LIST OF PUBLICATIONS

1. **Jameel Ahmed S. Mulla, Mohammed Iqbal A. Khazi, Ashraf Y. Khan, Young-Dae Gong, Imtiyaz Ahmed M. Khazi.**
   *Drug Invention Today*, 2012, 4(8), 420-423

   Rational design of antibacterial thienopyrimidines by 2D-QSAR study.
   *J Drug Del Therap.* 2012, 2(2), 55-66

   *Int J Drug Des Disc.* 2012, 3(2), 784-797

   *Archiv der Pharmazie.* 2011, 344, 358-365

5. **JS Mulla, AY Khan, SI Panchamukhi, MA Khazi, MB Kalashetti, IM Khazi.**

   Formulation, Characterization and in vitro Evaluation of Novel Thienopyrimidines and Triazolothienopyrimidines Loaded Solid Lipid Nanoparticles.
   *Int J Res Ayu Pharm.* 2010, 1(1), 192-200

7. **JS Mulla, IM Khazi.**
   Influence of process variables on particle size of solid lipid nanoparticles.
   *Indian J Nov Drug Del.* 2009, 1(1), 47-49

8. **Jameel Ahmed S. Mulla, Mohammed Iqbal Khazi, Young-Dae Gong, Imtiyaz Ahmed M. Khazi.**
   *Med Chem Res (Communicated).*

   *Eur J Med Chem (Communicated).*
Design, Characterization and In vitro Evaluation of Imidazo[2,1-b][1,3,4]thiadiazole Derivative Loaded Solid Lipid Nanoparticles

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INTRODUCTION

Nanoparticles are one of the multiparticulate delivery systems and are prepared to obtain prolonged or controlled drug delivery, to improve bioavailability or stability and to target drug to specific sites [10]. Solid lipid nanoparticles (SLNs), introduced in 1991 are colloidial drug delivery systems with a mean size in the range between 50-1000 nm [12], with a matrix composed of lipids, dispersed in an aqueous medium and stabilized by surfactants. SLNs combines the advantages of traditional colloidal carriers such as liposomes, polymeric nanoparticles and emulsions, but avoids or minimizes the drawbacks associated with these. The use of lipids and/or excipients of physiological origin or accepted status are an exceptional advantage since it decreases the risk of acute and chronic toxicity [15]. Good tolerability depends firstly on the added surfactant and secondly on the lipid composition. In formulation of parenteral SLNs, surfactants that are generally recognized as safe (GRAS) by US Food and Drug Administration, should be preferred, e.g., polysorbates and poloxamers [15]. Moreover, SLNs are biodegradable and biocompatible, and able to incorporate both lipophilic and hydrophilic drugs in considerable amounts within the lipid matrix.

Tuberculosis (TB) is a chronic necrotizing bacterial infection with wide variety of manifestations caused by Mycobacterium tuberculosis, which has been a scourge of humanity for thousands of years and remains one of the prevalent health tribulations in the world [15]. Tuberculosis (TB) is contagious and airborne. It is a disease of poverty affecting mostly young adults in their most productive years. 95% of TB deaths are in the developing world. TB is among the three greatest causes of death among women aged 15-44, 320,000 women died from TB in 2010 [15]. The WHO estimated that 17% of the 9.2 million new cases of active TB had some form of drug-resistant TB (DR-TB); of these, 5.1% or 440000 individuals had multidrug-resistant tuberculosis [2,1-4][1,3,4]thiadiazole derivatives were first discovered in the early 1950s and, since then, the research work on this heterocyclic system has led to significant developments in their chemistry and biology. Recently, these derivatives have attracted the interest of researchers as antituberculosis agents. Some members of the imidazo[2,1-b][1,3,4]thiadiazoles family displayed good activity against M. tuberculosis H37Rv [16].

We have reported the synthesis of some novel Mannich bases of imidazo[2,1-b][1,3,4]thiadiazoles derivatives with Antitubercular Activity. Among the series the compound 2-(2-chlorophenoxymethyl)-6-(4-bromophenyl)-5,7a-dihydro-5-morpholino-t-ylmethylimidazo l2J-bJll,3,4jtluadiazole (ITD) has shown excellent inhibition against M. tuberculosis with minimum inhibitory concentration (MIC) 1.6 μg/mL [17].

In view of these reports and in continuation of our work on biologically active nitrogen and sulfur heterocycles, we now report herein the design, characterization and evaluation of ITD loaded solid lipid nanoparticles.

MATERIALS AND METHODS

Materials

ITD (Fig. 1) form our lab (Dr. IMK Group, Karnatak University, India), tristearin from Himedia (Mumbai, India), tween 80 by Merck Ltd (Mumbai, India), egg lecithin from Himedia (Mumbai, India) and Millipore water by Millipore (India) Pvt. Ltd (Bangalore, India). Other chemicals are of analytical grades.

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RATIONAL DESIGN OF ANTIBACTERIAL THIENOPYRIMIDINES BY 2D-QSAR STUDY

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ABSTRACT

QSAR studies were performed on a set of 43 analogs of thienopyrimidine using V-Life Molecular Design Suite (MDS 3.5) QSAR plus module by using Multiple Linear Regression (MLR) and Partial Least Squares (PLS) Regression methods against a gram positive (S.aureus) and a gram negative (E.coli) bacteria. MLR method has shown a very promising prediction results in both S.aureus and E.coli. QSAR model was generated by a training set of 34 molecules with correlation coefficient (r²) of 0.9849, 0.8719, significant cross validated correlation coefficient (q²) of 0.8881, 0.7811 and F test of 40.4301, 40.4768 respectively. In the selected descriptors, alignment independent descriptors such as T_C_C_7, T_N_0_3, T_2_N_1, T_N_O_1, T_Q_O_7 and T_N_Cl_4 were the most important descriptors in predicting antibacterial activity.

Keywords: Thienopyrimidine, Antibacterial, Multiple Linear Regression (MLR), Partial Least Squares (PLS) Regression

INTRODUCTION

Inappropriate and irrational use of antimicrobial medicines provides favourable conditions for resistant microorganisms to emerge, spread and persist. Infections caused by resistant microorganisms often fail to respond to conventional treatment, resulting in prolonged illness and greater risk of death. Antimicrobial resistance (AMR) is resistance of a microorganism to an antimicrobial medicine to which it was previously sensitive. Resistant organisms (they include bacteria, viruses and some parasites) are able to withstand attack by antimicrobial medicines, such as antibiotics, antivirals, and antimalarials, so that standard treatments become ineffective and infections persist and may spread to others. AMR is a consequence of the use, particularly the misuse, of antimicrobial medicines and develops when a microorganism mutates or acquires a resistant gene. AMR reduces the effectiveness of treatment because patients remain infectious for longer, thus potentially spreading resistant microorganisms to others. The achievements of modern medicine are put at risk by AMR. Without effective antimicrobials for care and prevention of infections, the success of treatments such as organ transplantation, cancer chemotherapy and major surgery would be compromised.

Quantitative structure activity relationship (QSAR) searches information relating chemical structure to biological and other activities by developing a QSAR model. Several molecular descriptors are used to quantify the structural feature of lead molecule. The purpose of using QSAR-Descriptors is to calculate the properties of molecules that serve as numerical descriptions or characterizations of molecules in other calculations such as diversity analysis or combinatorial library design. Using such an approach one could predict the activities of newly designed compounds before a decision is being made whether these compounds should be really synthesized and tested. Recently, Cao H et al., have reported the 3D QSAR study on a series of thienopyrimidines as highly selective inhibitors of three receptor tyrosine kinases (RTKs). Singh M et al., have reported a novel QSAR model of a series of thienopyrimidine derivatives for evaluating and predicting the inhibition activity of H1-receptor antagonists.

Thienopyrimidines and other fused pyrimidines continue to attract considerable attention of researchers in different countries because of their great practical usefulness, primarily due to a wide spectrum of their biological activities. Thienopyrimidines occupy a special position among these compounds. Along with some other pyrimidine systems containing an annealed five membered heteroaromatic ring, thienopyrimidines are structural analogs of biogenic purines and can be considered as potential nucleic acid antimetabolites. Consequently, thienopyrimidines have become a well sought-privileged class of compounds in drug discovery programs due to their wide variety of interesting biological activities observed for these compounds, such as antimicrobial, antitumor and anti-inflammatory activity.

In view of the above facts and scope a 2D-QSAR study is performed on structurally-related thienopyrimidine derivatives against a gram positive (S.aureus) and a gram...
2D-QSAR Study of Thienopyrimidine Derivatives: An Approach to Design Effective Anti-bacterial Agents

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ABSTRACT: QSAR studies were performed on a set of 35 analogs of thienopyrimidine using V-Life Molecular Design Suite (MDS 3.5) QSAR plus module by using Multiple Linear Regression (MLR) and Partial Least Squares (PLS) Regression methods against a gram positive (B.subtilis) and a gram negative (P.aeruginosa) bacteria. MLR and PLS methods have shown a very promising prediction results in B.subtilis and P.aeruginosa respectively. QSAR model was generated by a training set of 27 molecules with correlation coefficient ($r^2$) of 0.9886, 0.8671, significant cross validated correlation coefficient ($q^2$) of 0.9020, 0.7369 and F test of 37.8697, 50.0378 respectively. In the selected descriptors, alignment independent descriptors such as T_2_N_1, T_0_0_6, T_N_CI_7, T_N_0_3, T_T_N_3, T_C_0_1, T_N_N_7, T_N_N_3, T_N_0_6, T_2_T_1 and individual descriptor such as XlogP were the most important descriptors in predicting antibacterial activity.

KEYWORDS: Thienopyrimidine; antibacterial; multiple linear regression (MLR); partial least squares (PLS) regression.

Introduction

Antimicrobial resistance (AMR) is resistance of a microorganism to an antimicrobial medicine to which it was previously sensitive. Resistant organisms (they include bacteria, viruses and some parasites) are able to withstand attack by antimicrobial medicines, such as antibiotics, antivirals, and antimalarials, so that standard treatments become ineffective and infections persist and may spread to others. AMR is a consequence of the use, particularly the misuse, of antimicrobial medicines and develops when a microorganism mutates or acquires a resistance gene. Infections caused by resistant microorganisms often fail to respond to the standard treatment, resulting in prolonged illness and greater risk of death. Resistance to earlier generation antimalarial medicines such as chloroquine and sulfadoxine-pyrimethamine is widespread in most malaria-endemic countries. Inappropriate and irrational use of antimicrobial medicines provides favourable conditions for resistant microorganisms to emerge, spread and persist. When infections become resistant to first-line medicines, more expensive therapies must be used. The longer duration of illness and treatment, often in hospitals, increases health-care costs and the financial burden to families and societies. The emergence of AMR is a complex problem driven by many interconnected factors; single, isolated interventions have little impact. A global and national multi-sectoral response is urgently needed to combat the growing threat of AMR.1

Fused pyrimidines continue to attract considerable attention of researchers in different countries because of their great practical usefulness, primarily, due to a very wide spectrum of their biological activities. Thienopyrimidines occupy a special position among these compounds. Along with some other pyrimidine systems containing an annelated five membered heteroaromatic ring, thienopyrimidines are structural analogs of biogenic purines and can be considered as potential nucleic acid antimetabolites2. Consequently, thienopyrimidines3'4 have become a well sought-privileged class of compounds in drug discovery programs due to their wide variety of interesting biological activities observed for these compounds, such as antimicrobial5'9, anticancer10, antiviral11, antitumor12, and anti-inflammatory activity13.

Quantitative structure activity relationship (QSAR) searches information relating chemical structure to biological and other activities by developing a QSAR model. Several molecular descriptors are used to quantify the structural feature of lead molecule. The purpose of using QSAR-Descriptors is to calculate the properties of molecules that serve as numerical descriptions or characterizations of molecules in other calculations such as diversity analysis or combinatorial library design. Using such an approach one could predict the activities of newly designed compounds before a decision is being made whether these compounds should be really synthesized and tested. Recently, Cao H et al., have reported the 3D QSAR study on a series of thienopyrimidines as highly selective inhibitors of three receptor tyrosine kinases (RTKs)14. Singh M et al., have reported a novel QSAR model of a series of thienopyrimidine derivatives for evaluating and...
Full Paper

Benzothieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidines: Synthesis, Characterization, Antimicrobial Activity, and Incorporation into Solid Lipid Nanoparticles

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Fused triazolothienopyrimidines were prepared from the corresponding 2-amino-4,5,6,7-tetrahydrobenzo[thiophene-3-carbonitrile, These precursors were intern prepared by employing the Gewald's reaction. All the newly synthesized compounds were characterized by spectral and analytical data. Title compounds displayed promising antibacterial and antifungal activities. Compound 3h which exhibited good antimicrobial activity was incorporated into SLN and characterized for particle size, entrapment efficiency (EE%), scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and in-vitro release studies. It showed narrow particle size distribution with high entrapment efficiency. In-vitro release study of compound loaded SLNs in phosphate buffer of pH 7.4, exhibited a biphasic pattern with an initial burst and prolonged release over 24 h.

Keywords: Antimicrobial activity / Gewalt reaction / In-vitro release study / Solid lipid nanoparticles / Triazolothienopyrimidines

Introduction

Synthesis of novel fused heterocycles is an important task for heterocyclic chemists from various points of view for the development of compounds of pharmacological and industrial importance. Pyrimidine derivatives and heterocyclic annulated pyrimidines continue to attract great interest due to their wide variety of interesting biological activities observed for these compounds, such as antimicrobial [1, 2], anticancer [3], antiviral [4], antitumor [5], and anti-inflammatory activity [6]. Furthermore, many condensed heterocyclic systems, especially when linked to thiophene ring as thienopyrimidine plays an important role in the field of medicinal chemistry [7–9]. The rapid growth in the literature dealing with the synthesis and biological activities of the thienopyrimidine derivatives prompted us to undertake the synthesis of novel fused thienopyrimidine derivatives.

Solid lipid nanoparticles (SLNs) possess a combined advantage of overcoming the problems associated with other colloidal carriers. Hence it has attracted much attention in recent years, and is regarded as an alternative carrier system to traditional colloidal systems, such as emulsions, liposomes and polymeric micro particles and nanoparticles [10–12]. Proposed advantages include possibility of controlled drug release and drug targeting, increased drug stability, high drug payload, incorporation of lipophilic and hydrophilic drugs. Furthermore, it doesn’t involve biotoxicity of the carrier, and avoids the use of organic solvents and provides the scope of large scale production and sterilization [13]. Many pharmaceutical researchers have prepared SLNs as alternative colloidal therapeutic systems, utilizing different approaches like modified high shear homogenization and ultrasound techniques [10], emulsification-diffusion [14], solvent injection [15], solvent diffusion [16], micro emulsion method [17], and hot homogenization technique [18].

Recently we have reported the synthesis of 1,2,4-triazolo[1,5-e]pyrimidine derivatives [2]. Here, we report the synthesis, characterization, and the incorporation into solid lipid nanoparticles of isomeric 1,2,4-triazolo[4,3-c]pyrimidine derivatives.
A series of 5,6-disubstituted imidazo[2,1-b][1,3,4]thiadiazoles were synthesized. The structures of newly synthesized compounds were characterized by spectral and analytical data. All the title compounds were tested for their in-vitro antitubercular activity against Mycobacterium tuberculosis H37RV using Alamar-Blue susceptibility test, and the activity is expressed as the minimum inhibitory concentration (MIC) in pg/mL. Among the series, compounds 3a, 3c, 4a, 5c, and 6a displayed an encouraging antitubercular activity profile as compared to the reference drug, rifampicin.

**INTRODUCTION**

Tuberculosis (TB) is a chronic necrotizing bacterial infection with wide variety of manifestations caused by *Mycobacterium tuberculosis*, which has been a scourge of humanity for thousands of years and remains one of the prevalent health tribulations in the world [5]. Tuberculosis (TB) is contagious and airborne. It is a disease of poverty affecting mostly young adults in their most productive years. 95% of TB deaths are in the developing world. TB is among the three greatest causes of death among women aged 15-44. 320,000 women died from TB in 2010 [2]. The WHO estimated that 17% of the 9.2 million new cases of active TB had some form of drug-resistant TB (DR-TB); of these, 3.1% or 440,000 individuals had multidrug-resistant (MDR)-TB (defined as resistance to rifampicin and isoniazid) [6].

In developing countries where rates of both infection and active disease have always been high, the number of cases skyrocketed, so dramatic was the increase that the World Health Organization (WHO) declared TB a global health emergency in 1993, for the first time an infectious disease achieved that dubious distinction [46].

Furthermore, the co-infection with human immunodeficiency virus (HIV) has worsened the situation. The convergence of HIV and TB also poses difficult problems, not only because viral infection increase mortality from TB but also optimization of further difficulties such as the rifampicin induces CYP 450 enzymes along with inhibition of RNA polymerization [7-9]. Further, rifampicin is known to have major pharmacokinetic interactions with certain anti-HIV drugs [9,10].

Almost one in four deaths among people with HIV is due to TB. In 2010 350,000 people died of HIV-associated TB. It is also the most common presenting illness among people living with HIV, including those who are taking antiretroviral treatment. There were an estimated 1.1 million HIV positive new TB cases globally in 2010. Around 82% of patients live in sub-Saharan Africa. At least one-thrd of the 34 million people living with HIV worldwide are infected with TB. Persons co-infected with TB and HIV are 21-34 times more likely to develop active TB disease than persons without HIV [11]. These problems demand renewed efforts towards the development of novel chemical entities to control the mortality from TB.

Imidazo[2,1-b][1,3,4]thiadiazole derivatives were first discovered in the early 1950s and, since then, the research work on this heterocyclic system has led to significant
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ABSTRACT
Thienopyrimidines and triazolothienopyrimidines loaded solid lipid nanoparticles (SLNs) were produced by microemulsion method. All the formulations were subjected to particle size analysis, zeta potential, compound entrapment efficiency and in vitro release studies. The SLNs formed were in nano-size range with maximum entrapment efficiency. Formulation with 195 nm in particle size and 84.20% of compound entrapment was subjected to scanning electron microscopy (SEM) for surface morphology, differential scanning calorimetry (DSC) for thermal analysis and short term stability studies. SEM confirms that the SLNs are circular in shape. The compound release behavior from SLN suspension exhibited biphasic pattern with an initial burst and prolonged release over 24 h.

KEY WORDS: Thienopyrimidines; Triazolothienopyrimidines; Solid lipid nanoparticles (SLNs); Particle size analysis; Entrapment efficiency; In vitro release study

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Short Communication

Influence of process variables on particle size of solid lipid nanoparticles

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ABSTRACT

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Solid lipid nanoparticles (SLNs) were prepared via microemulsion method. SLNs formulation consists of lipid (glyceryl monostearate (GMS), stearic acid (SA) and trilaurin ("LN")), stabilizers (soy lecithin and tween 80) and water. Influence of type of lipid, concentration of lipid, individual and in combination of stabilizers and homogenizer speed on particle size were studied intensively. Particle sizes were determined by laser scattering using a Malvern Mastersizer 2000 particle size analyzer. A higher concentration of lipid was found to rapidly increase the size of nanoparticles. In contrast, an increase in stirring rate and concentration of stabilizer agent were found to reduce moderately the size of the nanoparticles.

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Solid lipid nanoparticles (SLNs), introduced in 1991, as an alternative carrier system to traditional colloidal carriers, such as emulsions, liposomes and polymeric microparticles and nanoparticles (1-3). It has been claimed that SLNs combine the advantages and avoid disadvantages of other colloidal carriers. Proposed advantages include, possibility of controlled drug release and drug targeting, increased drug stability, high drug payload, incorporation of lipophilic and hydrophilic drugs feasible, no bioxicity of the carrier, avoidance of organic solvents, no problems with respect to large scale production and sterilization (4). SLNs formulations for various application routes (parenteral, oral, dermal, ocular, pulmonary, and rectal) have been developed and thoroughly characterized in vitro and in vivo (5).

Many of pharmaceutical researchers have prepared SLNs as an alternative colloidal therapeutic systems, utilizing different approaches like modified high shear homogenization and ultrasound techniques (6), emulsification-diffusion method (6), solvent injection method (7), solvent diffusion method (8), microemulsion method (9) and hot homogenization technique (10).

The current work endeavors to design optimal SLNs via microemulsion method. Different process variables like type of lipid and their concentration, individual and combination of emulsifier/s and their concentration and homogenizers speed on size of nanoparticles have studied.

Glycerol monostearate and stearic acid are purchased from Loba chemie Pvt Ltd (Mumbai, India), trilaurin and soy lecithin are from Himedia Laboratories Pvt. Ltd. (Mumbai, India), tween 80 by Merck Ltd (Mumbai, India) and Millipore water by Millipore (India) Pvt. Ltd (Bangalore, India). Other chemicals are of analytical grades.

Trilaurin based SLNs containing Tmx citrate were prepared according to Gasco and group; developed and optimized a suitable method for the preparation of SLNs via microemulsion (11,12). Briefly, warm microemulsion is prepared by stirring, containing molten state of trilaurin, soy lecithin and tween 80. To the molten lipid solution, Tmx citrate was dispersed. The warm microemulsion is then dispersed carefully drop wise using high speed homogenizer (T25 basic Ultra Turrax IKA, USA) in excess cold water (1:50, 2-3 °C) using an specially developed thermostated syringe. The excess water is removed by lyophilization in order to increase the particle concentration.

The SLNs were prepared under different processing parameters to study the effect of a number of variables on their particle size. Processing parameters varied as follows; the type lipid used, concentration of lipid varied from 2.5 to 10.0%w/w, soy lecithin surfactant individual and in combination with tween 80 (1-5%w/w) and homogenizers speed (6,500-24,500 rpm).

The size analysis of nanoparticles was performed by laser scattering using a Malvern Mastersizer 2000 particle size analyzer (Malvern Instruments Ltd, Worcestershire, UK). The aqueous nanoparticulate dispersion was added to the sample dispersion unit containing a stirrer and then stirred to minimize the interparticle interactions, and the laser obscuration range was maintained between 10% and 20%. The analysis was performed 3 times, and the average values were taken.

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