Journal of Pharmaceutical and Scientific Innovation
www.jpsionline.com
Research Article

ANTI-MICROBIAL EVOLUTION OF NOVEL THIAZOLES

R. Sumathi[1], A. Sultan[2], S. Syed Shafi*
[1]Department of Chemistry, Thiruvalluar University, Serkadu, Vellore, Tamil Nadu, India
[2]Department of chemistry, Islamiah College, Vaniyambadi
*Corresponding Author Email: Suban_shafi@yahoo.com
DOI: 10.7897/2277-4572.032125
Published by Moksha Publishing House. Website www.mokshaph.com

Received on: 01/02/14 Revised on: 02/03/14 Accepted on: 10/03/14

ABSTRACT
A vast array of thiazole derivatives having excellent broad spectrum activity forms an invaluable part of the present armory of the clinicians. A novel series of thiazole compounds were synthesized and screened for the anti-bacterial and anti-fungal activity. The structures of these compounds were ascertained by IR H^1 NMR, mass spectra and elemental analysis. The anti-bacterial activity of the synthesized compounds were evaluated against gram positive bacteria and gram negative bacteria all the compounds had shown moderate to significant anti-bacterial activity. The anti-fungal activity of the compounds is more significant than anti-bacterial activity.
Keywords: Thiazole moiety, pyrazole moiety, anti-microbial activity

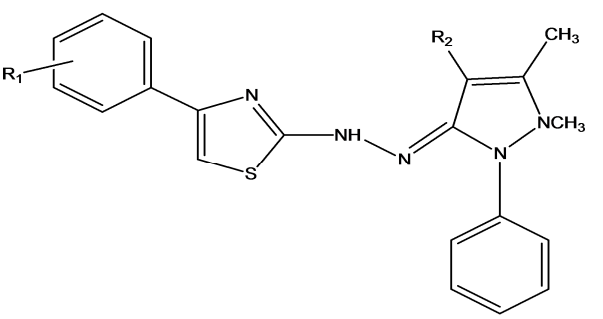
INTRODUCTION

The thiazole chemistry has been extensively developing because of their unique physiological properties. Thiazoles are stable, non-carcinogenic aromatic compounds with relatively small size. Heterocyclic systems containing thiazole show wide range of activities. The versatility of these nuclei is demonstrated by the fact that some of these compounds exhibit antifungal, antibacterial, antihistaminic, anti thyroid and anti tubercular activities. The synthetic importance of thiazoles, thiadiazoles, thiadiazines and their condensed heterocyclic systems have been increased much by their recent uses as anthelmintics, anti neoplastic, vulcanization accelerators and photographic sensitizers Thiazoles and pyrazoles are highly versatile ring systems displaying a large number of mild to potential pharmacological activities. Some of them are utilized as medicines[1]. According to literature survey, Thiazoles were reported to possess anti-microbial[2], analgesic[3], antiinflammatory[4], anti-cancer[5], anti-tubercular[6], anthelmintic[7] and diuretic[8] activities. Anti-microbial activities of some substituted thiazoles are well established because it posses (S-C=N) toxophoric unit. Thiazoles have enhanced lipid solubility with hydrophilicity. Thiazoles are easily metabolized by routine biochemical reactions and are non-carcinogenic in nature[9]. In addition, pyrazoles are reported as anti-microbial[10], analgesic[11], anti-inflammatory[12], anti hypertensive[13], anti-depressant[14] and anticancer[15] agents. We herewith proposed to synthesize novel compounds containing both pyrazole and thiazole moieties. Antipyrine was the first pyrazolin-5-one derivative used as an analgesic and antipyrine derivatives have been synthesized and evaluated as potent anti-inflammatory, analgesic and anti-microbial agents[16-19]. Also the chemistry of antipyrine and its derivatives has been extensively investigated due to its physiological properties. Pyrazoline derivatives have also been reported in the literature to exhibit various pharmacological activities such as antimicrobial[20-26], Anti inflammatory[27] and hypertensive[28].

MATERIALS AND METHODS

The commercially available AR and LR grade chemicals were used without further purification. Chemical reagents and solvents were purchased from sigma aldrich. Melting points were determined in an open glass capillaries on gallen camp apparatus and corrected. The percentage compositions of the elements (CHNS) for the compounds were determined using an elemental analyzer CHNS model fison EA 1108. The infrared spectra were recorded as potassium bromide disc using a perkin-elmer spectrophotometer GX. The 'H and 1^3c nuclear magnetic resonance spectra were recorded using JEOL JNM-ECP 400 spectrometer in DMSO-d_6 as the solvent using TMS as an internal standard, and chemical shifts are expressed as ppm. Mass spectra were recorded on micro-mass Q-TOF and shizmadzu LCMS 2010A mass spectrometer and the reactions were followed by TLC (silica gel, aluminium sheets 60 $F_{254,}$ Merck).

Final compound;



S. No.	R1	R2	Melting point	Yield	Molecular Formula	Molecular Weight
2a).	4-Cl	H	94°C	72 %	$C_{20}H_{18}ClN_5S$	395.91
2b).	4-CN	H	120°C	67 %	$C_{21}H_{18}N_6S$	386.4
2c).	4-NO_2	NH_2	115°C	74 %	$C_{20}H_{19}N_7O_2S$	421.48
2d).	-OCH_3	H	126°C	64 %	$C_{21}H_{21}N_5OS$	391.49
2e).	2-NO_2	NH_2	142°C	78 %	$C_{20}H_{19}N_7O_2S$	421.48
2f).	2,4,dibromo	H	108°C	69 %	$C_{20}H_{17}Br_2N_5S$	519.26
2g).	4-Cl	NH_2	98°C	72 %	$C_{20}H_{19}ClN_6S$	410.92
2h).	H	H	87°C	64 %	$C_{20}H_{19}N_5S$	361.46
2i).	-OCH_3	NH_2	116°C	62 %	$C_{21}H_{22}N_6O_6$	406.51
2j).	4-CN	NH_2	111°C	69 %	$C_{21}H_{19}N_7S$	401.49
2k).	4-NO_2	H	132°C	71 %	$C_{20}H_{18}N_6O_2S$	406.46
2l).	H	NH_2	92°C	64 %	$C_{20}H_{2O}N_6S$	376.48
2m).	2,4,dibromo	NH_2	105°C	69 %	$C_{20}H_{18}Br_2N_6S$	534.27

Spectral Data

2a) IR(KBr):μ(cm^{-1}) 3277(NHR str), 1645(C=N str)1550, 1519(Ar C-C str), 563(C-S-C str), CH_3-N (2750 cm^{-1}) ^{1}H NMR(DMSO, $_{ppm}$) :7.49(S,1H,CH of thiazole) 6.66(1-N-N) 8.35(S,1H_1-N=CH-), 6.6-7.23(m,9H,Ar-h); MS(E1); 394.10(M^+): E. Analysis. Found: C, 60.37; H,4.58; Cl, 8.95; N,17.69; S,8.10 .Calculated: C,60.45; H, 4.52; Cl,8.92;N,17.58; S,8.07 mol. formula: $C_{20}H_{18}ClN_5S$.

RESULT AND DISCUSSION

Most of the synthesized compounds exhibited mild to moderate antimicrobial activity against the tested micro organisms compound 2d and 2h where found to posses significant anti-bacterial and anti-fungal activity when compared to standard drug Compounds 2d and 2h displayed moderate anti-bacterial activity where as the remaining compounds show lesser activity. All the compounds displayed moderate anti-fungal activity. The entire synthesized compound exhibited better anti-fungal activity than anti-bacterial activity. In addition to that, many compounds are most active against gram positive bacteria than the gram negative one. The potent anti-microbial activity exhibited by 2d and 2h is due to the incorporation of electron donating groups. The interesting results we observed that both electrons donating as well as electron with drawing groups was found to increase the anti-microbial properties, where as un substituted derivatives exhibited lesser degree of activity. In conclusion, the present study highlights the importance of pyrazole and thiazole ring features responsible for the anti-microbial activities and therefore may serve as a lead molecule for further modification to obtain clinically useful novel entities.

Antimicrobial Activity

The compounds were screened for their antibacterial activity against four strains of bacteria *Staphylococcus aureus*, *Bacillius substilis*, *Escherichia coli* and *Candida albicans* and *Aspergillus niger* using paper disc technique. The zone of the inhibition against all the micro organisms was measured in millimeter the antifungal activity studies were carried out against *Candida albicans*, *Aspergillus niger*, *Aspergillus niger* fumigatus, *Rhizopus* sps, *Penicillium* sps, *Mucor* sps. The results are present in the Table 1, 2, 3 and 4.

Antimicrobial Assay

Antimicrobial analysis was followed using standard agar well diffusion method to study the antimicrobial activity of compounds[29]. Each bacterial isolate was suspended in Brain Heart Infusion (BHI) broth and diluted to approximately 10^5 colony forming unit (CFU) per mL. They were flood-inoculated onto the surface of BHI agar and then dried. Five-millimeter diameter wells were cut from the agar using a sterile cork-borer and 30 µL (5 µg compound in 500 µL DMSO) of the sample solution were poured into the wells. The plates were incubated for 18 h at 37C for bacteria. Antimicrobial activity was evaluated by measuring the diameter of the zone of inhibition in mm against the test microorganisms and the solvent. DMSO was used as solvent control. Ciprofloxacin was used as reference antibacterial agent. The tests were carried out in triplicates.

Brain Heart Infusion (BHI) Agar

Composition

Calf brains (infusion from 200 g) 12.5
Beef heart (infusion from 250 g) 5.0
Protease peptone 10.0
Sodium chloride 5.0
D (+)- Glucose 2.0
Disodium hydrogen phosphate 2.5
Agar 10.0
Final pH 7.4 +/- 0.2 at 37°C
Store prepared media below 8°C, protected from direct light. Store dehydrated powder, in a dry place, in tightly-sealed containers at 2-25°C.

Directions

Suspend the above ingredients in 1 liter of distilled water. Boil to dissolve the medium completely. Distribute into tubes, plates or flasks and sterilize by autoclaving at 121°C for 15 minutes.

Table 1

S. No	Microorganisms	Control	2a	2b	2c	2d	Ciprofloxacin
1.	*Klebsiella pneumoniae*	-	7 mm	8 mm	9 mm	21 mm	20 mm
2.	*Staphylococcus aureus*	-	16 mm	15 mm	20 mm	18 mm	20 mm
3.	*Escherichia coli*	-	20 mm	20 mm	22 mm	25 mm	24 mm
4.	*Streptococcus faecalis*	-	10 mm	20 mm	8 mm	24 mm	26 mm
5.	*Bacillus subtilis*	-	10 mm	15 mm	13 mm	22 mm	24 mm
6.	*Pseudomonas aeruginosa*	-	10 mm	14 mm	30 mm	21 mm	15 mm

Note: - no zone of inhibition

Table 2

S. No.	Microorganisms	Control	2e	2f	2g	2h	Ciprofloxacin
1.	*Klebsiella pneumoniae*	-	-	-	-	21 mm	22 mm
2.	*Staphylococcus aureus*	-	-	10 mm	-	20 mm	22 mm
3.	*Escherichia coli*	-	-	10 mm	-	26 mm	25 mm
4.	*Streptococcus faecalis*	-	-	6 mm	-	29 mm	30 mm
5.	*Bacillus subtilis*	-	-	5 mm	-	27 mm	26 mm
6.	*Pseudomonas aeruginosa*	-	-	5 mm	-	14 mm	15 mm

Note: - no zone of inhibition

Antifungal Activity

Table 3

S. No.	Microorganisms	Control	2a	2b	2c	2d	Ketoconazole
1.	*Candida albicans*	-	34 mm	45 mm	32 mm	42 mm	30 mm
2.	*Aspergillus niger*	-	35 mm	50 mm	30 mm	29 mm	13 mm
3.	*Aspergillus fumigatus*	-	35 mm	52 mm	40 mm	32 mm	20 mm
4.	*Rhizopus sps*	-	26 mm	45 mm	22 mm	42 mm	26 mm
5.	*Penicillium sps*	-	25 mm	41 mm	32 mm	40 mm	17 mm
6.	*Mucor Sps*	-	40 mm	54 mm	42 mm	47 mm	20 mm

Note: - no zone of inhibition

Table 4

S. No.	Micro organisms	Control	2e	2f	2g	2h	Ketoconazole
1.	*Candida albicans*	-	10 mm	9 mm	5 mm	22 mm	35 mm
2.	*Aspergillus niger*	-	11 mm	9 mm	5 mm	14 mm	10 mm
3.	*Aspergillus fumigatus*	-	20 mm	16 mm	10 mm	18 mm	14 mm
4.	*Rhizopus sps*	-	13 mm	11 mm	9 mm	12 mm	8 mm
5.	*Penicillium sps*	-	11 mm	13 mm	10 mm	11 mm	18 mm
6.	*Mucor Sps*	-	17 mm	25 mm	8 mm	16 mm	12 mm

Note: - no zone of inhibition

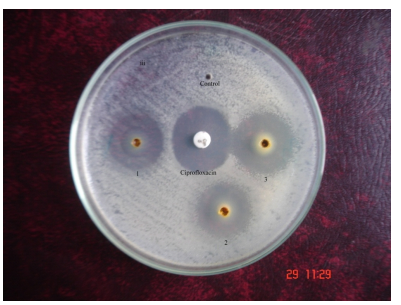


Figure 1

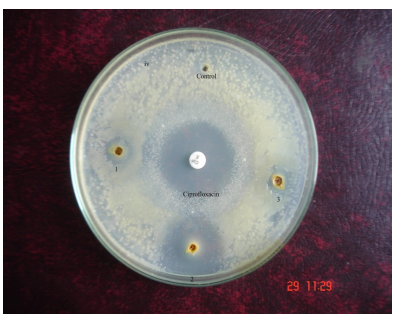


Figure 2

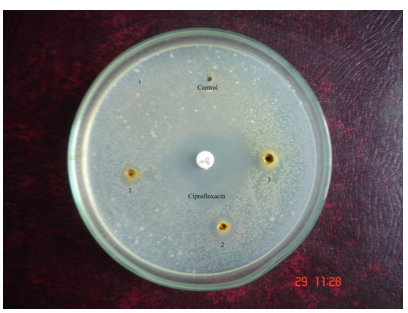


Figure 3

Figure 4

CONCLUSION

The main aim of the present study is to synthesize and investigate the anti microbial activity of the heterocyclic derivatives containing pyrazole and thiazole moieties with the hope of discovering new structures serving as potential broad spectrum antimicrobial agents. The antibacterial and antifungal data revealed that the compounds showed good to moderate antimicrobial activity. Basically introduction of pyrazole moiety in the structure of the final compound has increased the antifungal activity compared to the other. From the study, it can be concluded that all the synthesized compounds demonstrated potential antimicrobial activity.

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Source of support: Nil, Conflict of interest: None Declared

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	Website http://www.jpsionline.com

How to cite this article:

R. Sumathi, A. Sultan, S. Syed Shafi. Anti-microbial evolution of novel thiazoles. J Pharm Sci Innov. 2014;3(2):139-142 http://dx.doi.org/10.7897/2277-4572.032125