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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 1, 3, 4-THIADIAZOLE

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ABSTRACT

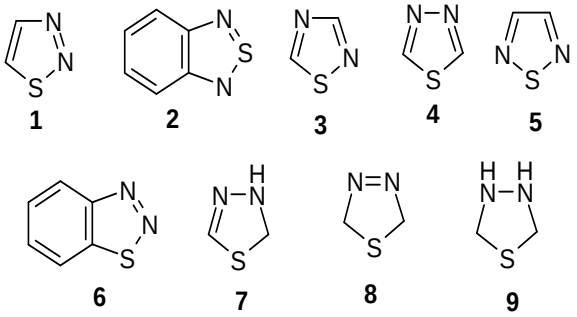
Several five membered aromatic systems having three heteroatoms at symmetrical positions such as thiadiazoles have been studied for their interesting pharmacological activities. This research article covers the most active thiadiazole derivatives that have shown excellent antibacterial activity. This research work also discusses the structure-activity relationship of the most potent compounds. It can act as an important tool for medicinal chemists to develop newer compounds possessing thiadiazole moiety that could be better agents in terms of efficacy and safety.

KEYWORDS: Thiadiazoles, Antibacterial activity.

INTRODUCTION

The resistance towards available drugs is becoming a major worldwide problem. The need to design new compounds to deal with this resistance has become one of the most important areas of research today. Thiadiazole exhibits a wide variety of biological activities. Thiadiazole moiety acts as "hydrogen binding domain" and "two-electron donor system". It also acts as a pharmacophore. Many drugs containing thiadiazole nucleus are available in the market such as methazolamide, acetazolamide, etc. Thiadiazole can act as the bio-isosteric replacement of the thiazole moiety. So it acts like third and fourth generation cephalosporin's, hence can be used in antibiotic preparations. Thiadiazole is a 5-membered ring system containing two nitrogen and one sulphur atom.

The thiadiazole system contains the following members the 1,2,3-thiadiazoles (**1**) and their benzo derivatives (**2**), the 1,2,4-thiadiazoles (**3**), the 1,3,4-thiadiazoles (**4**) and the 1,2,5-thiadiazles (**5**) and their benzo derivatives (**6**). Most of the published work, by far, is on 1,3,4-thiadiazoles. Between 1967 and March 1, 1982 chemical abstracts lists 724 references for this ring system. This includes the 1,3,4-thiadiazolines (**7**) and (**8**) and the 1,3,4-thiadiazolidines (**9**).[1,2]



MATERIAL AND METHODS

Anti-Bacterial Activity[3,4,5]

Method: Cup-plate agar diffusion method using nutrient agar.

In a radial or 2D technique, Petri dishes of agar are prepared by pouring melted agar media previously inoculated with selected microorganism. After the solidification agar cups are made with the help of borer and cups are filled with solution of suitable concentration of sample and standard respectively and are inoculated at 37°C for 24 hours. The anti-microbial agents diffuses through the agar around its cup and produces a characteristic zone of inhibition of the microorganism sensitive to the sample, the diameter of which can be measured.

Experimental

Melting points were determined in open capillary method and are uncorrected. Purity of the compound was

checked on Silica gel TLC plates. IR spectra were recorded on Thermo Nicolate IR 200 spectrophotometer using KBr disc method. ^{1}H NMR spectra were recorded on Bruker AMX-400, DMSO d6 as internal standard. Combustion analyses were found to be within the limits of permissible errors.

Synthesis of Isonicotinoyl-3-methyl-1H-pyrazol-5(4H)-one (I)[6]:-(1)

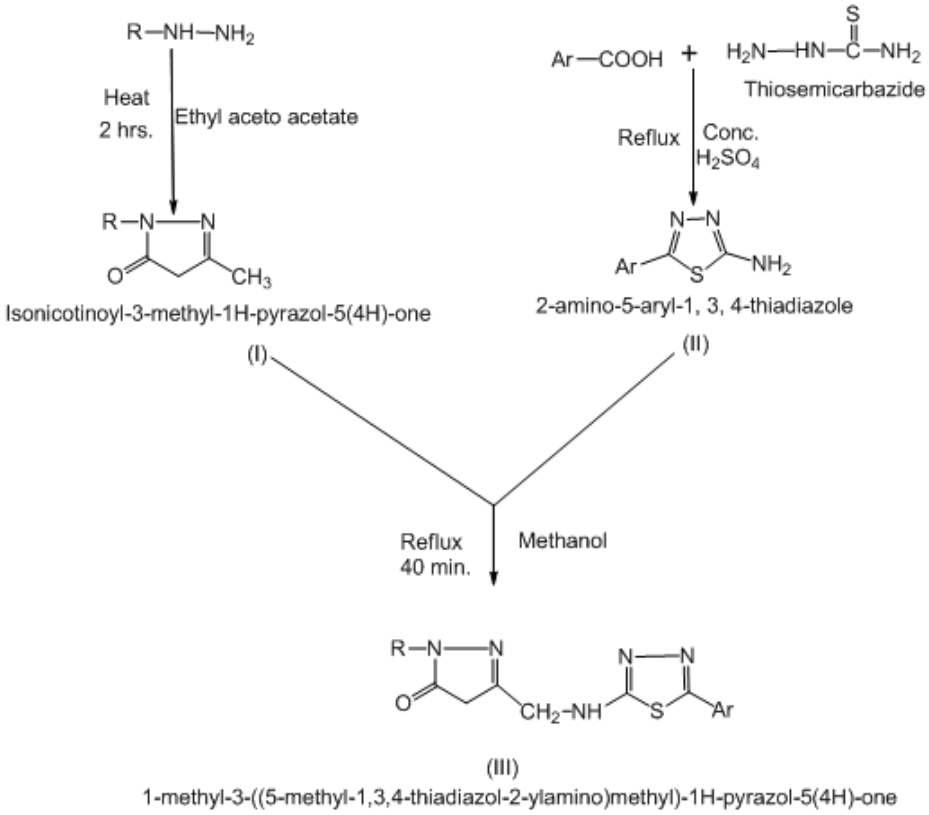
A mixture of 0.01mole (1.37gm) of hydrazides and 0.01 mole (1.3mL) ethylacetoacetate were heated on water bath for 2 hrs. and was stirred from time to time with glass rod. The resultant heavy reddish syrup was allowed to cool. It was washed thoroughly with ether to remove colored impurities. The solid thus separated out was filtered and dried. The same was recrystallized from ethanol.

Synthesis of 2-amino-5-aryl-1, 3, 4-thiadiazole (II)[6,7,8]

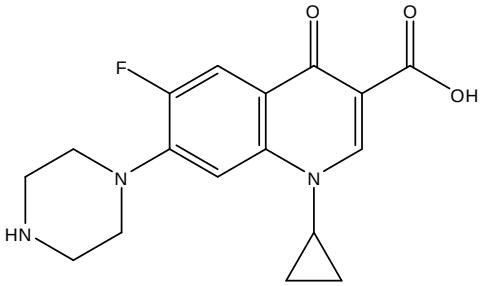
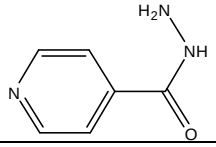
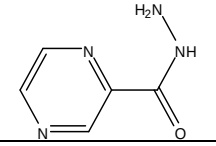
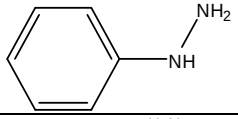
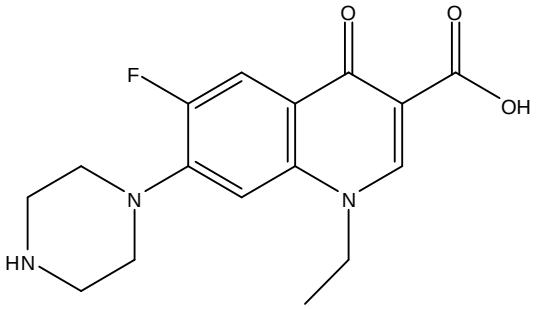
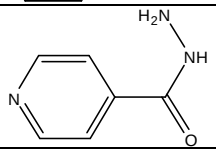
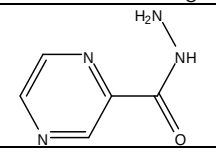
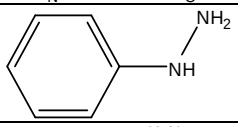
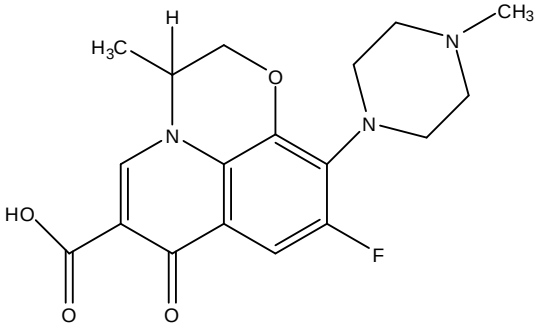
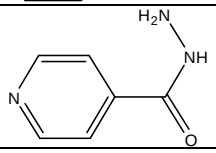
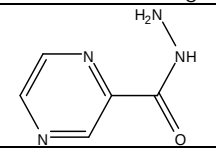
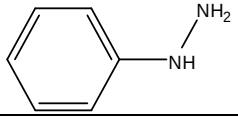
A mixture of thiosemicarbazide (0.1mole), aryl carboxylic acid (0.1 mole) & conc. Sulphuric acid (10 drops) in 50 mL of ethanol was refluxed for 1 hr & poured onto crushed ice. The solid separated out was filtered, washed with water & recrystallized from ethanol to give 2-amino-5-aryl-1, 3, 4-thiadiazole (II).

Synthesis of 1-methyl-3-((5-methyl-1,3,4-thiadiazol-2-ylamino)methyl)-1H-pyrazol-5(4H)-one (III)[6,7,8]

A mixture of 0.1 mole of substituted 1,3-dimethyl-1H-pyrazol-5(4H)-one (I) and 0.1 mole of 2-amino-5-aryl-1,3,4-thiadiazole (II) in 40 mL of methanol was refluxed for 40 min. The solid separated out was filtered & recrystallized from ethanol to give 1-methyl-3-((5-methyl-1,3,4-thiadiazol-2-ylamino)methyl)-1H-pyrazol-5(4H)-one (III).



SCHEME -1

COMP.	Ar	R
A_1		
A_2		
A_3		
B_1		
B_2		
B_3		
C_1		
C_2		
C_3		

Analytical, Physicochemical & TLC data of the synthesized compounds (scheme I).

Comp.	Mol. Formula	Mol. Wt.	Melting point (^{0}C)	R_f Value	Yield %	Elemental Analysis Calculated		
						C	H	N
A_1	$C_{28}H_{26}FN_9O_3S$	587.63	170-172	0.56	75.12	57.23	4.46	21.46
A_2	$C_{27}H_{25}FN_{10}O_3S$	588.62	180-182	0.52	80.28	55.09	4.28	23.80
A_3	$C_{28}H_{27}FN_8O_2S$	558.63	174-176	0.54	72.34	60.20	4.87	20.06
B_1	$C_{27}H_{26}FN_9O_3S$	575.62	178-180	0.52	72.08	56.34	4.55	21.90
B_2	$C_{26}H_{25}FN_{10}O_3S$	576.61	178-180	0.54	74.68	54.16	4.37	24.29
B_3	$C_{27}H_{27}FN_8O_2S$	546.62	176-178	0.54	75.24	59.33	4.98	20.50
C_1	$C_{29}H_{28}FN_9O_4S$	617.65	182-184	0.56	82.12	56.39	4.57	20.41
C_2	$C_{28}H_{27}FN_{10}O_4S$	618.64	170-172	0.51	78.44	54.36	4.40	22.64
C_3	$C_{29}H_{29}FN_8O_3S$	588.66	170-172	0.52	80.14	59.17	4.97	19.04

Spectral Data

A_1: IR (KBr) cm^{-1}: 3238(-NH str.), 3046 (Ar-CH str.), 1689 (C=O), 1501 (Ar-C-C str.), 1331 (C-O str.). ^{1}H NMR (d ppm): 11.59 (s, 1H, NH), 7.52-7.62 (m, 8H, Ar-H). **A_2:** IR (KBr) cm^{-1}: 3232(-NH str.), 3055 (Ar-CH str.), 1652 (C=O), 1500 (Ar-C-C str.), 1331 (C-O str.). ^{1}H NMR (d ppm): 11.89 (s, 1H, NH), 7.0-7.63 (m, 8H, Ar-H), 6.56 (d, 2H, NH_2) **A_3:** IR (KBr) cm^{-1}: 3238(-NH

str.), 3085(Ar-CH str.), 1651 (C=O), 1501 (Ar-C-C str.), 1301 (C-O str.). ^{1}H NMR (d ppm): 10.73 (s, 1H, NH), 7.0 -7.63 (m, 8H, Ar-H), 6.96 (d, 2H, CH_2). **B_1:** IR (KBr) cm^{-1}: 3073 (Ar-CH str.), 1661 (C=O), 1516 (Ar-C-C str.), 1280 (NO_2.), 679 (-Cl str.). ^{1}H NMR (d ppm): 6.94-7.64 (m, 8H, Ar-H). **B_2:** IR (KBr) cm^{-1}: 3062 (Ar-CH str.), 1682 (C=O), 1588(Ar-C-C str.), 1452 (C-N str.), 1360 (C-O str.), 1263 (-CN str.). ^{1}H NMR (d ppm): 6.94-7.64 (m, 8H, Ar-H).

Anti-bacterial activity of synthesized compounds

Compound	Zone of inhibition at 100µcg/mL (in mm.)		
	E. coli	***B. Subtilis***	***S. aureus***
A_1	16	23	20
A_2	18	24	26
A_3	18	20	21
B_1	26	23	26
B_2	23	19	22
B_3	25	21	23
C_1	26	24	25
C_2	16	18	19
C_3	25	19	24
Ciprofloxacin	28	24	26

RESULT AND DISCUSSION

A new series of some 1, 3, 4-thiadiazole derivatives were synthesized. The synthesized compounds were subjected to antibacterial activity by Cup-plate agar diffusion method result obtained were found to be promising A_1, A_2, B_1 and C_1 have shown excellent antibacterial activity against Ciprofloxacin as a standard drug.

CONCLUSION

These compounds exhibit a wide range of biological activities and with a suitable molecular modifications these compounds may prove as potent antibacterial agents in future.

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