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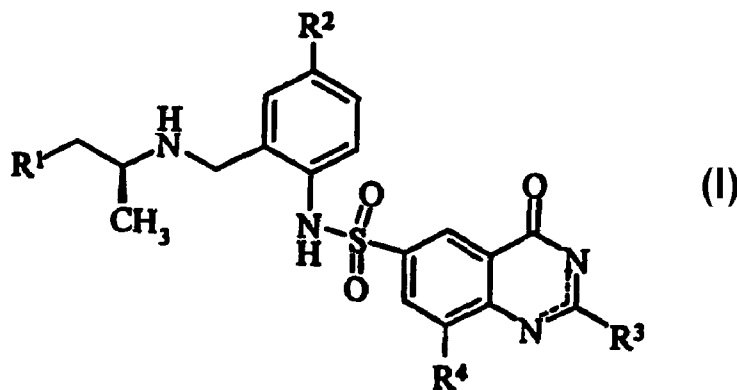
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(54) **Title:** HETEROCYCLIC SULFONAMIDES AS INHIBITORS OF TRANSFER RNA SYNTHETASE FOR USE AS ANTIBACTERIAL AGENTS



(57) **Abstract:** The present invention provides aromatic sulphonamides as tRNA synthetase inhibitors and process for their synthesis, pharmaceutical composition and method for treatment. Compounds disclosed can be used as antibacterial agents for the treatment or prevention of conditions caused by or contributed by aerobic and anaerobic Gram-positive pathogens, more particularly against bacterium, for example *Staphylococcus*, *Enterococci* and *Streptococci*. Compounds disclosed are used in particular for the treatment of skin and soft tissue infection, Formula (I).

HETEROCYCLIC SULFONAMIDES AS INHIBITORS OF TRANSFER RNA SYNTHETASE FOR USE AS ANTIBACTERIAL AGENTS

Field of the Invention

The present invention provides aromatic sulphonamides as tRNA synthetase inhibitors and process for their synthesis, pharmaceutical composition and method for treatment. Compounds disclosed can be used as antibacterial agents for the treatment or prevention of conditions caused by or contributed by aerobic and anaerobic Gram-positive pathogens, more particularly against bacterium, for example, *Staphylococcus*, *Enterococci* and *Streptococci*. Compounds disclosed are used in particular for the treatment of skin and soft tissue infection.

Background of the Invention

Resistant Gram-positive organisms have emerged over the past two decades and pose significant public health concerns because of the serious types of infections they cause, the vulnerable patient populations they infect, and their ability to spread within the hospital environment and from the hospital to the community. Clinically relevant organisms include methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, penicillin-resistant *Streptococcus*, macrolide resistant *Streptococcus*, and more recently, fluoroquinolone resistant *Staphylococcus* and *Streptococcus*. *Staphylococcus aureus*, the most virulent *Staphylococcus* species, is also the most prevalent pathogen isolated from hospitalized patients and the second most common from patients in outpatient settings. *S. aureus* causes a wide range of syndromes, from minor skin and soft tissue infection to life-threatening pneumonia and toxinoses such as toxic shock syndrome. *Staphylococcus aureus*, once largely susceptible to antibiotics, is now often resistant to multiple classes, including β -lactams, macrolides, aminoglycosides, and fluoroquinolones. Since methicillin-resistant *S. aureus* (MRSA) was first described in 1961 in England, it has become an important problem in hospitals around the world. The community-acquired MRSA (CA-MRSA) strains, first described in 1981 and responsible for recent outbreaks in diverse settings and groups, such as schools, prisons, athletic teams, the homeless, drug users, and the military, are usually involved in skin disease but have also been linked to lethal pneumonia and sepsis. To date CA-MRSA strains remain susceptible to a variety of other antibiotic classes.

MRSA, pathogen that causes both hospital and community-acquired infections thus represent a prime target in the current search for new antimicrobials.

Many new generation antibiotics of known classes were designed using structural modifications. This strategy is leading to cross resistance between the same class of antibiotics. Identifying new scaffold classes that hit new molecular targets is the obvious approach to maintain a pipeline of effective antibiotics. In the past years, only a few antibiotics representing new scaffold classes linezolid and daptomycin have been approved in the United States. This creates a compelling need for new classes of antibacterial agents with novel mechanisms of action. While genomics has offered the potential to identify novel druggable antibacterial targets, this has not yet proven successful. Bacterial phenylalanyl (Phe)-tRNA synthetase (FRS) is one such novel molecular target which is being explored extensively.

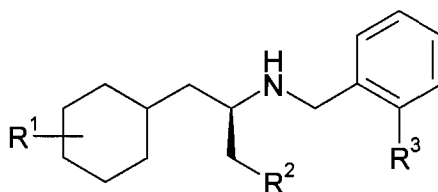
The amino acyl tRNA synthetases are essential enzymes found in all living organisms. These enzymes have emerged as an attractive target for the development of new antibiotics. Amino acyl tRNA synthetases charge tRNA molecules with their corresponding amino acid, an essential step in protein synthesis. There are 20 tRNA synthetases, most of which correspond to attractive broad-spectrum antibacterial targets. This is a validated target class in that pseudomonic acid A, also known as mupirocin, a natural product from *Pseudomonas fluorescens*, inhibits isoleucyl tRNA synthetase and is marketed as a topical antibiotic Bactroban. Other known natural products directed against amino acyl tRNA synthetases include borrelidin, furanomycin, granaticin, indolmycin, ochartoxin A, and cispentacin. None of them has been developed as antibiotic compounds. Phenylalanyl (Phe)-tRNA synthetase (FRS) is responsible for coupling the amino acid Phe to the corresponding Phe-specific tRNA (tRNA^{Phe}). The catalytic reaction proceeds in two steps and includes, first, the activation of Phe by adenylation, yielding Phe-AMP as an intermediate, and, subsequently, the transfer of the amino acid to the 3' end of the cognate tRNA^{Phe}. The charged Phe-tRNA^{Phe} is then able to interact with the elongation factor Tu and with the ribosomal A site to elongate the nascent protein chain.

FRS is the only class II enzyme which attaches the amino acid to the 2' OH group of the tRNA's 3' terminal ribose. The sequences of bacterial FRS are well conserved but

differ significantly from those of their eukaryotic counterparts. As FRS is indispensable for growth in all organisms, this suggests an interesting target for antibacterial therapy.

U.S. Patent Application Nos. 2004/0224981 and 2003/0013724 disclose tRNA synthetase inhibitors. WO 00/18772 discloses condensed imidazolidinone as tRNA synthetase inhibitors. U.S. Patent No. 5,191,093 discloses crystalline pseudomona-
5 process for its production and its use in human and veterinary medicines. U.S. Patent No. 4,916,155 discloses crystalline calcium pseudomona- or the hydrate thereof, and their use in human and veterinary medicine. WO 2006/083424 discloses radiolabeled compounds and uses thereof. U.S. Patent Application No. 2005/0187277 discloses substituted azole
10 derivatives, compositions, and methods of use. WO 2004/099127 discloses novel compounds as kinase inhibitors. U.S. Patent Application No. 2002/0091116 discloses novel compounds as inhibitors of factor X. WO 01/12611 discloses pyrimidine-2,4,6-trione metalloproteinase inhibitors. WO 99/32477 discloses ortho-anthranilamide derivatives as anti-coagulants. WO 96/40100 discloses arylsulfonylaminobenzene
15 derivatives and the use thereof as factor Xa inhibitors. WO 96/37204 discloses inhibitors of farnesyl-protein transferase.

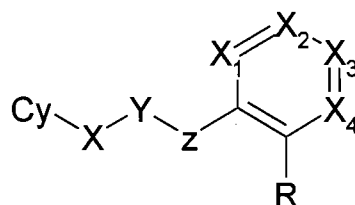
Compounds which inhibit tRNA synthetase are known, for example from WO 2007/017267, which relates to compounds of the general formula:



20 in which R¹ is H, trifluoromethyl or C₁-C₆ alkyl;
R² is H or C₁-C₆ alkyl; and
R³ is hydrogen or OR⁴, where R⁴ can be selected from a number of groups including alkyl, alkenyl and cyclic groups.

WO 2006/117762 also relates to compounds which are tRNA synthase inhibitors
25 and which have the general formula:

4

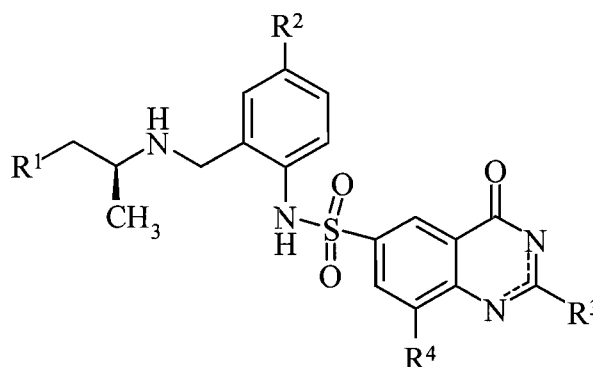


where Cy is cycloalkyl or heterocyclyl, X and Z are alkylene, Y is NH, N-alkyl or NOC(O)alkyl, X₁, X₂, X₃ and X₄ are CH or N and R is a number of groups including NHSO₂R₆.

5

Summary of the Invention

In one aspect of the present invention, there is provided compounds having structure of Formula I



Formula I

- 10 pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereoisomers, prodrugs, metabolites or *N*-oxide thereof,

wherein

----- is absent or represents a bond;

R¹ is cyclobutyl, cyclopentyl or cyclohexyl;

- 15 R² is hydrogen, fluorine or chlorine;

R³ is hydrogen, oxo or methyl;

R⁴ is fluorine or chlorine.

In another aspect, provided are compounds selected from:

- N*-[2-({[(1*S*)-2-Cyclohexyl-1-methylethyl]amino}methyl)phenyl]-8-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-sulfonamide (Compound No. 1);
- N*-[2-({[(2*S*)-1-Cyclohexylpropan-2-yl]amino}methyl)-4-fluorophenyl]-8-fluoro-4-oxo-3,4-dihydroquinazoline-6-sulfonamide (Compound No. 2);
- 5 *N*-[2-({[(2*S*)-1-Cyclobutylpropan-2-yl]amino}methyl)phenyl]-8-fluoro-2-methyl-4-oxo-3,4-dihydroquinazoline-6-sulfonamide (Compound No. 3);
- N*-[2-({[(2*S*)-1-Cyclopentylpropan-2-yl]amino}methyl)-4-fluorophenyl]-8-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-sulfonamide (Compound No. 4);
- 10 *N*-[2-({[(2*S*)-1-Cyclopentylpropan-2-yl]amino}methyl)-4-fluorophenyl]-8-fluoro-4-oxo-3,4-dihydroquinazoline-6-sulfonamide (Compound No. 5);
- N*-[2-({[(2*S*)-1-Cyclohexylpropan-2-yl]amino}methyl)-4-fluorophenyl]-8-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-sulfonamide (Compound No. 6);
- N*-[2-({[(1*S*)-2-Cyclopentyl-1-methylethyl]amino}methyl)phenyl]-8-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-sulfonamide (Compound No. 7);
- 15 *N*-[2-({[(2*S*)-1-Cyclohexylpropan-2-yl]amino}methyl)phenyl]-8-fluoro-4-oxo-3,4-dihydroquinazoline-6-sulfonamide (Compound No. 8);
- N*-[2-({[(2*S*)-1-Cyclobutylpropan-2-yl]amino}methyl)phenyl]-8-fluoro-4-oxo-3,4-dihydroquinazoline-6-sulfonamide (Compound No. 9);
- 20 *N*-[4-Chloro-2-({[(2*S*)-1-cyclohexylpropan-2-yl]amino}methyl)phenyl]-8-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-sulfonamide (Compound No. 10),
- pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereoisomers, prodrugs, metabolites or *N*-oxide thereof

The compounds of the present invention are useful in the treatment of bacterial infections, including infections by bacteria which are resistant to conventional antibiotic

25 drugs.

In addition, unlike the compounds exemplified in WO 2006/117762, preferred compounds of the present invention are effective for treatment of skin and soft tissue mixed infections caused by both aerobic and anaerobic gram positive pathogens.

In particular, suitable compounds of the present invention are, bicyclic

30 heterocycle-quinazoline having a substitution of R⁴, wherein R⁴ is fluorine. It was originally thought that it was advantageous to have a heterocyclic-sulphonamide as R in WO 2006/117762; and, almost all the exemplified compounds of WO 2006/117762 have heterocyclic-sulphonamide as R.

Surprisingly, however, the compounds with bicyclic heterocycle, quinazoline

35 having a substitution of R⁴ have greatly improved activity against *S. aureus* as well as

similar or better potency against *Streptococci* (*S. pyogenes*, Viridans group β -haemolytic group B) and *Enterococci* compared with compounds in which R⁴ is absent or have a different heterocycle as disclosed in WO 2006/117762.

5 The compounds of the present invention are tRNA synthetase inhibitors and therefore have antibacterial activity. Therefore, in a further aspect of the present invention there is provided a compound of general Formula (I) for use in medicine, particularly as an antibacterial agent.

10 There is also provided a method for the treatment of a bacterial condition, the method comprising administering to a subject in need of such treatment an effective amount of a compound of general Formula (I).

The invention further provides the use of a compound of general Formula (I) in the preparation of an agent for the treatment of a bacterial condition.

Typically, the compounds of general Formula (I) may be used to treat bacteria, for example *staphylococci*, *streptococci* and *enterococci*.

15 The compounds of the invention are especially useful in the treatment of methicillin-sensitive *Staphylococcus aureus* (MSSA), methicillin resistant *Staphylococcus aureus* (MRSA), *Streptococcus agalactiae* and *Streptococcus viridans* (Group B *streptococci*), *Streptococcus pyogenes* (group A *streptococcus*), Vancomycin resistant *enterococci* (VRE) including *E. faecalis*, *E. faecium* and *S. pneumoniae*, particularly when
20 R⁴ is F.

The compounds of general Formula I may be provided as a pharmaceutical composition and therefore in a further aspect of the invention there is provided a pharmaceutical composition comprising a compound of general Formula (I) together with a pharmaceutically acceptable excipient.

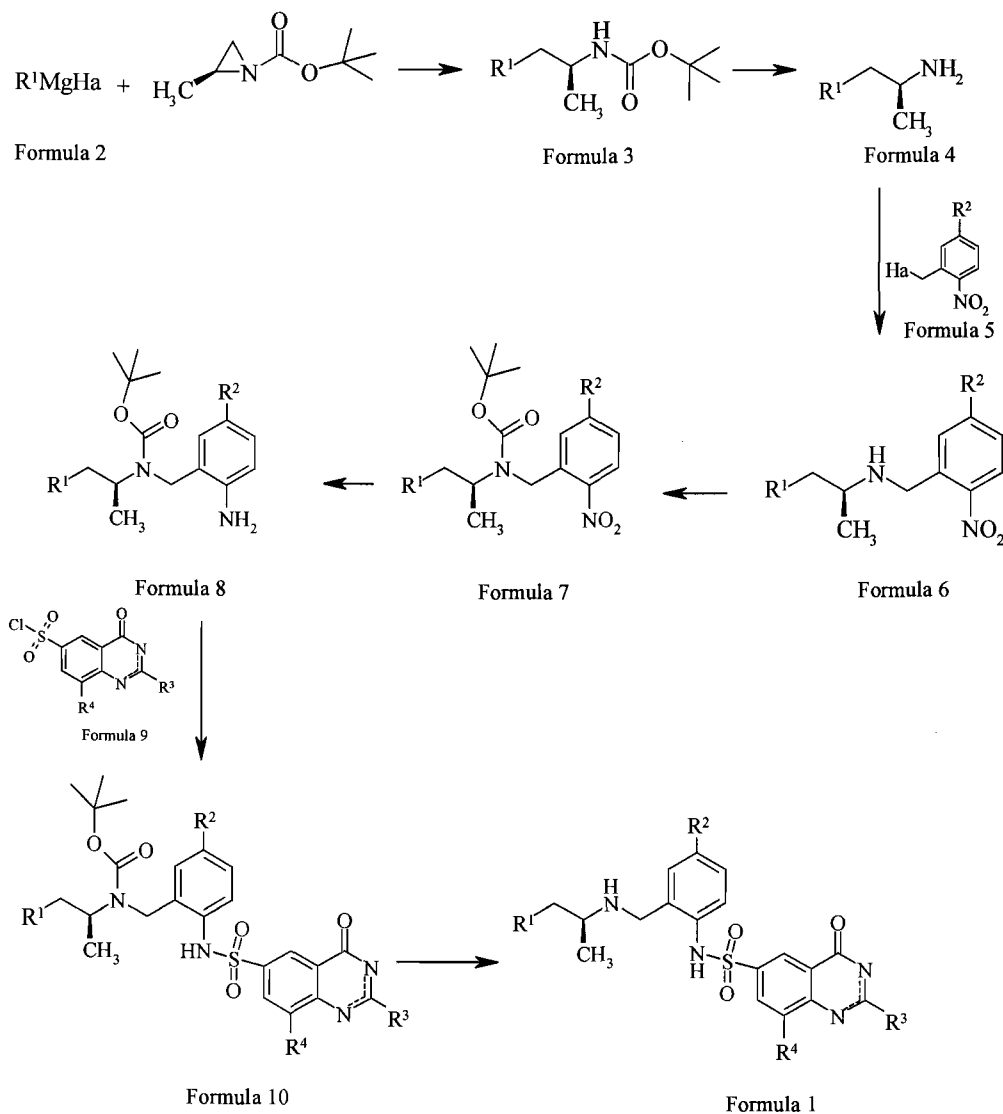
25 The composition may be adapted for administration by any suitable route, for example oral, nasal, buccal, transdermal or rectal administration or a parenteral route such as intravenous, intramuscular or intraperitoneal administration

In another aspect, there are provided processes for the preparation of compounds disclosed.

Detailed Description of the Invention

The compounds disclosed herein may be prepared by techniques well known in the art and familiar to the person having ordinary skills in the art. In addition, compounds of the present invention may be prepared as depicted in Scheme I.

5 Scheme I



The compound of Formula 1 can be prepared according to, for example, Scheme I. The reaction of a compound of Formula 2 (wherein Ha is halogen, *e.g.*, F, Cl, Br or I and R¹ is same as defined earlier) with *tert*-butyl (2*S*)-2-methylaziridine-1-carboxylate to give a compound of Formula 3, which upon deprotection gives a compound of Formula 4. The compound of Formula 4 upon alkylation with a compound of Formula 5 (wherein Ha and

R^2 is same as defined earlier) gives a compound of Formula 6 which is *N*-protected to give a compound of Formula 7. The compound of Formula 7 on reduction gives a compound of Formula 8 which upon coupling with a compound of Formula 9 gives a compound of Formula 10. The compound of Formula 10 upon deprotection gives a compound of Formula 1.

The reaction of a compound of Formula 2 with *tert*-butyl(2*S*)-2-methylaziridine-1-carboxylate to give a compound of Formula 3 can be carried out in one or more solvents, for example, ethers (diethyl ether, dioxane, or tetrahydrofuran), chlorinated solvents (dichloromethane, chloroform or carbon tetrachloride), or mixtures thereof.

The deprotection of a compound of Formula 3 to give a compound of Formula 4 can be carried in the presence of one or more mineral acids, for example, hydrochloric, hydrobromic, hydroiodic acid or in the presence of one or more organic acids, for example, trifluoroacetic acid, *p*-toluenesulphonic acid or camphor sulphonic acid in one or more solvents, for example, polar protic solvents (water, methanol, ethanol, propanol, isopropanol or *tert*-butanol), polar aprotic solvent (diethyl ether, acetonitrile or dioxane), or chlorinated solvent (dichloromethane, chloroform or carbon tetrachloride).

The reaction of a compound of Formula 4 with a compound of Formula 5 to give a compound of Formula 6 can be carried out in the presence of a base, for example, cesium carbonate, lithium carbonate, barium carbonate, magnesium carbonate, sodium carbonate, potassium carbonate, sodium bicarbonate in one or more solvents, for example, diethyl ether, acetonitrile or dioxane.

The *N*-protection of a compound of Formula 6 to give a compound of Formula 7 can be carried out with di-*tert*-butyl dicarbonate, in the presence of one or more organic solvents, for example, triethylamine, trimethylamine, *N*-ethyldiisopropylamine, 2,6-lutidine, pyridine or *tert*-butylamine, DMAP in one or more chlorinated solvents (dichloromethane, dichloroethane, chloroform, or tetrachloromethane), or dioxane.

The reduction of a compound of Formula 7 to give a compound of Formula 8 can be carried out in the presence of a reducing agent, for example, lithium aluminum hydride, Pd/C, Raney Nickel in hydrazine hydrate or zinc, tin or iron in the presence of hydrochloric acid.

The coupling of a compound of Formula 8 with a compound of Formula 9 to give a compound of Formula 10 can be carried out in one or more organic bases, for example, pyridine, triethylamine, trimethylamine, tributylamine, *N*-ethyldiisopropylamine, 4-*N,N*-dimethylaminopyridine, *N*-methylmorpholine or 2,6-lutidine.

- 5 The deprotection of a compound of Formula 10 to give a compound of Formula 1 can be carried out under similar conditions as that of deprotection of a compound of Formula 3 to give a compound of Formula 4.

Experimental Examples

Microbiological activity

- 10 Microbroth minimum inhibitory concentration (MIC) was performed using NCCLS method in Cation adjusted Muller Hinton broth for facultative cultures (*S. aureus*, *Enterococcus*) and Cation adjusted Mueller Hinton broth +2.5% lysed horse blood for *S. pneumonia*. Overnight grown cultures were adjusted to 0.5 McFarland using normal saline and diluted 100 times. 1mg/mL concentration of stock solution of drug in
- 15 DMSO/distilled water/solvent given in NCCLS manual was prepared. NCCLS double dilutions were done to get the required concentration range of the drugs in the 96 well microtiter plates using the respective media. About 100µl of broth containing antibiotic to get approximately $3-7 \times 10^5$ CFU/mL was prepared. The plates were incubated at 37°C for about 18 hours to 24 hours. The concentration of drug at which there was complete
- 20 disappearance of growth was considered as MIC.

Table 1

Compound	IC50 (nM)		MIC range (µg/ml)					
	S.aur	S.pn	S. aureus	S. pneumoniae	Streptococci			Enterococci
					S. pyogenes	Viridans group	β-haemolytic group B	
Compound No. 6	<5	<5	0.25-0.5	0.125-0.25	0.06-0.5	0.25-0.5	0.125-0.25	0.25-0.5
Compound No. 2	<5	<5	0.25-0.5	0.25-0.5	0.125-0.5	0.25-0.5	0.125-0.5	
Compound No. 8	14	68	0.125-0.5	0.125-0.25	0.25-0.5	0.125-0.25	0.125-0.5	0.25-0.5
Compound No. 9	15	37	0.25-2	0.125-0.5	0.5-2	0.25-1	0.5-1	2-4
Compound No. 10	<5	9	0.25-0.5	0.25-1	0.5-2	0.5-1	1-2	4-8
Compound No. 3	<5	<5	0.25-1	0.125-0.5	0.25-1	0.25-0.5	0.5-1	1-2
Compound No. 593 of WO 2006/117762	<5	<5	2-8	0.25-1	0.5-4	1-2	1-2	4-8

Compound	IC50 (nM)		MIC range (µg/ml)					Enterococci
	S.aur	S.pn	S. aureus	S. pneumoniae	Streptococci			
					S. pyogenes	Viridans group	β-haemolytic group B	
Compound No. 592 of WO 2006/117762	<5	<5	4-16	0.25-1	1-4	1-2	1-2	8->16
Compound No. 470 of WO 2006/117762	72	132	>16	>16	>16	>16	>16	>16
Compound No. 463 of WO 2006/117762	60	23	2-16	0.25-0.5	16- >16	16->16	16->16	>16
Compound No. 1	<5	<5	0.125-1	0.06-0.125	0.125-0.25	0.125-0.25	0.125-0.25	0.125-0.5
Compound No. 7	<5	<5	0.25-0.5	0.06-0.125	0.125-0.25	0.125-0.25	0.125-0.25	0.5-1

Compound	IC50 (nM)		MIC range (µg/ml)					Enterococci
	<i>S.aur</i>	<i>S.pn</i>	<i>S. aureus</i>	<i>S. pneumoniae</i>	Streptococci			
					<i>S. pyogenes</i>	Viridans group	β-haemolytic group B	
Compound No. 4	<5	<5	0.5-1	0.125-0.25	0.06-0.5	0.125-0.25	0.125-0.25	1-2
Compound No. 5	<5	<5	0.25-0.5	0.125-0.25	0.25-0.5	0.125-0.25	0.125-0.25	0.5-1

s it is apparent from the experimental results given in Table 1, compounds of the invention have better potency to the closely related compounds of WO 2006/117762 in *S. aureus*, *S. pyogenes*, Group B *streptococci*, and *Enterococci*. Such an effect as above caused by the introduction of Fluorine at R4 position is quite unexpected. Therefore, compounds of the present invention are of value for treatment of skin and soft tissue mixed infections caused by gram positive pathogens

Example

Various solvents used were dried using drying reagents according to procedures described in the literature. Wherever room temperature or ambient temperature is used, it is 25°C to 30°C.

Synthesis of *tert*-butyl (2*S*)-2-methylaziridine-1-carboxylate

Step a: Synthesis of *tert*-butyl[(2*S*)-1-hydroxypropan-2-yl]carbamate

To a solution of L-alaninol (1.0 equiv.) in dichloromethane (10 times) was added di-*tert*-butyl dicarbonate (1.1 equiv.) slowly at about 0°C to 5°C. The reaction mixture was allowed to stir for about 3 hours at ambient temperature. After completion, the reaction mixture was diluted with dichloromethane and washed with water, brine, dried over anhydrous sodium sulphate and evaporated in *vacuo* to get the desired product as a white solid. Yield: 75%

Step b: Synthesis of *tert*-butyl (2*S*)-2-methylaziridine-1-carboxylate

To a solution of compound obtained from step a (1.0 equiv.) in ether (20-30 ml) was added tosyl chloride (1.3 equiv.). The reaction mixture was stirred for about 15 minutes and then cooled to 0°C. To this solution was added crushed potassium hydroxide (8 equiv.) portion-wise and the mixture was stirred for an additional 15 minutes. The reaction mixture was then refluxed at about 40°C to 45°C for about 3 hours, diluted with water, and extracted with ether. The organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure to get desired compound. Yield: 67%

Synthesis of 2-(bromomethyl)-4-fluoro-1-nitrobenzene

To a solution of 5-fluoro-2-nitrotoluene (14 g, 1 equiv.) in carbon tetrachloride (140 ml) was added *N*-bromosuccinamide (20.01 g, 1.25 equiv.), and the reaction mixture

was heated to 50°C. To this reaction mixture was added benzoyl peroxide (26.78 g, 0.9 equiv.) portion-wise within 5 to 10 minutes and refluxed at 80°C for 4 to 5 hours. After completion, the reaction mixture was diluted with dichloromethane and washed with water. The organic layer was separated, dried over anhydrous sodium sulphate and evaporated under vacuum to get the crude product, which was purified on a silica gel column (60-120 mesh) using 10% dichloromethane:hexane solvent system. The solvent was evaporated off to afford the desired compound. Yield: 7.2 g

Synthesis of 2-(bromomethyl)-4-chloro-1-nitrobenzene

To a solution of 5-chloro-2-nitro benzyl alcohol (15 g) in dichloromethane (100 ml) was added carbon tetrabromide (39.7 g). The reaction mixture was allowed to cool to 0°C and triphenyl phosphine (41.9 g) dissolved in dichloromethane (100 ml) was added drop-wise and stirred at room temperature for one hour. After complete consumption of starting material, solvent was evaporated under reduced pressure and crude product obtained was purified by column chromatography (100-200 mesh) using 5% ethyl acetate: hexane as eluent to afford the desired compound. Yield: 12 g.

Synthesis of 8-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazoline

3-Fluoro anthranilic acid (3 g) was mixed with urea (6.97 g) in a two-neck round bottom flask fitted with an open condenser and heated up to 190°C to 200°C with stirring for 2 hours. During heating, the solid first melted and then started solidifying. After all the liquid became solid, heating was removed and the reaction mixture was allowed to come to room temperature. To this reaction mixture, water was added and stirred at same temperature for one hour. The solid so obtained was filtered out, washed with diethyl ether and dried over anhydrous phosphorous pentoxide. Yield: 3.0 g

Synthesis of 8-fluoro-2-methylquinazolin-4(3H)-one

Step a: Preparation of 8-fluoro-2-methylquinazolin-4(3H)-one

To an ice-cooled solution of 3-fluoroanthranilic acid (50 g) in dichloromethane (250 ml) were added triethylamine (89.5 ml) and acetic anhydride (60.5 ml) and stirred at ambient temperature for 4 hours to 6 hours. After completion of reaction, solvent was evaporated under vacuum to yield a brown colored crude compound. The crude compound was cooled to about 0°C and aqueous ammonia (500 ml) was added to it

portion wise. The reaction mixture was stirred at 60°C for overnight. After completion, the reaction mixture was cooled to 10°C and solid so formed was filtered. The solid was washed with water and dried under vacuum to afford a desired compound. Yield: 40 g.

Step b: Preparation of 8-fluoro-2-methyl-6-nitroquinazolin-4(3H)-one

5 To a solution of compound obtained from Step a (5 g) was added slowly sulphuric acid (50 ml, 1:10 w/v) at room temperature and stirred at room temperature for 30 minutes. After complete dissolution of the starting material, potassium nitrate (4.24 g) was added and reaction mixture was stirred for six hours. After completion, reaction mixture was cooled to 0°C and pH was adjusted to about 2-3 by adding sodium hydroxide
10 solution (10N, ~300 ml) while maintaining temperature to about 0°C. A bright yellow precipitate was obtained which was filtered, washed with water and dried under vacuum to get desired compound. Yield: 4g.

Step c. Preparation of 6-amino-8-fluoro-2-methylquinazolin-4(3H)-one

To a solution of compound obtained from Step b (1 g) in methanol (500 ml) was
15 added Raney Nickel (0.5 g) and cooled to 0°C. To this solution was added hydrazine hydrate (5 ml) drop wise and again stirred at room temperature for about 6 hours. After completion, the reaction mixture was filtered through celite bed and washed with methanol. The organic layer was concentrated under vacuum to get a yellowish solid mass. The solid mass was stirred with water and the insoluble product so obtained was
20 filtered and washed with water and dried under vacuum to afford desired compound. Yield: 0.7 g.

Synthesis of 8-fluoroquinazolin-4(3H)-one

3-Fluoro anthranilic acid (20 g) was mixed with formamide (10ml) and fused at 180°C for 2 hours to 3 hours. After completion, the reaction mixture was allowed to cool
25 to 30°C and ethanol was added to remove excess of formamide. The solid so obtained was filtered out, washed with hexane and dried under vacuum to get the desired compound. Yield: 18 g

Synthesis of 8-Fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-sulfonyl chloride

8-Fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazoline (6 g) was added portion wise in chlorosulphonic acid (22.8 ml) at 0°C and stirred at same temperature for 15 minutes. After 15 minutes, it was allowed to cool to room temperature and thionyl chloride (12.5 ml) was added. The reaction mixture was heated at 90°C for 3 hours to 4 hours. After completion, the reaction mixture was poured into ice water and the solid so obtained was filtered, washed with water, ether and dried over P₂O₅ under *vacuum*. Yield: 7.7g

Synthesis of 8-fluoro-4-oxo-3,4-dihydroquinazoline-6-sulfonyl chloride

In a three-necked round bottom flask fitted with stoppers and a guard tube was added dry sodium chloride (15 g) and cooled to 0°C. To this cooled solution was added chlorosulphonic acid slowly (86 ml) which was followed by portion wise addition of 8-fluoroquinazolin-4(3*H*)-one (15 g) and stirred for about 10 minutes. The reaction mixture was allowed to reflux at about 180°C for about 24 hours. After complete conversion of the starting material, the reaction mixture was allowed to cool to room temperature and poured into crushed ice. The solid precipitating out was separated and dried to get the desired compound. Yield: 11.27g

8-Fluoro-2-methyl-4-oxo-3,4-dihydroquinazoline-6-sulfonyl chloride

To a solution of concentrated hydrochloric acid (2 ml) and glacial acetic acid (0.62 ml) was added 6-amino-8-fluoro-2-methylquinazolin-4(3*H*)-one (1g) at room temperature. The reaction mixture was vigorously stirred at -5°C to -10°C and a solution of sodium nitrite (0.46 g in 0.67 ml of water) was added dropwise. The addition should be at such a rate that temperature shouldn't exceed -5°C. The resulting diazotized mixture was stirred for about 45 minutes at 0°C to -5°C. When diazotization was complete, glacial acetic acid (6.25 ml) was taken in round bottom flask and sulfur dioxide gas was bubbled into it for about 30 minutes. To this reaction mixture, CuCl (0.15 g) was added while bubbling of sulphur dioxide was continued for about 30 minutes (until solution becomes blue-green). The reaction mixture was allowed to cool to 0°C and diazotized reaction mixture was added in portion wise over about 30 minutes. After complete addition of the diazotized salt mixture, it was stirred at room temperature for 15 minutes to 20 minutes and quenched with ice-water and stirred for 20 minutes to 30 minutes resulting in separation of yellowish

solid. The solid was filtered, washed with water and dried under vacuum to get title compound. Yield: 0.74 g.

Example 1: Synthesis of *N*-[2-({[(2*S*)-1-Cyclobutylpropan-2-yl]Amino}Methyl)Phenyl]-8-Fluoro-2-Methyl-4-Oxo-3,4-Dihydroquinazoline-6-Sulfonamide (Compound No. 3)

5 Step a: Synthesis of *tert*-butyl[(2*S*)-1-cyclobutylpropan-2-yl]carbamate

In a two-neck round bottom flask was added Mg (9.16 g) and a crystal of iodine in dry tetrahydrofuran (100-125 ml). To this reaction mixture was added cyclobutyl bromide (5 g out of 51.5 g) through addition funnel under argon atmosphere until the reaction initiates (violet color disappears). The remaining cyclobutyl bromide was added drop wise
10 in one hour. After complete addition, the reaction mixture was allowed to stir at room temperature for one hour. After one hour, the reaction mixture was diluted with dry tetrahydrofuran (1.2 l) and cooled to -40°C. CuBr-Me₂S complex (5.21 g) was added to the reaction mixture and stirred at same temperature for about 20 minutes. To this solution *tert*-butyl (2*S*)-2-methylaziridine-1-carboxylate (20 g) dissolved in
15 tetrahydrofuran was added drop wise at -40°C and stirred for 2 hours. After 2 hours, the reaction mixture was allowed to warm to room temperature. After completion of reaction, reaction mixture was cooled to -20°C and quenched by adding saturated ammonium chloride solution. The reaction mixture was extracted with ethyl acetate, dried and evaporated under reduced pressure to get a crude product. The crude product so obtained
20 was purified by column chromatography eluting with 5% ethyl acetate:hexane to afford the desired compound. Yield: 40 g

Electron Impact Ionization Mass Spectrometry (EIMS) (m/z): 214.31

Step b: Synthesis of (2*S*)-1-cyclobutylpropan-2-amine

To an ice-cooled solution of compound obtained from Step a (50 g) in
25 dichloromethane (200 ml) was added trifluoroacetic acid (60 ml) and stirred for 3 hours. After completion, the solvent was evaporated and crude product so obtained was dissolved in ethyl acetate (200 ml) and cooled to 0°C. To this cooled solution was added sodium hydroxide (5N) and stirred at room temperature for 1 hour to 2 hours. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined
30 organic layer was stirred with 5N sodium hydroxide solution (250 ml) for 1 hour to 2

hours. The organic layer was separated and dried over anhydrous sodium sulphate and evaporated under vacuum to get a brown oily compound. Yield: 20 g.

EIMS (m/z): 114.06

Step c: Synthesis of (2*S*)-1-cyclobutyl-*N*-(2-nitrobenzyl)propan-2-amine

5 To a solution of compound obtained from Step b (10 g) in acetonitrile (400 ml) was added cesium carbonate (85 g), and after 10 minutes was added 2-nitro benzyl bromide (15.29 g) in acetonitrile (20 ml) and stirred for 6 hours. After completion of the reaction, the solvent was evaporated and the residue so obtained was quenched with water. The reaction mixture was extracted with ethyl acetate. The combined organic layer was
10 dried over anhydrous sodium sulphate and evaporated under vacuum to yield a brown colored oily mass. The crude product was purified by column chromatography to afford the desired product. Yield: 13 g

EIMS (m/z): 249.04

**Step d: Synthesis of *tert*-butyl [(2*S*)-1-cyclobutylpropan-2-yl](2-nitrobenzyl)
15 carbamate**

To an ice-cooled solution of a compound obtained from Step c (13 g) in dichloromethane (100 ml) was added triethylamine (7.9 g) and di-*tert*-butyldicarbonate (13.71 g) drop wise. The reaction mixture was allowed to stir at an ambient temperature overnight. After completion, the organic layer was evaporated under vacuum to get crude
20 product which was purified by column chromatography eluting with ethyl acetate in hexane to afford the desired compound. Yield: 15 g

EIMS (m/z): 349.15

Step e: Synthesis of *tert*-butyl (2-aminobenzyl)[(2*S*)-1-cyclobutylpropan-2-yl]carbamate

25 To an ice-cooled solution of compound obtained from Step d (15 g) in methanol (150 ml) was added Raney Nickel (2g, w/w) followed by drop wise addition of hydrazine hydrate (15 ml). The reaction mixture was allowed to stir at 0°C for 30 minutes and at ambient temperature for about 6 hours. After completion, reaction mixture was filtered through celite pad. The filtrate was washed with methanol and concentrated. The concentrated

mixture was dissolved in water and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulphate, filtered and evaporated under vacuum to yield crude product. The crude product was purified by column chromatography to afford the desired compound. Yield: 12 g.

5 ***EIMS (m/z): 319.47***

Step f: Synthesis of *tert*-butyl [(2*S*)-1-cyclobutylpropan-2-yl](2-[(8-fluoro-2-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)sulfonyl]amino)benzyl)carbamate

To a solution of a compound obtained from Step e (3.07 g) in acetone (25 ml) was added 8-fluoro-2-methyl-4-oxo-3,4-dihydroquinazolin-6-sulfonyl chloride (4 g) in
10 pyridine (1.27 g) and stirred at room temperature for overnight. After complete consumption of the starting material, solvent was evaporated to yield a crude product. The crude product was purified by column chromatography using silica gel (100-200 mesh) and eluting with 5% methanol in dichloromethane to get a desired compound. Yield: 4.5g.

EIMS (m/z): 559.29

15 **Step g: Synthesis of *N*-[2-([(2*S*)-1-cyclobutylpropan-2-yl]amino)methyl]phenyl]-8-fluoro-2-methyl-4-oxo-3,4-dihydroquinazoline-6-sulfonamide**

To an ice-cooled solution of compound obtained from Step f (4.5 g) in dichloromethane (50 ml) was added trifluoroacetic acid (11.9 ml in 10 ml of dichloromethane) drop wise. The reaction mixture was stirred at room temperature for 6
20 hours. After completion, solvent was evaporated and the crude product so obtained was dissolved in ethyl acetate. The reaction mixture was washed with saturated sodium bicarbonate solution. The organic layer was separated, dried over anhydrous sodium sulphate and evaporated to get crude product which was purified by column chromatography using silica gel (100-200 mesh) and eluting with 5% methanol in
25 dichloromethane to get a desired compound. Yield: 2.5 g.

EIMS (m/z): 458.95; M.Pt.: 187°-188°C

¹HNMR (CDCl₃+MeOD) δ ppm: 8.45(s,1H), 7.92(dd, J_{1,2}=1.92, J_{2,4}=9.64Hz), 7.13-7.11(m,2H), 7.05(d,1H,J=7.08Hz), 6.83-6.79(m,1H), 4.02-3.91(m,2H), 2.50(s,3H), 2.45-2.41(m,1H), 2.15-2.06(m,2H), 1.80-1.95(m,3H), 1.72-1.58(m,3H), 1.27(d,3H,J=6.52Hz).

The compounds mentioned below were prepared by following the same route of synthesis as above:

- 5 *N*-[2-({[(2*S*)-1-Cyclohexylpropan-2-yl]amino}methyl)-4-fluorophenyl]-8-fluoro-4-oxo-3,4-dihydroquinazoline-6-sulfonamide (Compound No. 2);
EIMS (*m/z*): 491.27 (*M*+1); *M.Pt.*: 201°-203°C
- N*-[2-({[(2*S*)-1-Cyclopentylpropan-2-yl]amino}methyl)-4-fluorophenyl]-8-fluoro-4-oxo-3,4-dihydroquinazoline-6-sulfonamide (Compound No. 5);
EIMS (*m/z*): 477.42(*M*+1); *M.Pt.*: 201°-203°C
- 10 *N*-[2-({[(2*S*)-1-Cyclohexylpropan-2-yl]amino}methyl)-4-fluorophenyl]-8-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-sulfonamide (Compound No. 6);
EIMS (*m/z*): 507.28 (*M*+1); *M.Pt.*: 230°-231°C
- N*-[2-({[(1*S*)-2-Cyclopentyl-1-methylethyl]amino}methyl)phenyl]-8-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-sulfonamide (Compound No. 7);
EIMS (*m/z*): 475.20 (*M*+1); *M.Pt.*: 232°-234°C
- 15 *N*-[2-({[(2*S*)-1-Cyclohexylpropan-2-yl]amino}methyl)phenyl]-8-fluoro-4-oxo-3,4-dihydro quinazoline-6-sulfonamide (Compound No. 8);
EIMS (*m/z*): 472.57 (*M*+1);
- 20 *N*-[2-({[(2*S*)-1-Cyclobutylpropan-2-yl]amino}methyl)phenyl]-8-fluoro-4-oxo-3,4-dihydro quinazoline-6-sulfonamide (Compound No. 9);
EIMS (*m/z*): 444.52 (*M*+1); *M.Pt.*: 174°-175°C
- N*-[4-Chloro-2-({[(2*S*)-1-cyclohexylpropan-2-yl]amino}methyl)phenyl]-8-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-sulfonamide (Compound No. 10)
EIMS (*m/z*): 522.08 (*M*+1); *M.Pt.*: 270°-271°C

- 25 Example 2: Synthesis of *N*-[2-({[(2*S*)-1-Cyclopentylpropan-2-Yl]Amino}Methyl)-4-Fluorophenyl]-8-Fluoro-2,4-Dioxo-1,2,3,4-Tetrahydroquinazoline-6-Sulfonamide (Compound No. 4)

Step a: Preparation of *tert*-butyl [(2*S*)-1-cyclopentylpropan-2-yl]carbamate

- 30 In a two-neck round bottom flask was added Mg (11.4 g) and a crystal of iodine in dry tetrahydrofuran (50-60 ml). To this reaction mixture was added cyclopentyl bromide (10 ml out of 51.21 ml) through addition funnel under argon atmosphere till the reaction initiates (violet color disappears). The remaining cyclopentyl bromide in tetrahydrofuran (60 ml) was added drop wise in one hour. After complete of addition, reaction mixture was allowed to stir at room temperature for one hour. After 1.5 hrs, reaction mixture was
- 35 diluted with dry tetrahydrofuran (1.2 liter) and cooled to -40°C. CuBr-Me₂S complex (2.9 g) was added to the reaction mixture and stirred at same temperature for 30 minutes. To

this solution *tert*-butyl (2*S*)-2-methylaziridine-1-carboxylate (15 g) dissolved in tetrahydrofuran (50 ml) was added drop wise and stirred for 2 hours. After 2 hours, reaction mixture was allowed to warm to room temperature. After completion, reaction mixture was cooled to -20°C and quenched by adding saturated ammonium chloride solution. The reaction mixture was extracted with ethyl acetate, dried and evaporated under reduced pressure to get a crude product. The crude product so obtained was purified on silica gel column (100-200 mesh) eluting with 5% ethyl acetate:hexane to afford the desired compound. Yield: 12.1g

EIMS (m/z): 228.295

10 Step b: Preparation of (2*S*)-1-cyclopentylpropan-2-amine

To an ice-cooled solution of compound obtained from Step a (60 g) in dichloromethane (360 ml) was added drop wise trifluoroacetic acid (120 ml) and stirred for 4 hours to 5 hours. After completion, the solvent was evaporated and crude product so obtained was dissolved in ethyl acetate (200 ml) and cooled to 0°C. To this cooled solution was added potassium hydroxide (5N) and stirred at room temperature for 1 hour to 2 hours. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was stirred with 5N potassium hydroxide solution (250 ml) for 1 hour to 2 hours. The organic layer was separated and dried over anhydrous sodium sulphate and evaporated under vacuum to get brown oily compound. Yield: 38 g.

EIMS (m/z): 128.18

Step c: Preparation of (2*S*)-1-cyclopentyl-*N*-(5-fluoro-2-nitrobenzyl)propan-2-amine

To a solution of compound obtained from Step b (5.8 g) in acetonitrile (20 ml) was added cesium carbonate (9.75 g) and after 10 minutes was added 2-(bromomethyl)-4-fluoro-1-nitrobenzene (7.123 g) in acetonitrile (20 ml) and stirred for 15 minutes to 30 minutes. After completion of the reaction, solvent was evaporated and residue so obtained was quenched with water (250 ml). The reaction mixture was extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulphate and evaporated under vacuum to yield brown colored oily mass. The crude product was purified by column chromatography to afford the desired product. Yield: 9 g

EIMS (m/z): 281.26

Step d: Preparation of *tert*-butyl[(2*S*)-1-cyclopentylpropan-2-yl](5-fluoro-2-nitrobenzyl)carbamate

To an ice-cooled solution of compound obtained from Step c (15.4 g) in dichloromethane (150 ml) was added triethylamine (15.22 ml) and di-*tert*-butyldicarbonate (18.93 g) drop wise. The reaction mixture was allowed to stir at ambient temperature for overnight. After completion, the reaction mixture was diluted with dichloromethane and washed with water. The organic layer was separated, dried over anhydrous sodium sulphate and evaporated under vacuum to afford a crude product. The crude product obtained was purified on silica gel column (60-120 mesh) using 2% to 3% ethyl acetate:hexane as eluent to get the desired compound. Yield: 18.5 g.

EIMS (m/z): 381.26

Step e: Preparation of *tert*-butyl(2-amino-5-fluorobenzyl)[(2*S*)-1-cyclopentylpropan-2-yl]carbamate

To an ice-cooled solution of a compound obtained from Step d (18.5 g) in methanol (540 ml) was added Raney Nickel (~2.5 g) and hydrazine hydrate (22 ml) drop wise. The reaction mixture was stirred for about one hour. After complete consumption of starting material, reaction mixture was filtered through celite bed. The filtrate was evaporated under reduced pressure to obtain residues. The residues obtained was washed with water, dried over anhydrous sodium sulphate and evaporated under reduced pressure to afford the desired compound. Yield: 15g.

EIMS (m/z): 351.32

Step f: Preparation of *tert*-butyl [(2*S*)-1-cyclopentylpropan-2-yl](5-fluoro-2-[(8-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-6-yl)sulfonyl]amino}benzyl)carbamate

To an ice-cooled solution of compound obtained from Step e (15 g) in acetone/pyridine (300 ml/15 ml) was added 8-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-sulfonyl chloride (17.87 g) portion wise (2-3 portions in 10 minutes). The reaction mixture was stirred at room temperature for about 2 hours. After complete consumption of starting material, reaction mixture was filtered to remove insoluble impurities. The filtrate so collected was evaporated under reduced pressure and residues

obtained were purified on silica gel column (60-120 mesh) using 50% ethyl acetate: hexane to afford the desired compound. Yield: 23.9 g.

EIMS (m/z): 593.25

Step g: Preparation of *N*-[2-({[(2*S*)-1-cyclopentylpropan-2-yl]amino}methyl)-4-fluorophenyl]-8-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-sulfonamide

To an ice-cooled solution of compound obtained from Step f (23.9 g, 1 equiv.) in dichloromethane (150 ml) was added trifluoroacetic acid (50 ml, 10 equiv.) drop wise. The reaction mixture was allowed to stir for one hour at room temperature. After complete consumption of the starting material, reaction mixture was evaporated to remove dichloromethane and excess of trifluoroacetic acid. The residue obtained was diluted with ethyl acetate and neutralized with sodium bicarbonate solution. The organic layer was separated, washed with water, dried over anhydrous sodium sulphate and evaporated under reduced pressure to get crude product. The crude product obtained was purified by washing with 50% ethyl acetate:hexane and then with 2% methanol:dichloromethane. The solid was filtered and triturated with hexane to get desired compound. Yield: 13 g

EIMS (m/z): 493.36 ($M+1$); *M.Pt.*: 214-216°C

¹HNMR (CDCl₃+MeOD) δ ppm: 8.26(m,1H), 7.83(dd,1H, J_{1,2}=1.84, J_{2,4}=9.76Hz), 7.07-7.03(m,1H), 6.86-6.82(m,2H), 4.00-3.90 (m, 2H), 3.05-3.00(m,1H), 1.95-1.53(m,9H), 1.32(d, 3H,J=6.48Hz), 1.07-1.29(m,2H)

Example 3: Synthesis of *N*-[2-({[(1*S*)-2-Cyclohexyl-1-Methylethyl]Amino}Methyl)Phenyl]-8-Fluoro-2,4-Dioxo-1,2,3,4-Tetrahydroquinazoline-6-Sulfonamide (Compound No. 1)

Step a: Preparation of *tert*-butyl [(2*S*)-1-cyclohexylpropan-2-yl]carbamate

In a two-neck round bottom flask was added Mg (19.1 g) and a crystal of iodine in dry tetrahydrofuran (100-125 ml). To this reaction mixture was added cyclohexyl bromide (5 g out of 129 g) through addition funnel under argon atmosphere until the reaction initiates (violet color disappears). The remaining cyclohexyl bromide (124 g) was added drop wise in about one hour. After completion of addition, reaction mixture was allowed to stir at room temperature for about one hour. After one hour, reaction mixture was diluted with dry tetrahydrofuran (1.2 liter) and cooled to -40°C. CuBr-Me₂S complex (9.8

g) was added to the reaction mixture and stirred at same temperature for about 30 minutes. To this solution *tert*-butyl (2*S*)-2-methylaziridine-1-carboxylate (50 g) dissolved in tetrahydrofuran was added drop wise at -40°C and stirred for about 2 hours. Reaction mixture was allowed to warm to room temperature. After completion of reaction, reaction mixture was cooled to -20°C and quenched by adding saturated ammonium chloride solution. The reaction mixture was extracted with ethyl acetate, dried and evaporated under reduced pressure to get a crude product. The crude product so obtained was purified by column chromatography eluting with ethyl acetate:hexane to afford the desired compound. Yield: 70% (53.7g)

EIMS (*m/z*): 242.34

Step b: Preparation of (2*S*)-1-cyclohexylpropan-2-amine

To an ice-cooled solution of compound obtained from Step a (60 g) in dichloromethane (360 ml) was added trifluoroacetic acid (120 ml) and stirred for 3 hours. After completion, the solvent was evaporated and crude product so obtained was dissolved in ethyl acetate (200 ml) and cooled to 0°C. To this cooled solution was added potassium hydroxide (5N) and stirred at room temperature for 1 hour to 2 hours. The organic layer was separated and aqueous layer was extracted with ethyl acetate. The combined organic layer was stirred with 5N potassium hydroxide solution (250 ml) for 1 hour to 2 hours. The organic layer was separated and dried over anhydrous sodium sulphate and evaporated under vacuum to get brown oily compound. Yield: 90% (31.6g)

EIMS (*m/z*): 142.42

Step c: Preparation of (2*S*)-1-cyclohexyl-*N*-(2-nitrobenzyl)propan-2-amine

To a solution of compound obtained from Step b (2.5 g) in acetonitrile (25 ml) was added anhydrous cesium carbonate (5.75 g) and stirred for 10 minutes. To this stirred solution was added 2-nitrobenzyl bromide (3.8 g) and again stirred for 4 hours at room temperature. After complete consumption of starting material, reaction mixture was diluted with ethyl acetate and quenched with water. The organic layer was separated, dried over anhydrous sodium sulphate and evaporated under reduced pressure to get crude compound. The crude compound obtained was purified by column chromatography. The

non-polar impurities were removed using 5% to 10% dichloromethane in hexane and desired compound was eluted using 10% ethyl acetate in hexane. Yield: 3.28 g

EIMS (*m/z*): 277.38

Step d: Preparation of *tert*-butyl [(2*S*)-1-cyclohexylpropan-2-yl](2-nitrobenzyl) carbamate

To an ice-cooled solution of compound obtained from Step c (7.9 g) in dichloromethane (80 ml) were added di-*tert*-butyldicarbonate (6.4 g) drop wise. The reaction mixture was allowed to stir at ambient temperature for overnight. After completion, the reaction mixture was diluted with water and organic layer was separated. The organic layer was washed with water, dried over anhydrous sodium sulphate and evaporated under vacuum to afford a crude product. The crude product so obtained was purified by column chromatography to get the desired compound. Yield: 10 g

EIMS (*m/z*): 377.24

Step e: Preparation of *tert*-butyl (2-aminobenzyl)[(2*S*)-1-cyclohexylpropan-2-yl]carbamate

To an ice-cooled solution of a compound obtained from Step d (13 g) in methanol (540 ml) was added Raney Nickel (~2.5 g) and hydrazine hydrate (22 ml) drop wise. The reaction mixture was stirred for 2 hours to 5 hours. After complete consumption of starting material, reaction mixture was filtered through celite bed. The filtrate was evaporated under reduced pressure and residues so obtained were diluted with dichloromethane. The reaction mixture was washed with water, dried over anhydrous sodium sulphate and evaporated under reduced pressure to afford the desired compound. Yield: 15g.

EIMS (*m/z*): 347.20

Step f: Preparation of *tert*-butyl [(2*S*)-1-cyclohexylpropan-2-yl][2-({[(8-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-6-yl)methyl]sulfonyl}amino)benzyl]carbamate

To a solution of compound obtained from Step e (8 g) in pyridine (70 ml) was added 8-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-sulfonyl chloride (9.64 g). The reaction mixture was allowed to stir at room temperature for 3 hours to 4 hours. After

complete consumption of starting material, pyridine was evaporated, residue obtained was dissolved in ethyl acetate and water was added. The organic layer was separated, washed with brine and dried over anhydrous sodium sulphate, concentrated under vacuum to get crude product. The crude product obtained was purified on silica gel (100-200 mesh) column chromatography using ethyl acetate:hexane as eluent to afford desired compound. Yield: 12.85 g

EIMS (m/z): 589.20

Step g: Preparation of *N*-[2-({[(2*S*)-1-cyclohexylpropan-2-yl]amino}methyl)phenyl]-1-(8-fluoro-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-6-yl)methanesulfonamide

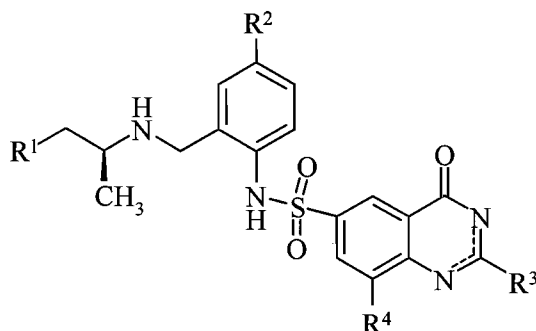
To an ice-cooled solution of compound obtained from Step f (10.85 g) in dichloromethane (100 ml) was added trifluoroacetic acid (31.93 g/21 ml) drop wise. The reaction mixture was allowed to stir at room temperature for one hour. After complete consumption of the starting material, solvent was evaporated and residues were diluted with ethyl acetate and washed with sodium bicarbonate solution. The organic layer was separated, washed with water, dried over anhydrous sodium sulphate and evaporated under reduced pressure to get crude product. The crude product obtained was purified by silica gel column chromatography using dichloromethane:methanol as eluent to afford a pure compound. Yield: 6.75 g.

EIMS (m/z): 489.25 (M+1); M.Pt.: 236°-239°C

¹HNMR (CDCl₃+MeOD) δ ppm: 8.29 (s,1H), 7.14-7.05 (m,3H), 6.83-6.80 (m,1H), 4.07-3.97 (m,2H), 3.17-3.10 (m,1H), 1.67-0.86 (m,1

Claims:

- 1 1. A compound of Formula I

**Formula I**

2
3
4 its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereoisomers,
5 prodrugs, metabolites or *N*-oxide thereof,

6 wherein

7 ----- indicates that a bond may or may not be present;

8 R^1 is cyclobutyl, cyclopentyl or cyclohexyl;

9 R^2 is hydrogen, fluorine or chlorine;

10 R^3 is hydrogen, oxo or methyl;

11 R^4 is fluorine or chlorine.

- 1 2. A compound, which is:

2 *N*-[2-({[(1*S*)-2-Cyclohexyl-1-methylethyl]amino}methyl)phenyl]-8-fluoro-2,4-
3 dioxo-1,2,3,4-tetrahydroquinazoline-6-sulfonamide (Compound No. 1);

4 *N*-[2-({[(2*S*)-1-Cyclohexylpropan-2-yl]amino}methyl)-4-fluorophenyl]-8-fluoro-4-
5 oxo-3,4-dihydroquinazoline-6-sulfonamide (Compound No. 2);

6 *N*-[2-({[(2*S*)-1-Cyclobutylpropan-2-yl]amino}methyl)phenyl]-8-fluoro-2-methyl-
7 4-oxo-3,4-dihydroquinazoline-6-sulfonamide (Compound No. 3);

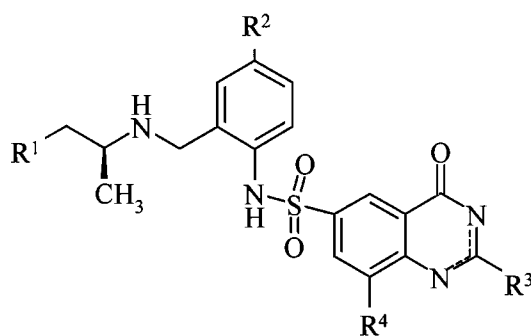
8 *N*-[2-({[(2*S*)-1-Cyclopentylpropan-2-yl]amino}methyl)-4-fluorophenyl]-8-fluoro-
9 2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-sulfonamide (Compound No. 4);

10 *N*-[2-({[(2*S*)-1-Cyclopentylpropan-2-yl]amino}methyl)-4-fluorophenyl]-8-fluoro-
11 4-oxo-3,4-dihydroquinazoline-6-sulfonamide (Compound No. 5);

12 *N*-[2-({[(2*S*)-1-Cyclohexylpropan-2-yl]amino}methyl)-4-fluorophenyl]-8-fluoro-
13 2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-sulfonamide (Compound No. 6);

- 14 *N*-[2-({[(1*S*)-2-Cyclopentyl-1-methylethyl]amino}methyl)phenyl]-8-fluoro-2,4-
15 dioxo-1,2,3,4-tetrahydroquinazoline-6-sulfonamide (Compound No. 7);
- 16 *N*-[2-({[(2*S*)-1-Cyclohexylpropan-2-yl]amino}methyl)phenyl]-8-fluoro-4-oxo-3,4-
17 dihydroquinazoline-6-sulfonamide (Compound No. 8);
- 18 *N*-[2-({[(2*S*)-1-Cyclobutylpropan-2-yl]amino}methyl)phenyl]-8-fluoro-4-oxo-3,4-
19 dihydroquinazoline-6-sulfonamide (Compound No. 9);
- 20 *N*-[4-Chloro-2-({[(2*S*)-1-cyclohexylpropan-2-yl]amino}methyl)phenyl]-8-fluoro-
21 2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-sulfonamide (Compound No. 10); and
- 22 its pharmaceutically acceptable salts, pharmaceutically acceptable solvates,
23 stereoisomers, prodrugs, metabolites or *N*-oxide thereof
- 1 3. A pharmaceutical composition comprising a therapeutically effective amount of a
2 compound according to any one of claims 1 to 2, together with a pharmaceutically
3 acceptable carrier, excipient or diluent.
- 1 4. A compound according to any one of claims 1-2, for use in treating bacterial
2 infections, including infections by bacteria which are resistant to conventional antibiotic
3 drugs.
- 1 5. A compound according to any one of claims 1-2, for use in treating skin and soft
2 tissue mixed infections caused by both aerobic and anaerobic gram positive pathogens.
- 1 6. A compound according to claim 4, for use in treating bacterial infections wherein
2 bacterial infections arise from the contact with an organism selected from *staphylococci*,
3 *streptococci* and *enterococci*.
- 1 7. A compound according to any one of claims 1-2, for use in the treatment of
2 methicillin sensitive *Staphylococcus aureus* (MSSA), methicillin resistant *Staphylococcus*
3 *aureus* (MRSA), *Streptococcus agalactiae* and *Streptococcus viridans* (Group B
4 streptococci), *Streptococcus pyogenes* (group A streptococcus), vancomycin resistant
5 *enterococci* (VRE) including *E. faecalis*, *E. faecium* and *S. pneumoniae*.
- 1 8. A process for the preparation of compounds of Formula I,

29

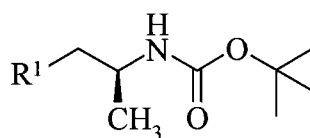


Formula 1

2

3 comprising:

- 4 a) reacting a compound of Formula 2 with *tert*-butyl (2*S*)-2-methylaziridine-1-
5 carboxylate to give a compound of Formula 3

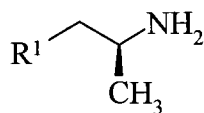


6 R^1MgHa
Formula 2

Formula 3

6

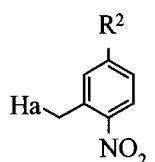
- 7 b) deprotecting a compound of Formula 3 to give a compound of Formula 4



Formula 4

8

- 9 c) reacting a compound of Formula 4 with a compound of Formula 5

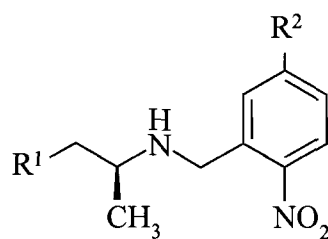


Formula 5

10

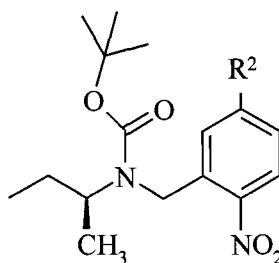
- 11 to give a compound of Formula 6

30



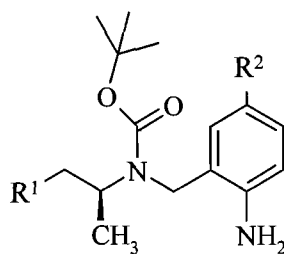
Formula 6

d) *N*-protecting a compound of Formula 6 to gives a compound of Formula 7



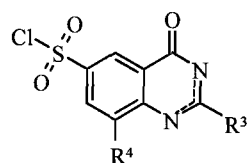
Formula 7

e) reducing a compound of Formula 7 to give a compound of Formula 8



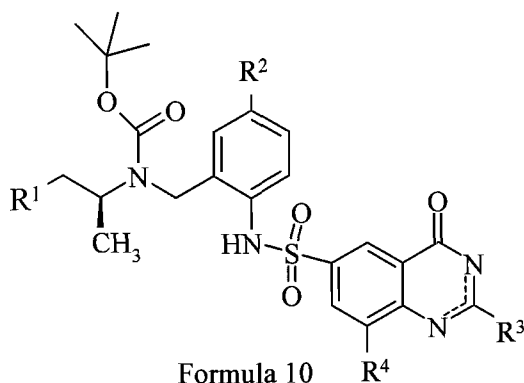
Formula 8

f) coupling of a compound of Formula 8 with a compound of Formula 9



Formula 9

to give a compound of Formula 10



g) deprotecting a compound of Formula 10 to give a compound of Formula 1

wherein

----- indicates that a bond may or may not be present;

R¹ is cyclobutyl, cyclopentyl or cyclohexyl;

R² is hydrogen, fluorine or chlorine;

R³ is hydrogen, oxo or methyl;

R⁴ is fluorine or chlorine;

Ha is halogen such as F, Cl, Br or I.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/053090

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D239/88 C07D239/96 A61K31/517 A61P31/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EP0-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2006/117762 A2 (RANBAXY LAB LTD [IN]; DAS BISWAJIT [IN]; ARORA JASBIR SINGH [IN]; AHME) 9 November 2006 (2006-11-09) cited in the application compounds 592, 593 the whole document -----	1-8



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

23 November 2011

Date of mailing of the international search report

05/12/2011

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Authorized officer

Sarakinos, Georgios

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2011/053090

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006117762 A2	09-11-2006	AU 2006242824 A1	09-11-2006
		CA 2606804 A1	09-11-2006
		EP 1879877 A2	23-01-2008
		KR 20080014812 A	14-02-2008
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		WO 2006117762 A2	09-11-2006
