JMBFS
Journal of Microbiology, Biotechnology and Food Sciences
International peer-reviewed scientific online journal
Published by Faculty of Biotechnology and Food Sciences

CYCLOHEXANE AND ITS FUNCTIONALLY SUBSTITUTED DERIVATIVES: IMPORTANT CLASS OF ORGANIC COMPOUNDS WITH POTENTIAL ANTIMICROBIAL ACTIVITIES

*Muhammad Shoaib, Aygun Alimardan Israyilova, Khudaverdi Ganbarov**

Address(es): Khudaverdi Ganbarov
Department of Microbiology, Faculty of Biology, Baku State University, Azerbaijan.

*Corresponding author: khuda1949@mail.ru

doi: 10.15414/jmbfs.2019.9.1.84-87

ARTICLE INFO

Received 31. 1. 2019
Revised 15. 3. 2019
Accepted 15. 3. 2019
Published 1. 8. 2019

Review

OPEN ACCESS

ABSTRACT

Development of resistance to antimicrobial drugs is a global health concern not only for humans but also for animals. Rate of microbial resistance to antibiotics has alarmingly increased in last two decades. Factors responsible for this ever increasing antibiotic resistance are attributed to microorganisms as well as excessive and unwise use of antimicrobial drugs. Drug efflux pumps and biofilm formation are examples of microbial factors which contribute to antimicrobial resistance. It is dire need of hour to develop new antimicrobial drugs to ameliorate this condition. New antimicrobial agents with unique mode of action should be explored. In this regard, synthetic organic compounds are target of worldwide drug development studies which are being conducted for investigating new antimicrobial drugs. Cyclohexane and its functionally substituted derivatives are important compounds with diverse biological properties. These compounds can serve as probable alternatives to antibiotics with potential antimicrobial properties. This review summarizes the experimental evidences and studies exploring antimicrobial activities of cyclohexane and its functionally substituted derivatives as probable antimicrobial agents of future.

Keywords: Cyclohexane, functionally substituted derivatives, antimicrobial resistance, potential antimicrobial drugs, drug development

INTRODUCTION

Due to perpetual increasing resistance of microbes to antibiotics and shortage of new antimicrobial drugs, drug development studies are of supreme importance in the present time (**Vnutskikh *et al.*, 2006**). Irrational and overuse of antibiotics is the major reason for development of antimicrobial resistance. That's why use of antibiotics as growth promoters has been banned in livestock and poultry feed in many countries. Greater selective potential has been observed for long term low dose exposure to antimicrobials as compared to short term full dose usage (**Hao *et al.*, 2014**). There are numerous microorganisms like *Staphylococcus aureus, Escherichia coli, Mycobacterium tuberculosis* etc. which have acquired resistance against one or multiple types of antibiotics. Methicillin-resistant *Staphylococcus aureus* (MRSA) is a Gram-positive multidrug resistant pathogenic bacterium which causes infections in humans. It is also responsible for huge economic losses by causing diseases in food animals and poultry (**Iqbal *et al.*, 2016**). Multidrug resistant *Escherichia coli* is a Gram-negative bacterium which causes numerous diseases in humans, animals and poultry. There are 16 different types of genes for antimicrobial resistance against different antibiotics in *Escherichia coli*. These genes impart antimicrobial resistance to *Escherichia coli* against β-lactams, chloramphenicol, quinolones etc. (**Hussain *et al.*, 2017**).

Antimicrobial resistance has been described against different groups of antibiotics like β-lactams, quinolones, vancomycin, glycopeptides, macrolides etc. Leading cause of casualties due to infectious diseases is mainly attributed to development of multidrug resistant and extensively drug resistant bacteria. Recently, the number of multi drug resistant bacteria and extensively drug resistant microorganisms has increased many folds. Pan drug resistant bacteria which are resistant to almost all the available antibiotics have also been reported (**Bielawski *et al.*, 2017**). Worldwide many studies are being carried out to discover new antimicrobial compounds. Antimicrobial drug discovery studies are focused on development of hybrid organic compounds which combine two or more potentially bioactive substructures to make an integrated new organic compound. Furthermore, functional substitution of organic compounds imparts higher antimicrobial activities as compared to non substituted compounds (**Tsemeugne *et al.*, 2018**). It is dire need of hour to synthesize new and better therapeutic agents in order to overcome problem of antimicrobial resistance. New chemical organic compounds with potential antimicrobial properties and unique mode of action which is not affected by bacterial resistance should be investigated. The aim of this study is to provide current developments and experimental evidences of antimicrobial potential of cyclohexane and its functionally substituted derivatives. There are limited reports regarding antimicrobial properties of cyclohexane derivatives which are summarized in this review.

CYCLOHEXANE

Cyclohexane, also called Hexanaphthene, is an alicyclic hydrocarbon which consists of ring of six carbon atoms. Cyclohexane is a cycloalkane having molecular formula C_6H_{12} as shown in figure 1. It is a volatile organic compound having melting point 6.47°C and boiling point 80.74°C. It is most commonly used in preparation of precursors of nylon (**Campbell, 2011**).

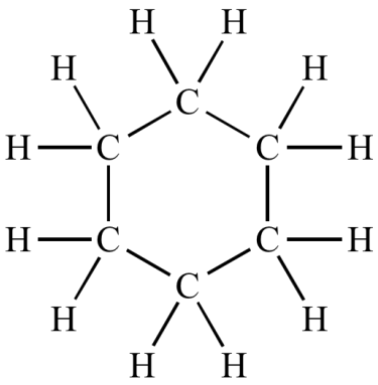

Figure 1 Structure of Cyclohexane (**Campbell, 2011**)

Cyclohexane triones are synthetic antibacterial agents which are lipophilic weak acids. The mode of action of these molecules is very unique. Unlike other cationic antibacterial molecules, cyclohexane triones don't disrupt the bacterial

cytoplasmic membranes. These molecules block the transport of low molecular weight hydrophilic substances into bacterial cells (**Lloyd *et al.*, 1988**).

DIVERSE BIOLOGICAL PROPERTIES OF CYCLOHEXANE DERIVATIVES

Numerous studies have been conducted to demonstrate wide range of biological activities of cyclohexane derivatives. These include anticancer activity, antioxidant activity, cytotoxic activity, analgesic activity, anti-inflammatory activity and antithrombin activity. Antimicrobial activity and inhibition of different enzymes which are part of treatment of diabetes mellitus and hypertension have also been reported.

A new polyoxygenated cyclohexane compound, 3-acetyl-4-benzoyl-1-benzoyloxymethyl-1,6-diepoxycyclohexan-2,3,4,5-tetrol was isolated and evaluated for cytotoxic activity against pancreatic and breast cancer cell lines and normal cell lines. Tested compound showed remarkable cytotoxic activity against cancer cell lines. No cytotoxic activity was observed against normal cell lines (**Lallo *et al.*, 2014**). The effect of 2-[(4-hydroxy-phenylamino)-methylene]-5,5-dimethyl-cyclohexane was investigated against breast cancer treatment in rats. It was found that this cyclohexane derivative remarkably decreased the number of rats with mammary tumor. Furthermore, the number of tumors per rat and tumor volume was also significantly reduced. So this compound can be used as potential therapeutic in treatment of mammary carcinogenesis (**Song *et al.*, 2015**). Antimicrobial and anticancer activities of cyclohexyl diamine based derivatives have been reported. Structure activity relationship studies show that by introduction of aliphatic chains in the benzene ring leads to manifold increase in antimicrobial and anticancer potential of these cyclohexane derivatives (**Sharma *et al.*, 2011**). A series of new spiro (cyclohexane-1,2′-thiazolidine) derivatives and spiro(cyclohexane1,2′-thiazolo-pyridine) derivatives were prepared and tested for their antibacterial, antioxidant and anticancer properties. Some of the compounds showed significant antioxidant and anticancer properties (**Flefel *et al.*, 2014**). A library of 3 H-spiro [1-benzofuran-2, 1'cyclohexane] derivatives has been tested for antiproliferative activities. These compounds have shown significant antiproliferative activities and can be used as potential alternatives for antineoplastic therapy (**Modak *et al.*, 2011**).

A series of spiro cyclohexane-1,2'-quinazoline derivatives were synthesized and biological evaluation was performed. Compounds were tested for inhibition of enzyme called dipeptidyl peptidase IV and sitagliptin was used as reference drug. Inhibition of this enzyme is most current and potential therapy for treatment of Type 2 Diabetes Mellitus. Some of the tested compounds were potent than reference drug. This explains the potential use of these compounds in treatment of Type 2 Diabetes Mellitus (**Syam *et al.*, 2019**). A series of six 3*H*-spiro[benzofuran-2,1′-cyclohexane] derivatives were prepared and their classical complement pathway inhibiting ability was investigated. Classical complement pathway inhibiting ability of these derivatives was found to be comparable to that of natural complement inhibitor proteins. This demonstrates that these cyclohexane derivatives have anti-inflammatory potential (**Usegilo *et al.*, 2006**). Spiro [(2H,3H) quinazoline-2,1′-cyclohexan]-4(1H)-one derivatives have shown remarkable anti-inflammatory and analgesic activity in rats when compared to indomethacin and tramadol respectively, as reference drugs (**Amin *et al.*, 2010**). *N*-{[1-(2-Phenylethyl) pyrrolidin-2-yl] methyl} cyclohexane-carboxamides were prepared and evaluated for 5-HT_{1A} receptor agonists. It was concluded that these derivatives are potential 5-HT_{1A} receptor agonists. Hence these compounds can be used for decreasing blood pressure and heart rate (**Fujio *et al.*, 2000**). A series of tripeptide arginine aldehydes containing a central 1,2-disubstituted cyclohexane were prepared and tested for thrombin inhibition activity. Substitution in aromatic side chain of the compounds was responsible for selective thrombin inhibition activity of screened compounds (**Harmat *et al.*, 1998**).

ANTIMICROBIAL PROPERTIES OF CYCLOHEXANE DIAMINE DERIVATIVES

A series of forty two adamantyl based cyclohexane diamine derivatives as shown in figure 2 were prepared and screened for antimicrobial properties against 29 strains of Methicillin-resistant *Staphylococcus aureus* (MRSA) and a virulent strain of *Mycobacterium tuberculosis*. For *Mycobacterium tuberculosis*, moderate to weak antibacterial activity was noted while strong to moderate antibacterial activity was observed against MRSA. The compounds showed bactericidal properties against *Mycobacterium tuberculosis* with rapid kill kinetics showing 4 log decline in viability of microorganism (**Beena *et al.*, 2014a**).

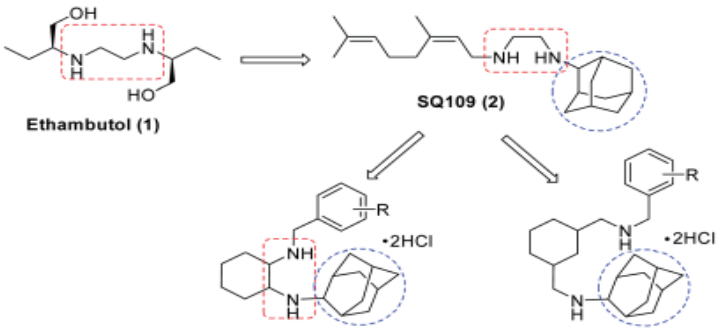

Figure 2 Design strategy for generation of Cyclohexane diamine scaffolds (**Beena *et al.*, 2014a**).

Cyclohexane-1,2-diamine derivatives with different substitution pattern on the benzene ring were synthesized as shown in figure 3. These 56 unsymmetrically substituted derivatives were tested for antibacterial properties against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Staphylococcus epidermidis*. By using 96-well micro titer plate, minimum inhibitory concentration of these derivatives was determined against these pathogens and tetracycline was used as standard drug for comparison. Compounds with halogen (chloro, bromo or fluoro groups) at para position of benzene ring were found to be better antimicrobial agents as compared to compounds in which halogen was present at meta position of benzene ring (**Kumar *et al.*, 2011**).

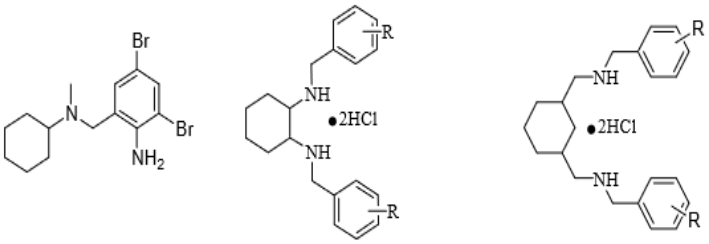

Figure 3 Prototype structures of cyclohexane diamine derivatives as antibacterial agents (**Kumar *et al.*, 2011**).

A series of 44 *N*,*N*-dibenzyl-cyclohexane-1,2-diamine derivatives were prepared as shown in figure 4. These derivatives were screened for antimicrobial properties against Gram-positive bacteria, Gram-negative bacteria and fungi like *Candida albicans*, *Candida glabrata* and *Geotrichum candidum*. Against these pathogens, minimum inhibitory concentrations were determined and tetracycline was used as standard drug for comparison. All the tested compounds showed variable antimicrobial activity but some compounds were found to be 37-6200 fold more active than reference compound against *Candida albicans*, *Candida glabrata* and *Geotrichum candidum*. None of compound was found to be toxic for mammalian red blood cells (**Sharma *et al.*, 2011**).

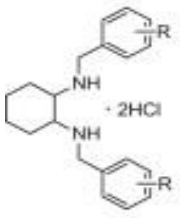

Figure 4 *N*,*N*-dibenzyl-cyclohexane-1,2-diamine derivative tested for antimicrobial properties (**Sharma *et al.*, 2011**).

A series of new cyclohexane-1,2-diamine derivatives were prepared by introducing long chain acetylenic groups into the aromatic ring. *In vitro* antituberculosis activity of 32 compounds was determined in liquid medium. Minimum inhibitory concentration values were determined using 96 well microtitre plates. Compounds with unsaturated chain at ortho/para position of benzene ring were found to be weakly active or partially active. Compounds having 5 and 6 carbon chain at para-position of the benzene ring were significantly active against *Mycobacterium tuberculosis*. It was concluded that with the increase in Carbon chain length, antimycobacterial activity of these derivatives decreases (**Beena *et al.*, 2014b**).

A library of novel 27 symmetrical trans-cyclohexane-1,4-diamine derivatives were synthesized and their antimycobacterial properties were evaluated. Compounds having substitutions at para position were found to have greater antimycobacterial potential. Propyl group at para position of benzene ring was responsible for maximum antimycobacterial activity (**Kumar *et al.*, 2014**).

ANTIMYCOBACTERIAL ACTIVITIES OF C-(3-AMINOMETHYL-CYCLOHEXYL)-METHYLAMINE DERIVATIVES

A series of C-(3-aminomethyl-cyclohexyl)-methylamine derivatives as shown in figure 5 were synthesized with the amino group at 1,3 position of the cyclohexyl ring. These twenty four new compounds were tested for their antibacterial properties against *Mycobacterium tuberculosis* and minimum inhibitory concentrations of these compounds were determined. Ethambutol was used as standard drug for comparison of antimycobacterial activity. The tested compounds showed variable activity against *Mycobacterium tuberculosis*. The compound with t-butyl at para position of the benzene ring exhibited maximum antimycobacterial activity even better than ethambutol. It was concluded from time kill kinetics study that *Mycobacterium tuberculosis* was rapidly killed in four days (**Kumar *et al.*, 2013**).

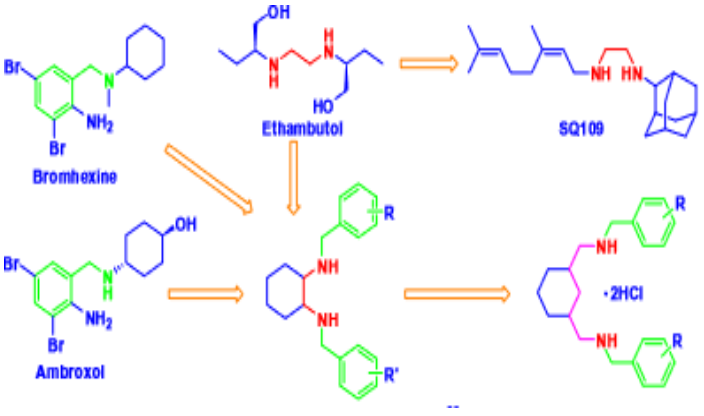

Figure 5 Design strategies for the synthesis of C-(3-aminomethyl-cyclohexyl)-methylamine derivatives (**Kumar *et al.*, 2013**).

A series of benzyl-[3-(benzyl aminomethyl) cyclohexyl methyl]-amine derivatives were synthesized with different substitution pattern on aromatic ring. Test compounds were dissolved in 5% dimethyl sulfoxide (DMSO) and *in vitro* antibacterial activity was measured. Using 96 well micro titer plates, minimum inhibitory concentration values were evaluated against *Staphylococcus aureus, Staphylococcus epidermidis, Pseudomonas aeruginosa* and *Escherichia coli*. Compounds with no substitution showed no antibacterial activity. Compounds with methyl group at different positions in the aromatic ring exhibited antibacterial properties against *Staphylococcus epidermidis* and *Pseudomonas aeruginosa*. Compounds with ethyl, propyl or butyl group at para position of phenyl ring showed remarkable antibacterial properties against all the tested microorganisms. Furthermore, these compounds were found to be non toxic and non hemolytic on mammalian red blood cells (**Kumar *et al.*, 2010**).

ANTIBACTERIAL PROPERTIES OF MISCELLANEOUS CYCLOHEXANE DERIVATIVES

Five chemical organic compounds: 3'-hydroxy-2',2',6'-trimethyl-3H-spiro[1-benzofuran-2,1'-cyclohexane]-5-carboxylic acid , methyl 3'-acetyloxy-2',2',6'-trimethyl-3Hspiro[1-benzofuran-2,1'-cyclohexane]-5-carboxylate, methyl 3'-isopentanoyloxy2',2',6'-trimethyl-3H-spiro[1-benzofuran-2,1'-cyclohexane]-5-carboxylate and methyl 3'-benzoyloxy-2',2',6'-trimethyl-3H-spiro[1-benzofuran-2,1'-cyclohexane]-5-carbox as shown in figure 6 were extracted from cuticular components of *Heliotropium filifolium*. These compounds were screened for antimicrobial activity against *Bacillus subtilis, Bacillus cereus, Micrococcus luteus* and *Staphylococcus aureus*. Minimum inhibitory concentration values of these organic compounds were determined by agar over lay method. These compounds were found to be active against Gram-positive bacteria, while no antimicrobial activity was seen against Gram-negative bacteria. Antibacterial activity of these compounds was comparable to that of antibiotics like chloramphenicol, ampicillin or tetracycline. Lipophilicity was an important factor which contributed in antibacterial activity of substances. The more the number of hydrophobic groups in the substance, more the antimicrobial activity was observed (**Urzúa *et al.*, 2008**).

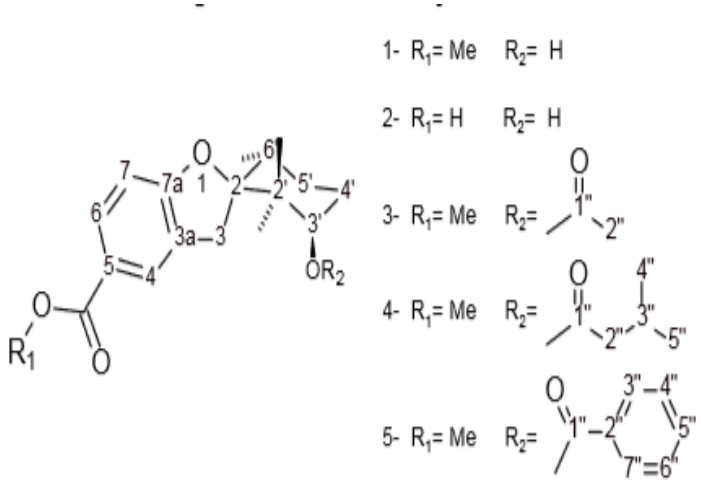

Figure 6 Structure of cyclohexane derivatives extracted from *Heliotropium filifolium* (**Urzúa *et al.*, 2008**).

Different cyclohexane triones were tested for their antimicrobial properties against *Staphylococcus aureus, Bacillus subtilis, Mycobacterium smegmatis, Streptococcus (Enterococcus) faecalis, Haemophilus influenzae, Klebsiella aerogenes, Salmonella typhimurium, Proteus mirabilis* and *Pseudomonas aeruginosa*. Minimum inhibitory concentrations were determined against these microbes using agar incorporation method. All the tested compounds were found to be active against Gram-positive bacteria, *Haemophilus influenzae* and *Mycobacterium smegmatis* but *Micrococcus, Staphylococcus, and Streptococcus species* were found to be more susceptible. Further it was observed that compounds with methyl, ethyl and allyl substituents showed better antimicrobial activity (**Lloyd *et al.*, 1988**).

A series of new (±)-4-(*N*,*N*-disubstituted-1-carbamoyl)-1*H*-spiro[benzo[*c*]pyran-3(4*H*),1′-cyclohexane]-1-ones were prepared and antimicrobial screening was performed against Gram-positive and Gram-negative bacteria. Minimum inhibitory concentration values were determined against all the test cultures. Tested compounds showed variable antibacterial activity against different bacteria. *Proteus vulgaris* and *Bacillus subtilis* were least sensitive while *Escherichia coli* was most sensitive microorganism to the tested compounds (**Bogdanov *et al.*, 2007**). A library of 10 novel 1,1 -Bis (4-aminophenyl) -4-Phenyl cyclohexane derivatives were prepared and screened for antibacterial activity. Disc diffusion method was used to determine antibacterial potential of these compounds against *Staphylococcus aureus, Staphylococcus pyogenes, Klebsiella pneumoniae* and *Escherichia coli*. Zone of growth inhibition for each compound was measured and DMSO was used as control. Derivatives showed variable antibacterial activity against all the test cultures but *Escherichia coli* was found to be most sensitive bacteria against these derivatives (**Nief *et al.*, 2017**). New Cyclohexane-1,3-dione ligands and their metal complexes were synthesized, characterized and evaluated for biological activities. These compounds were screened for antibacterial activity against *Escherichia coli, Enterococcus faecalis, Staphylococcus aureus and Salmonella typhimurium*. Zone of inhibition was measured for these derivatives against test cultures and ampicillin was used as reference drug. Mild antibacterial activity was observed for these compounds (**Turan *et al.*, 2015**).

CONCLUSION

Antimicrobial resistance is a serious global health problem for humans as well as animals. Emergence and increase in number of drug resistant, multi drug resistant, extensively drug resistant and pan drug resistant microorganisms is hazardous. Major obstacle in control of infectious diseases is the perpetual increasing antimicrobial resistance. Globally, numerous efforts are being made and new drug development studies are being conducted to overcome this problem. In this regard, cyclohexane and its functionally substituted compounds discussed in review are best available option for candidate antimicrobial drugs in the future. Subtle substitutions in the functional group of cyclohexane compounds have demonstrated the antimicrobial potential of these compounds. Further studies investigating the synthesis and antimicrobial activity of new functionally substituted cyclohexane derivatives should be conducted. It is need of time to expedite these efforts to overcome problem of antimicrobial resistance and to develop new antimicrobial drugs.

REFERENCES

AMIN, K.M., KAMEL, M.M., ANWAR, M.M., KHEDR, M., SYAM, Y.M. 2010. Synthesis, biological evaluation and molecular docking of novel series of spiro [(2H,3H) quinazoline-2,1′- cyclohexan]-4(1H)- one derivatives as anti-inflammatory and analgesic agents. *European Journal of Medicinal Chemistry*, 45(6), 2117-2131. https://dx.doi.org/10.1016/j.ejmech.2009.12.078

BAGDANOV, M.G., GOCHEVA, B.T., DIMITROVA, B.T., PALAMAREVA, M.D. 2007. Synthesis and Antimicrobial Activity of 4-Substituted (.+-.)-1H-Spiro[benzo[c]pyran-3(4H),1′-cyclohexane]-1-ones. *ChemInform*, 38(39), 1-7. https://dx.doi.org/10.1002/chin.200739122

BEENA, KUMAR, D., KUMBUKGOLLA, W., JAYAWEERA, S., BAILEY, M., ALLING, T., RAWAT, D.S. 2014a. Antibacterial activity of adamantyl substituted cyclohexane diamine derivatives against methicillin-resistant *Staphylococcus aureus* and *Mycobacterium tuberculosis*. *RSC Advances*, 4(23), 11962-11966. https://dx.doi.org/10.1039/c4ra00224e

BEENA, KUMARA, D., BAILEY, M.A., PARISH, T., RAWAT, D.S. 2014b. Synthesis and antituberculosis activity evaluation of cyclohexane-1,2-diamine derivatives. *Chemistry & Biology Interface*, 4(1), 23-36.

BIELAWSKI, K., LESZCZYŃSKA, K., KAŁUŻA, Z., BIELAWSKA, A., MICHALAK, O., DANILUK, T., STASZEWSKA-KRAJEWSKA, O., CZAJKOWSKA, A., PAWŁOWSKA, N., GORNOWICZ, A. 2017. Synthesis and antimicrobial activity of chiral quaternary N-spiro ammonium bromides with 3′,4′-dihydro-1′h-spiro[isoindoline-2,2′isoquinoline] skeleton. *Drug Design, Development and Therapy*, 11, 2015-2028. https://dx.doi.org/10.2147/DDDT.S133250

CAMPBELL, M.L. 2011. Cyclohexane. *Ullmann's Encyclopedia of Industrial Chemistry*. https://dx.doi.org/10.1002/14356007.a08_209.pub2

FLEFEL, E.M., SAYED, H.H., HASHEM, A.I., SHALABY, E.A., EL-SOFANY, W., ABDEL-MEGEID, F.M.E. 2014. Pharmacological evaluation of some novel synthesized compounds derived from spiro(cyclohexane-1,2′-thiazolidines). *Medicinal Chemistry Research*, 23(5), 2515-2527. https://dx.doi.org/10.1007/s00044-013-0830-y

FUJIO, M., TOGO, Y., TOMOZANE, H., KUROITA, T., MORIO, Y., KATAYAMA, J., MATSUMOTO, Y. 2000. *N*-{[1-(2-Phenylethyl)pyrrolidin-2-yl]methyl}cyclohexane-carboxamides as selective 5-HT_{1A} receptor agonists. *Bioorganic & Medicinal Chemistry Letters*, 10(5), 509-512. https://dx.doi.org/10.1016/S0960-894X(00)00030-5

HAO, H., CHENG, G., IQBAL, Z., AI, X., HUSSSAIN, H.I., HUANG, L., DAI, M., WANG, Y., LIU, Z., YUAN, Z. 2014. Benefits and risks of antimicrobial use in food-producing animals. *Frontiers in Microbiology*, 5, 1-11. https://doi.org/10.3389/fmicb.2014.00288

HARMAT, N.J.S., BUGNO, C.D., CRISCUOLI, M., GIORGI, R., LIPPI, A., MARTENLI, A., MONTI, S., SUBISSI, A., 1998. ,2-Disubstituted cyclohexane derived tripeptide aldehydes as novel selective thrombin inhibitors. *Bioorganic & Medicinal Chemistry Letters*, 8(10), 1249-1254. https://dx.doi.org/10.1016/S0960-894X(98)00200-5

HUSSAIN, H.I., IQBAL, Z., SALEEM, M.N., HUANG, D., SATTAR, A., HAO, H., YUAN, Z. 2017. Virulence and transcriptome profile of multidrug-resistant Escherichia coli from chicken. *Scientific Reports*, 7, *1-15.* https://dx.doi.org/10.1038/s41598-017-07798-1

IQBAL, Z., SALEEM, M.N., HUSSAIN, H.I., HUANG, L., HAO, H., YUAN, Z. 2016. Comparative virulence studies and transcriptome analysis of Staphylococcus aureus strains isolated from animals. *Scientific Reports*, 6, 1-12. https://dx.doi.org/10.1038/srep35442

KUMAR, D., JOSHI, S., ROHILLA, R.K., ROY, N., RAWAT, D.S. 2010. Synthesis and antibacterial activity of benzyl-[3-(benzyl aminomethyl) cyclohexyl methyl]-amine derivatives. *Bioorganic and Medicinal Chemistry Letters*, 20, 893-895. https://doi.org/10.1016/j.bmcl.2009.12.074

KUMAR, D., ROHILLA, R.K., ROY, N., RAWAT, D.S. 2011. Synthesis and Antibacterial Activity Evaluation of Unsymmetrically Substituted Cyclohexane-1,2-diamine Derivatives. *Chemistry & Biology Interface*, 1(2), 263-278.

Kumar, D., Raja, K.K., Bailey, M.A., Alling, T., Parishb, T., Rawat, D.S. 2013. Antimycobacterial activity evaluation, time-kill kinetic and 3D-QSAR study of C-(3-aminomethyl-cyclohexyl)-methylamine derivatives. *Bioorganic & Medicinal Chemistry Letters*, 23(5), 1365-1369. http://dx.doi.org/10.1016/j.bmcl.2012.12.083

KUMAR, N., KAPOOR, E., SINGH, R., KIDWAI, S., KUMBUKGOLLA, W., BHAGAT, S., RAWAT, D.S. 2014. ChemInform Abstract: Synthesis and Antibacterial/Antitubercular Activity Evaluation of Symmetrical trans-Cyclohexane-1,4-diamine Derivatives. *Chem Inform*, 45(12), 1-5. https://dx.doi.org/10.1002/chin.201412062

LALLO, S., LEE, S., DIBWE, D.F., TEZUKA, Y., MORITA, H., 2014. A new polyoxygenated cyclohexane and other constituents from *Kaempferia rotunda* and their cytotoxic activity. *Natural Product Research*, 28(20), 1754-1759. https://dx.doi.org/10.1080/14786419.2014.945175

LLOYD, W.J., BROADHURST, A.V., HALL, M.J., ANDREWS, K.J.M., BARBER, W.E., WONG-KAI-IN, P. 1988. Cyclohexane Triones, Novel Membrane-Active Antibacterial Agents. *Antimicrobial Agents and Chemotherapy*, 32(6), 814-818.

MODAK, B., TORRES, R., PIERRE, D.S., MICHELLE, KATHERINE, S., ADRIANA, A., RAÚL, C., PABLO, C. 2011. In vitro antiproliferative activity of 3 H-spiro [1-benzofuran-2,1'-cyclohexane] derivatives. *Boletín Latinoamericano y del Caribe de*, 10(3), 281-288.

NEIF, O.A., SALMAN, H.N., AHAMED, L.S., 2017. Synthesis, Characterization, Biological Activity Studies of Schiff Bases and 1,3-Oxazipene Derived from 1,1 -Bis (4-aminophenyl) -4-Phenyl Cyclohexane. *Journal of Science*, 58(4B), 1998-2011. https://dx.doi.org/10.24996/ ijs.2017.58.4B.2

SHARMA, M., JOSHI, P., KUMAR, N., JOSHI, S., .ROHILLA, R.K., ROY, N., RAWAT, D.S. 2011. Synthesis, antimicrobial activity and structure–activity relationship study of *N*,*N*-dibenzyl-cyclohexane-1,2-diamine derivatives. *European Journal of Medicinal Chemistry*, 46(2), 480-487. https://doi.org/10.1016/j.ejmech.2010.11.027

SONG, L., KANG, H., LIU, D., DAI, Z., HE, J. WANG, B., ZHAO, W., WANG, X., XI, W. 2015. Dimedone Derivative {2-[(4-Hydroxy-phenylamino)-methylene]-5,5-dimethyl-cyclohexane-1,3-dione} Plays an Important Role in Breast Cancer Treatment. *Tropical Journal of Pharmaceutical Research*, 14(9), 1719-1722. http://dx.doi.org/10.4314/tjpr.v14i9.25

SYAM, Y.M., ABD EL-KARIM, S.S., NASR, T., ELSEGINY, S.A., ANWAR, M.M., KAMEL, M.M., ALI, H.F. 2019. Design, Synthesis and Biological Evaluation of Spiro Cyclohexane-1,2- Quinazoline Derivatives as Potent Dipeptidyl Peptidase IV Inhibitors. *Mini-Reviews in Medicinal Chemistry*, 19(3), 250-269. http://dx.doi.org/10.2174/1389557517666170828121018

TSEMEUGNE, J., FONDJO, E.S., TAMOKOU, J., ROHAND, T., NGONGANG, A.D., KUIATE, J.R., SONDENGAM, B.L. 2018. Synthesis, Characterization, and Antimicrobial Activity of a Novel Trisazo Dye from 3-Amino-4H-thieno [3,4-c][1]benzopyran-4-one. *International Journal of Medicinal Chemistry*, 2018(2), 1-8. https://dx.doi.org/10.1155/2018/9197821

TURAN, N., KORKOCA, H., ADIGZEL, R., COLAK, N., BULDURUM, K. 2015. Synthesis, Structural Characterization and Biological Activity of Novel Cyclohexane-1,3-dione Ligands and Their Metal Complexes. *Molecules*, 20(5), 9309-9325. https://dx.doi.org/10.3390/molecules20059309

URZÚA, A., ECHEVERRÍA, J., REZENDE, M.C., WILKENS, M., 2008. Antibacterial Properties of 3 H-Spiro[1-benzofuran-2,1'cyclohexane] Derivatives from *Heliotropium filifolium*. *Molecules*, 13, 2385-2393. https://dx.doi.org/10.3390/molecules13102385

USEGLIO, M., CASTELLANO, P.M., OPERTO, M.A., TORRES, R., KAUFMAN, T.S. 2006. Synthesis of 3*H*-spiro[benzofuran-2,1′-cyclohexane] derivatives from naturally occurring filifolinol and their classical complement pathway inhibitory activity. *Bioorganic & Medicinal Chemistry Letters*, 16(19), 5097-5101. https://dx.doi.org/10.1016/j.bmcl.2006.07.029

VNUTSKIKH, Z.A., SHKLYAEV, Y.V., ODEGOVA, T.F., CHEKRYSHKIN, Y.S., TOLSTIKOV, A.G., EL'CHISHCHEVA, N.V., SYROPYATOV, B.Y. 2006. Synthesis and antimicrobial activity of mono-and biquaternized derivates of dipyridylethanes and dipyridylethylenes. *Pharmaceutical Chemistry Journal*, 40(4), 194-198. https://dx.doi.org/10.1007/s11094-006-0090-y