RJC

RASĀYAN *J. Chem.*
Vol. 6 | No.3 | 196-200 | July- September | 2013
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

SYNTHESES AND CHARACTERIZATION OF SOME NOVEL SUBSTITUTED PYRIDOSULFONAMIDE DERIVATIVES AS ANTIMICROBIAL AGENTS

Shweta Singh[1], Pooja Chawla[2], Viney Chawla[1] and Shailendra K. Saraf[1,*]
[1]Faculty of Pharmacy, Babu Banarasi Das Northern India Institute of Technology, Lucknow-226028, India.
[2]School of Pharmacy, Babu Banarasi Das Univesity, Lucknow-226028, India.
*E-mail: dirpharmniec@gmail.com

ABSTRACT

Increasing incidences of antimicrobial resistance are proving to be a menace for the society. There is a demand for the synthesis of some new antimicrobial agents which can overcome this problem. In the present study, a series of pyridosulfonamide derivatives have been synthesized, to exploit the combined potential of pyridine and sulphonamide nuclei. Different derivatives were synthesized through a three step process. The success of syntheses was confirmed through physical and spectral characterization on the basis of IR spectroscopy, Mass spectrometry and PNMR spectroscopy. These derivatives were evaluated at varying concentrations for antimicrobial activity by cup plate method using Co-trimoxazole and Fluconazole were used as the standard drug for antimicrobial and antifungal activity respectively. The synthesized compounds were found to be active against the tested strains of Gram positive (*Bacillus subtilis* and *Staphylococcus aureus*) and Gram negative (*Escherchia coli* and *Psuedomonas. aeruginosa*) organisms. However, none of the compounds was active against *Candida albicans*.

Keywords: Pyridosulfonamide derivatives, antimicrobial resistance, antibacterial activity, cup plate method.

INTRODUCTION

The deterioration of human life due to the enhanced prevalence of infectious diseases is becoming a worldwide problem. Medicinal chemists are hard pressed to bring out new molecules which can overcome antimicrobial resistance. Heterocyclic compounds, if properly manipulated, hold the key to this problem. They are widely distributed in nature and are essential to life as they play a vital role in the metabolism of all living cells. For example pyrimidine and purine bases of the genetic material DNA; the essential amino acids proline, histidine and tryptophan; the vitamins and coenzyme precursors thiamine, riboflavine, pyridoxine, folic acid and biotin; the B_{12} and E families of vitamins etc. are all examples of heterocyclic compounds. Not only this, heterocycles are also the basis of the majority of medicines. Pyridines belong to the category of such compounds. Pyridine derivatives have been found to exhibit antimicrobial, anti-inflammatory[1-5] and antitumor [6] activities.

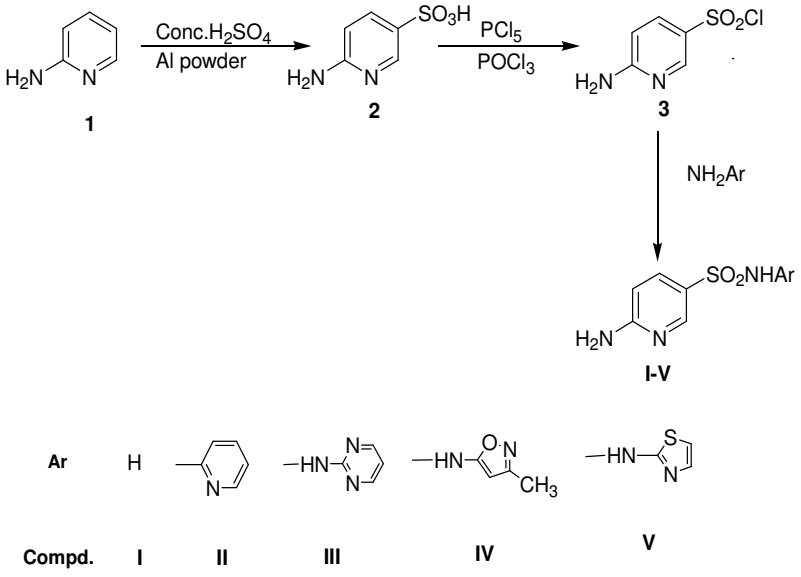
The sulfonamides and sulfones have a relatively broad antibacterial spectrum. Individual sulfonamides do differ in their antibacterial spectrum. The bacteria most susceptible to sulfonamides include *Pneumococci*, *Streptococci*, *Meningococci*, *Staphylococci*, some coliform bacteria, and *Shigellae*. They have been extensively studied in the past. The presence of a *p*-aminobenzenesulfonyl radical seems inevitable for maintaining good activity and practically all the attention was focused on N^1-substitutents. These substituents appeared to affect mainly the physicochemical and the pharmacokinetic characteristic of the drugs[7]. However, the main drawback of sulfonamides, as antimicrobial agents, is the development of resistance which has been studied by a number of workers[8].

The conjugation of sulfonamides with pyridine nucleus has been proven to yield potent antiproliferative[9-10], antitubercular[11] and antimicrobial agents[12].

Antimicrobials are the current need of the society and they influence the human community very much. Among the existing antimicrobial agents, sulpha drugs are reported to have an enormous potential to

serve in the different areas of chemotherapy and a lot of SAR studies have been done. This looks incomplete due to the lack of information about bioisosteric replacement of benzene ring and cyclization of the amine functionality attached to $^{-}SO_2$. The manuscript reports the synthesis and evaluation of some novel therapeutic agents.

Instead of simple aromatic ring, heteroaromatic rings have been used. Substitution with more lipophilic groups was carried out to produce more potent derivative of sulfonamides.

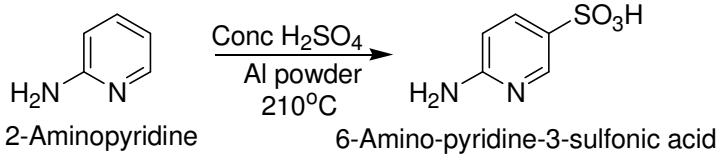


Scheme-1: Synthetic route to novel sulfonamides.

EXPERIMENTAL

All research chemicals were purchased from Sigma-Aldrich and S.D. Fine Chemicals India Pvt. Ltd. and used as such for the reactions. Reactions were monitored by thin-layer chromatography (TLC), on pre-coated silica gel plates. Melting points of the synthesized compounds were determined by open capillary method and are uncorrected. UV spectra were recorded on a Shimadzu 1700 UV–Visible spectrophotometer and IR spectra were recorded on a Shimadzu 8400S FTIR spectrometer using KBr pellets. High-Resolution Mass spectra were recorded on a JEOL-Accu TOF JMS-T100LC spectrometer. The ^{1}H NMR were recorded on a Bruker WM-300 (at 300 MHz) using $CDCl_3$ as solvent. Chemical shifts are reported in δ ppm units with respect to TMS as internal standard. Purity of the compounds was checked on precoated TLC plates, using silica gel G plates, and iodine vapors as visualizing agent. The antimicrobial activity was evaluated using the cup plate method.

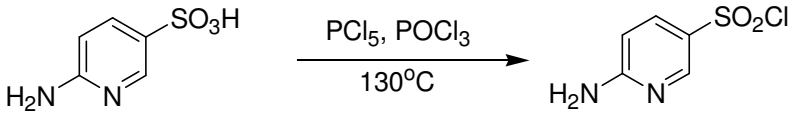
Synthesis of 6-aminopyridine-3-sulfonic acid (2)



A mixture of 2-aminopyridine (1 mole), and concentrated sulfuric acid (3 moles) was stirred with small amount of aluminium powder in the presence of ethanol, for about 5 hours at a temperature of 210°C. After cooling to room temperature, the reaction mixture was poured on to crushed ice. The precipitate thus obtained was washed and combined with further fractions from the mother liquor. The product was

filtered, washed and recrystallized from hot water to get 6-aminopyridine-3-sulfonic acid as the first intermediate[13].

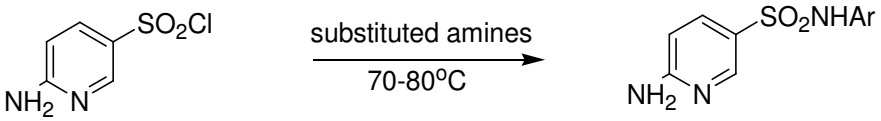
Synthesis of 6-aminopyridine-3-sulfonyl chloride (3)



6-Amino-pyridine-3-sulfonic acid 6-Amino-pyridine-3-sulfonyl chloride

6-Aminopyridine-3-sulfonic acid (0.5 mole), obtained in step I, was ground with phosphorus pentachloride (1 mole), in the presence of a few drops of phosphorus oxytrichloride. The reaction mixture was refluxed for 5 hours at 130°C. The reaction mixture was cooled to room temperature and poured on to crushed ice. The solid mass, 6-aminopyridine-3-sulfonyl chloride, was filtered followed by washing with water and sodium bicarbonate solution and dried under vacuum[14].

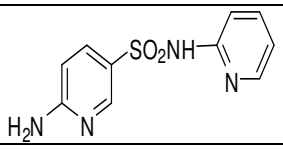
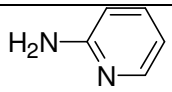
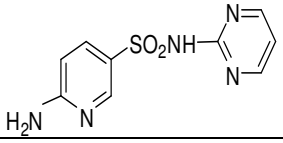
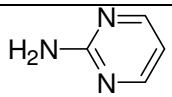
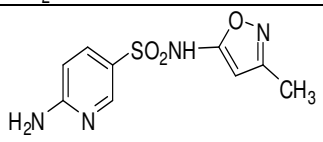
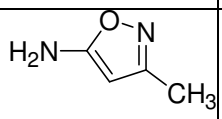
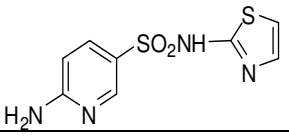
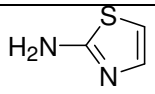
Synthesis of 6-aminopyridine-3-substituted sulfonamides (I-IV)



6-Amino-pyridine-3-sulfonyl chloride 6-Amino-pyridine-3-sulfonic acid substituted-amide

A mixture of substituted amines and a suitable solvent was slowly added to the crude form of 6-aminopyridine-3-sulfonyl chloride in a reaction flask. The contents of the flask were mixed thoroughly, followed by heating at 70-80°C with occasional stirring for about 1 hr. The reaction mixture was cooled and the product was filtered, washed with cold water and vacuum dried[3,15] . The physicochemical and spectral data of the compounds has been recorded in Table-1.

Table-1: Physical and spectral data of the synthesized compounds (1-4).

S.No.	Structure	Amine used	Solvent used	Melting Range (°C)	IR (ν: cm^{-1})	Mass (M+1)	NMR (δ: ppm)
1.			Dry acetone, dry pyridine	250-253	C-H (3026), C-H out of plane (738), N-H (3355), C=N (1618-1444)	251.2	6.91-8.21 (m, 7H, aromatic), 7.41 (s, 2H, NH_2), 11.25 (s, 1H, NH)
2.			Dry acetone, dry pyridine	292-294	C-H (3126), N-H (3352), C-N (1357-1224), C=N (1649-1475)	252.0	6.92-8.40 (m, 6H, aromatic), 7.41 (s, 2H, NH_2), 11.20 (s, 1H, NH)
3.			Dry acetone, dry pyridine	150-154	C-H (3149), N-H (3415), C=N (1629,1479), N-O (893,1280)	256.4	6.94-8.27 (m, 4H, aromatic), 7.42 (s, 2H, NH_2), 9.01 (s, 1H, NH), 2.31 (s, 3H, CH_3)
4.			Methanol, dry pyridine	300-302	C-H (3176), N-H (3334), C-S (703), C=N (1665, 1485)	257.1	6.98-8.20 (m, 5H, aromatic), 7.45 (s, 2H, NH_2), 12.50 (s, 1H, NH)

Antimicrobial Screening

The antimicrobial activity of synthesized compounds was screened by cup plate method[16]. Two Gram positive (*Bacillus subtilis* MTCC 441, *Staphylococcus aureus* MTCC 1430) and three Gram negative (*Escherchia coli* MTCC 1573, *Psuedomonas aeruginosa* MTCC 424, *Streptococcus pneumoniae* MTCC 655, and one fungal strain *Candida albicans* MTCC 183) were used for the activity. The strains were of MTCC type and procured from Institute of Microbial Technology, Chandigarh, India. The test samples of compounds 1, 2, 3, and 4 were prepared in the concentrations of 100 µg/ml and 150 µg/ml, using water as the solvent, for antimicrobial activity. Co-trimoxazole (combination of Sulphamethoxazole and Trimethoprim) and Fluconazole were used as the standard drug for antimicrobial and antifungal activity respectively. The diameters of zones of inhibition are shown in Table-2.

Table-2: Mean Zone diameters of Compounds 1-4 at various concentrations.

Sample	Conc. (µg/ml)	Mean Zone Diameter (mm)					
		SA	EC	BS	SP	PA	CA
Compound 1	100	16	15	24	18	-	-
	150	20	18	26	30	-	-
Compound 2	100	19	14	25	27	-	-
	150	21	15	18	28	-	-
Compound 3	100	-	-	13	-	-	-
	150	-	-	-	-	-	-
Compound 4	100	18	20	25	26	-	-
	150	20	18	31	30	-	-
Co-trimoxazole	100	20	18	24	20	-	-
Fluconazole	100	-	-	-	-	-	26

SA = *S. aureus*; EC = *E. coli*; BS = *B. subtilis*; SP = *S. pneumoniae*; PA = *P. aerugenosa,* CA=*C albicans*

RESULTS AND DISCUSSION

A series of substituted pyridosulfonamide derivatives were synthesized by the reaction of 6-aminopyridine-3-sulfonic acids with substituted heterocyclic aromatic amines, through the formation of 6-aminopyridine-3-sulfonyl chloride. The success of the syntheses was confirmed through physical and spectral characterization. The peaks observed at 3300-3400 cm^{-1} for NH group and 1440-1670 cm^{-1} for C=N group in the IR spectra of the synthesized compounds matched well with their structure. Chemical shifts observed in the range of 9-12ppm for NH group and 2.31ppm for CH_3 group (compound 4) in the NMR spectra of synthesized compounds had delta values attributable to corresponding protons in their structures. This was further supported by their mass spectra, where characteristic M+1 peaks were observed clearly. Antimicrobial activity of synthesized compounds was screened by the cup plate method. In the present study, most of the compounds have shown good anti-microbial activity at 100 µg/kg and 150 µg/kg. This increase in anti-microbial activity may be due to the molecular modification, i.e. introduction of a heterocyclic ring in sulphonamide nucleus. From the present study, it is clear that the increase in the number of N-atoms may lead to increase in the anti-microbial activity. The amino and sulfonyl groups on the benzene ring should be in the 1,4-disposition for activity: the amino group should be unsubstituted or have a substituent that is removed readily *in vivo.* Compounds 1, 2 and 4 exhibited a remarkable activity against the used bacterial strains. Activity increased by introducing a heteroaromatic ring at the sulfonyl group. Also, the activity increased with the increase in the number of nitrogen or sulfur and nitrogen containing rings. However, it was observed that the replacement of thiazole ring by oxazole ring with methyl group drastically diminished the activity. None of the compounds showed activity against *Streptococcus pneumoniae* and *Candida albicans*.

REFERENCES

1. M. Mader, A. Dios, C. Shih, R. Bonjouklian, T. Li, W. White, B.L. Uralde, C. Sánchez-Martinez, M. Prado, C. Jaramillo, E. Diego, L.M. Cabrejas, C. Dominguez, C. Montero, T. Shepherd, R. Dally, J.E. Toth, A. Chatterjee, S. Pleite, J. Blanco-Urgoiti, *Bioorg. Med. Chem. Lett.*, **18**, 179 (2008).

2. A.E. Amr, A.M. Mohamed, A.A. Ibrahim, *Z. Naturforsch*., **58b**, 861 (2003).
3. L.W. Deady, *Synth. Comm.,* **7**, 509 (1977).
4. M.H. Abo-Ghalia, A.M. Mohamed, A.E. Amr, A.A. Ibrahim, *Z. Naturforsch*., **58b**, 903 (2003).
5. L.R.S. Dias, M.J. Alvim, A.C. Freitas, E.J. Barreiro, A.L. Miranda, *Pharma. Acta. Helv.,* **69**, 163 (1994).
6. L. Racane, S.K. Pavelic, I. Ratkaj, V. Stepanic, K. Pavelic, V.T. Kulenovic, G. K. Zamola, *Eur. J. Med. Chem.,* **55**, 108 (2012).
7. M.R. Stetten, C.L. Fox, *J. Biol. Chem.,* **161**, 333 (1945).
8. H. Pentti, S. Lars, S. Gote, S. Ola, *Antimicrob. Agents. Chemother.,* **39**, 279 (1995).
9. L. Hu, Z. Li, Y. Wang, J.D. Jiang, D.W. Boykin, *Bioorg. Med. Chem. Lett*., **17**, 1193 (2007).
10. O. Takashi, Y. Hiroshi, O. Tadashi, O. Yoichi, S.H. Naoko, Y. Kentaro, N. Takeshi, K. Nozomu, K. Kyosuke, *Bioorg. Med. Chem. Lett.,* **12**, 2097 (2002).
11. A. Scozzafava, A. Mastrolorenzo, C.T. Supuran, *Bioorg. Med. Chem. Lett.,* **11**, 1675 (2001).
12. D. Rai, Singh R.K, *Indian. J. Chem.,* **50B**, 931 (2011).
13. S.M. McElvain, M.A. Goese, *J. Am. Chem. Soc.,* **65**, 2233 (1943).
14. B.S. Furniss, A.J. Hannaford, P.W.G. Smith, A.R. Tatchell, Vogel's Textbook of Practical Organic Chemistry, Pearson Education, New Delhi, p. 191 (2008).
15. Y. Morisawa, M. Kataoka, H. Nagahori, T. Sakamoto, N. Kusano, K. Sato, *J. Med. Chem.,* **23**, 1376 (1980).
16. Indian Pharmacopoeia, Cup plate method, Govt. of India, New Delhi, **1**, 54 (2010).

[RJC-1051/2013]