pharm Sci (Assiut University). 2009;32(1):125-140.
- Shen LL, Pernet AG. Mechanism of inhibition of DNA gyrase by analogues of nalidixic acid: The target of the drugs is DNA. Proc Natl Acad Sci. 1985;82:307-311.
- Aggarwal N, Kumar R, Dureja P, Khurana JM. Synthesis, antimicrobial evaluation and QSAR analysis of novel nalidixic acid based 1,2,4-triazole derivatives. Eur J. Med Chem. 2011;46(9):4089-4099.
- King DE, Malone R, Lilley SH. New classification and update on the quinolone antibiotics. Am Fam Physician. 2000;6(9):2741-2748.
- Pedrini AM, Geroldi D, Siccardi A, Balaschi A. Studies on the mode of action of nalidixic acid. Eur J. Biochem. 1972;25:359-365.
- Aboul-Fadl T, Radwan AA, Abdel-Aziz HA, Baseeruddin M, Attia MI, Kadi A. Novel Schiff bases of indoline-2,3-dione and nalidixic acid hydrazide: Synthesis, *in vitro* antimycobacterial and *in silico* *Mycobacterium tuberculosis* (MTB) DNA gyrase inhibitory activity. Dig J. Nanomater Bios. 2012;7(1):329-338.
- Crumplin GC, Smith JT. Nalidixic acid: An antibacterial paradox. Antimicrob Agents Chemother. 1975;8(3):251-261.
- Grover G, Kini SG. Synthesis and evaluation of new quinazolone derivatives of nalidixic acid as potential antibacterial and antifungal agents. Eur J. Med Chem. 2006;41(2):256-62.
- Deeba F, Khan MN, Abbas N, Khan MA, Khan RA. Synthesis and biological evaluation of *N'*-(2-hydroxybenzylidene)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazide and its complexes with Cu(II), Ni(II), Zn(II) and Fe(III). Asian J Chem. 2013;25(15):8351-8354.
- Waheed A, Alorainy MS, Alghasham AA, Khan SA, Raza M. Synthesis of a new series of substituted pyrimidines and its

- evaluation for antibacterial and antinociceptive effects. *Int J Health Sci.* 2008;2(1):39-48.
11. Aggarwal N, Kumar R, Dureja P, Khurana JM. Synthesis of novel nalidixic acid-based 1,3,4-thiadiazole and 1,3,4-oxadiazole derivatives as potent antibacterial agents. *Chem Biol Drug Des.* 2012;79(4):384-397.
 12. Rollas S, Küçükgülzel SG. Biological activities of hydrazone derivatives. *Molecules.* 2007;12(8):1910-1939.
 13. Waśkiewicz A, Irzykowska L, Karolewski Z, Bocianowski J, Goliński P, Weber Z. Mycotoxins biosynthesis by *Fusarium oxysporum* and *F. proliferatum* isolates of *Asparagus* origin. *J Plant Prot Res.* 2009; 49(4):369-372.
 14. Lass-Flörl C, Griff K, Mayr A, Petzer A, Gastl G, Bonatti H, et al. Epidemiology and outcome of infections due to *Aspergillus terreus*: 10-year single centre experience. *Br J Haematol.* 2005;131(2):201-207.
 15. Gräser Y, Scott J, Summerbell R. The new species concept in dermatophytes-a polyphasic approach. *Mycopathologia.* 2008;16(5-6):239-256.
 16. Aggarwal N, Kumar R, Srivastava C, Dureja P, Khurana JM. Synthesis of nalidixic acid based hydrazones as novel pesticides. *J Agric Food Chem.* 2010;58(5):3056-3061.
 17. Aggarwal N, Kumar R, Srivastava C, Dureja P, Khurana JM. Synthesis, biological activities and SAR studies of novel 1-Ethyl-7-methyl-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid based diacyl and sulfonyl acyl hydrazines. *Pest Manag Sci.* 2014;70(7):1071-1082.

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