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Diphenyl(piperidin-4-yl)methanol Derivatives as an Antimicrobial Agents

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ABSTRACT

Developing antimicrobial drugs keeping their potency, resistance to classes of microorganism are the major concern for the scientists in the area of medicinal chemistry. The diphenyl(piperidin-4-yl)methanol derivatives 1a-n and 2a-i were evaluated for antimicrobial activity. The results are encouraging, Compounds 1b and 1g are the most potent among the sulfonamide series whereas compound 2h is the most potent among urea series.

Keywords: Piperidine, Sulfonyl chloride, Isocyanates, Antimicrobial activity, Gram-positive, Gram-negative

INTRODUCTION

Infectious microbial diseases are serious menace in the health care practice. These microbial diseases connected to the most of the other diseases, whenever human system is debilitated (weakened). In order to combat them number of drugs are used in clinical practice, ranging from natural product antibacterial to antibacterial designed by using molecular modeling techniques. Developing antimicrobial drugs keeping their potency, resistance to different classes of microorganism and broad spectrum of activity against different microorganism are the major concern of the research scientists in this area. In spite of many developments in antimicrobial treatment, plenty of problems need to be solved including multidrug resistance of different microorganism, a different adverse reaction (Ototoxicity in case of gentamycin, hepatotoxicity in case of bacitracin and nephrotoxicity in case of ampicillin B) and different organelles of the bacterial cellular system get mutated or equipped with constant exposure to different antibacterial agents, for instance biosynthesis of penicillinace enzyme by certain microorganism, which works against penicillin and mutation of the enzyme bacterial DNA gyrase, exposure to fluoroquinolone antibiotics. Highlight the need for advent of safe, novel, effective and bioavailable antibacterial compounds [1].

Sulfonamide constitute an important class of drug, with several types of pharmacological agents possessing antibacterial, anticarbonic anhydrous, diuretic, hypoglysonic, HIV protease inhibition, antithyroid activity and antitumour activity [2]. Heterocyclic sulfonamides have variety of activity on different cellular system, responsible for the mechanism of these compounds such as disruptions of microtubule assembly, suppression of the transcriptional activator NF-Y and matrix metalloproteinase (angiogenesis) [3].

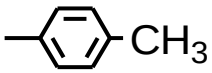
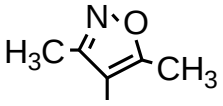
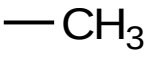
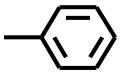
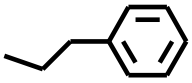
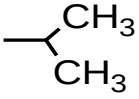
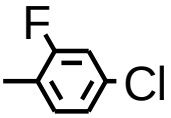
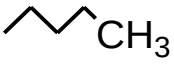
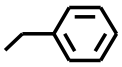
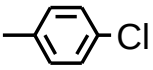
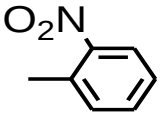
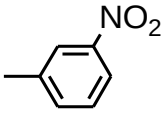
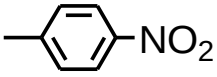
Piperidine and its analogues, an important pharmacophore of many drug molecules, are reported to act as antibacterial [4], antitubercular agents [5], AChE inhibitors [6] and other biological application as mentioned in our previous paper [7], herewith, in continuation of our research on the modification of functional group in the diphenyl(piperidin-4-yl)methanol scaffold [7,8], the antimicrobial activity for the derivatives 1a-n and 2a-i is reported.

MATERIALS AND METHODS

Chemistry

The target compound diphenyl(piperidin-4-yl)methanol was synthesized as reported earlier [7,8]. Synthesis and *in vitro* antiproliferative activity of diphenyl(sulfonylpiperidin-4-yl)methanol derivatives 1a-n against human cancer cell lines has been reported [8]. The chemical structure of the compounds 1a-n is given in Table 1. The compounds 1a [9], 1k [10] and 1l [11] was structurally characterized by X-ray crystallographic studies.

Table 1: Chemical structure of the compounds 1a-n

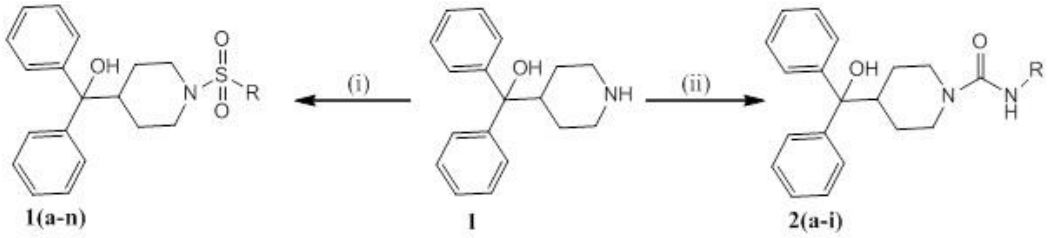
Compound	R
1a	
1b	
1c	
1d	
1e	
1f	
1g	
1h	
1i	
1j	
1k	
1l	
1m	
1n	

Experimental

The instrumental details are same as reported [8].

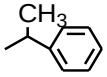
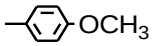
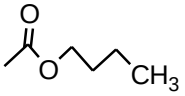
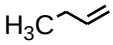
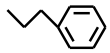
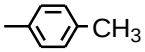
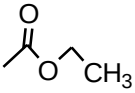
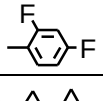
General procedure for the synthesis of diphenyl(piperidin-4-yl)methanol urea derivatives 2a-i

A solution of diphenyl(piperidin-4-yl)methanol **(1)** (1.0 eq) in dry dichloromethane was taken and cooled to 0-5°C in an ice bath. Triethylamine (3 eq) was added to the cold reaction mixture and stirred for 10 min, then different isocyanates (1.0 eq) was added, the reaction mixture was allowed to room temperature under stirring for 5-6 h. The reaction mixture was monitored by TLC. Upon completion, the solvent was removed under reduced pressure and residue was taken in water and extracted with ethyl acetate. The organic layer was washed with 10% ammonium chloride solution and finally water wash was given to organic layer and dried with anhydrous sodium sulphate, the solvent was evaporated to get crude product which was purified by column chromatography over silica gel (60-120 mesh) using Hexane: Ethyl acetate (8:2) as an eluent. The formation of our products was confirmed by Proton Nuclear Magnetic Resonance (^{1}H-NMR), Infra-Red (IR) and Liquid Chromatography–Mass Spectrometry (LC-MS) analysis. Synthesized compounds 2a-i was obtained in good yield and the schematic representation is shown in Scheme 1. The yield, physical data and chemical structures of the derivatives are shown in Table 2.



Scheme 1: Reagents and conditions: (i) Sulfonyl chlorides, TEA, MDC, Retention time 4-5 h, (ii) Isocyanates, TEA, MDC, and Retention time 4-5 h

Table 2: Chemical structure, yield and melting point of the synthesized compounds 2a-i

Compound	R	Yield (%)	Melting point (°C)
2a		84	102-104
2b		90	241-243
2c		91	99-101
2d		89	260-262
2e		90	214-216
2f		82	194-196
2g		93	169-171
2h		91	223-225
2i		86	145-147

Synthesis of 4-(hydroxydiphenylmethyl)-*N*-(1-phenylethyl)piperidine-1-carboxamide (2a): Compound 2a obtained was pale yellow solid from diphenyl(piperidin-4-yl)methanol (0.5 g, 1.77 mmol), 1-(1-isocyanatoethyl) benzene (0.26 g, 1.77 mmol) and triethylamine (0.667 g, 6.81 mmol). ^{1}H-NMR (DMSO-*d6*, 400 MHz), δ=7.52 (m, 4H, Ar-H), 7.32 (m, 4H, Ar-H), 7.25 (m, 2H, Ar-H), 7.06-7.15 (m, 5H, Ar-H), 5.48 (s, 1H, -NH), 5.05 (s, 1H, -CH_2), 3.1 (d, 2H, -CH_2), 2.68 (t, 2H, -CH_2), 2.4 (m, 1H, -CH), 2.23 (s, 1H, -OH), 1.62 (s, 3H, -CH_3), 1.5 (d, 4H, -CH_2). IR (KBr, cm^{-1}): 3509, 1638, 1460, 1350. MS (ESI) *m/z*: 415.54 ($M+H^+$).

Synthesis of 4-(hydroxydiphenylmethyl)-*N*-(4-methoxyphenyl)piperidine-1-carbox- amide (2b): Compound 2b obtained was white amorphous solid from diphenyl(piperidin-4-yl)methanol (0.5 g, 1.77 mmol), 4-methoxy phenyl-isocyanate (0.263 g, 1.77 mmol) and triethylamine (0.667 g, 6.81 mmol). ^{1}H-NMR (DMSO-*d6*, 400 MHz), δ=8.22 (s, 1H, -NH), 7.52 (m, 4H, Ar-H), 7.32 (m, 4H, Ar-H), 7.25 (m, 2H, Ar-H), 7.12 (t, 2H, Ar-H), 6.79 (d, 2H, Ar-H), 3.8 (s, 3H, -OCH_3), 3.1 (d, 2H, -CH_2), 2.68 (t, 2H, -CH_2), 2.4 (m, 1H, -CH), 2.2 (s, 1H, -OH), 1.5 (d, 4H, -CH_2). IR (KBr, cm^{-1}): 3500, 2810, 1630. MS (ESI) *m/z*: 417.21 ($M+H^+$).

Synthesis of butyl 2-(4-(hydroxydiphenylmethyl)piperidine-1-carboxamido)acetate (2c): Compound 2c obtained was white amorphous solid from diphenyl(piperidin-4-yl)methanol (0.5 g, 1.77 mmol), butyl isocyanatoacetate (0.278 g, 1.77 mmol) and triethylamine (0.667 g, 6.81 mmol). ^{1}H-NMR (DMSO-*d6*, 400 MHz), δ=7.49 (m, 4H, Ar-H), 7.35 (m, 4H, Ar-H), 7.19 (m, 2H, Ar-H), 5.36 (s, 1H, -NH), 4.15 (s, 2H, -CH_2), 4.08 (t, 2H, -CH_2), 3.15 (d, 2H, -CH_2), 2.68 (t, 2H, -CH_2), 2.4 (m, 1H, -CH), 2.2 (s, 1H, -OH), 1.61 (m, 2H, -CH_2), 1.5 (d, 4H, -CH_2), 0.94 (t, 3H, -CH_3). IR (KBr, cm^{-1}): 3509, 2830, 1638, 1460, 1350, 1730. MS (ESI) *m/z*: 411.22 ($M+H^+$).

Synthesis of *N*-allyl-4-(hydroxydiphenylmethyl)piperidine-1-carboxamide (2d): Compound 2d obtained was white amorphous solid from diphenyl(piperidin-4-yl)methanol (0.5 g, 1.77 mmol), allyl isocyanate (0.146 g, 1.77 mmol) and triethylamine (0.667 g, 6.81 mmol). ^{1}H-NMR (DMSO-*d6*, 400 MHz), δ=7.50 (m, 4H, Ar-H), 7.35 (m, 4H, Ar-H), 7.19 (m, 2H, Ar-H), 5.83 (s, 1H, C=CH), 5.36 (s, 1H, -NH), 5.17 (s, 1H, C=CH), 5.13 (s, 1H, C=CH), 3.82 (d, 2H, -CH_2), 3.15 (d, 2H, -CH_2), 2.68 (t, 2H, -CH_2), 2.4 (m, 1H, -CH), 2.2 (s, 1H, -OH), 1.5 (d, 4H, -CH_2). IR (KBr, cm^{-1}): 3500, 1640, 1456, 1350, 740. MS (ESI) *m/z*: 351.20 ($M+H^+$).

Synthesis of 4-(hydroxydiphenylmethyl)-*N*-phenethylpiperidine-1-carboxamide (2e): Compound 2e obtained was white amorphous solid from diphenyl(piperidin-4-yl)methanol (0.5 g, 1.77 mmol), 1-(2-isocyanatoethyl)benzene (0.26 g, 1.77 mmol) and triethylamine (0.667 g, 6.81 mmol). ^{1}H-NMR (DMSO-*d6*, 400MHz), δ=7.46 (m, 4H, Ar-H), 7.28 (m, 4H, Ar-H), 7.20 (m, 2H, Ar-H), 7.15-7.20 (m, 5H, Ar-H), 5.36 (s, 1H, -NH), 3.49 (m, 2H, -CH_2), 3.09 (d, 2H, -CH_2), 2.82 (t, 2H, -CH_2), 2.62 (t, 2H, -CH_2), 2.41 (m, 1H, -CH), 2.3 (s, 1H, -OH), 1.48 (d, 4H, -CH_2). IR (KBr, cm^{-1}): 3509, 1638, 1460, 1350. MS (ESI) *m/z*: 415.23 (M+H$^+$).

Synthesis of 4-(hydroxydiphenylmethyl)-*N*-p-tolylpiperidine-1-carboxamide (2f): Compound 2f obtained was white crystalline solid from diphenyl(piperidin-4-yl)methanol (0.5 g, 1.77 mmol), 1-isocyanato-4-methylbenzene (0.235 g, 1.77 mmol) and triethylamine (0.667 g, 6.81 mmol). ^{1}H-NMR (DMSO-*d6*, 400 MHz), δ=9.03 (s, 1H, -NH), 7.55 (m, 2H, Ar-H), 7.51 (m, 4H, Ar-H), 7.33 (m, 4H, Ar-H), 7.21 (m, 2H, Ar-H), 7.02 (m, 2H, Ar-H), 3.07 (d, 2H, -CH_2), 2.65 (t, 2H, -CH_2), 2.38 (m, 1H, -CH), 2.30 (s, 3H, -CH_3), 2.18 (s, 1H, -OH), 1.56 (d, 4H, -CH_2). IR (KBr, cm^{-1}): 3515, 1650, 1466, 1346. MS (ESI) *m/z*: 401.22 (M+H$^+$).

Synthesis of ethyl 2-(4-(hydroxydiphenylmethyl)piperidine-1-carboxamido)acetate (2g): Compound 2g obtained was white amorphous solid from diphenyl(piperidin-4-yl)methanol (0.5 g, 1.77 mmol), ethyl 2-isocyanatoacetate (0.228 g, 1.77 mmol) and triethylamine (0.667 g, 6.81 mmol). ^{1}H-NMR (DMSO-*d6*, 400MHz), δ=7.45 (m, 4H, Ar-H), 7.32 (m, 4H, Ar-H), 7.17 (m, 2H, Ar-H), 5.36 (s, 1H, -NH), 4.12 (d, 2H, -CH_2), 3.95 (s, 2H, -CH_2), 3.12 (d, 2H, -CH_2), 2.68 (t, 2H, -CH_2), 2.4 (m, 1H, -CH), 2.2 (s, 1H, -OH), 1.5 (d, 4H, -CH_2) 1.28 (s, 3H, -CH_3). IR (KBr, cm^{-1}): 3500, 2835, 1638, 1460, 1350, 1730. MS (ESI) *m/z*: 397.20 (M+H$^+$).

Synthesis of *N*-(2,4-difluorophenyl)-4-(hydroxydiphenylmethyl)piperidine-1-carbox-amide (2h): Compound 2h obtained was pale yellow crystalline solid from diphenyl(piperidin-4-yl)methanol (0.5 g, 1.77 mmol), 2,4-difluoro-1-isocyanatobenzene (0.274 g, 1.77 mmol) and triethylamine (0.667 g, 6.81 mmol). ^{1}H-NMR (DMSO-*d6*, 400 MHz), δ=8.95 (s, 1H, -NH), 7.52 (m, 4H, Ar-H), 7.33 (m, 4H, Ar-H), 7.26 (m, 2H, Ar-H), 7.14 (m, 2H, Ar-H), 7.05 (s, 1H, Ar-H), 3.1 (d, 2H, -CH_2), 2.68 (t, 2H, -CH_2), 2.42 (m, 1H, -CH), 2.25 (s, 1H, -OH), 1.56 (d, 4H, -CH_2). IR (KBr, cm^{-1}): 3509, 1628, 1160. MS (ESI) *m/z*: 423.18 (M+H$^+$).

Synthesis of *N*-(2,4-difluorophenyl)-4-(hydroxydiphenylmethyl)piperidine-1-carbox-amide (2i): Compound 2i obtained was white amorphous from diphenyl(piperidin-4-yl)methanol (0.5 g, 1.77 mmol), N-1-isocyanatohexane (0.224 g, 1.77 mmol) and triethylamine (0.667 g, 6.81 mmol). ^{1}H-NMR (DMSO-*d6*, 400MHz), δ=7.50 (m, 4H, Ar-H), 7.27 (m, 4H, Ar-H), 7.15 (m, 2H, Ar-H), 5.26 (s, 1H, -NH), 2.95 (m, 2H, -CH_2), 2.58 (m, 2H, -CH_2), 2.43 (m, 1H, -CH), 2.22 (s, 1H, -OH), 1.58 (d, 4H, -CH_2), 1.12-1.45 (bs, 10H, -$(CH_2)_6$), 0.85 (s, 3H, -CH_3). IR (KBr, cm^{-1}): 3509, 1638, 1460, 1350. MS (ESI) *m/z*: 395.26 (M+H$^+$).

Pharmacological screening

In vitro evaluation of antimicrobial activity

The standard strains were procured from the American Type Culture Collection (ATCC) Rockville, USA, and the pathological strains were procured from the Department of Microbiology, University of Mysore, Mysore, India. The antibacterial activity of the synthesized compounds was screened against the following standard Bacterial strains: *Staphylococcus aureus* ATCC 25953, *Streptococcus pneumoniae* ATCC 49619, *Bacillus cereus* 11778, *Bacillus subtilis* 6051, *Escheriea coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 2853, *P. vulgaris* ATCC 2853, and *Salmonella typhi* ATCC 9484.

Paper disc diffusion method

Preliminary antibacterial screening was performed by the agar diffusion method using a paper disc. The sterilized (autoclaved at 120°C for 30 min), liquefied Mueller Hinton agar (40-50°C) was inoculated (1 ml/100 ml of medium) with the suspension of the microorganism (matched to McFarland Barium sulphate standard) and poured in to a petri dish to give a depth of 3-4 mm. The paper discs impregnated with the test compounds 500 µg/ml^{-1} in Dimethyl Sulfoxide (DMSO) were placed on the solidified medium. The plates were refrigerated at 4°C for 2 h and then incubated at 37°C for 24 h.

Minimum inhibitory concentration (MIC)

A series of glass tubes containing different concentrations of the synthesized compounds (1-500 µg/ml^{-1} in DMSO) with Mueller Hinton broth was inoculated with the required amount of the inoculum to obtain a suspension of microorganism, which contains 10^5 colony-forming units per milliliter. One growth control tube was prepared with the addition of the compound and one blank tube was prepared without the addition of microorganism. The tubes were incubated at 37°C for 24 h. The turbidity produced in each tube was recorded by using a UV-Visible spectrometer. The minimum inhibitory concentration (MIC-µg/ml^{-1}) was considered to be the lowest concentration, which exhibited the same turbidity as the blank tube. The observed MICs (µg/ml^{-1}) are given in Tables 3-6.

Table 3: Inhibition zone (diameter in mm) of compounds 1a-n and 2a-i against Gram-positive bacterial strains by paper disc diffusion method

Compound	*Bacillus cereus*	*Bacillus subtilis*	*Staphylococcus aureus*	*Staphylococcus epidermidis*
1a	14	12	11	10
1b	**26**	**23**	**24**	**28**
1c	8	7	10	11
1d	11	9	12	8
1e	16	15	13	11
1f	9	11	13	10
1g	**25**	**27**	**22**	**24**
1h	13	10	12	9
1i	14	13	15	11
1j	11	14	12	12
1k	18	17	19	15
1l	20	17	15	16
1m	21	18	19	22
1n	18	16	20	23
2a	14	12	10	13
2b	19	17	18	22

2c	11	9	13	12
2d	16	18	15	14
2e	15	12	13	16
2f	11	13	15	12
2g	Nil	Nil	Nil	Nil
2h	**23**	**24**	**22**	**26**
2i	8	7	9	8
Streptomycin	**23**	**20**	**21**	**23**

Zone of inhibition zone in mm

Table 4: Minimum inhibitory concentration (µg/ml) of compounds 1a-n and 2a-i against Gram-positive bacterial strains by micro dilution method

Compound	*Bacillus cereus*	*Bacillus subtilis*	*Staphylococcus aureus*	*Staphylococcus epidermidis*
1a	180	174	186	183
1b	**38**	**34**	**36**	**39**
1c	134	129	125	138
1d	125	133	136	130
1e	114	108	109	113
1f	159	154	163	158
1g	**68**	**64**	**70**	**65**
1h	148	143	146	151
1i	153	149	155	153
1j	84	82	88	83
1k	82	79	81	84
1l	80	76	78	81
1m	94	90	98	95
1n	88	84	85	90
2a	148	151	153	155
2b	86	84	87	82
2c	128	131	130	123
2d	164	169	172	167
2e	134	138	142	145
2f	189	184	186	187
2g	Nill	Nill	Nill	Nill
2h	**63**	**60**	**58**	**59**
2i	172	170	176	177
Streptomycin	**156**	**213**	**229**	**132**

Minimum inhibitory concentration in µg/ml

Table 5: Inhibition zone (diameter) mm of compounds 1a-n and 2a-i against Gram-negative bacterial strains by paper disc diffusion method

Compounds	*Pseudomonas aeruginosa*	*Escheriea coli*	*Proteus vulgaris*	*Salmonella typhi*
1a	13	12	10	12
1b	**22**	**25**	**26**	**28**
1c	8	11	13	14
1d	12	14	11	11
1e	14	16	14	15
1f	11	13	16	17
1g	**24**	**23**	**25**	**27**
1h	16	14	13	11
1i	14	15	12	14
1j	12	13	15	12
1k	17	15	17	16
1l	18	19	18	17
1m	20	21	19	15
1n	**24**	**24**	**25**	**26**
2a	18	15	17	13
2b	14	12	11	13
2c	19	18	14	15
2d	12	11	13	13
2e	15	14	16	17
2f	16	15	12	14
2g	12	11	9	13
2h	**23**	**24**	**26**	**26**
2i	9	10	12	11
Streptomycin	**21**	**22**	**23**	**23**

Zone of inhibition zone in mm

Table 6: Minimum inhibitory concentration (µg/ml) of compounds 1a-n and 2a-i against Gram-negative bacterial strains by micro dilution method

Compounds	*Pseudomonas aeruginosa*	*Escheriea coli*	*Proteus vulgaris*	*Salmonella typhi*
1a	174	169	167	176
1b	**46**	**54**	**56**	**61**
1c	142	139	132	142
1d	148	143	141	143
1e	129	127	132	138
1f	172	165	163	169
1g	**59**	**62**	**48**	**64**
1h	112	121	125	128
1i	117	124	119	123
1j	121	116	120	122
1k	132	127	125	129
1l	128	118	118	112
1m	140	134	130	134
1n	**67**	**64**	**61**	**58**
2a	154	162	158	163
2b	149	155	159	161
2c	134	138	142	139
2d	138	143	146	144
2e	139	144	152	143
2f	185	182	190	194
2g	Nill	Nill	Nill	Nill
2h	**52**	**54**	**47**	**49**
2i	162	164	147	194
Streptomycin	**151**	**176**	**143**	**192**

Minimum inhibitory concentration in µg/ml

RESULTS AND DISCUSSION

Antibacterial activity of the synthesized compounds were tested against different pathogenic bacterial strains i.e., *S. aureus*, *S. epidermis*, *B. cereus*, *B. subtilis*, *E. coli*, *P. aeruginosa*, *P. vulgaris* and *S. typhi* using the paper disc diffusion and micro dilution method. Streptomycin was used as reference drug for both Gram-positive and Gram-negative bacterias.

Gram-positive bacteria

In general, the synthesised compounds exhibit significant, moderate and less active inhibitory activity against Gram-positive bacteria. From the sulfonamides 1a-n, compounds 1b and 1g shows significant inhibitory activity against pathogenic bacterial strains with the zone of inhibition in the range of (23-28 mm), (22-27 mm) respectively. Compounds 1k, 1l, 1m and 1n show moderate activity against pathogenic bacterial strains with the zone of inhibition in the range of (15-19 mm), (15-20 mm), (18-22 mm) and (16-23 mm) respectively. Compounds 1c and 1f show less active against pathogenic bacterial strains with the zone of inhibition in the range of (7-11 mm) and (9-13 mm) respectively. Compound 1b shows significant activity against *B. subtilis* (23 mm), *S. aureus* (24 mm) *B. cereus* (26 mm) and *S. epidermis* (28 mm) bacterias. Compound 1g shows significant activity against *S. aureus* (22 mm), *S. epidermis* (24 mm), *B. cereus* (25 mm), *B. subtilis* (27 mm) bacterias. Isoxazole present in compound 1b, fluoro at 2^{nd} position and chloro at 4^{th} position in 1g is probably responsible for the significant antibacterial activity. Compound 1b shows observable antibacterial activity in the least concentration of 34 µg/ml against *B. subtilis* bacteria and compound 1g shows observable antibacterial activity in the least concentration of 64 µg/ml against *B. subtilis* bacteria.

Among urea series 2a-i, compound 2h shows significant inhibitory activity against pathogenic bacterial strains with the zone of inhibition in the range of (22-26 mm). Compounds 2b, 2d and 2e shows moderate activity against bacterial strains with the zone of inhibition in the range of (17-22 mm), (14-18 mm) and (12-16 mm) respectively. Whereas, the compound 2g has no inhibitory activity against bacterial strains. Compound 2h shows significant activity against *S. epidermis* (26 mm), *B. subtilis* (24 mm), *B. cereus* (23 mm) and *S. aureus* (22 mm). Fluorine at 2^{nd} and 4^{th} position present in 2h could be responsible for the significant antibacterial activity. Compound 2h shows observable antibacterial activity in the least concentration of 58 µg/ml against *S. aureus* bacteria, 59 µg/ml against *S. epidermis* bacteria, 60 µg/ml against *B. subtilis* bacteria and 63 µg/ml against *B. cereus* bacteria.

Gram-negative bacteria

Title compounds shows significant, moderate and less inhibitory activity against Gram-negative bacteria. In the sulfonamide series 1a-n, compounds 1b, 1g and 1n shows significant inhibitory activity against pathogenic bacterial strains with the zone of inhibition in the range of (22-28 mm), (23-27 mm) and (24-26 mm) respectively. Compounds 1k, 1l and 1n shows moderate activity against bacterial strains with the zone of inhibition in the range of (15-17 mm), (17-19 mm) and (15-20 mm) respectively. Compound 1c shows less active against bacterial strains with the zone of inhibition in the range of (8-14 mm). Compound 1b shows significant inhibitory activity against *S. typhi* (28 mm), *P. vulgaris* (26 mm), *E. coli* (25 mm) and *P. aeruginosa* (22 mm) bacterias. Compound 1g shows significant inhibitory activity against *S. typhi* (27 mm), *P. vulgaris* (25 mm), *P. aeruginosa* (24 mm) and *E. coli* (23 mm) bacterias. Compound 1n shows significant inhibitory activity against *Salmonella typhi* (25 mm), *P. vulgaris* (25 mm), *P. aeruginosa* (24 mm) and *E. coli* (24 mm) bacterias. Isoxazole group present in 1b, chlorine at 4^{th} position and fluorine at 2^{nd} position in 1g and nitro group at 4^{th} position in 1n are probably responsible for the significant antibacterial activity. Compound 1b shows observable antibacterial activity in the least concentration of 46 µg/ml against *P. aeruginosa* bacteria, compound 1g shows observable antibacterial activity in the least concentration of 48 µg/ml against *P. vulgaris* bacteria and 1n shows observable antibacterial activity in the least concentration of 58 µg/ml against *S. typhi* bacteria.

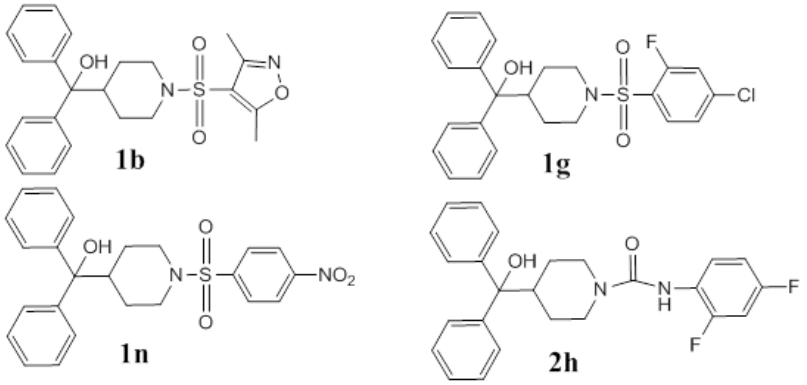


Figure 1: The structure of the potent antimicrobial agents

Among urea series 2a-i, compounds 2h shows significant inhibitory activity against pathogenic bacterial strains with the zone of inhibition in the range of (23-26 mm). The compounds 2a, 2c and 2e showed moderate activity against bacterial strains with the zone of inhibition in the range of (13-18 mm), (14-19 mm) and (14-17 mm) respectively. Whereas, the compound 2i shows less inhibitory activity against bacterial strains. Compound 2h shows significant activity against *S. typhi* (23 mm), *P. vulgaris* (23 mm), *E. coli* (22 mm) and *P. aeruginosa* (21 mm) bacterias. Fluorine at 2nd and 4th position present in compound 2h could be responsible for the significant antibacterial activity. The fluorine atom has a profound effect on drug disposition, in terms of distribution, drug clearance, route and extent of drug metabolism [12]. Compound 2h shows observable antibacterial activity in the least concentration of 47 µg/ml against *P. vulgaris* bacteria.

The structural correlation of the synthesized compounds reveal that, by keeping the same substituents on substituted phenyl ring of both sulfonamide and urea series (1a-2f) found that, the urea series shows relatively significant antibacterial activity. Another structural correlation is that, by changing the substituents on phenyl ring but doesn't change the position of the substituents (1g-2h) and (1n-2f), found that sulfonamide series show relatively significant antibacterial activity. This is because of the nature of the substituents influences the antibacterial activity. The above two structural correlation studies reveal that both nucleus and substituents are responsible for the antibacterial activity of the drugs.

CONCLUSION

From the results obtained, it reveals that the antibacterial activity of synthesized compounds could be attributed to isoxazole and chlorofluoroaryl moiety. The tested compounds 1a-n and 2a-i showed relatively better activity against Gram-negative bacteria compare to Gram-positive. Compounds 1b and 1g are the most potent among the sulfonamide series whereas compound 2h is the most potent among urea series. The structures of the potent antibacterial are shown in Figure 1.

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