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Comparative Study of the Antibacterial Activity of N, N-Diethylamido Substituted p-Toluenesulfonamides to their α-Toluenesulfonamide Counterparts

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ABSTRACT
Reaction of p-toluenesulfonyl chloride with amino acids gave sulfonamides p-T1a-k which upon amidation afforded p-T2a-k. Similarly, treatment involving α-toluenesulfonyl chloride and amino acids afforded the sulfonamides α-T1a-k. These two classes of sulfonamides were synthetically modified at their COOH end position to achieve N,N-diethylamido substituted p-toluenesulfonamides p-T2a-k and α-toluenesulfonamides α-T2a-k, respectively. The chemical structures of the compounds were validated with IR, Mass spectra, NMR as well as elemental analytical data. Both classes of compounds were screened against *Escherichia coli* and *Staphylococcus aureus* and their activity were compared. It was remarkable to note that the α-toluene sulfonamides α-T2a-k were more active than their p-toluenesulfonamide counterparts p-T2a-k. Compound 1-(benzylsulfonyl)-N,N-diethylpyrrolidine-2-carboxamide α-T2a was the most potent antibacterial compound on *S. aureus* with MIC value of 3.12 μg mL^{-1} while N,N-Diethyl-3-phenyl-2-(phenylmethylsulfonamide) propanamide α-T2j emerged as the best antibacterial motif against *E. coli* with MIC value of 12.5 μg mL^{-1}. Hence, these compounds especially the α-toluenesulfonamide core structural templates are good candidates for further study for future drug discovery.

Key words: Sulfonamide, bacterial infection, drug resistance, zone of inhibition, *Escherichia coli*

INTRODUCTION

Sulfonamide drugs which have brought about an antibiotic revolution in medicine are associated with a wide range of biological activities. Sulfonamides inhibit the multiplication of bacteria by acting as competitive inhibitors of p-aminobenzoic acid (PABA) in the folic acid metabolism cycle. They have been in clinical use since 1968 (Connor, 1998) and are known to represent a class of medicinally important compounds which are extensively used as antibacterial agents (Chohan *et al*., 2010). Sulfonamides possess many types of biological activities and many of them are widely used in therapeutic medicine as analgesic (Zebardast *et al*., 2009), antimicrobial (Ozbek *et al*., 2007), anticancer (Lopez *et al*., 2010), antileishmanial (Bhattacharya *et al*., 2002), antitumor (Alqasoumi *et al*., 2010), antidiabetic (Berredjem *et al*., 2015), antioxidant (Saeedi *et al*., 2014), anticonvulsant (Kiran *et al*., 2009), anti-HIV (Al-Soud *et al*., 2008) antihypertensive (Bhagwat *et al*., 2014), anti-inflammatory (Chowdhury *et al*., 2009), antimalarial (Miller *et al*., 2002), antitubercular (Papadopoulou *et al*., 2014), antiviral, antiplatelet aggregation (Wang *et al*., 2003), diuretic (Supuran and Scozzafava, 2000) and anti-carbonic anhydrase (Bertucci *et al*., 2009; Eroglu, 2008) activities among others.

Recently, a host of structurally novel sulfonamide derivatives have been reported to show substantial antitumor activity *in vitro* and/or *in vivo* (Ismail *et al*., 2006). The chemistry of sulfonamides has recently shown them to be highly efficient synthons in the preparation of various valuable biologically active compounds (Bahrami *et al*., 2009). A novel series of potent thioether benzenesulfonamide inhibitors of carbonic anhydrases II and IV was discovered using structure-based drug design (Vernier *et al*., 2010). The sulfonamide dyes, especially secondary sulfonamide dyes, exhibited superior dye exhaustion and color fastnesses to washing, sublimation and rubbing on fine denier PP fabrics (Cui *et al*., 2009). Many of the 9-sulfonylamino derivatives exhibited improved antibacterial activity against a number of tetracycline and minocycline resistant gram-positive pathogens (Sum *et al*., 2006).

Epidemiological studies have revealed that the emergent of new diseases is on the increase and quite alarming (Jones *et al*., 2008). Multi-drug resistance is also one of the major immediate threats to human health today (Dyatkina *et al*., 2002). For instance, methicillin-resistant staphylococci are resistant to many antibiotics such as penicillin, carbapenems, cephems and beta-lactam, quinolone, amino glycosides and tetracycline (Jain *et al*., 2004), whereas sulfonamides and their combination therapies are gaining more attention by the day in antimicrobial drug research (Genc *et al*., 2008). Thus, it is conceivable to develop a series of functionalized sulfonamides with dialkylated amide side chain modification on carboxyl functionality for possible antibacterial efficacy. In view of the challenges above and other wide pharmacological activities of sulfonamide derivatives, we have herein embarked on the synthesis and antibacterial study of p-toluenesulfonamides and α-toluenesulfonamides in order to compare their biological efficiency for future drug design.

MATERIALS AND METHODS

General: The melting points were determined on XT-4 Digital Binocular Microscope melting point apparatus manufactured by Beijing, Technical Instrument Co. Ltd. and were uncorrected. The IR spectra were run on Varian Excalibur HE 3100 FT-IR Spectrometer while, the mass spectra were obtained using Waters GCT Premier Spectrometer. The ^{1}H-NMR spectra were recorded in either $CDCl_3$ or DMSO-d_6 on NMR Bruker DPX 400 spectrometer operating at 400 MHz. Tetramethyl silane (TMS) was used as internal standard with the deuterium signal of the solvent as the lock and chemical shifts δ recorded in ppm. The elemental analyses (C, H, N) of the compounds were performed using Flash EA 1112 Elemental Analyzer. The pH was monitored using Portable pH Meter Model PHB4. All drying were conducted at reduced pressure with DHG-9023A Vacuum Oven. In addition, column chromatographic purifications were carried out on the products using $CHCl_3/CH_3OH$ (9:1) solvent system and Merck silica gel F (Mesh 200-300). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated with a RE-2000B Buchi Rotary Evaporator. Commercially available materials were used without further purification while other reagents were used directly after ascertaining the purity condition.

Synthesis

General procedure for p-toluenesulfonamide p-T1a-k: To a solution of amino acid (12.5 mmol) in water (15 mL) was added Na_2CO_3 (2.785 g, 26.25 mmol) at 0°C and p-toluenesulfonyl chloride, p-TsCl (2.86 g, 15 mmol) in three portions over a period of 1 h. The slurry was then warmed to room temperature and allowed to stir for 48 h. Upon completion of the reaction which was TLC monitored using $CHCl_3/CH_3OH$ solvent system (9:1), the reaction mixture was acidified with 20% concentrated aqueous HCl solution to pH 2, after which crystallization occurred and the product was obtained via suction filtration. The filtered crude product was washed with pH 2.2 buffer and dried in a vacuum oven at 60°C for 12 h to afford p-toluenesulfonamides p-T1a-k.

General procedure of α-tolylsulfonamide derivatives p-T2a-k: To a solution of L-amino acid (5 mmol) in H_2O (6 mL) was added Na_2CO_3 (1.113 g, 10.5 mmol) with continuous stirring until all the solutes had dissolved. The clear solution was cooled to -10°C and α-toluenesulfonyl chloride, α-TsCl (1.144 g, 6 mmol) was added in three batches over a period of 1 h. It was warmed up to 0°C and stirred there for 1 h. Finally, the reacting mixture was then warmed up to room temperature and allowed to stir there for 48 h. The reaction was quenched by addition of DCM (10 mL) and transferred into separatory funnel where the excess of α-TsCl was removed by extraction. The aqueous layer was then worked up to give a clear solution by addition of 2 N HCl until the pH 2.2 was attained. The clear liquid was then lyophilized at -52°C under reduced pressure for 12 h to obtain the crude solid product which was purified by column chromatography ($CHCl_3/CH_3OH$, 3:1) to afford α-toluene sulfonamides p-T2a-k in excellent yields.

General procedure of N,N-diethyl-2-(phenylmethylsulfonamido) propanamide, a-T2a-k: To a solution of α-tolylsulfonamide derivatives a-T1a-k (2.96 mmol) in H_2O (10 mL) in a streaming flow of nitrogen gas, was added oxalyl chloride (0.34 mL, 3.85 mmol, 1.30 eq.) via dropping pipette followed by carefully controlled addition of 1 drop of DMF. The resulting mixture was stirred at room temperature for 2 h to get crude acid chloride which was kept air-tighted prior to use. In a separate 250 mL three-necked round bottom flask, equipped with a magnetic stirring bar, was added Na_2CO_3 (0.628 g, 5.92 mmol, 2 equiv.) to H_2O

(10 mL) followed by diethyl amine DEA (0.4 mL, 3.85 mmol, 1.3 equiv.) in continuous stirring and cooled to -15°C. Then, earlier kept acid chloride was added in such a way to maintain the internal temperature of the reaction mixture at around-10°C. The reacting mixture was then stirred at -10°C for 1 h; at 0°C for 1 h and finally at room temperature for 1 h. The reaction was terminated, worked up by acidifying with 2 N HCl and concentrated in rotary evaporator. The clear solution obtained was freeze-dried to get crude solid product which was purified by column chromatography ($CHCl_3/CH_3OH$, 3:1) to afford N,N-diethylalkanamide of α-tolylsulfonamide derivatives α-T2a-k.

Antibacterial activity assays: The antimicrobial properties of the sulfonamides were investigated in form of the general sensitivity testing and Minimum Inhibitory Concentration (MIC) with respect to freshly cultured targeted organisms. The two organisms of interest in this present study are one gram positive (*Staphylococcus aureus* ATCC 6538) and one gram negative (*Escherichia coli* ATCC 25922) organisms which are associated with the gastrointestinal tract damage in man and animal.

Preparation of the inoculum: The standard strains of *S. aureus* and *E. coli* used were obtained from Test Center of Antimicrobial Materials, TIPC, Beijing. No clinically isolated organism was used based on in-availability of such as at the time of this study. The strains were propagated on nutrient agar plates and maintained on the plate at 4°C. The isolates were sub-cultured in nutrient broth at 37°C for 8 h prior to antibacterial testing.

Antibacterial sensitivity testing of the synthesized compounds: Agar well diffusion technique as described by Russell and Furr (1977), was used to determine the antibacterial activity of the synthesized compounds (Russell and Furr, 1977). Sensitivity test agar plates were seeded with 0.1 mL of an overnight culture of each bacterial strain (equivalent to 10^7-10^8 CFU mL^{-1}). The seeded plates were allowed to set and a standard cork borer of 8 mm diameter was used to cut uniform wells on the surface of the agar. The wells were then filled with 0.3 mL of each sulfonamide solution in appropriate solvent at a concentration of 1000 μg mL^{-1} (0.02 g of sulfonamide dissolved in 20 mL distilled water). All the plates were incubated at 37°C for 24 h. The assay was conducted at regular intervals of 24 h until marked decline in the potency of the sulfonamide solution to inhibit the growth of the test organisms was noticed. Zones of clearance round each well means inhibition and the diameter of such zones were measured. The procedure was repeated for the streptomycin (standard).

Determination of Minimum Inhibitory Concentration (MIC): Agar well dilution method as described by Russell and Furr (1977) was used to determine the Minimum Inhibitory Concentration (MIC) of the sulfonamides and streptomycin (Russell and Furr, 1977). Different dilutions of the sulfonamides were prepared first at ≤100 μg mL^{-1} to give final concentrations in the range of 100, 50, 25, 12.5, 6.25 and 3.13 μg mL^{-1}. The different dilutions of sulfonamide derivatives that could not inhibit the microbial growth at ≤100 μg mL^{-1} were later prepared at ≤1000 μg mL^{-1} to give final concentrations in the range of 1000, 500, 250, 125, 62.5 μg mL^{-1}. Two milliliter of each dilution was mixed with 18 mL of Mueller Hinton agar (MHA, Difco, France) and poured into petri-dishes and allowed to set. The agar was streaked with an overnight broth culture of the bacterial strains and incubated overnight. The plates were then examined for the presence or absence of growth. The minimum concentration that completely inhibited macroscopic growth was regarded as the minimum inhibitory concentration of the respective sulfonamide. The procedure was repeated for streptomycin (standard).

RESULTS AND DISCUSSION

Chemistry: In the continuation of our effort on the exploration of sulfonamide derivatives as potential antibacterial agent for future drug discovery (Ajani *et al*., 2013), we have herein evaluated the *in vitro* antibacterial screening using α-toluene sulfonamide and their N,N-diethyl substituted amido bearing template. The activity recorded therein was compared with that of p-toluene in order to establish the relevance of CH_2/CH_3 in specific position requested via structure-activity relationship study. The reaction of p-toluenesulfonyl chloride (p-TsCl) with a typical amino acid, L-proline resulted in the formation of p-toluenesulfonamide p-T1a in excellent yield. Molecular diversity was further expanded by the reaction of the p-TsCl with ten other amino acids to afford p-toluene sulfonamides p-T2b-k. These sulfonamide derivatives were further reacted with diethylamine under swern oxidation strategy, making use of oxalyl chloride/DMF, to afford various N,N-diethylamido bearing p-toluenesulfonamides p-T2a-k (Fig. 1). In a similar manner, reaction of α-toluenesulfonyl chloride with various amino acids gave α-toluene sulfonamides α-T1a-k which upon subsequent amidation gave their N,N-diethylamido bearing α-toluenesulfonamides α-T2a-k (Fig. 2). Comparative study of the synthesis of p-toluenesulfonamides p-T1a-k with that of α-toluenesulfonamides α-T1a-k was evaluated. From the reaction optimization study, it was discovered that when the α-toluenesulfonyl chloride (α-TsCl) synthon was replaced with p-toluenesulfonyl chloride, there was an entirely different chemical behavioral pattern exhibited due to high polarity of

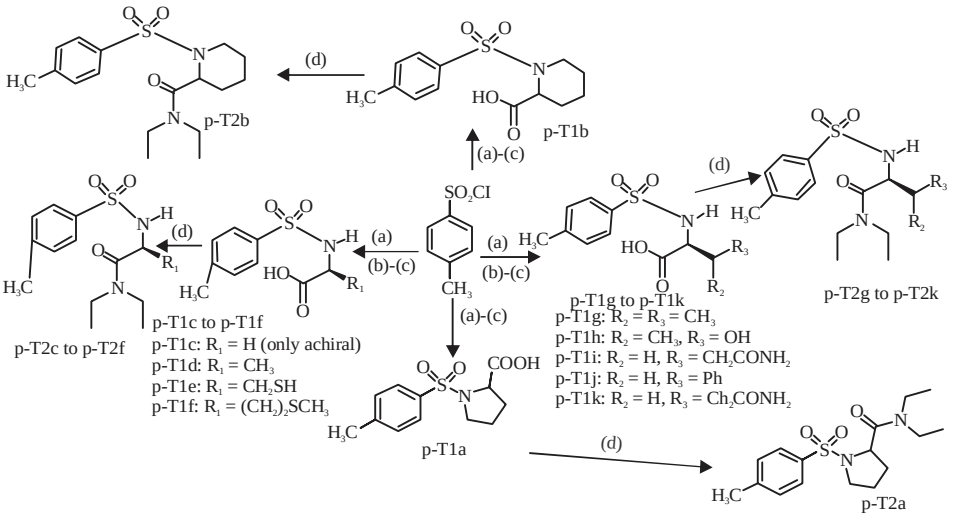

Fig. 1: Synthetic conversion of p-tolylsulfonamide intermediates to N,N-diethylamido-s-sulfonamides, reaction condition, (a) Na_2CO_3/H_2O, (b) 0°C to rt, 4 h, (c) 20% HCI to pH 2.2, (d) $(COCI)_2$, DMF, H_2O, $NH(CH_2CH_3)_2$, TEA, DCM, -10°C (1 h), 0°C (1 h), rt, (1 h)

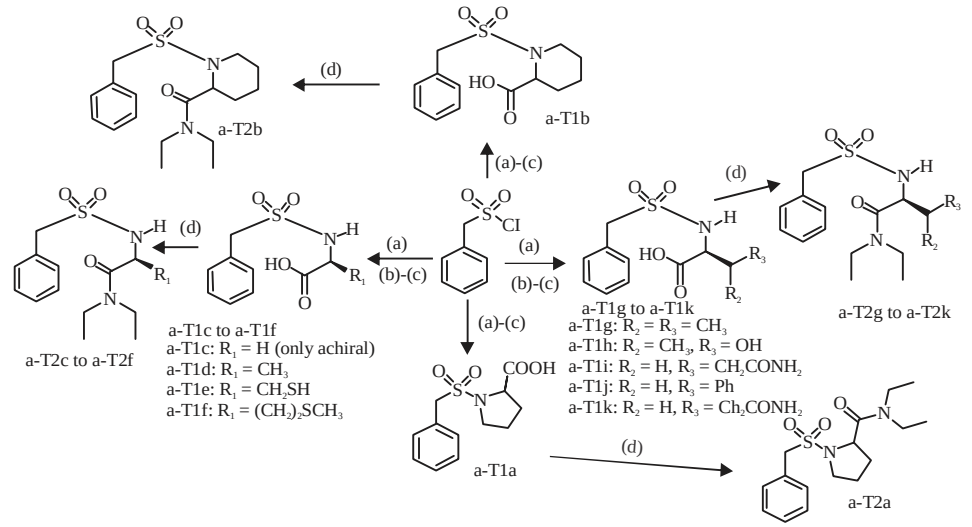

Fig. 2: Synthetic conversion of α-tolylsulfonamide intermediates to N,N-diethylamido-s-sulfonamides, reaction condition, (a) Na_2CO_3/H_2O, (b) 0°C to rt, 48 h, (c) 2N HCI to pH 2.2, (d) $(COCI)_2$, DMF, H_2O, $NH(CH_2CH_3)_2$, Na_2CO_3, H_2O, -10°C (1 h), rt, (1 h)

the sulfonamides α-T1a-k obtained from the α-toluenesulfonyl chloride as compared with that of p-toluenesulfonamides p-T1a-k obtained from p-toluenesulfonyl chloride. This was because p-toluenesulfonamides p-T1a-k easily crystallized out of water after acidification to pH 2 whereas, that of α-toluenesulfonamides α-T1a-k still remained in solution at that same pH. In fact, all effort to crystallized α-toluenesulfonamides α-T1a-k from water after acidification proved abortive, until the solution was lyophilized in the freeze drier, after which the α-toluenesulfonamides α-T1a-k were obtained in excellent yields.

Antibacterial activity: The antimicrobial sensitivity testing of the twenty-two sulfonamide derivatives synthesized were assayed using agar diffusion technique against the test organisms. Prior to the assay, the bacterial isolates were tested for viability by resuscitating the organisms in buffered peptone broth, after which it was sub-cultured into nutrient agar medium and incubated at 37°C for 24 h. The isolates were sub-cultured in a nutrient broth at 37°C for 8 h prior to antibacterial testing. The Mueller Hinton agar was inoculated with the test organisms and solutions of the different synthesized compounds dissolved in DMSO were aseptically

introduced into the bored holes. Streptomycin was used as reference clinical standards for the antibacterial activities. In addition, the choice of *S. aureus* and *E. coli* as the targeted organisms in this study was due to wide range of infectious diseases and life threatening conditions associated with such isolates. *S. aureus* which produces heat stable toxin, is among the invasive gram positive known as pyogenic cocci implicated in several diseases of human (Nwinyi *et al*., 2009). From literatures, *S. aureus* had shown to be very resistant to a wide variety of antibiotics (Nwinyi *et al*., 2008). Infections caused by methicillin resistant *S. aureus* (MRSA) and vancomycin resistant *S. aureus* are associated with high morbidity and mortality, high treatment cost and long stays in hospitals (Nwinyi *et al*., 2008). *Escherichia coli*, a facultative anaerobe of wide distribution in the environment, has been implicated in the cause of urinary tract infections, meningitis, sepsis, wound infections, nosocomial pneumonia and arthritis. A subgroup enterohemorrhagic *E. coli* (EHEC) can cause severe potentially fatal illness known as hemorrhagic colitis with symptoms of blood diarrhea and severe abdominal pain (Dolores and Doyle, 2001). The result of the zones of inhibition of the p-toluenesulfonamides p-T2a-k as compared with that of α-toluenesulfonamides α-T2a-k was as presented in Fig. 3. The zones of inhibition of the p-T2a-k on *S. aureus* ranged from 10-28 mm while that of α-T2a-k was observed to range from 6-32 mm. All α-toluenesulfonamides had larger zones of inhibition compared to their corresponding p-toluenesulfonamide derivatives p-T2a-k against *S. aureus* except in α-T2e and α-T2j. When compared with streptomycin, four compounds (p-T2j, p-T2k, α-T2a and α-T2j) showed larger zones of inhibition than streptomycin against *S. aureus*. Although, most of the p-toluenesulfonamide derivatives p-T2a-k showed larger zones of inhibition than their α-toluene sulfonamide counterparts p-T2a-k, yet the largest zone of inhibition against *E. coli* still emanated from the α-toluene sulfonamide motif α-T2j with zones of inhibition of 33 mm (Fig. 4).

Furthermore, Minimum Inhibitory Concentration (MIC) test was carried out on the tested organisms using methods of Russell and Furr (1977). The result is shown in Table 1. The MIC values of the p-T2a-k ranged from 25-1000 mg mL^{-1} against *S. aureus* while that of α-T2a-k against the same organism varied between 3.2 and 500 mg mL^{-1}. On the other hand, the MIC values of both p-T2a-k and α-T2a-k against *E. coli* ranged from 12.5 to 500 mg mL^{-1}. From the overview of the Structure Activity Relationship (SAR) study, it was discovered that the insertion of CH_2 between Ph and SO_2 contributed immensely to the increase in antibacterial activity observed in α-T2a-k as compared with p-T2a-k, where the SO_2 is directly linked to the Ph ring. The results showed that this skeletal framework exhibited marked potency as antibacterial agents. The most active antibacterial agent against *S. aureus* and *E. coli* were α-T2a and α-T2j respectively. The significant antibacterial activity of the synthesized compounds may be explained by the ability of its sulfonamide binding site to mimic p-aminobenzoic acid (PABA) which is an essential

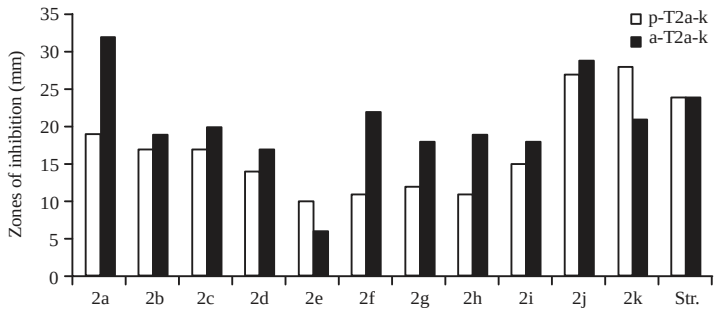

Fig. 3: Comparative study of antibacterial activity of p-T2a-k and α-T2a-k against *Staphylococcus aureus*

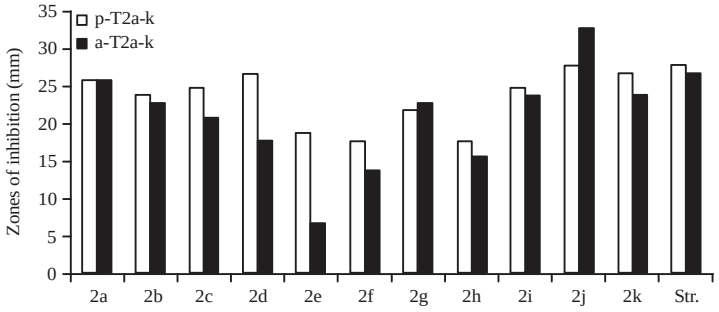

Fig. 4: Comparative study of antibacterial activity of p-T2a-k and α-T2a-k against *Escherichia coli*

Table 1: Result of MIC test of p-T2a-k and α-T2a-k on targeted organisms (mg mL^{-1})

Comp No.	*S. aureus*	*E. coli*	Comp No.	*S. aureus*	*E. coli*
p-T2a	100	50	*α*-T2a	3.12	50
p-T2b	125	62.5	*α*-T2b	250	250
p-T2c	250	50	*α*-T2c	62.5	50
p-T2d	250	25	*α*-T2d	500	250
p-T2e	250	500	*α*-T2e	50	62.5
p-T2f	250	250	*α*-T2f	25	62.5
p-T2g	1000	62.5	*α*-T2g	500	500
p-T2h	250	125	*α*-T2h	125	62.5
p-T2i	250	125	*α*-T2i	125	62.5
p-T2j	25	12.5	*α*-T2j	25	12.5
p-T2k	125	25	*α*-T2k	25	25
Str.	125	6.25	Str.	125	6.25

MIC: Minimum inhibitory concentration (mg mL^{-1}), *E. coli* ATCC 25922, *S. aureus* ATCC 6538, Str.: Streptomycin clinical reference

growth factor in the targeted organisms as earlier documented in literatures. The explanation for this encouraging activity of the synthesized sulfonamides could be traceable to the mode of action of sulfonamide drugs. This is based on the inhibition of DNA synthesis (Perez-Trallero and Iglesias, 2003) by interfering with para-aminobenzoic acid (PABA) in biosynthesis of folic acid (Levin *et al*., 2007).

CONCLUSION

Accordingly, the need to develop new and safer therapeutic agents has motivated the present design, synthesis and comparative study of antibacterial activity of two series of sulfonamides p-T2a-k and α-T2a-k derivatives as potential antibacterial agent against *S. aureus* and *E. coli* infection. The syntheses were successfully achieved and duly validated with physico-chemical analysis and spectroscopic means. The results herein suggest that these α-toluenesulfonamides α-T2a-k may have potential as structural templates in the subsequent design and development of new antibacterial agent against the action of *S. aureus* and *E. coli*. Hence, compounds α-T2a and α-T2j are good candidates for further study for future drug discovery.

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