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

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ABSTRACT

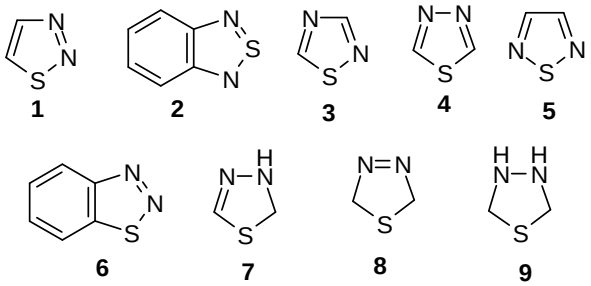
Some five membered aromatic systems having three heteroatoms at symmetrical positions such as 1,3,4-thiadiazoles have been studied for their antifungal activity. This research article covers the most active 1,3,4-thiadiazole derivatives that have shown excellent antifungal activity. This research work 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 1,3,4-thiadiazole moiety that could be better agents in terms of efficacy and safety.

KEYWORDS: Thiadiazoles, Antifungal 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. 1,3,4-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. 1,3,4-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-Fungal Activity[3]

Method: Cup-plate agar diffusion method.

Sabouraud-Dextrose agar plates were prepared by pouring 15-20 mL of the medium into each sterilized petridish and were allowed to set at room temperature. The cell suspension was standardized to a density of 530nm using a spectrophotometer and was inoculated over the surface of medium using a sterile cotton swab. Three cups were scooped in each plate using a sterile cork borer of 6mm diameter, standard and test solution. The solution of each test compound (0.10 mL/0.15 mL) was added in the cups by using micropipettes and these plates were subsequently incubated at 28°C for 48 hrs. The zone of inhibition was measured in mm for each organism.

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)[4]

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.

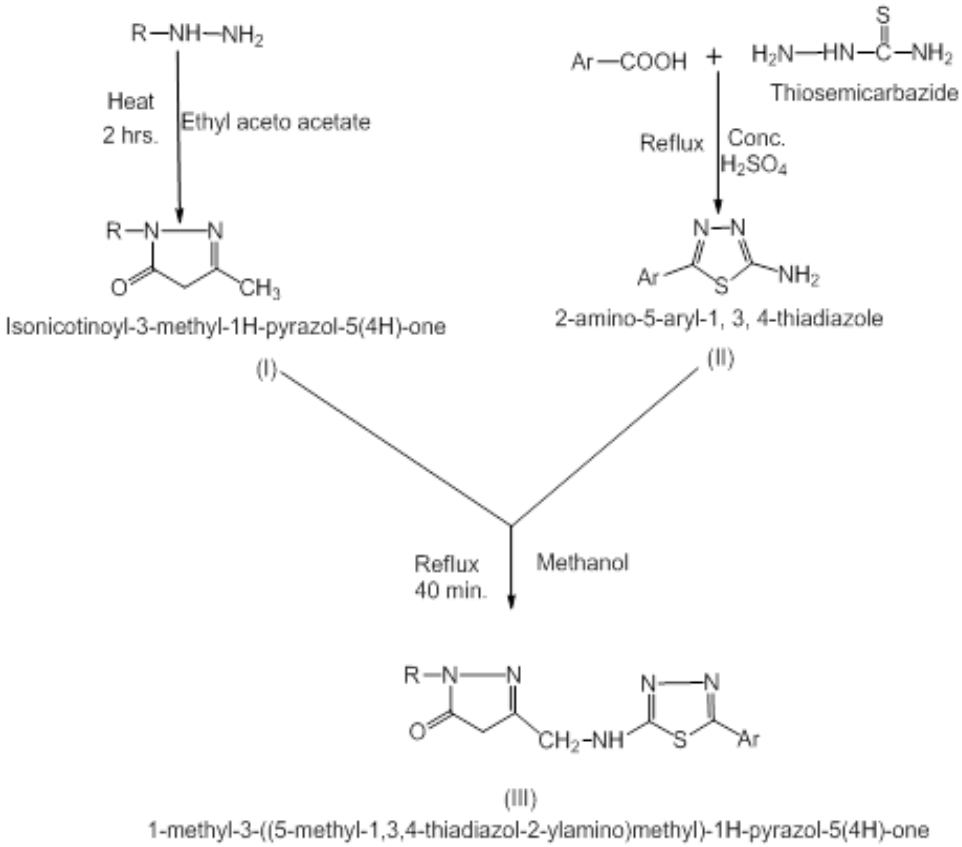
Synthesis of 2-amino-5-aryl-1, 3, 4-thiadiazole (II)[4,5,6]

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)[4,5,6]

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



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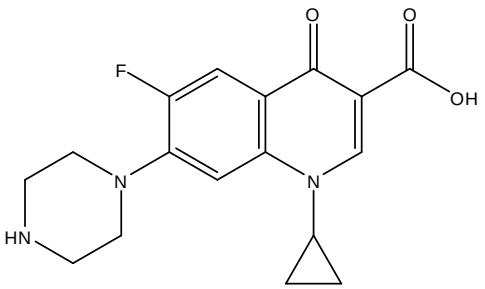
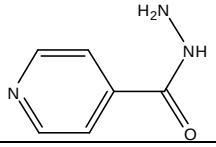
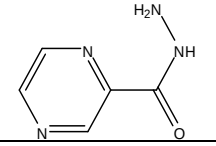
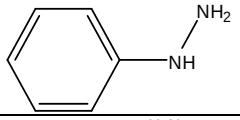
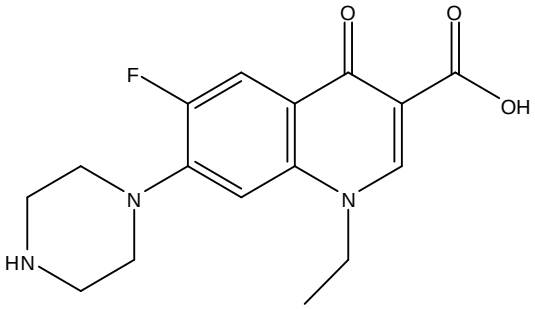
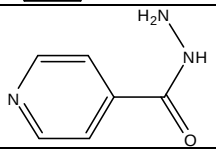
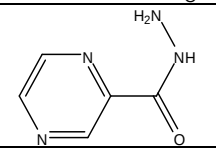
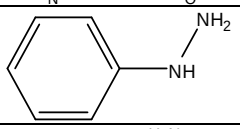
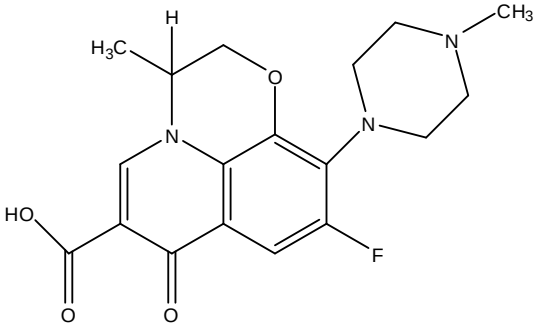
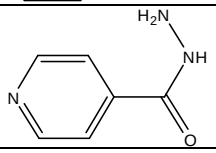
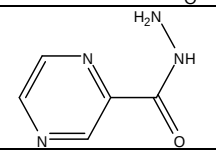
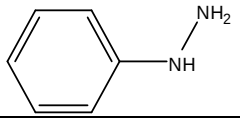
A_1		
A_2		
A_3		
B_1		
B_2		
B_3		
C_1		
C_2		
C_3		

Analytical, Physicochemical & TLC data of the synthesized compounds

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
$_3$	$C_{29}H_{29}FN_8O_3S$	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-fungal activity of synthesized compounds

Compound	Zone of inhibition at 100µcg/mL (in mm.)	
	C. albicans	*A. niger*
A_1	27	24
A_2	26	25
A_3	25	24
B_1	23	18
B_2	27	24
B_3	22	18
C_1	25	23
C_2	26	24
C_3	21	19
Fluconazole	28	25

RESULT AND DISCUSSION

A new series of some 1, 3, 4-thiadiazole derivatives were synthesized. The synthesized compounds were subjected to antifungal activity by Cup-plate agar diffusion method result obtained were found to be promising A_1, A_2, B_2 and C_2 have shown excellent antifungal activity against Fluconazole as a standard drug.

CONCLUSION

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

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