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Rapid and efficient synthesis of newer heterocyclic 2-azetidinone and 5-benzylidine-4-oxo-thiazolidine compounds and their pharmacological studies

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A straightforward rapid and efficient protocol for the synthesis of 2-azetidinone (D_{1-10}) and 5-benzylidine-4-oxo-thiazolidine (F_{1-10}) has been designed and synthesized in order to find newer antimicrobial compounds. The structure of entitle compounds have been evaluated on the basis of various spectroscopic techniques FTIR, ^{1}H-NMR, ^{13}C-NMR as well as elemental microanalysis. The title compounds were screened for their preliminary *in vitro* antibacterial activity against a panel of selected pathogenic bacterial strains, *Staphylococcus aureus (MTCC 96), Escherichia coli (MTCC 443), Proteus vulgaris (MTCC 426)* and *Pseudomonas aeruginosa (MTCC 424)* using cup-plate agar diffusion method at 40 µg/ml concentration. Out of synthesized compounds, compound nos. D_4, D_5, D_7, D_8, D_9 and D_{10} have shown outstanding inhibitory effect against all pathogens and consider as the best bioactive desired antibacterial analogue of the series as compare to standard drugs ampicilline and chloramphenicol.

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Capsule Summary: Heteroaryl substituted analogs of 2-azetidinone and 5-benzylidine-4-oxo-thiazolidine were prepared via conventional method. Results of pharmacological study revealed the future hope of the potent antibiotic drug.

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INTRODUCTION

Over the past years, potency of antimicrobial therapy is somewhat in hesitate due to bacterial resistance to antibiotics. Quick development of drug resistant strains exerts a severe threat in present years (Overbye and Barrett, 2005). The lack of effective treatment is the main cause of this problem (Alekshun and Levy, 2007). The main challenge plunge into two parts: suitable target selection, mainly the requirement of pursuing molecular targets that are not susceptible to rapid resistance development and enhancement of chemical libraries to defeat limitations of diversity, particularly that which is essential to defeat barriers to bacterial species especially in Gramnegative organisms (Silver, 2011). Even though advancement in expansion of antibacterial agents, there are still exceptional needs to find new antibacterial agents due to enlargement of multidrug resistant bacteria (Wise et al., 1998). This incentive led us to the formation of some newer antibacterial agents.

Imines, well-known even as Schiff bases or azomethines (Vigato and Tamburini, 2004) are compounds that are symbolized by the general formula R1N=CHR2 are an important and distinct class of organic compounds. Their chemistry has attracted the interest of many researchers in

the world. The chemical reactivity and physical properties of Schiff bases are continue to be studied by more than a hundred years (Layer, 1963). They are synthetically versatile substrate that can be used to synthesize a large variety of various heterocyclic compounds and as a raw material for drug synthesis (Kouznetsov, 2009; Palomo et al., 2004; Solankee et al., 2008). Schiff bases are further known to possess wide spectrum of pharmacological activities such as antiviral (Kumar et al., 2010), antimycobacterial (Hearn et al., 2009), antimicrobial (Shi et al., 2007), anti-inflammatory (Sondhi et al., 2006), cytotoxic (Miri et al., 2013) etc.

Azetidine is a parent heterocyclic ring in azetidinones. Azetidine is a 4 member heterocyclic ring system with nitrogen as hetero atom. 2-Azetidinones or 2-oxoazetidines are known as β-lactams consists of a carbonyl group at the second position and it is one of the most common heterocyclic ring found in antibiotics including penicillins, cephalosporins, carbapenems, nocardicin A, monobactams, clavulanic acid, sulbactams and tazobactams which have been widely used as chemotherapeutic agents to treat bacterial infection and microbial diseases (Maiti et al., 2006; Singh, 2004). The chemistry of 2-azetidinone has taken a vital place in organic chemistry since the discovery of penicillin by Sir Alexander Fleming in 1928. The azetidinone moiety is reported as a potent mechanism based inhibitor of several enzymes like human leukocyte elastase, tryptase, chymase, thrombin, serine protease and human cytomegalovirus protease enzyme (Knight et al., 1992; Firestone et al., 1990; Vergely et al., 1996). The pharmacological activity of the 2-azetidinone is normally assumed to be related with the chemical reactivity of their 2-azetidinone ring and on the substituents particularly at nitrogen of the 2-azetidinone ring. Generally β-lactam derivatives have great importance because of widely used as antibacterial agent (Halve et al., 2007; Solankee et al., 2007; Singh and Mmolotsi, 2005). Recently, these compounds are also reported various pharmacological properties like cholesterol absorption inhibitors (Wang et al., 2009), anti-inflammatory agent (Kumar et al., 2007), cytotoxic (Veinberg et al., 2003), antiplasmodial (Singh et al., 2011), antitubercular (Thaker et al., 2003) etc. These activities stimulated our attention and prompted us to synthesize some 2-azetidinone derivatives.

4-Oxo-thiazolidines are thiazolidine derivatives having a sulfur atom at position 1, nitrogen at position 3 and a carbonyl group at position 4. The thiazolidinone scaffold is very versatile and has featured in a number of clinically used drugs such as Darbufelon (dual COX-2/5-LOX inhibitors), Pioglitazone and its analogs (hypoglycemic thiazolidinediones), Etozolin (new generation diuretics) (Lesyk and Zimenkovsky, 2004) etc… . Several reports have appeared in the literature which highlights their chemistry and pharmacological uses (Verma and Saraf, 2008; Hamama et al., 2008). Moreover they have been reported as novel inhibitors of the bacterial enzyme Mur B which was a antecedent during the biosynthesis of peptidologycan, HIV-1 integrase inhibitors, non-nucleoside inhibitors of HIV-RT (Rawal et al., 2005; Unangst et al., 1993; Dayam et al., 2005). They are also known for their broad spectrum of biological activities, including anticancer effect (Lesyk et al., 2007), anti-apoptotic Bcl-2 proteins (Degterev et al., 2001), *in vivo* anti-inflammatory (Ottana et al., 2005), antimicrobial (Solankee et al., 2012), antiparasitic (Mahran et al., 2003), antiviral (Barreca et al., 2001) etc. In view of the literature regarding biological potency of 2-azetidinone and 4-oxo-thiazolidines and in continuation of our research work on diverse heterocycles (Solankee and Patel, 2013), herein we synthesize some 2-azetidinones (D_{1-10}) and 5-benzylidene-4-oxo-thiazolidines (F_{1-10}) from schiff base (C_{1-10}) with a view to carry out their potency as better antibacterial agents.

MATERIAL AND METHODS

Commercial reagents (AR grade) and solvents were used without further purification. Melting points of the synthesized compounds were determined in open-glass capillaries and were uncorrected. IR spectra (KBr disc) were recorded on Perkin–Elmer-838 FT-IR spectrometer using KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were scanned on Bruker Avance II 400 spectrometer at 400 MHz and 100 MHz respectively. Chemical shifts are expressed in δ (ppm) relative to TMS as an internal standard using $CDCl_3$ as solvent. The purity of each compound was verified by TLC-silica gel plates (Merck). The elution was realized in the methanol-toluene as mobile phase. The spots visualization was done either with UV light or with iodine vapour. Elemental analyses of the newly synthesized compounds were performed on Perkin-Elmer 2400 series-II elemental analyzer (Perkin-Elmer, USA). Reference drugs for antibacterial activity Ampicillin and Chloramphenicol of commercial grade were used.

The building blocks *N*-(3-phenoxyphenyl) benzylidine amine/ substituted amine (C_{1-10}) and *N*-2-(3'-phenoxyphenyl)-3-phenyl/substituted phenyl-4-oxo-thiazolidine (E_{1-10}) were synthesized in toluene using Dean-Stark water separator as the reported method described previously by solankee et al (Solankee, 2011).

General procedure for the preparation of 1-(phenyl/substitutedphenyl)-3-chloro-4-(3'-phenoxyphenyl)-2-azetidinone (D_{1-10})

A mixture of *N*-(3-phenoxyphenyl) benzylidine amine/ substituted amine (C_{1-10}) (0.01 mol) and triethylamine (0.02 mol) was dissolved in 1, 4-dioxane (50 ml) and kept in an ice bath. To this well stirred cooled solution of chloroacetylchloride (0.02 mol) was added drop wise during 30 min. The reaction-mixture was then stirred for further 3 hrs and left at room temperature for three days. The precipitated of triethylammonium chloride was filtered off and 1,4-dioxane was removed by distillation. The reaction was monitored by TLC on silica gel using toluene : methanol (10:4 V/V). After completion of the reaction, the mixture was poured into crushed ice. The product thus obtained was

filtered, washed with water and recrystallized from methanol. The analytical and spectral data of the entire synthesized compounds (D_{1-10}) are given below.

1-(2'-Ethoxyphenyl)-3-chloro-4-(3'-phenoxyphenyl)-2-azetidinone (D_1)

IR (KBr, ν_{max}, cm^{-1}): 3034 (aromatic =CH str.), 2921 (C-H str. of azetidinone), 1730 (C=O str. of azetidinone), 1541 (C-N str. of azetidinone), 1532 (aromatic C=C str.), 1220 (asymmetric C-O-C str. ether linkage of phenoxy ring), 795 (C-Cl str. of azetidinone), 688 and 775 (C-H bending 1,3 and 1,2 disubstituted benzene ring); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.2 (t, 3H, $OCH_2C\underline{H}_3$), 3.8 (q, 2H, $OC\underline{H}_2CH_3$), 4.5 (d, *J* = 9.3 Hz, 1H, -C<u>H</u>-Cl, azitidinone ring), 4.0 (d, *J* = 9.0 Hz, 1H, -C<u>H</u>-N, azitidinone ring), 6.9-8.1 (m, 13H, Ar-<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 21.2 (CH_3), 64.5 (OCH_2), 66.1 (CH-Cl of azetidinone moiety), 69.8 (CH-N of azetidinone moiety), 111.5 (CH), 113.7 (CH), 114.0 (CH), 116.2 (CH), 118.6 (CH), 121.3 (CH), 122.4 (CH), 125.9 (CH), 129.7 (CH), 131.1 (C), 139.5 (C), 148.6 (C), 154.1 (C), 157.0 (C-OCH_2CH_3), 170.0 (C=O of azetidinone moiety).

1-(2'-Methoxyphenyl)-3-chloro-4-(3'-phenoxyphenyl)-2-azetidinone (D_2)

IR (KBr, ν_{max}, cm^{-1}): 3052 (aromatic =CH str.), 2931 (C-H str. of azetidinone), 1716 (C=O str. of azetidinone), 1524 (C-N str. of azetidinone), 1518 (aromatic C=C str.), 1230 (asymmetric C-O-C str. ether linkage of phenoxy ring), 1142 (OCH_3 str.), 791 (C-Cl str. of azetidinone), 681 and 770 (C-H bending 1,3 and 1,2 disubstituted benzene ring); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.7 (s, 3H, $OC\underline{H}_3$), 5.2 (d, *J* = 6.8 Hz, 1H, -C<u>H</u>-Cl, azitidinone ring), 4.9 (d, *J* = 6.4 Hz, 1H, -C<u>H</u>-N, azitidinone ring), 7.1-8.1 (m, 13H, Ar-<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 54.2 (OCH_3), 63.7 (CH-Cl of azetidinone moiety), 69.5 (CH-N of azetidinone moiety), 111.8 (CH), 113.4 (CH), 115.2 (CH), 117.8 (CH), 119.4 (CH), 121.6 (CH), 126.0 (CH), 128.5 (CH), 131.0 (CH), 132.7 (C), 141.5 (C), 153.4 (C), 156.3 (C), 157.1 (C-OCH_3), 167.5 (C=O of azetidinone moiety).

1-(2'-Phenoxyphenyl)-3-chloro-4-(3'-phenoxyphenyl)-2-azetidinone (D_3)

IR (KBr, ν_{max}, cm^{-1}): 3076 (aromatic =CH str.), 2957 (C-H str. of azetidinone), 1702 (C=O str. of azetidinone), 1535 (C-N str. of azetidinone), 1524 (aromatic C=C str.), 1231 (asymmetric C-O-C str. ether linkage of phenoxy ring), 784 (C-Cl str. of azetidinone), 671 and 777 (C-H bending 1,3 and 1,2 disubstituted benzene ring); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 4.3 (d, *J* = 7.7 Hz, 1H, -C<u>H</u>-Cl, azitidinone ring), 3.5 (d, *J* = 7.8 Hz, 1H, -C<u>H</u>-N, azitidinone ring), 6.7-8.3 (m, 18H, Ar-<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 57.4 (CH-Cl of azetidinone moiety), 65.1 (CH-N of azetidinone moiety), 109.5 (CH), 111.3 (CH), 113.2 (CH), 115.8 (CH), 117.4 (CH), 118.0 (CH), 121.5 (CH), 124.9 (CH), 127.1 (CH), 129.0 (CH), 131.8 (CH), 133.7 (CH), 137.1 (C), 141.5 (C), 146.9 (C), 151.5 (C), 154.2 (C), 168.1 (C=O of azetidinone moiety).

1-(3'-Chlorophenyl)-3-chloro-4-(3'-phenoxyphenyl)-2-azetidinone (D_4)

IR (KBr, ν_{max}, cm^{-1}): 3041 (aromatic =CH str.), 2955 (C-H str. of azetidinone), 1721 (C=O str. of azetidinone), 1532 (C-N str. of azetidinone), 1521 (aromatic C=C str.), 1222 (asymmetric C-O-C str. ether linkage of phenoxy ring), 778 (C-Cl str. of azetidinone), 650 (C-H bending 1,3 disubstituted benzene ring); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 5.8 (d, *J* = 7.3 Hz, 1H, -C<u>H</u>-Cl, azitidinone ring), 5.2 (d, *J* = 7.3 Hz, 1H, -C<u>H</u>-N, azitidinone ring), 7.0-8.0 (m, 13H, Ar-<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 65.4 (CH-Cl of azetidinone moiety), 67.2 (CH-N of azetidinone moiety), 111.4 (CH), 112.8 (CH), 114.1 (CH), 116.7 (CH), 118.5 (CH), 120.9 (CH), 122.2 (CH), 125.1 (CH), 127.8 (CH), 130.5 (C), 135.2 (C), 140.4 (C-Cl), 153.1 (C), 158.9 (C), 170.7 (C=O of azetidinone moiety).

1-(3'-Methylphenyl)-3-chloro-4-(3'-phenoxyphenyl)-2-azetidinone (D_5)

IR (KBr, ν_{max}, cm^{-1}): 3049 (aromatic =CH str.), 2962 (C-H str. of azetidinone), 1719 (C=O str. of azetidinone), 1537 (C-N str. of azetidinone), 1513 (aromatic C=C str.), 1378 (CH_3 str.), 1238 (asymmetric C-O-C str. ether linkage of phenoxy ring), 795 (C-Cl str. of azetidinone), 670 and 821 (C-H bending 1,3 and 1,4 disubstituted benzene ring); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.2 (s, 3H, $C\underline{H}_3$), 5.1 (d, *J* = 8.7 Hz, 1H, -C<u>H</u>-Cl, azitidinone ring), 4.6 (d, *J* = 8.3 Hz, 1H, -C<u>H</u>-N, azitidinone ring), 6.7-8.2 (m, 13H, Ar-<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 32.5 (CH_3), 66.1 (CH-Cl of azetidinone moiety), 75.4 (CH-N of azetidinone moiety), 114.8 (CH), 116.1 (CH), 117.4 (CH), 119.6 (CH), 121.0 (CH), 122.9 (CH), 124.8 (CH), 126.0 (CH), 128.2 (CH), 130.0 (C), 133.6 (C), 139.4 (C), 152.7 (C), 155.1 (C), 172.6 (C=O of azetidinone moiety).

1-(4'-Acetamidophenyl)-3-chloro-4-(3'-phenoxyphenyl)-2-azetidinone (D_6)

IR (KBr, ν_{max}, cm^{-1}): 3083 (aromatic =CH str.), 2969 (CH_3 str.), 1715 (-$COCH_3$ str.), 1688 (C=O str. of thiazolidinone), 1341 (C-N str.), 1529 (-$NHCOCH_3$ str.), 1523 (aromatic C=C str.), 1226 (asymmetric C-O-C str. ether linkage of phenoxy ring), 670 and 861 (C-H bending 1,3 and 1,4 disubstituted benzene ring), 740 (C-H bending of mono substituted benzene), 665 (C-S-C str. of thiazolidinone); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.8 (s, 3H, $C\underline{H}_3$), 4.7 (s, 1H, -C<u>H</u>-Ar, thiazolidinone ring), 6.6 (s, 1H, Ar-C<u>H</u>=, benzylidene ring), 7.2-8.0 (m, 18H, Ar-<u>H</u>), 8.3 (s, 1H, N<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 29.2 (CH_3), 68.4 (CH-Ar of thiazolidinone ring), 112.6 (CH), 113.5 (CH), 118.7 (CH), 119.2 (CH), 121.7 (CH), 124.5 (CH), 126.1 (CH=C of benzylidene ring), 128.0 (CH), 131.3 (CH), 132.4 (CH), 133.5 (C=CH of thiazolidinone ring), 136.1 (C), 138.4 (C-CH of benzylidene ring), 139.0 (C), 141.9 (C), 152.1 (C), 166.0 (C=O of thiazolidinone ring), 169.8 (C=O of acetamido ring).

1-(4'-Bromophenyl)-3-chloro-4-(3'-phenoxyphenyl)-2-azetidinone (D_7)

IR (KBr, ν_{max}, cm^{-1}): 3048 (aromatic =CH str.), 2954 (C-H str. of azetidinone), 1722 (C=O str. of azetidinone), 1531 (C-N str. of azetidinone), 1520 (aromatic C=C str.), 1229 (asymmetric C-O-C str. ether linkage of phenoxy ring), 789 (C-Cl str. of azetidinone), 656 and 875 (C-H bending 1,3 and 1,4 disubstituted benzene ring), 593 (C-Br str.); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 5.7 (d, *J* = 7.4 Hz, 1H, -C<u>H</u>-Cl, azitidinone ring), 5.0 (d, *J* = 7.2 Hz, 1H, -C<u>H</u>-N, azitidinone ring), 6.8-8.0 (m, 13H, Ar-<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 64.3 (CH-Cl of azetidinone moiety), 70.4 (CH-N of azetidinone moiety), 111.8 (CH), 112.2 (CH), 116.4 (CH), 118.0 (CH), 119.6 (CH), 120.4 (CH), 124.3 (CH), 126.1 (CH), 128.7 (CH), 131.8 (C), 142.3 (C), 144.7 (C-Cl), 150.0 (C), 157.8 (C), 172.3 (C=O of azetidinone moiety).

1-(4'-Chlorophenyl)-3-chloro-4-(3'-phenoxyphenyl)-2-azetidinone (D_8)

IR (KBr, ν_{max}, cm^{-1}): 3043 (aromatic =CH str.), 2953 (C-H str. of azetidinone), 1719 (C=O str. of azetidinone), 1526 (C-N str. of azetidinone), 1525 (aromatic C=C str.), 1220 (asymmetric C-O-C str. ether linkage of phenoxy ring), 770 (C-Cl str. of azetidinone), 663 and 869 (C-H bending 1,3 and 1,4 disubstituted benzene ring); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 5.9 (d, *J* = 6.8 Hz, 1H, -C<u>H</u>-Cl, azitidinone ring), 5.1 (d, *J* = 7.2 Hz, 1H, -C<u>H</u>-N, azitidinone ring), 7.1-8.0 (m, 13H, Ar-<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 63.1 (CH-Cl of azetidinone moiety), 66.5 (CH-N of azetidinone moiety), 109.7 (CH), 112.2 (CH), 115.3 (CH), 116.9 (CH), 117.0 (CH), 119.3 (CH), 121.4 (CH), 123.2 (CH), 125.7 (CH), 128.9 (C), 133.1 (C), 138.2 (C-Cl), 152.4 (C), 154.2 (C), 164.0 (C=O of azetidinone moiety).

1-(4'-Ethylphenyl)-3-chloro-4-(3'-phenoxyphenyl)-2-azetidinone (D_9)

IR (KBr, ν_{max}, cm^{-1}): 3006 (aromatic =CH str.), 2960 (C-H str. of azetidinone), 2954 and 2930 (CH_3 and CH_2 asymmetric str), 1713 (C=O str. of azetidinone), 1540 (C-N str. of azetidinone), 1525 (aromatic C=C str.), 1221 (asymmetric C-O-C str. ether linkage of phenoxy ring), 781 (C-Cl str. of azetidinone), 649 and 863 (C-H bending 1,3 and 1,4 disubstituted benzene ring); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.4 (t, 3H, $CH_2C\underline{H}_3$), 2.9 (q, 2H, $C\underline{H}_2CH_3$), 4.9 (d, *J* = 8.4 Hz, 1H, -C<u>H</u>-Cl, azitidinone ring), 5.8 (d, *J* = 8.4 Hz, 1H, -C<u>H</u>-N, azitidinone ring), 7.0-8.2 (m, 13H, Ar-<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 19.4 (CH_3), 26.5 (CH_2), 59.1 (CH-Cl of azetidinone moiety), 66.3 (CH-N of azetidinone moiety), 110.5 (CH), 112.2 (CH), 117.9 (CH), 122.4 (CH), 124.3 (CH), 126.8 (CH), 128.2 (CH), 130.0 (CH), 131.4 (CH), 132.1 (C), 138.0 (C), 140.5 (C), 154.1 (C), 159.2 (C), 172.1 (C=O of azetidinone moiety).

1-(4'-Methoxyphenyl)-3-chloro-4-(3'-phenoxyphenyl)-2-azetidinone (D_{10})

IR (KBr, ν_{max}, cm^{-1}): 3059 (aromatic =CH str.), 2934 (C-H str. of azetidinone), 1712 (C=O str. of azetidinone), 1520 (C-N str. of azetidinone), 1517 (aromatic C=C str.), 1239 (asymmetric C-O-C str. ether linkage of phenoxy ring), 1150 (OCH_3 str.), 798 (C-Cl str. of azetidinone), 653 and 860 (C-H bending 1,3 and 1,4 disubstituted benzene ring); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.4 (s, 3H, $OC\underline{H}_3$), 5.1 (d, *J* = 6.8 Hz, 1H, -C<u>H</u>-Cl, azitidinone ring), 4.6 (d, *J* = 6.4 Hz, 1H, -C<u>H</u>-N, azitidinone ring), 6.7-7.8 (m, 13H, Ar-<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 52.4 (OCH_3), 62.1 (CH-Cl of azetidinone moiety), 69.5 (CH-N of azetidinone moiety), 111.0 (CH), 112.2 (CH), 114.5 (CH), 117.3 (CH), 120.7 (CH), 122.3 (CH), 128.0 (CH), 130.2 (CH), 132.8 (CH), 134.6 (C), 140.5 (C), 151.9 (C), 154.6 (C), 156.8 (C-OCH_3), 165.4 (C=O of azetidinone moiety).

General procedure for the preparation of 2-(3'-phenoxyphenyl)-3-(phenyl/substituted phenyl)-5-benzylidene-4-oxo-thiazolidine (F_{1-10})

An equimolar amount of 2-(3'-phenoxyphenyl)-3-phenyl/substituted phenyl-4-oxo-thiazolidine (0.01mol) (E_{1-10}) and benzaldehyde (0.01 mol) dissolved in freshly prepared sodium ethoxide solution taken in 250 ml round bottomed flask, fitted with a reflux condenser and were refluxed for 6 hours with occasional shaking. The progress of the reaction was monitored by TLC using toluene: methanol (10:8 V/V) eluent as mobile phase. The reaction mixture was cooled and poured into crushed ice. The solid thus obtained was filtered, washed with water, and the product was recrystallized from methanol. Synthetic pathway for formation of title compounds is presented in Scheme 1. The analytical and spectral data of the entire synthesised compounds (F_{1-10}) are given below.

2-(3'-Phenoxyphenyl)-3-(2'-ethoxyphenyl)-5-benzylidene-4-oxo-thiazolidine (F_1)

IR (KBr, ν_{max}, cm^{-1}): 3050 (aromatic =CH str.), 1666 (C=O str. of thiazolidinone), 1554 (aromatic C=C str.), 1349 (C-N str.), 1238 (asymmetric C-O-C str. ether linkage of phenoxy ring), 680 and 770 (C-H bending 1,3 and 1,2 disubstituted benzene ring), 731 (C-H bending of mono substituted benzene), 635 (C-S-C str. of thiazolidinone); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.9 (t, 3H, $OCH_2C\underline{H}_3$), 3.6 (q, 2H, $OC\underline{H}_2CH_3$), 4.2 (s, 1H, -C<u>H</u>-Ar, thiazolidinone ring), 6.6 (s, 1H, Ar-C<u>H</u>=, benzylidene ring), 6.9-8.0 (m, 18H, Ar-<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 29.2 (CH_3), 62.6 (OCH_2), 67.5 (CH-Ar of thiazolidinone ring), 112.5 (CH), 114.3 (CH), 116.1 (CH), 118.2 (CH), 120.1 (CH), 122.5 (CH), 124.6 (CH=C of benzylidene ring), 126.9 (CH), 130.1 (CH), 134.1 (CH), 135.8 (C=CH of thiazolidinone ring), 137.0 (C), 139.5 (C-CH of benzylidene ring), 142.4 (C), 152.3 (C), 156.1 (C-OCH_2CH_3), 167.1 (C=O of thiazolidinone ring).

2-(3'-Phenoxyphenyl)-3-(2'-methoxyphenyl)-5-benzylidene-4-oxo-thiazolidine (F_2)

IR (KBr, ν_{max}, cm^{-1}): 3015 (aromatic =CH str.), 1694 (C=O str. of thiazolidinone), 1519 (aromatic C=C str.), 1328 (C-N str.), 1234 (asymmetric C-O-C str. ether linkage of phenoxy ring), 1133 (OCH_3 str.), 721 (C-H bending of mono substituted benzene), 690 and 771 (C-H bending 1,3 and 1,2 disubstituted benzene ring), 679 (C-S-C str. of thiazolidinone); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.9 (s, 3H, OCH_3), 4.1 (s, 1H, -CH-Ar, thiazolidinone ring), 7.0 (s, 1H, Ar-CH=, benzylidene ring), 7.2-8.1 (m, 18H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 53.1 (OCH_3), 66.4 (CH-Ar of thiazolidinone ring), 112.5 (CH), 113.9 (CH), 115.1 (CH), 117.5 (CH), 118.4 (CH), 120.5 (CH), 122.1 (CH=C of benzylidene ring), 124.6 (CH), 127.5 (CH), 130.1 (CH), 132.7 (C=CH of thiazolidinone ring), 133.2 (C), 136.4 (C-CH of benzylidene ring), 138.9 (C), 155.2 (C), 158.6 (C-OCH_3), 161.8 (C=O of thiazolidinone ring).

2-(3'-Phenoxyphenyl)-3-(2'-phenoxyphenyl)-5-benzylidene-4-oxo-thiazolidine (F_3)

IR (KBr, ν_{max}, cm^{-1}): 3053 (aromatic =CH str.), 1663 (C=O str. of thiazolidinone), 1544 (aromatic C=C str.), 1332 (C-N str.), 1247 (asymmetric C-O-C str. ether linkage of phenoxy ring), 695 and 768 (C-H bending 1,3 and 1,2 disubstituted benzene ring), 740 (C-H bending of mono substituted benzene), 625 (C-S-C str. of thiazolidinone); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 5.3 (s, 1H, -CH-Ar, thiazolidinone ring), 6.8 (s, 1H, Ar-CH=, benzylidene ring), 6.9-8.3 (m, 23H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 69.4 (CH-Ar of thiazolidinone ring), 112.4 (CH), 114.6 (CH), 116.3 (CH), 118.1 (CH), 120.1 (CH), 122.2 (CH), 124.7 (CH=C of benzylidene ring), 126.3 (CH), 129.0 (CH), 130.6 (CH), 131.5 (CH), 133.7 (CH), 135.4 (CH), 138.1 (C=CH of thiazolidinone ring), 140.2 (C), 141.4 (C), 142.3 (C-CH of benzylidene ring), 143.0 (C), 154.5 (C), 165.3 (C=O of thiazolidinone ring).

2-(3'-Phenoxyphenyl)-3-(3'-cholorphenyl)-5-benzylidene-4-oxo-thiazolidine (F_4)

IR (KBr, ν_{max}, cm^{-1}): 3038 (aromatic =CH str.), 1650 (C=O str. of thiazolidinone), 1569 (aromatic C=C str.), 1373 (C-N str.), 1220 (asymmetric C-O-C str. ether linkage of phenoxy ring), 648 (C-H bending 1,3 disubstituted benzene ring), 751 (C-Cl str.), 730 (C-H bending of mono substituted benzene), 681 (C-S-C str. of thiazolidinone); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 4.9 (s, 1H, -CH-Ar, thiazolidinone ring), 6.8 (s, 1H, Ar-CH=, benzylidene ring), 7.2-8.0 (m, 18H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 64.1 (CH-Ar of thiazolidinone ring), 110.5 (CH), 112.4 (CH), 114.1 (CH), 116.5 (CH), 118.2 (CH), 122.4 (CH), 124.8 (CH=C of benzylidene ring), 126.1 (CH), 129.5 (CH), 130.1 (CH), 131.4 (C=CH of thiazolidinone ring), 134.5 (C), 136.6 (C), 137.1 (C-CH of benzylidene ring), 142.5 (C), 153.7 (C), 163.5 (C=O of thiazolidinone ring).

2-(3'-Phenoxyphenyl)-3-(3'-methylphenyl)-5-benzylidene-4-oxo-thiazolidine (F_5)

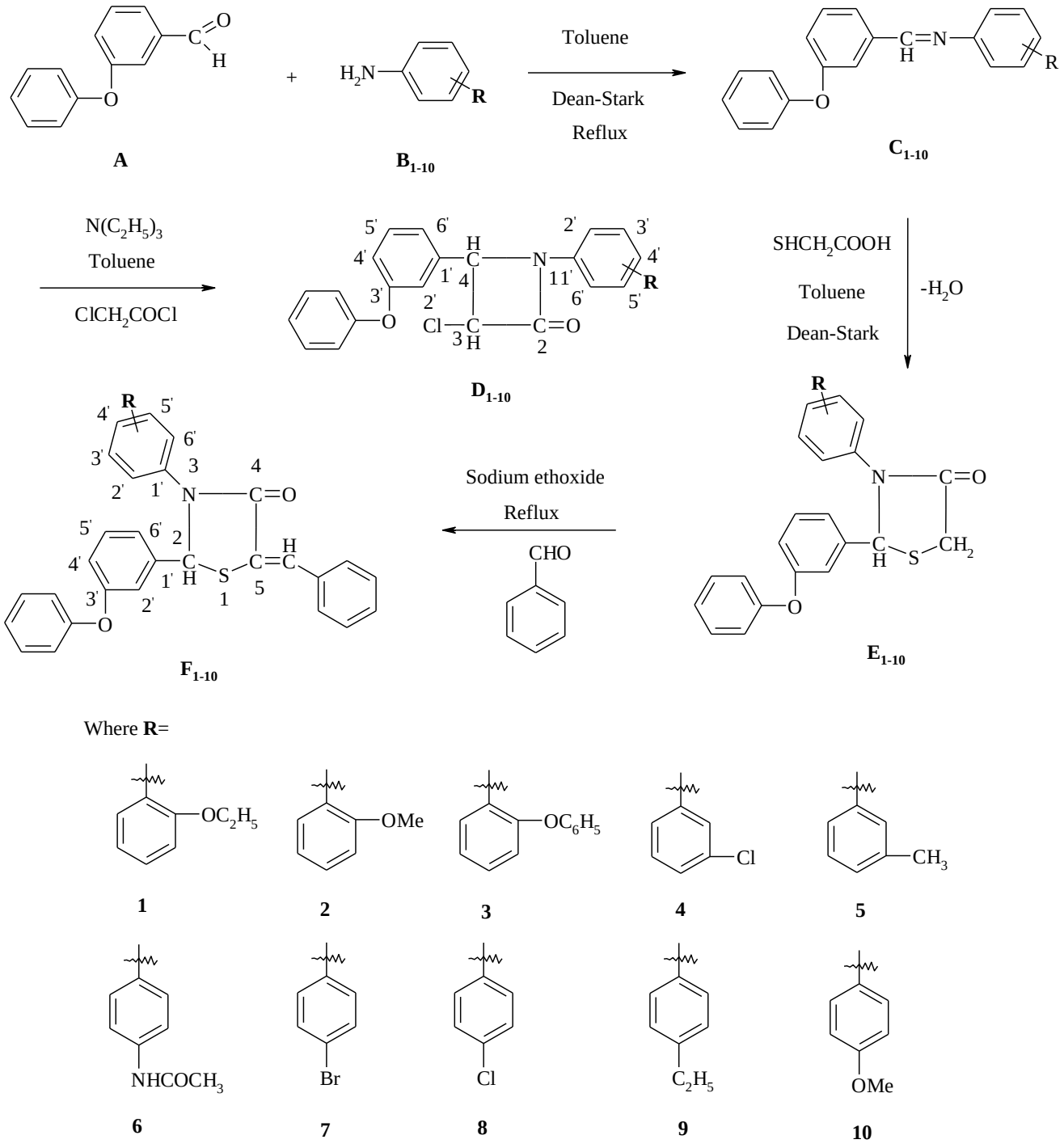
IR (KBr, ν_{max}, cm^{-1}): 3030 (aromatic =CH str.), 1671 (C=O str. of thiazolidinone), 1589 (aromatic C=C str.), 1382 (CH_3 str.), 1372 (C-N str.), 1216 (asymmetric C-O-C str. ether linkage of phenoxy ring), 664 (C-H bending 1,3 disubstituted benzene ring), 745 (C-H bending of mono substituted benzene), 696 (C-S-C str. of thiazolidinone); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.3 (s, 3H, CH_3), 4.5 (s, 1H, -CH-Ar, thiazolidinone ring), 6.5 (s, 1H, Ar-CH=, benzylidene ring), 6.9-8.2 (m, 18H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 32.4 (CH_3), 64.2 (CH-Ar of thiazolidinone ring), 113.5 (CH), 115.6 (CH), 117.3 (CH), 119.0 (CH), 121.8 (CH), 123.5 (CH), 125.9 (CH=C of benzylidene ring), 127.2 (CH), 128.3 (CH), 131.4 (CH), 132.5 (C=CH of thiazolidinone ring), 134.3 (C), 136.1 (C-CH of benzylidene ring), 140.8 (C), 142.6 (C), 156.1 (C), 162.0 (C=O of thiazolidinone ring).

2-(3'-Phenoxyphenyl)-3-(4'-acetamidophenyl)-5-benzylidene-4-oxo-thiazolidine (F_6)

IR (KBr, ν_{max}, cm^{-1}): 3086 (aromatic =CH str.), 2969 (CH_3 str.), 1715 (-$COCH_3$ str.), 1689 (C=O str. of thiazolidinone), 1521 (-$NHCOCH_3$ str.), 1518 (aromatic C=C str.), 1341 (C-N str.), 1221 (asymmetric C-O-C str. ether linkage of phenoxy ring), 651 and 865 (C-H bending 1,3 and 1,4 disubstituted benzene ring), 730 (C-H bending of mono substituted benzene), 651 (C-S-C str. of thiazolidinone); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.9 (s, 3H, CH_3), 4.2 (s, 1H, -CH-Ar, thiazolidinone ring), 6.4 (s, 1H, Ar-CH=, benzylidene ring), 7.2-8.0 (m, 18H, Ar-H), 8.2 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 25.5 (CH_3), 66.1 (CH-Ar of thiazolidinone ring), 110.4 (CH), 112.2 (CH), 114.1 (CH), 116.3 (CH), 119.6 (CH), 121.5 (CH), 123.8 (CH=C of benzylidene ring), 125.6 (CH), 128.1 (CH), 130.2 (CH), 131.9 (C=CH of thiazolidinone ring), 133.2 (C), 135.0 (C-CH of benzylidene ring), 137.4 (C), 141.5 (C), 152.1 (C), 168.1 (C=O of thiazolidinone ring), 172.3 (C=O of acetamido ring).

2-(3'-Phenoxyphenyl)-3-(4'-bromophenyl)-5-benzylidene-4-oxo-thiazolidine (F_7)

IR (KBr, ν_{max}, cm^{-1}): 3031 (aromatic =CH str.), 1642 (C=O str. of thiazolidinone), 1575 (aromatic C=C str.), 1360 (C-N str.), 1223 (asymmetric C-O-C str. ether linkage of phenoxy ring), 661 and 874 (C-H bending 1,3 and 1,4 disubstituted benzene ring), 738 (C-H bending of mono substituted benzene), 631 (C-S-C str. of thiazolidinone), 589 (C-Br str.); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 4.4 (s, 1H, -CH-Ar, thiazolidinone ring), 7.0 (s, 1H, Ar-CH=, benzylidene ring), 7.3-8.2 (m, 18H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 69.1 (CH-Ar of thiazolidinone ring), 111.4 (CH), 112.8 (CH), 114.1 (CH), 116.5 (CH), 118.4 (CH), 120.3 (CH), 122.1 (CH=C of benzylidene ring), 124.6 (CH), 126.5 (CH), 130.0 (CH), 131.4 (C=CH of thiazolidinone ring), 134.2 (C), 137.8 (C), 139.2 (C-CH of benzylidene ring), 141.4 (C), 150.2 (C), 161.3 (C=O of thiazolidinone ring).



Scheme 1: Systematic path to synthesize design compounds (D_1-D_{10}) and (F_1-F_{10})

2-(3'-Phenoxyphenyl)-3-(4'-chlorophenyl)-5-benzylidene-4-oxo-thiazolidine (F_8)

IR (KBr, ν_{max}, cm^{-1}): 3051 (aromatic =CH str.), 1672 (C=O str. of thiazolidinone), 1567 (aromatic C=C str.), 1353 (C-N str.), 1229 (asymmetric C-O-C str. ether linkage of phenoxy ring), 659 and 867 (C-H bending 1,3 and 1,4 disubstituted benzene ring), 738 (C-Cl str.), 726 (C-H bending of mono substituted benzene), 661 (C-S-C str. of thiazolidinone); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 4.9 (s, 1H, -C<u>H</u>-Ar, thiazolidinone ring),

6.8 (s, 1H, Ar-CH=, benzylidene ring), 7.0-8.2 (m, 18H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 64.5 (CH-Ar of thiazolidinone ring), 113.2 (CH), 114.5 (CH), 116.4 (CH), 119.3 (CH), 121.7 (CH), 124.0 (CH), 126.1 (CH=C of benzylidene ring), 128.9 (CH), 130.5 (CH), 132.4 (CH), 134.8 (C=CH of thiazolidinone ring), 135.9 (C), 138.2 (C), 140.1 (C-CH of benzylidene ring), 142.3 (C), 148.9 (C), 162.6 (C=O of thiazolidinone ring).

2-(3'-Phenoxyphenyl)-3-(4'-ethylphenyl)-5-benzylidene-4-oxo-thiazolidine (F_9)

IR (KBr, ν_{max}, cm^{-1}): 3020 (aromatic =CH str.), 2959 and 2926 (CH_3 and CH_2 asymmetric str.), 1669 (C=O str. of thiazolidinone), 1580 (aromatic C=C str.), 1389 (C-N str.), 1238 (asymmetric C-O-C str. ether linkage of phenoxy ring), 663 and 889 (C-H bending 1,3 and 1,4 disubstituted benzene ring), 742 (C-H bending of mono substituted benzene), 682 (C-S-C str. of thiazolidinone); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.4 (t, 3H, CH_2CH_3), 2.3 (q, 2H, CH_2CH_3), 4.2 (s, 1H, -CH-Ar, thiazolidinone ring), 7.1 (s, 1H, Ar-CH=, benzylidene ring), 6.9-7.9 (m, 18H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 20.5 (CH_3), 32.2 (CH_2), 69.5 (CH-Ar of thiazolidinone ring), 113.4 (CH), 115.2 (CH), 116.8 (CH), 118.4 (CH), 120.7 (CH), 122.3 (CH), 124.9 (CH=C of benzylidene ring), 127.7 (CH), 128.0 (CH), 129.4 (CH), 130.2 (C=CH of thiazolidinone ring), 132.4 (C), 135.9 (C), 137.0 (C-CH of benzylidene ring), 140.2 (C), 151.3 (C), 162.1 (C=O of thiazolidinone ring).

2-(3'-Phenoxyphenyl)-3-(4'-methoxyphenyl)-5-benzylidene-4-oxo-thiazolidine (F_{10})

IR (KBr, ν_{max}, cm^{-1}): 3016 (aromatic =CH str.), 1692 (C=O str. of thiazolidinone), 1519 (aromatic C=C str.), 1332 (C-N str.), 1234 (asymmetric C-O-C str. ether linkage of phenoxy ring), 1139 (OCH_3 str.), 669 and 861 (C-H bending 1,3 and 1,4 disubstituted benzene ring), 750 (C-H bending of mono substituted benzene), 653 (C-S-C str. of thiazolidinone); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.4 (s, 3H, OCH_3), 3.9 (s, 1H, -CH-Ar, thiazolidinone ring), 6.4 (s, 1H, Ar-CH=, benzylidene ring), 7.0-8.1 (m, 18H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 56.1 (OCH_3), 68.4 (CH-Ar of thiazolidinone ring), 112.2 (CH), 113.1 (CH), 114.5 (CH), 116.6 (CH), 118.0 (CH), 121.9 (CH), 123.0 (CH=C of benzylidene ring), 125.2 (CH), 128.4 (CH), 130.3 (CH), 132.5 (C=CH of thiazolidinone ring), 134.1 (C), 136.0 (C-CH of benzylidene ring), 139.2 (C), 156.3 (C), 160.2 (C-OCH_3), 164.0 (C=O of thiazolidinone ring).

Pharmacological assay

The synthesized compounds were screened for their antibacterial activity by employing cup-plate agar diffusion method (Barry, 1976) against Gram positive and Gram negative bacteria such as *Staphylococcus aureus* (MTCC 96), *Escherichia coli* (MTCC 443), *Proteus vulgaris* (MTCC 426) and *Pseudomonas aeruginosa* (MTCC 424). The compounds were tested at 40 µg/ml concentration and DMF was used as solvent. The sterilized nutrient agar media [2.4% (w/v) agar-agar, 5% (w/v) NaCl, peptone, pH (6.8 to 7.0)] was poured into a petridish (9.0 cm in diameter) and allowed to set for 2 hours. On the surface of the media microbial suspension was spread over the agar plates to solidify. A stainless steel cylinder (pre-sterilized) was used to bore the cavities. All the synthesized compounds (100 µg/ml) in DMF were placed serially in the cavities with the help of micropipette. It is then allowed to diffuse for 10 minutes in refrigerator. The plates were incubated at 37 ^{0}C for 24 hours. The control was also maintained with 0.1 ml of DMF in similar manner and the zone of inhibition of the growth was measured in mm (Table 1). The standard knows antibiotics like Ampicilline and Chloramphenicol were used.

RESULTS AND DISCUSSION

Chemistry

Numerous procedures for the synthesis of 2-azetidinones and 5-benzylidene-4-oxo-thiazolidines from Schiff base are available in the literature (Desai et al., 2001; Hassaneen et al., 2002; Solankee et al., 2012). Herein we report the synthesis of 2-azetidinones (D_{1-10}) by reacting *N*-(3-phenoxyphenyl) benzylidine amine/substituted amine (C_{1-10}) with triethylamine and 5-benzylidene-4-oxo-thiazolidines by applying Knoevenagel reaction condensation of 2-(3'-phenoxyphenyl)-3-phenyl/substituted phenyl-4-oxo-thiazolidine (F_{1-10}) with benzaldehyde dissolved in freshly prepared sodium ethoxide solution as per the systematic path describe in the scheme 1. The 2-azetidinone and 5-benzylidene-4-oxo-thiazolidines structure were confirmed based on the FTIR, ^{1}H- NMR, ^{13}C-NMR as well as elemental analysis. The spectral data of the isolated product were in complete agreement with the assigned structure. For example, the IR spectrum of the reaction product D_1 showed absorption band at 2921, 1730, 1541 and 795 cm^{-1} regions conforming the presence of CH, C=O, C-N and C-Cl functionality of azetidinone moiety respectively. The asymmetric C-O-C stretching ether linkage of phenoxy ring was observed at 1220 cm^{-1} which confirmed the 3-phenoxy ring. Moreover, the C-H bending vibrations for 1,3, and 1,2 disubstituted benzene ring, C=C as well as =CH functionality of aromatic ring were observed at 688, 775, 1532 and 3034 cm^{-1} respectively. ^{1}H NMR spectrum of compound D_1 was more informative. In addition to the peak of azetidinone moiety, characteristic signal were observed at δ 4.5 (d, *J* = 8.6 Hz, 1H, -CH-Cl), 4.0 (d, *J* = 8.6 Hz, 1H, -CH-N) confirming the structure of azetidinone ring. The other remaining thirteen aromatic protons resonated as a multiplet signal at δ 6.9-8.1 ppm. The ^{13}C NMR spectrum of D_1 was recorded in $CDCl_3$ and the spectral signals were in good agreement with the proposed structure. In the ^{13}C NMR spectrum of compound D_1, the most shielded and deshielded signal that appeared at δ 66.1, 69.8 and 170.0 ppm were assigned to the CH-Cl, CH-N and carbonyl carbon of the azetidinone moiety respectively.

Table 1: *In Vitro* antibacterial activity of synthesized compounds (D_1-D_{10}) and (F_1-F_{10}) (Zone of Inhibition in mm at 40 µg/mL concentration)

Compounds	*S. aureus* MTCC 96	*E. coli* MTCC443	*P. vulgaris* MTCC 426	*P. aerugenosa* MTCC 424
	Gram positive		Gram negative	
D_1	12	10	-	-
D_2	24	18	10	10
D_3	18	19	10	8
D_4	25	24	21	11
D_5	30	28	17	24
D_6	18	18	10	9
D_7	22	17	18	19
D_8	25	14	21	11
D_9	25	13	18	17
D_{10}	22	17	17	21
F_1	11	-	9	-
F_2	-	-	-	-
F_3	15	11	9	11
F_4	13	10	11	-
F_5	-	9	-	11
F_6	10	9	-	-
F_7	12	10	-	-
F_8	15	12	14	11
F_9	15	12	10	-
F_{10}	11	10	9	-
Ampicillin	23	12	12	12
Chloramphenicol	20	14	15	15

The signals for aromatic carbons appeared between at δ 111.5-157.0 ppm.

The formation of the product F_1 was confirmed by a sharp absorption band at 1666 cm^{-1} for C=O group along with a band at 1349 and 635 cm^{-1} for C-N and C-S-C stretching of thiazolidinone ring in the IR spectrum. The mono substituted benzene ring was exerted at 731 cm^{-1} which confirmed the attachment of benzylidine ring with thiazolidinone moiety. Further, the aromatic C=C stretching, C-H bending vibrations for 1,3 and 1,2 disubstituted benzene ring and asymmetric C-O-C stretching ether linkage of phenoxy ring were appeared at 1554, 680, 770 and 1238 cm^{-1} respectively. The ^{1}H NMR spectrum of compound F_1 showed a sharp singlet at δ 4.2 and 6.6 ppm due to the CH-Ar proton of thiazolidinone ring and Ar-C<u>H</u>= proton of benzylidene ring respectively. The other remaining eighteen aromatic protons resonated as a multiplet signal at δ 6.9-8.0 ppm. ^{13}C NMR spectrum of compound F_1 showed most shielded signal at 67.5 and deshielded signal at 167.1 ppm due to the CH-Ar and CO carbon of thiazolidinone moiety. The signal observed at δ 124.6 ppm due to the CH=C carbon of benzylidene unit and the signals for aromatic carbons appeared between at δ 112.5-156.1 ppm in the ^{13}C spectrum. Furthermore, triplete and quatrate of $OCH_2C\underline{H}_3$ and $OC\underline{H}_2CH_3$ protons were observed around at δ 1.0-2.0 ppm and 2.0-3.0 ppm in ^{1}H NMR of D_1 and F_1 stands for ethoxy group of aryl ring attached to 2-azetidinone and 4-thiazolidinone unit. The elemental analysis (C, N and H) found for all the condensed products were in close agreement with the calculated values.

Evaluation of antibacterial activity

The antibacterial activity of all the synthesized compounds were tested *in-vitro* against pathogenic *Staphylococcus aureus*, *Escherichia coli*, *Proteus vulgaris*, *Pseudomonas aeruginos.* The obtained scrineening results were compared with standard drugs (Ampicilline and Chloramphenicol) and tabulated in Table 2.

Table 1: The analytical and physical data of synthesized compounds (D_1-D_{10}) and (F_1-F_{10})

Compds	R	Molecular Formula	Yield (%)	M. P. ^{0}C	Elemental analysis Calculated (Found) %		
					C	H	N
D_1	2 - Ethoxy phenyl	$C_{23}H_{20}ClNO_3$	79	limpid	70.14 (70.10)	5.11 (5.13)	3.56 (3.51)
D_2	2 - Methoxy phenyl	$C_{22}H_{18}ClNO_3$	81	limpid	69.57 (69.54)	4.77 (4.79)	3.69 (3.73)
D_3	2 - Phenoxy phenyl	$C_{27}H_{20}ClNO_3$	74	limpid	73.39 (73.43)	4.56 (4.60)	3.17 (3.14)
D_4	3 - Chloro phenyl	$C_{21}H_{15}Cl_2NO_2$	83	limpid	65.64 (65.68)	3.93 (3.90)	3.65 (3.61)
D_5	3 - Methyl phenyl	$C_{22}H_{18}ClNO_2$	81	limpid	72.63 (72.60)	4.98 (4.92)	3.85 (3.82)
D_6	4 - Acetamido phenyl	$C_{23}H_{19}ClN_2O_3$	72	limpid	67.90 (67.86)	4.70 (4.68)	6.89 (6.86)
D_7	4 - Bromo phenyl	$C_{21}H_{15}BrClNO_2$	76	limpid	58.84 (58.89)	3.52 (3.48)	3.27 (3.30)
D_8	4 - Chloro phenyl	$C_{21}H_{15}Cl_2NO_2$	80	limpid	65.64 (65.67)	3.93 (3.97)	3.65 (3.62)
D_9	4 - Ethyl phenyl	$C_{23}H_{20}ClNO_2$	69	limpid	73.11 (73.08)	5.33 (5.29)	3.71 (3.75)
D_{10}	4 - Methoxy phenyl	$C_{22}H_{18}ClNO_3$	73	limpid	69.57 (69.55)	4.77 (4.80)	3.69 (3.65)
F_1	2 - Ethoxy phenyl	$C_{30}H_{25}NO_3S$	82	limpid	75.13 (75.10)	5.25 (5.21)	2.92 (2.88)
F_2	2 - Methoxy phenyl	$C_{29}H_{23}NO_3S$	85	69	74.82 (74.79)	4.98 (4.95)	3.01 (3.07)
F_3	2 - Phenoxy phenyl	$C_{34}H_{25}NO_3S$	65	63	77.40 (77.43)	4.77 (4.73)	2.65 (2.61)
F_4	3 - Chloro phenyl	$C_{28}H_{20}ClNO_2S$	77	84	71.56 (71.51)	4.29 (4.33)	2.98 (2.93)
F_5	3 - Methyl phenyl	$C_{29}H_{23}NO_2S$	70	limpid	74.82 (74.78)	4.98 (4.99)	3.01 (3.06)
F_6	4 - Acetamido phenyl	$C_{30}H_{24}N_2O_3S$	79	105	73.15 (73.12)	4.91 (4.96)	5.69 (5.64)
F_7	4 - Bromo phenyl	$C_{28}H_{20}BrNO_2S$	82	97	65.38 (65.34)	3.92 (3.87)	2.72 (2.76)
F_8	4 - Chloro phenyl	$C_{28}H_{20}ClNO_2S$	73	98	71.56 (71.53)	4.29 (4.25)	2.98 (2.94)
F_9	4 - Ethyl phenyl	$C_{30}H_{25}NO_2S$	78	81	77.73 (77.70)	5.43 (5.40)	3.02 (3.06)
F_{10}	4 - Methoxy phenyl	$C_{29}H_{23}NO_3S$	81	89	74.82 (74.86)	4.98 (4.95)	3.01 (3.03)

In case of Gram positive bacteria, compounds D_2 (30 mm), D_4, D_8, and D_9 (25 mm), D_2 (24 mm), D_7 and D_{10} (22 mm) displayed an outstanding inhibitory effect against *Staphylococcus aureus* as compared to Ampicillin (23 mm) and Chloramphenicol (20 mm). Compounds D_3, and D_6 (18 mm), F_3, F_8, and F_9 (15 mm), F_4 (13 mm), D_1, and F_7 (12 mm), F_1, and F_{10} (11 mm) and F_6 (10 mm) depicted moderate activity against *Staphylococcus aureus* compared to Ampicillin (23 mm) and Chloramphenicol (20 mm) while compounds F_2 and F_5 showed no zone of inhibition. In the case of inhibiting Gram negative bacteria, compounds D_5 (28 mm), D_4 (24 mm), D_3 (19 mm), D_2, and D_6 (18 mm), D_7, and D_{10} (17 mm), D_8 (14 mm) and D_9 (13 mm) demonstrated excellent activity compared to Ampicillin (12 mm) and

modest to Chloramphenicol (14 mm) against *Escherichia coli*. Compound D_8 (14 mm) found more potency to Ampicillin (12 mm) and equally potency to Chloramphenicol (14 mm) while compound F_8 and F_9 (12 mm) showed equally potency to Ampicillin (12 mm) and less potency to Chloramphenicol (14 mm) against *Escherichia coli*. Compounds F_3 (11 mm), D_1, F_4, F_7, and F_{10} (10 mm), F_5 and F_6 (9 mm) exerted poor activity while compounds F_1 and F_2 showed no zone of inhibition against *Escherichia coli* compared to Ampicillin (12 mm) and Chloramphenicol (14 mm). In the case of inhibiting *Proteus vulgaris* compounds D_4, and D_8 (21 mm), D_7, and D_9 (18 mm), D_5, and D_{10} (17 mm) and F_8 (14 mm) exhibited excellent activity while compounds D_2, D_3, D_6, and F_9 (10 mm), F_1, F_3 and F_{10} (9 mm) showed less potency compared to Ampicillin (12 mm) and moderate to Chloramphenicol (15 mm). Compounds D_1, F_2, F_5, F_6 and F_7 are not showed zone of inhibition against *Proteus vulgaris*. Against *Pseudomonas aeruginosa*, compounds D_5 (24 mm), D_{10} (21 mm), D_7 (19 mm) and D_9 (17 mm) displayed outstanding inhibitory effect whereas compounds D_4, D_8, F_3, F_5, and F_8 (11 mm), D_2 (10 mm), D_6 (9 mm) and D_3 (8 mm) found moderately active while compounds D_1, F_1, F_2, F_4, F_6, F_7, F_9 and F_{10} showed no zone of inhibition compared to Ampicillin (12 mm) and Chloramphenicol (15 mm). The methods was efficient for the synthesis of 2-azetidinone and 5-benzylidene-4-oxo-thiazolidine derivatives with potentially interesting biological antibacterial properties (Frick et al., 2003; Gurupadayya et al., 2008; Maffii et al., 1959; Mehta et al., 2010; Pawar et al., 2012).

CONCLUSIONS

The results of the study explained above have led to the development of a simple and efficient method for the synthesis of a new class of 2-azetidinone and 5-benzylidene-4-oxo-thiazolidine derivatives with potentially interesting biological antibacterial properties. From the screening result it is clear that the introduction of appropriate chloro, bromo, methyl, ethyl, methoxy substituent on the phenyl ring would lead to the more active antibacterial derivatives. Among the twenty synthesized compounds, compounds D_4, D_5, D_7, D_8, D_9 and D_{10} were the best bioactive desired antibacterial derivatives and most proficient member of the series. From the results of pharmacological activities it is clear that these compounds would be of better use in drug development to fight against bacterial infections in the future.

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