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"Synthesis, Antimicrobial Screening and Spectral Studies of Novel Derivatives of 1, 2, 4-Triazole and 1, 3, 4-Thiadiazole"

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ABSTRACT: Heterocycles bearing a symmetrical 1,2,4-oxadiazole-2-thione, and 1,3,4-thiadiazole-2-thione moieties, represent an interesting class of compounds possessing promising biological activities. Triazole ring is a quite important five-member heterocycle with three nitrogen atoms, possesses aromaticity and rich electrons. Thiadiazole is a five membered ring system containing two nitrogens and one sulphur atom. 1, 3, 4-Thiadiazole moiety when interacts with receptor acts as "hydrogen binding domain" and "Two-electron donor system. The present study entitled "Synthesis, antimicrobial screening and spectral studies of novel derivatives of 1, 2, 4-triazole and 1, 3, 4-thiadiazole" was carried out to synthesize and to screen the newly developed compounds for its antimicrobial activity. The stationary phase used were Silica gel G coated plate and mobile phase used were Chloroform: methanol (8:2). The spots were observed by the UV- light and iodine fumes. A single spot obtained were confirmed the purity of compounds. All the newly synthesized compounds were then identified for their structure and functional groups by using various analytical studies like IR, Mass and ^{1}HNMR spectra. Antifungal activity was performed in- vivo. The both results were correlated by minimum inhibitory concentration

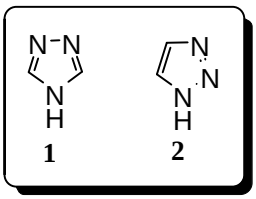
Keywords: - Antimicrobial activity, Antifungal activity, UV- light, IR, HNMR.

I. INTRODUCTION

A survey of literature reveals that heterocycles make up an exceedingly important class of compounds. Heterocycles bearing a symmetrical 1,2,4-oxadiazole-2-thione, and 1,3,4-thiadiazole-2-thione moieties, represent an interesting class of compounds possessing promising biological activities.

1,2,4-Triazole

Triazole ring is a quite important five-member heterocycle with three nitrogen atoms, possesses aromaticity and rich electrons. There are two possible isomers of triazole, 1,2,3- (1,2,5-) **1**, 1,2,4- (1,3,4) **2** depending on the position of nitrogen atom in the ring as shown below.



1 **2**

Fig.1. 1,3,4- Triazole Fig.2. 1,2,3- Triazole

Out of the two isomers shown in Fig.1 and 2, 1,2,4- triazole have drawn great attention to medicinal chemists from last few decades due to its readily binding property with a variety of enzymes and receptors in biological system via diverse non-covalent interactions such as coordination bonds, hydrogen bonds, ion-dipole, cation -π, π-π stacking, hydrophobic effect, Vander Waals force and so on. Because of this, triazole derivatives display a broad spectrum of biological activities, exhibit low toxicity and good pharmacokinetic and pharmacodynamic profiles [1]. Moreover, triazoles can function as attractive linker units which could connect two pharmacophores to give an innovative bifunctional drug, and thus have become increasingly useful and important in constructing bioactive and functional molecules [2].

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1, 3, 4-Thiadiazole

Thiadiazole is a five membered ring system containing two nitrogens and one sulphur atom. It occurs in nature in four isomeric forms viz. 1,2,3 - Shown in fig. **13**, 1,2,4- Shown in fig. **14**, 1,2,5- Shown in fig. **15** and 1,3,4- Shown in fig. **16**. The 1,3,4 -thiadiazole isomer of thiadiazole series and its dihydro-derivatives provide a bulk of literature on thiadiazole. A glance at the standard reference work shows that more work has been carried out on the 1,3,4- thiadiazole than all other isomers combined [3].

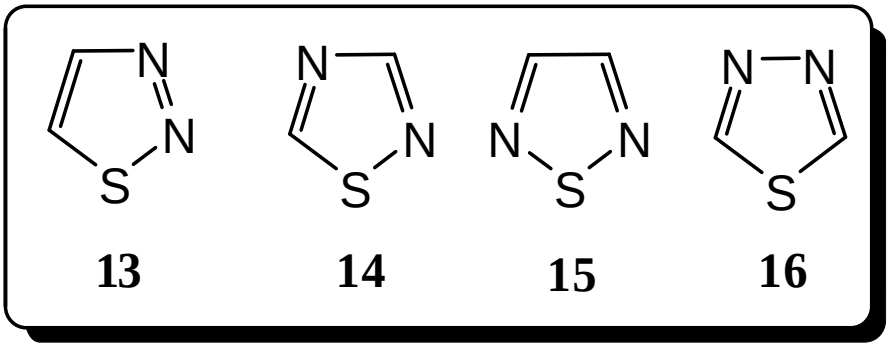

Fig. 13- 1,2,3 -thiadiazole

Fig. 14- 1,2,4 -thiadiazole

Fig. 15- 1,2,5 -thiadiazole

Fig. 16- 1,3,4 -thiadiazole

II. RESULT AND DISCUSSION

Three novel series of paracetamol derivatives has been prepared in an attempt to find out new derivatives with potent antimicrobial activity. The target compounds were synthesized as depicted, Ethyl-2-(4-acetamidophenoxy) acetate **5**, the starting material, was prepared by esterification of N-(4-hydroxyphenyl) acetamide **4** which when reacted with hydrazine hydrate gave N-[4-(2-hydrazinyl-2-oxoethoxy) phenyl] acetamide **6**. Compound **7** was obtained from the reaction of N-[4-(hydrazinyl methoxy) phenyl] acetamide **6** with carbon disulfide in basic media in good yield. Compound **7** when treated with cold concentrated H_2SO_4 gave compound **8**.

A series of targeted phenoxy acetylamino-thidiazole compounds (**9a-h**) were then condensed using the reaction of potassium salt of **N-{4-[(5-sulfanyl-1,3,4-thiadiazole-2-yl)methoxy]phenyl} acetamide** (**8**) and various N-substituted- β-chloropropionamides (**3a-h**), with stirring at 60 to 65°C by conventional method. The structures of various synthesized **3- [(5-{[4 (acetylamino) phenoxy] methyl}-1,3,4-thiadiazol-2-yl)sulfanyl] N-substituted propanamide** (**9a-h**) were assigned on the basis of chromatographic and spectral data available. The formation hydrazide **6** from ethyl-4-acetamido phenoxy acetate **5**, was confirmed using its IR spectrum. This spectrum showed absorption bands at 32668, 3198, 2986, 1690,1633 and 1565 $cm^{-1}$for NH_2, NH, Ar, C=O, C=C_{bend}, and NH_{bend} respectively.

Conversion of **7** to N-{4-[(5-sulfanyl-1,3,4-thiadiazole-2-yl)methoxy]phenyl} acetamide, **8 was confirmed by IR** absorption bands at 3298 cm^{-1} (N-H), 2462 cm^{-1} (S-H), 2896 cm^{-1} (C-H) and 1527 cm^{-1} (C-N str). Being acidic nature hydrogen of SH can be easily substituted in basic reaction conditions.

IR spectra of the title compounds **9a-h** confirmed the formations, after appearance of absorption bands in the ranges of 3264-3410, 3015-3120, 1618-1725 and 1572-1652 cm^{-1} due to NH, C-H, C=O and C=N respectively. ^{1}H NMR spectrum of the synthesized compounds showed that, all protons were in good agreements with the expected chemical signals and integral values. In these PMR spectra of new compounds **9a-h** chemical shifts between 3.82-3.87, 1.50-1.57, 6.94-8.77 and 8.10-8.19 were noticed for CH_2, CH_3, Aromatic and NH protons respectively. The structures of all these novel molecules were further confirmed with elemental analyses and mass spectroscopic results.

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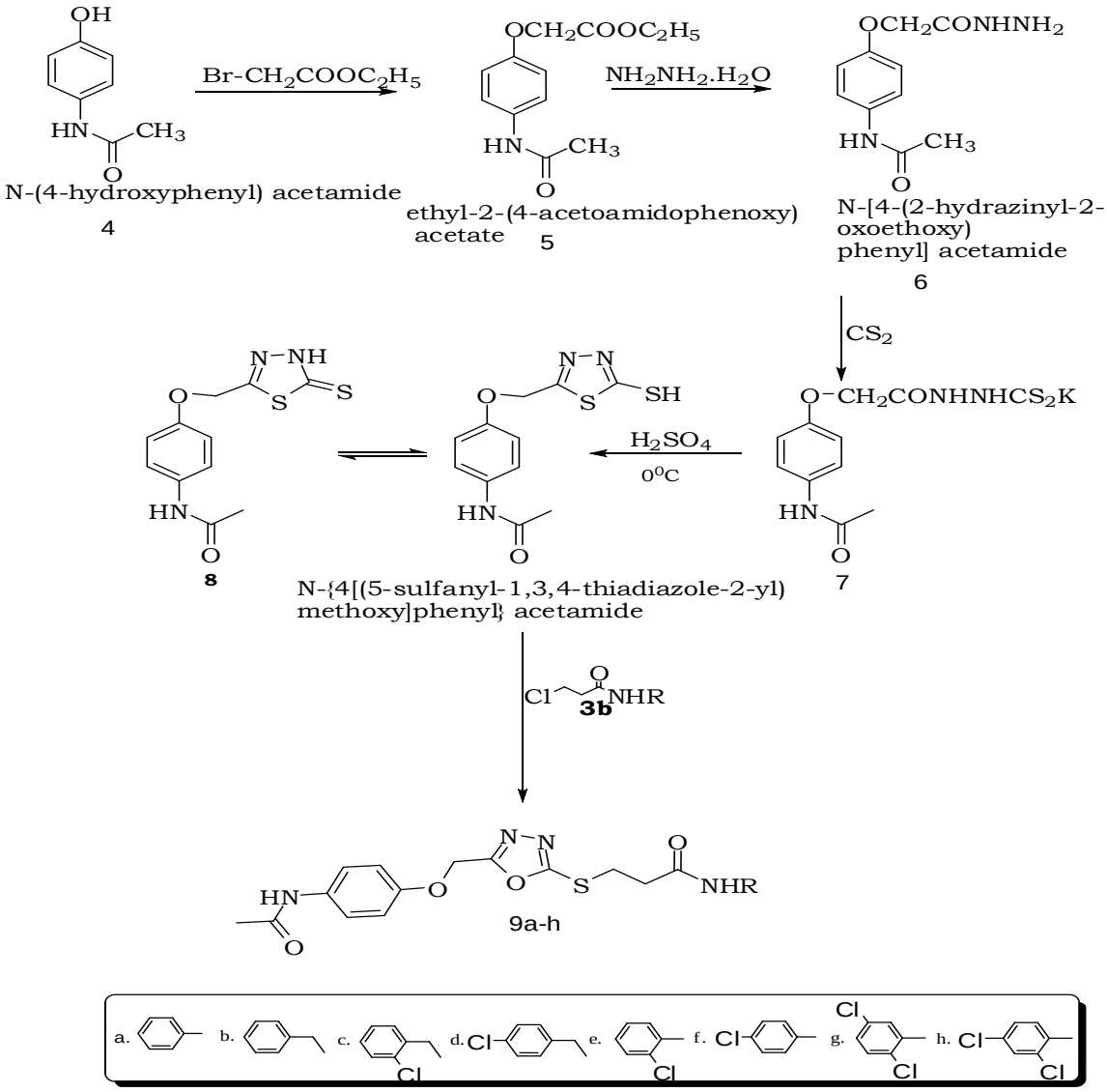

fig I: Synthesis of 9a-h

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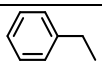
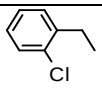
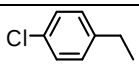
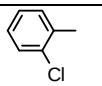
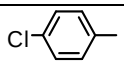
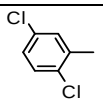
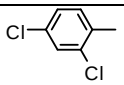
Table No. I: Spectral data of compounds 9a-h.

No.	Ar	IR (KBr)cm^{-1}	^1H NMR ($CDCl_3$)	Mass m/z
9a		3285 (NH), 3146 (Ar-H), 1088 (C-S), 1675 (C=O)	2.2 (s, 3H, CH_3), 2.3 (t, 2H, CH_2), 3.1 (t, 2H, CH_2), 5.4 (s, 2H, OCH_2), 6.7-7.8 (m, 9H-Ar), 10.01 (s, 1H, NH).	$(M+1)^+$ 427.1
9b		3255 (NH), 3164 (Ar-H), 1081 (C-S), 1702 (C=O)	2.1 (s, 3H, CH_3), 2.3 (t, 2H, CH_2), 3.3 (t, 2H, CH_2), 2 (s, 3H, CH_3), 4.46-4.47 (s, 2H, CH_2), 5.2 (s, 2H, OCH_2), 6.9-7.6 (m, 8H-Ar), 9.9 (s, 2H, 2NH).	(M^+)
9c		3265 (NH), 3166 (Ar-H), 1078 (C-S), 1685 (C=O), 746 (C-Cl)	2.2 (s, 3H, CH_3), 2.63-2.64 (t, 2H, CH_2-CH_2), 3.30-3.32 (t, 2H, CH_2-CH_2), 4.47-4.48 (s, 2H, CH_2), 5.4 (s, 2H, OCH_2), 7.00-7.61 (m, 8H, ArH, 8.0-8.1 (br, 1H, NH),	(M^+)
9d		3244 (NH), 3169 (Ar-H), 1090 (C-S), 1672 (C=O), 772 (C-Cl)	2.2 (s, 3H, CH_3), 2.58-2.59 (t, 2H, CH_2-CH_2), 3.27-3.29 (t, 2H, CH_2-CH_2), 4.42-4.44 (s, 2H, CH_2), 5.4 (s, 2H, OCH_2), 7.00-7.81 (m, 8H, ArH), 8.0-8.1 (br, 1H, NH),	(M^+)
9e		3275(NH), 3152 (Ar-H), 1088 (C-S), 1696 (C=O), 752 (C-Cl)	2.2 (s, 3H, CH_3), 2.60-2.62 (t, 2H, CH_2-CH_2), 3.31-3.32 (t, 2H, CH_2-CH_2), 5.4 (s, 2H, OCH_2), 6.94-7.67 (m, 8H, ArH), 8.0-8.1 (br, 1H, NH),	(M^+)
9f		3254 (NH), 3158 (Ar-H), 1081 (C-S), 1690 (C=O), 735 (C-Cl)	2.2 (s, 3H, CH_3), 2.60-2.62 (t, 2H, CH_2-CH_2), 3.28-3.29 (t, 2H, CH_2-CH_2), 5.4 (s, 2H, OCH_2), 7.25-7.27 (d, 2H, ArH), 7.58-7.59 (d, 2H, ArH), 7.60-7.61 (d, 2H, Pyridine-H), 8.65-8.66 (d, 2H, Pyridine-H), 8.0-8.1 (br, 1H, NH),	(M^+)
9g		3282 (NH), 3167 (Ar-H), 108 (C-S), 1688 (C=O), 735 (C-Cl)	2.2 (s, 3H, CH_3), 2.59-2.60 (t, 2H, CH_2-CH_2), 3.28-3.30 (t, 2H, CH_2-CH_2), 5.4 (s, 2H, OCH_2), 7.19-7.80 (m, 7H, ArH), 8.0-8.1 (br, 1H, NH),	(M^+)
9h		3268 (NH), 3172 (Ar-H), 1058 (C-S), 1670 (C=O), 711 (C-Cl)	2.2 (s, 3H, CH_3), 2.62-2.63 (t, 2H, CH_2-CH_2), 3.30-3.31 (t, 2H, CH_2-CH_2), 5.4 (s, 2H, OCH_2), 7.13-7.82 (m, 7H, ArH), 8.0-8.1 (br, 1H, NH),	(M^+)

Antimicrobial activity of [(5-{[4-(acetylamino) phenoxy] methyl}-1,3,4-thiadiazol-2-yl)sulfanyl] N-substituted 3-propanamide. (9a-h)

In case of **5e** with o-chloro phenyl substitution improvement in activity was noticed. Similar attempt with the benzyl substitution (**5c**) exhibited better result but with (**5d**) disappointing results with no further increase in activity. Assuming, chlorine has vital role to play in the orientation and receptor bindings, **5g** and **5h** were synthesized but failed to reflect the potentiation. Close look at SAR revealed that "small changes make big difference", thus wondering if one carbon elongation or branching will embark any betterment in inhibition.

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Table IV: Data of Antimicrobial activities of compounds 9a-h.

Comp	MIC values (µg/ml)					
	Antibacterial activity				Antifungal activity	
	Gram-positive		Gram-negative			
	Sa	Bs *	Ec	Pa	An	Ca
9a	62.5	62.5	62.5	62.5	125	125
9b	31.25	16	16	16	125	62.5
9c	16	8	8	8	31.25	31.25
9d	31.25	31.25	16	16	62.5	62.5
9e	16	16	16	8	31.25	62.5
9f	62.5	62.5	31.25	31.25	62.5	62.5
9g	62.5	31.25	31.25	31.25	125	125
9h	62.5	31.25	31.25	31.25	125	125
Nor[b]	<5	<1	<1	<5	-	-
Fluc[c]	-	-	-	-	0.25	0.25

III. CONCLUSION

The present study on synthesis, antimicrobial screening and molecular docking studies of novel derivatives of 1,2,4-triazole and 1,3,4-thiadiazole were carried out to synthesize and to screen the newly developed compounds for its antimicrobial activity. The melting point of the synthesized compound was determined by open capillary method. The purity and progress of reaction were monitored by thin layer chromatography. The stationary phase used were Silica gel G coated plate and mobile phase used were Chloroform: methanol (8:2). The spots were observed by the UV light and iodine fumes. A single spot obtained were confirmed the purity of compound. All the newly synthesized compounds were then identified for their structure and functional groups by using various analytical studies like IR, Mass and ^{1}HNMR spectra. The newly synthesized compounds were evaluated for the Antibacterial; Antifungal activity were performed in- vivo. The both results were correlated by minimum inhibitory concentration. All the synthesized compounds some of their derivatives show significant antimicrobial activity. This study should be proceed through molecular pharmacology and toxicological studies along with screening of therapeutic application of this drug as develop the potent drug in the management microbial diseases.

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