

Synthesis, antibacterial and electrochemical studies of 4-[(E)-{[(4-substituted)sulfonyl]substitutedimino}methyl](substituted)phenyl acetate

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Abstract : A new series of 4-[(E)-{[(4-substituted)sulfonyl]substitutedimino}methyl](substituted)phenyl acetate were synthesized by coupling of 3-methoxy-4-acetyloxy benzaldehyde with different sulphanalamide derivatives. Electrochemical behaviour of 4-[(E)-{[(4-substituted)sulfonyl]substitutedimino}methyl](substituted)phenyl acetate have been studied in Britton-Robinson buffers of pH 2.5–12.0 at dropping mercury and glassy carbon electrode. All the synthesized compounds gave 2-electron wave corresponding to the reduction of -N=N- bonds at mercury electrode. On the basis of differential pulse polarography, cyclic voltammetry, IR, mass and ¹H NMR spectral studies and product identification, a reduction mechanism has been suggested. Antibacterial studies of the compounds were found promising.

Keywords : Sulphonamides, antibacterial activity, differential pulse polarography, cyclic voltammetry.

Introduction

The combination of two or more moieties into one was a common procedure for manipulation in medicinal chemistry and this can possibly result in augmenting the activity towards infectious microorganisms. Synthesis of new beneficial azomethines^{1,3}, finding indole-induced azomethines was under taken in the hope of getting better bioactive agents. Convenient synthesis approach and antimicrobial screening of novel indole azomethines were also carried out. Mono and bis 2,2-(arylidineaminophenyl) indole azomethines have been synthesized by a condensation reaction of 2-(2-amino phenyl) indole with various mono and diketones RCO-R1/R-CO-X-CO-R1 (1 : 1/2 : 1 ratio) in ethanol media. The antimicrobial activity of these compounds against different bacteria and fungi was also evaluated⁴.

A number of significant curative compounds have been obtained from the Schiff base reactions which were also used as intermediates in polymer chemistry and organic synthesis as well⁵. Literature reveals that these compounds have shown a broad range of activities such as antimalarial⁶, anticancer^{7,8}, antitumor⁹, antibacterial¹⁰, antifungal¹¹, antitubercular¹², anti-HIV¹³, antimicrobial¹⁴ and

antiviral¹⁵. Some of them have been used as powerful corrosion inhibitors¹⁶ and also as complexing agents¹⁷. Medicinal importance and significance of Schiff bases¹⁸ in various areas have developed interest¹⁹.

Bacterial infections have been most deleterious to the human health and cause more deaths than HIV infections^{20,23}. The multidrug resistance both in the community and hospitals has been the major concerns to public health and scientific community worldwide^{24,25}. The incidence of bacterial resistance has been observed to different class of antibacterials such as β -lactams, macrolides, quinolones, glycopeptides, oxazolidinones etc. and by 2003 over 59% resistant isolates have been registered²⁶. Among the resistant strains, an infection caused by methicillin resistance *Staphylococcus aureus* (MRSA) and drug resistant enterococci is difficult to treat and as of now vancomycin is the last defense against these infections^{27,30}. In order to improve quality of life there was an urgent need for the development of new chemical entities that can solve the problem of drug resistance. To achieve this goal, different approaches such as identification of novel targets where no pre-existing resistance exist and exploration of existing clinically proven targets for new chemical entities are being explored³¹. Unfortunately, identifica-

tion of novel drug targets have not been successful due to issues associated with target validation and low hit rates from high throughput screening but the second approach has been used successfully by scientists across the globe to identify new chemical entities as antibacterial agents³².

Results and discussion

Differential pulse polarographic studies :

The differential pulse polarographic studies of compounds were carried out in BR buffers in the pH range 2.5 to 10.5. The polarographic reduction was found to be pH dependent. A typical polarogram was shown in Fig. 1 and the polarographic characteristics have been compiled in Table 1.

Each compound exhibited one sharp polarographic peak in the pH range 2.5 to 10.5. Two electron reduction process was observed due to the presence of the imine ($-\text{CH}=\text{N}-$) group. The peak potential shifted towards more negative potential with the rise in pH for all the compounds indicating the participation of protons in electrode process (Fig. 2). Neutral medium favoured the reduction due to the accessibility of the protons which favours the increase in the current due to the reduction of the preferred molecule. After pH 7.0, the peak current decreases in the basic medium this again confirms the participation of the protons in the reduction process. Thus pH 7.0 has been chosen for further analytical procedures. The polarographic wave was found to be pH dependent (Fig. 3).

Plot of i_d vs pulse amplitude at pH 7.0 and a concentration, of $1 \times 10^{-1} M$ for the compound 4-[(E)-{[(4-substituted)sulfonyl]substitutedimino}methyl](substituted)-

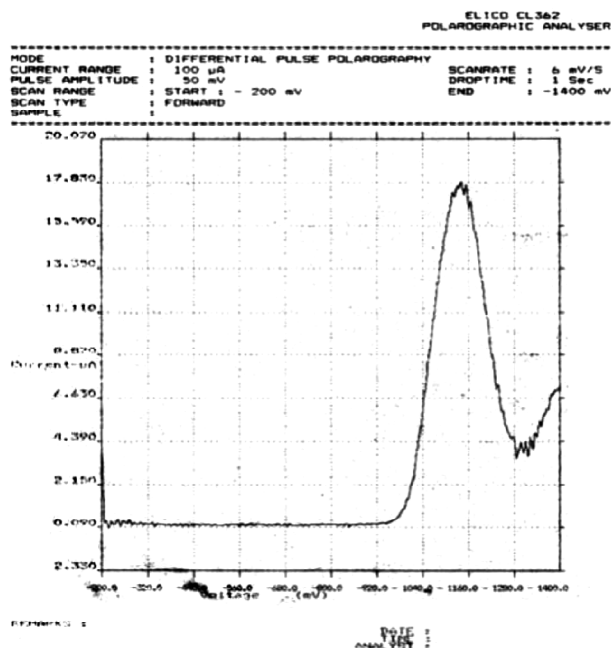


Fig. 1. A typical polarogram of 4-[(E)-{[(4-substituted)sulfonyl]substitutedimino}methyl](substituted)phenyl acetate, conc. $1 \times 10^{-1} M$, pH 7.

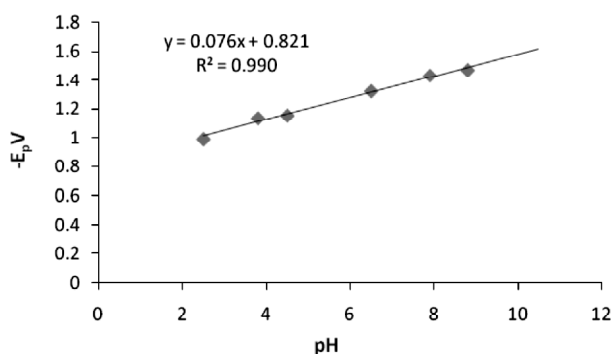


Fig. 2. Plot of pH vs $-E_p$ of 4-[(E)-{[(4-aminophenyl)sulphonyl]imino}methyl]-2-methoxyphenyl acetate.

Table 1. Differential pulse polarographic (DPP) characteristics of 4-[(E)-{[(4-substituted)sulfonyl]substitutedimino}methyl](substituted)phenyl acetate, conc. $1 \times 10^{-1} M$

Sr. no.	pH	Sulphanilamide		Sulphamethazine		Sulphathiazole		Sulphaguanidine	
		$-E_p$ (V)	i_d (μA)	$-E_p$ (V)	i_d (μA)	$-E_p$ (V)	i_d (μA)	$-E_p$ (V)	i_d (μA)
1.	2.5	0.99	19.27	1.04	12.32	1.00	5.23	0.99	13.23
2.	3.8	1.13	15.24	1.14	9.937	1.10	7.62	1.04	9
3.	4.5	1.15	16.85	1.16	10.618	1.12	4.11	1.13	10.31
4.	5.6	1.27	19.49	1.24	6.219	1.21	3.69	1.18	7.74
5.	6.5	1.32	20.22	1.28	7.106	1.22	6.06	1.24	11.03
6.	7.0	1.43	21.66	1.46	10.6	1.25	8.25	1.40	10.52
7.	8.2	1.47	18.22	1.50	13.5	1.37	12.07	1.42	12.09
8.	10.5	1.49	14.90	1.54	7.78	1.46	9.47	1.48	8.99

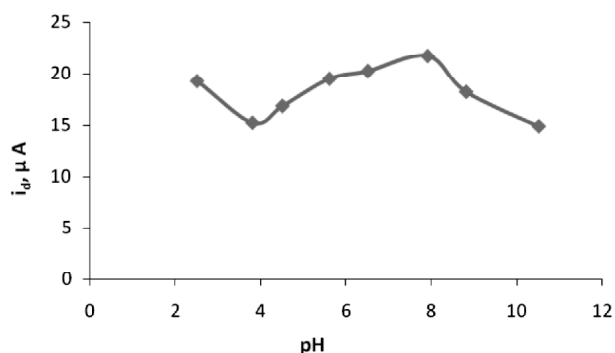


Fig. 3. Plot of pH vs i_d of 4-[(E)-{[(4-aminophenyl)sulphonyl]imino}methyl]-2-methoxyphenyl acetate.

phenyl acetate was shown in Fig. 4. It was found to be linear, passing through the origin confirming the diffusion controlled nature of the electrode process. The same behaviour has been observed for the remaining compounds of the series. Reversibility of the electrode process was checked by recording polarograms at different concentrations of the depolarizer (100×10^{-3} to 4×10^{-3} M) (Fig. 5).

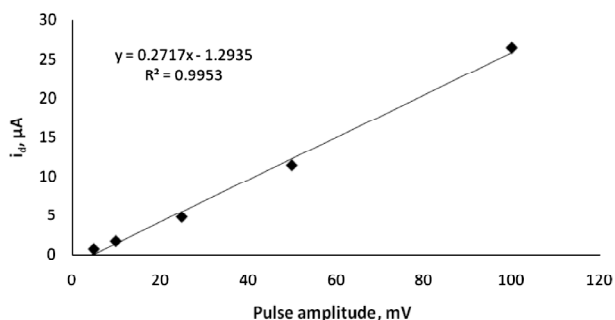


Fig. 4. Plot of i_d vs pulse amplitude of 2-methoxy-4-[(E)-{N-[(4-methylphenyl)sulphonyl]carbamidoyl}imino]methyl]phenyl acetate, at pH 7.0 and a concentration, of 0.01×10^{-3} M.

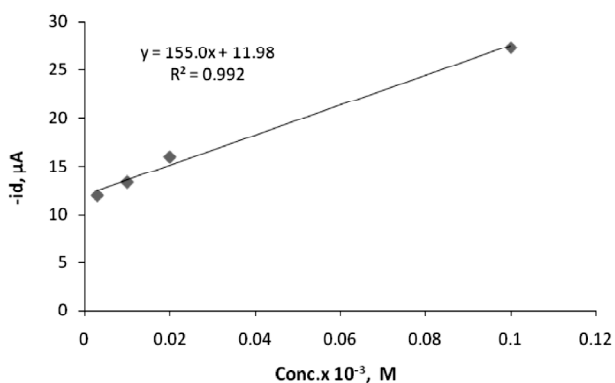


Fig. 5. Plot of i_d value of 2-methoxy-4-[(E)-{N-[(4-methylphenyl)sulphonyl]carbamidoyl}imino]methyl]phenyl acetate, at different concentrations at pH 7.0.

Half wave potential shifted towards more negative potential with increase in concentrations. This behaviour pointed towards the irreversible nature of the electrode process, which was further confirmed by log plots.

The slope of plot of $-E_p$ vs $[(\log i/i_d - i) - 0.546 \log t]$ of 4-[(E)-{[(4-substituted)sulphonyl]substitutedimino}methyl](substituted)phenyl acetate, confirm the irreversible nature of the electrode process (Fig. 6). The plot was found to be linear in nature with a good correlation value of 0.99.

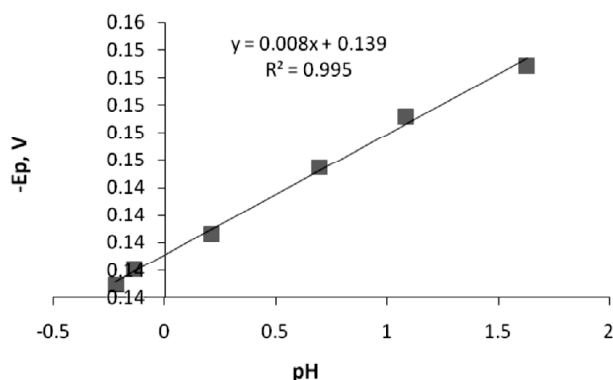


Fig. 6. Plot of $-E_{d,e}$ vs $[(\log i/i_d - i) - 0.546 \log t]$ of 4-[(E)-{N-[(4-aminophenyl)sulphonyl]imino}methyl]-2-methoxyphenyl acetate, at different concentration at pH 7.0.

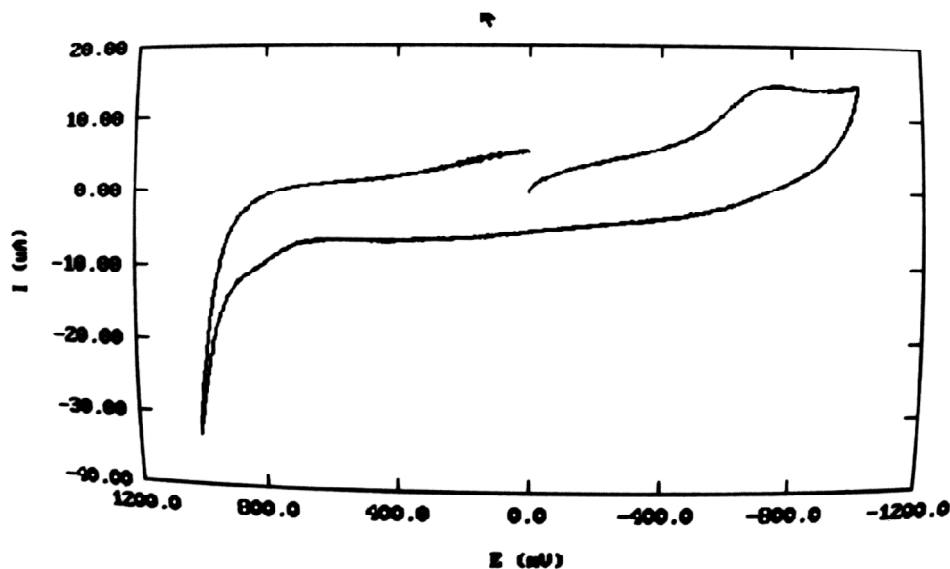
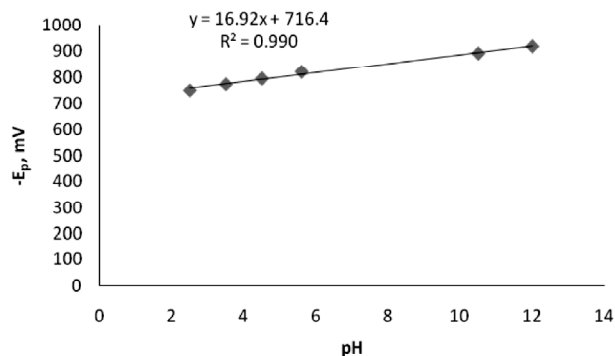
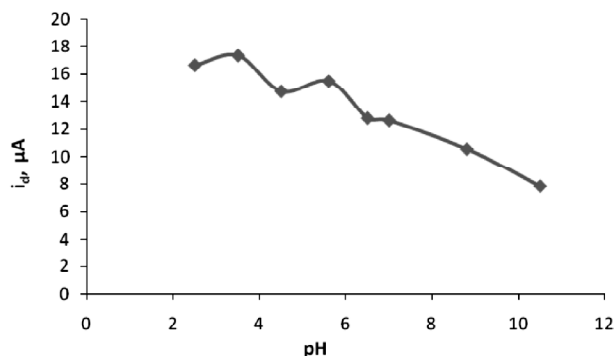
Cyclic voltammetry :

Cyclic voltammograms of 4-[(E)-{[(4-substituted)sulphonyl]substitutedimino}methyl](substituted)phenyl acetate, at glassy carbon exhibited one well defined cathodic peak in the potential range -1.000 V to $+1.000$ V, at all concentrations, assignable to the reduction of $CH=N$ - group in the pH range 2.5 to 10.5. A typical cyclic voltammogram for the reduction of 4-[(E)-{[(4-substituted)sulphonyl]substitutedimino}methyl](substituted)phenyl acetate was shown in Fig. 7.

For maintaining pH two buffer systems Britton-Robinson and phosphate buffers were used. The best results with respect to sensitivity accompanied with sharper response were obtained with Britton-Robinson buffer. With the rise in pH the peak potential shifted towards more negative potential indicating the existence of a protonation reaction coupled with reduction process (Fig. 8). The study was made in the pH range 2.5–12 in BR buffers at a concentration of 100×10^{-3} M. The relation between $E_{1/2}$ and pH of the medium over the range 2.5–

Table 2. Differential pulse polarographic characteristics of 4-[(E)-{(4-substituted)sulfonyl}substitutedimino}methyl](substituted)phenyl acetate, conc. $100 \times 10^{-3} M$, pH 7.0

Sr. no.	Compd.	$-E_{1/2}$ (V)	i_d (μA)	$\delta E_{1/2}/\delta pH$	α_{na}	I (μA)	$D_0^{1/2}$ (cm/s)	K_{fh}^0 (cm/s)
1.	16	1.56	21.66	78.27	0.01	65.63	5.40×10^{-2}	2.8×10^{-2}
2.	17	1.27	16.61	62.08	0.02	50.33	4.14×10^{-2}	1.9×10^{-2}
3.	18	1.54	12.11	56.12	0.02	36.71	3.02×10^{-2}	1.27×10^{-2}
4.	19	1.57	12.09	59.61	0.01	36.63	3.01×10^{-2}	1.7×10^{-2}

**Fig. 7.** A typical cyclic voltammogram for the reduction of 4-[(E)-{(4-substituted)sulfonyl}substitutedimino}methyl](substituted)phenyl acetate, conc. $100 \times 10^{-3} M$, pH 3.8.**Fig. 8.** Plot of $-E_p$ vs pH of 4-[(E)-{(4-substituted)sulfonyl}substitutedimino}methyl](substituted)phenyl acetate, conc. $1 \times 10^{-1} M$, scan rate 100 mV s^{-1} .**Fig. 9.** Plot of i_d vs pH of 4-[(E)-{(N-[(4-aminophenyl)sulfonyl]carbamimidoyl}imino)methyl]-2-methoxyphenyl acetate, conc. $1 \times 10^{-1} M$, scan rate 100 mV s^{-1} .

12 is expressed as $E_{p1} = 16.92 + 716.43$, $r^2 = 0.9905$ (Fig. 9).

The influence of scan rate on the electrode reduction of 4-[(E)-{(N-[(4-aminophenyl)sulfonyl]carbamimidoyl}imino)methyl]-2-methoxyphenyl acetate was examined in BR buffer of pH 3.8. The scan rate was varied from 50 to

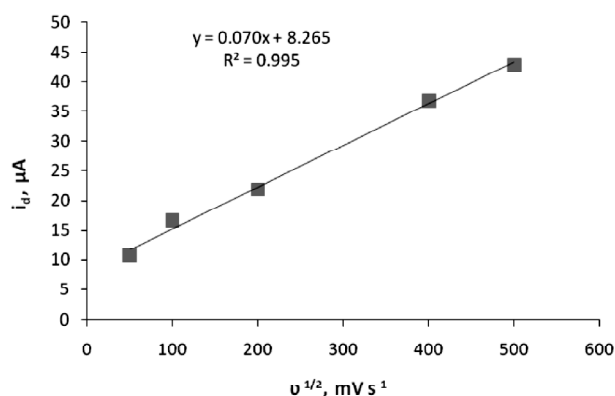
500 mV/s at a concentration of $100 \times 10^{-3} M$.

In all cases, the cathodic peak current varies linearly with the square root of the scan rate indicating diffusion controlled nature of the electrode process. The reduction peak shifted to more negative potential with increase in scan rate. A straight line was observed when cathodic

Table 3. Values of i_{pc} at different scan rate, at concentration $0.1 \times 10^{-1} M$ at pH 3.8 for 4-[(*E*)-{*N*-[(4-aminophenyl)sulfonyl]carbamidoyl}imino)methyl]-2-methoxyphenyl acetate

Sr. no.	$v^{1/2}$ (mV s ⁻¹)	i_d (μA)
1.	50	10.71
2.	100	16.63
3.	200	21.9
4.	300	25.4
5.	400	36.8
6.	500	42.9

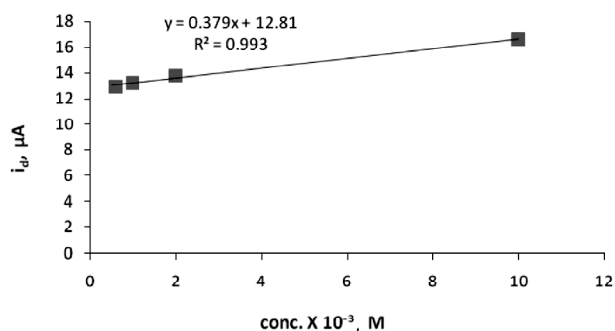
peak current (i_{pc}) was plotted against $v^{1/2}$ (Fig. 10). The cathodic peak shifts towards more negative potential with increase in scan rate, indicating irreversible electron transfer. From the plot of i_p versus $v^{1/2}$, regression equation was expressed as $i_{pc} = 0.0701 v^{1/2} + 8.2655$, between 50 and 500 mV s⁻¹ with good correlation ($r^2 = 0.9952$), confirming the diffusion controlled nature of the electrode process.

**Fig. 10.** Plot of i_d vs $v^{1/2}$ of 4-[(*E*)-{*N*-[(4-aminophenyl)sulfonyl]carbamidoyl}imino)methyl]-2-methoxyphenyl acetate at pH 3.8.

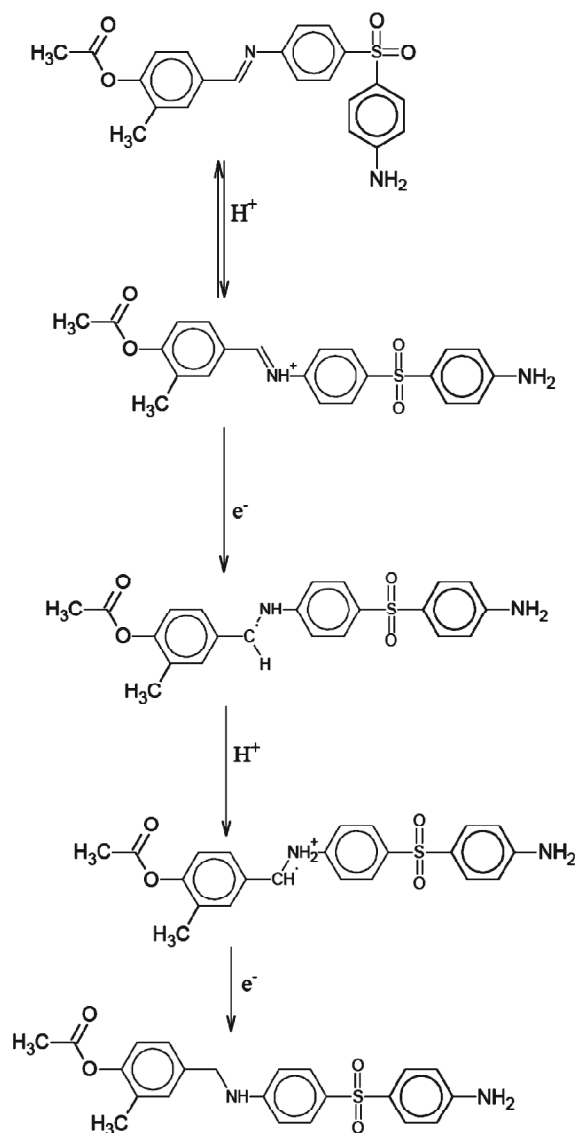
The plot of i_d vs concentration of 4-[(*E*)-{*N*-[(4-aminophenyl)sulfonyl]carbamidoyl}imino)methyl]-2-methoxyphenyl acetate, at scan rate 100 mV s⁻¹ at pH 3.5 was given in Fig. 11. Plot of peak current vs concentrations was straight line confirming the diffusion controlled nature of the electrode process.

Reduction mechanism :

A reduction mechanism of 4-[(*E*)-{[(4-substituted)sulfonyl]substitutedimino}methyl](substituted)phenyl acetate has been postulated on the basis of polarographic, coulometry and cyclic voltammetric studies from the

**Fig. 11.** Plot of i_d vs conc. of 4-[(*E*)-{*N*-[(4-aminophenyl)sulfonyl]carbamidoyl}imino)methyl]-2-methoxyphenyl acetate, at pH 3.8 at scan rate 100 mV s⁻¹.

polarograms and the cyclic voltamograms (Scheme 1).

**Scheme 1**

Experimental

All the melting points were determined in open glass capillary and was uncorrected. The purity of compounds was ascertained by TLC on silica gel plates and spots were visualized using iodine vapours. The IR spectra were recorded using KBr pellets on a Shimadzu, Japan, model Prestige IR 20, Spectrophotometer. ^1H NMR spectra were recorded on Bruker DRX 300 (300 MHz, FT NMR) in $\text{DMSO}-d_6$ using TMS as internal reference. All media employed in bacteriological studies were prepared by dissolving the required amount of individual component of the subjective media in Millipore water and then autoclaved at 121°C for 20 min. For carrying out the anti-bacterial studies, solid media and agar was added to the broth prior to autoclaving. The fresh media plates were prepared by pouring lukewarm (40°C) autoclaved agar medium in sterile petriplates inside a laminar flow cabinet and allowed it to solidify.

General procedure for synthesis of compounds :

3-Methoxy-4-acetyloxybenzaldehyde was refluxed with equimolar quantity of sulphonamide variants *p*-aminobenzenesulfonamide; 4-amino-*N*-[1,3-thiazole-2-yl] benzene sulfonamide; 4-amino-*N*-[aminoiminomethyl] benzene sulfonamide; [4-amino-*N*-(4,6-dimethyl-2-pyrimidinyl)benzenesulphonamide] in ethanol for 4 h to yield the target sulphonamide Schiff bases. The refluxing mixture was cooled overnight and poured over crushed ice. The precipitate thus obtained was filtered and recrystallized with ethanol. The IR spectra results of crystallized compounds are as follows : $\text{OCH}_3 = 1089.58\text{ cm}^{-1}$, $\text{CHO} = 2846.4\text{ cm}^{-1}$, $\text{O}-\text{C}=\text{O}-\text{CH}_3 = 1757.8\text{ cm}^{-1}$, $\text{C}=\text{N} = 1470\text{ cm}^{-1}$, $-\text{N}-\text{H} = 3342.03\text{ cm}^{-1}$, $-\text{S}=\text{O} = 1329.68\text{ cm}^{-1}$. The other compounds of the series were synthesized in the similar manner. The physical data and characteristics of the synthesized compounds have been compiled in Table 4.

Table 4. Physical characteristics of acetylated vanilin sulphonamide azomethines

Sr. no.	Molecular formula	Yield (%)	Colour	M.p. ($^\circ\text{C}$)
1.	$\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_5\text{S}$	55	Light yellow	86
2.	$\text{C}_{22}\text{H}_{22}\text{N}_4\text{O}_5\text{S}$	75	Creamy white	80
3.	$\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}_5\text{S}_2$	82	Off white	106
4.	$\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_5\text{S}$	79	Pale yellow	92

Reagents and material :

All chemicals were obtained from Aldrich Chemical Co., Germany. Double distilled water was obtained from Millipore (Milford, MA) Milli-Q plus system. 1.0 M KCl in double distilled water was prepared. Britton-Robinson buffers in the pH range 2.5 to 10.5 were prepared using boric acid, orthophosphoric acid, acetic acid and NaOH. All chemicals used were analytical reagents and were employed without further purification. Solutions for recording voltammograms were prepared by adding buffers of varying pH to the stock solution and 1 mL KCl (1.0 M) as supporting electrolyte. The stock solutions of 4-[(*E*)-{[(4-substituted)sulfonyl]substitutedimino}methyl]-(substituted)phenyl acetate ($1.0 \times 10^{-1}\text{ M}$) were prepared in DMF.

Apparatus :

The IR spectra of synthesized compounds were recorded using KBr pellets on a Shimadzu, Japan model Prestige IR 20 while ^1H NMR studies were performed on a Bruker NMR. The differential pulse polarographic (DPP) measurements were carried out using ELICO CL362 Polarographic Analyzer (India). The drop time of 1 s was electronically controlled using a 663 VA stand. A three-electrode system having a working dropping mercury electrode (DME), saturated calomel electrode (SCE) as reference electrode and platinum wire as an auxiliary electrode were used. Triple distilled mercury was used for this purpose. The pH-metric measurements were made on a Digital pH Meter MK VI provided with a glass electrode and a saturated calomel electrode as reference. It was standardized with buffers of known pH and used for ascertaining pH of the prepared buffers.

Cyclic voltammetry was performed on a potentiostat versastat EG & G II Princeton Applied Research model 273 coupled with 270/250 research electrochemistry software 4.30. A three electrode assembly consisting of a glassy carbon working electrode ($\phi = 2\text{ mm}$ EG & G/ PAR), Ag/AgCl as reference electrode and platinum wire as auxiliary electrode were used. Solutions were purged for 10 min with purified nitrogen gas to remove the dissolved oxygen, after which a blanket of pure nitrogen gas was maintained over the solutions throughout the experiment. The glassy carbon electrode was polished with fine grade emery paper followed by polishing alumina (0.5

μm). It was then washed and subsequently activated by triangular voltage sweeps from +1.0 to -1.4 V at the scan rate of 5 to 200 mV/s for 5 min. The activity of the electrode was tested for ferricyanide-ferrocyanide system in 0.1 M KCl.

Procedure :

Influence of various buffers (phosphate, acetate and Britton-Robinson) was compared for the analytical signals and it was observed that the diffusion current peaks were sharp and well defined in BR buffers. Diffusion currents were also compared using methanol and dimethylformamide for further investigation. Well defined peaks were observed in DMF for 4-[(E)-{[(4-substituted)sulfonyl]substitutedimino}methyl](substituted)phenyl acetate. The experiments were carried out to study the influence of different concentrations of the depolarizer and different pulse amplitude on reduction process of the synthesized 4-[(E)-{[(4-substituted)sulfonyl]substitutedimino}methyl](substituted)phenyl acetate. For cyclic voltammetric study, 0.1 M stock solution of depolarizer, 7.5 mL of BR buffer (pH 3.8), 1.0 mL of 1 M KCl and 1 mL of organic solvent (DMF) were used and studied the effect of different concentrations and scan rate on electrode process.

Assessment of antimicrobial activity of synthesized compounds :

Disc diffusion assay :

It is done by using Kirby-Bauer method to determine the antibacterial susceptibility of a compound at fixed concentrations. For this, few colonies of organism were inoculated in 2-5 mL broth and grown for 2.5 h. Using a micropipette, 1 ml of the inoculated broth was spreaded on the solidified nutrient agar using a spreader. Disc of 5 mm diameter (Whatman filterman No. 1) was autoclaved and then dried at 60 °C for 1 h. The sterile filter paper discs, impregnated with fixed concentrations viz. 10^{-5} , 10^{-4} , 10^{-3} , 10^{-2} , 10^{-1} of compound were placed on the pre-inoculated surface by flamed forceps. The disc bearing plates were incubated within 30 min at 37 °C for 24 h. After incubation, the inhibition zone diameter was measured.

The diameter of inhibition zone is directly proportional to the degree of sensitivity of the bacterial strain and concentration of compound under test. A systematic

perusal data of antibacterial activity reveals that, with the increase in concentration of drug, increase in zone of inhibition occur in Petri-plates.

The synthesized compounds were screened against selected strain of bacteria viz. *E. coli*, *P. aeruginosa*, *B. subtilis* and *M. luteus*, using disc-diffusion assay. Simultaneously, antibiotic sensitivity profile of the test bacteria was determined using standard drug chloramphenicol to compare relative activity of compound viz-a-viz known antibiotics as standard. The zone of inhibition around the disc against the test bacteria was determined at five different concentrations by disc diffusion assay as indicative of the antibacterial activity of sulphonamide derivatives. In the present work, some sulphanilamide derivatives were combined with the azomethine pharmacophore at the N⁴ nitrogen of the sulphanilamide molecule. The double bond at the N⁴ nitrogen of the substituted azosalicylaldehyde renders it readily reducible. In the work it has been observed that the sulphanilamide derivatives are found to exhibit noticeable antibacterial activity.

From the literature review it has been reported that *P. aureuginosa* is resistant to sulphonamide group of drugs and other antibiotics, but in the present work the compound 2-methoxy-4-[(E)-{N-[(4-methylphenylsulfonyl]carbamidoyl}imino)methyl]phenyl acetate was found to inhibit its growth. The compounds 4-[(E)-{[(4-aminophenyl)sulfonyl]imino}methyl]-2-methoxyphenyl acetate, 4-(3'-methoxy-4'-acetyloxy)benzylidene amine-N-(4,6-dimethylpyrimidin-2-yl)benzenesulfonamide and 2-methoxy-4-[(E)-{[(3-(1,3-thiazole-2-ylsulfonyl)phenyl]imino}methyl]phenyl acetate were found to be efficient against *E. coli*, 2-methoxy-4-[(E)-{N-[(4-methylphenylsulfonyl]carbamidoyl}imino)methyl]phenyl acetate was mildly active against *B. subtilis* while 4-[(E)-{[(4-aminophenyl)sulfonyl]imino}methyl]-2-methoxyphenyl acetate and 2-methoxy-4-[(E)-{N-[(4-methylphenylsulfonyl]carbamimido}imino)methyl]phenyl acetate showed efficient activity against *B. subtilis* and all the compounds show low activity against *M. leutus*.

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References

1. R. Pignatello, A. Panico, P. Mazzone, M. R. Pinizzotto, A. Garozzo and P. M. Fumeri, *Eur. J. Med. Chem.*, 1994, **29**, 781.
2. P. M. Reddy, Y. P. Ho, K. Shanker, R. Rohini and V. Ravinder, *Eur. J. Med. Chem.*, 2009, **44**, 2621.
3. R. Rohini, P. M. Reddy, K. Shanker and V. Ravinder, *Acta Chim. Slov.*, 2009, **56**, 900.
4. K. Shanker, R. Rohini, P. M. Reddy, Y. P. Ho and V. Ravinder, *Spectrochim. Acta A : Mol. Biomol. Spectrosc.*, 2009, **73**, 205.
5. C. P. Pulate, P. M. Gurubasavrajswamy, R. V. Antre and D. Goli, *Int. J. Drug Des. Discov.*, 2011, **2**, 483.
6. S. L. Vasoya, P. T. Chovatia, D. H. Purohit and H. S. Joshi, *J. Serb. Chem. Soc.*, 2005, **70**, 1163.
7. Y. Li, Z. S. Yang, H. Zhang, B. J. Cao and F. D. Wang, *Bioorg. Med. Chem.*, 2003, **11**, 4363.
8. R. Villar, I. Encio, M. Migliaccio, M. G. Gil and V. M. Merino, *Bioorg. Med. Chem.*, 2004, **12**, 963.
9. Z. Y. Shi, Y. Q. Li, Y. H. Kang, G. Q. Hu, C. S. Huang-Fu, J. B. Deng and B. Liu, 2010, **33**, 271.
10. G. Q. Hu, X. K. Wu, X. Wang, Z. Q. Zhang, S. Q. Xie, W. L. Huang and H. B. Zhang, *Acta Pharma. Sin.*, 2008, **43**, 1112.
11. K. N. Venugopal and B. S. Jayashree, *Ind. J. Pharm. Sci.*, 2008, **70**, 88.
12. S. N. Pandeya, D. Sriram, G. Nath and E. De Clercq, *Ind. J. Pharm. Sci.*, 2000, **61**, 358.
13. M. J. Hearn, M. H. Cynamon, M. F. Chen, R. Coppins, J. Davis, H. Joo-On Kang, A. Noble, B. Tu-Sekine, M. S. Terrot, D. Trombino, M. Thai, E. R. Webster and R. Wilson, *Eur. J. Med. Chem.*, 2009, **44**, 4169.
14. S. N. Pandeya, D. Sriram, G. Nath and E. De Clercq, *Eur. J. Pharm. Sci.*, 1999, **9**, 25.
15. S. J. Wadher, M. P. Puranik, N. A. Karande and P. G. Yeole, *Int. J. Pharm. Tech. Res.*, 2009, **1**, 22.
16. M. S. Karthikeyan, J. P. Dasappa, B. P. Subrahmanyam, K. Bhat and B. S. Holla, *Bioorg. Med. Chem.*, 2006, **14**, 7482.
17. V. S. Agarwal, K. S. Rajan and P. K. Sen, *U.S. Patent.*, 1992, **147**, 567.
18. P. A. Kulkarni, S. I. Habib, D. V. Saraf and M. M. Deshpande, *Res. J. Pharma. Bio. Chem. Sci.*, 2012, **3**, 107.
19. J. Patole, D. Shingnapurkar, S. Padhye and C. Ratledge, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1514.
20. K. E. Jones, N. G. Patel, M. A. Levy, A. Storeygard, D. Balk, J. L. Gittleman and P. Daszak, *Nature*, 2008, **45**, 1990.
21. D. M. Morens, G. K. Folkers and A. S. Fauci, *Nature*, 2004, **430**, 242.
22. J. R. Miller and G. L. Waldrop, *Drug Discov.*, 2010, **5**, 145.
23. S. B. Levy, *Adv. Drug Deliv. Rev.*, 2005, **57**, 1446.
24. H. Lode, *Clin. Microbiol. Infect.*, 2005, **11**, 778.
25. L. B. Rice, *Biochem. Pharmacol.*, 2006, **71**, 991.
26. National Nosocomial Infections Surveillance (NNIS) system report, *Am. J. Infect. Control*, 2004, **32**, 470.
27. K. C. Nicolaou, C. N. C. Boddy, S. Braese and N. Winssinger, *Angew. Chem. Int. Ed.*, 1999, **38**, 2097.
28. X. Fu, C. Albermann, J. Jiang, J. Liao, C. Zhang and J. S. Thorson, *Nat. Biotechnol.*, 2003, **21**, 1467.
29. Y. Cetinkaya, P. Falk and C. G. Mayhall, *Microbiol. Rev.*, 2000, **13**, 686.
30. R. O'Shea and H. E. Moser, *J. Med. Chem.*, 2008, **51**, 2871.
31. S. J. Projan, *Curr. Opin. Pharmacol.*, 2002, **2**, 513.
32. D. Kahne, C. Leimkuhler, W. Lu and C. Walsh, *Chem. Rev.*, 2005, **10**, 5425.