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SYNTHESIS AND ANTIMICROBIAL SCREENING OF SOME NOVEL TRIAZOLES THEIR SCHIFF'S BASES

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ABSTRACT

The 1, 2, 4-triazole is a versatile lead molecule for designing potential bioactive agents. Derivative of this particular lead structure have been evaluated for wide spectrum of biological activities such as antifungal, antitubercular, antibacterial. The target derivatives were synthesis by four steps. The methyl-2-(4-isobutylphenyl) propanoate [1b] and 2-(4-isobutylphenyl) prapanohydrazide [1c] were synthesis by reflux ibuprofen in methanol and few drop of sulphuric acid and hydrazine hydrate. The potassium salt of 2-[2-(4-isobutylphenyl) propanoyl] hydrazine-carbothioate [1d] synthesis by reaction of ibuprofen acid hydrazide in methanol, carban disulfide and alcoholic potassium hydroxide.The 4-amino -5-[(-4isobutylphenyl -1) ethyl]-1, 2,4triazole-thioal [1e] synthesis by reaction of potassium carbodithiote with hydrazine hydrate with evolution of hydrogen sulphide gas. The aromatic aldehyde was react with triazole [1e] and form 4-[(1Z)-(2/4substituted phenyl) methylene] amino-5-[1-(4-isobutylphenyl) ethyl]-1, 2, 4triazole-3-thiol [1f].
The structures of compounds were assigned on the basis of elemental analysis .IR, PMR, C^{13}NMR and MASS spectral data.

Keywords: 1, 2, 4 Triazoles, antifungal, antibacterial.

1. INTRODUCTION

The Triazoles is well known moiety for a wide range of biological activity, several Triazoles such as fluconazole, itraconazole are used as antifungal activity, the Triazoles were also used antibacterial, anticonvulsant, antiplatelates, hypoglycemic agent[4]. Therefore it was thought worthwhile to synthesize hybrids of substituted 1, 2, 4 triazoles. The compound [1f] was synthesis by four steps as;

The methyl-2-(4-isobutylphenyl) propanoate [1b] and 2-(4-isobutylphenyl) prapanohydrazide [1c] were synthesis by reflux ibuprofen in methanol and few drop of sulphuric acid and hydrazine hydrate.The potassium salt of 2-[2-(4-isobutylphenyl) propanoyl] hydrazine-carbothioate [1d] synthesis by reaction of ibuprofen acid hydrazide in methanol, carbon disulfide and alcoholic potassium hydroxide. The 4-amino -5-[(-4isobutylphenyl -1) ethyl]-1, 2,4triazole-thioal [1e] synthesis by reaction of potassium carbodithiote with hydrazine hydrate with evolution of hydrogen sulphide gas. The aromatic aldehyde was react with triazole [1e] and form 4-[(1Z)-(2/4substituted phenyl) methylene] amino-5-[1-(4-isobutylphenyl) ethyl]-1, 2, 4triazole-3-thiol [1f].

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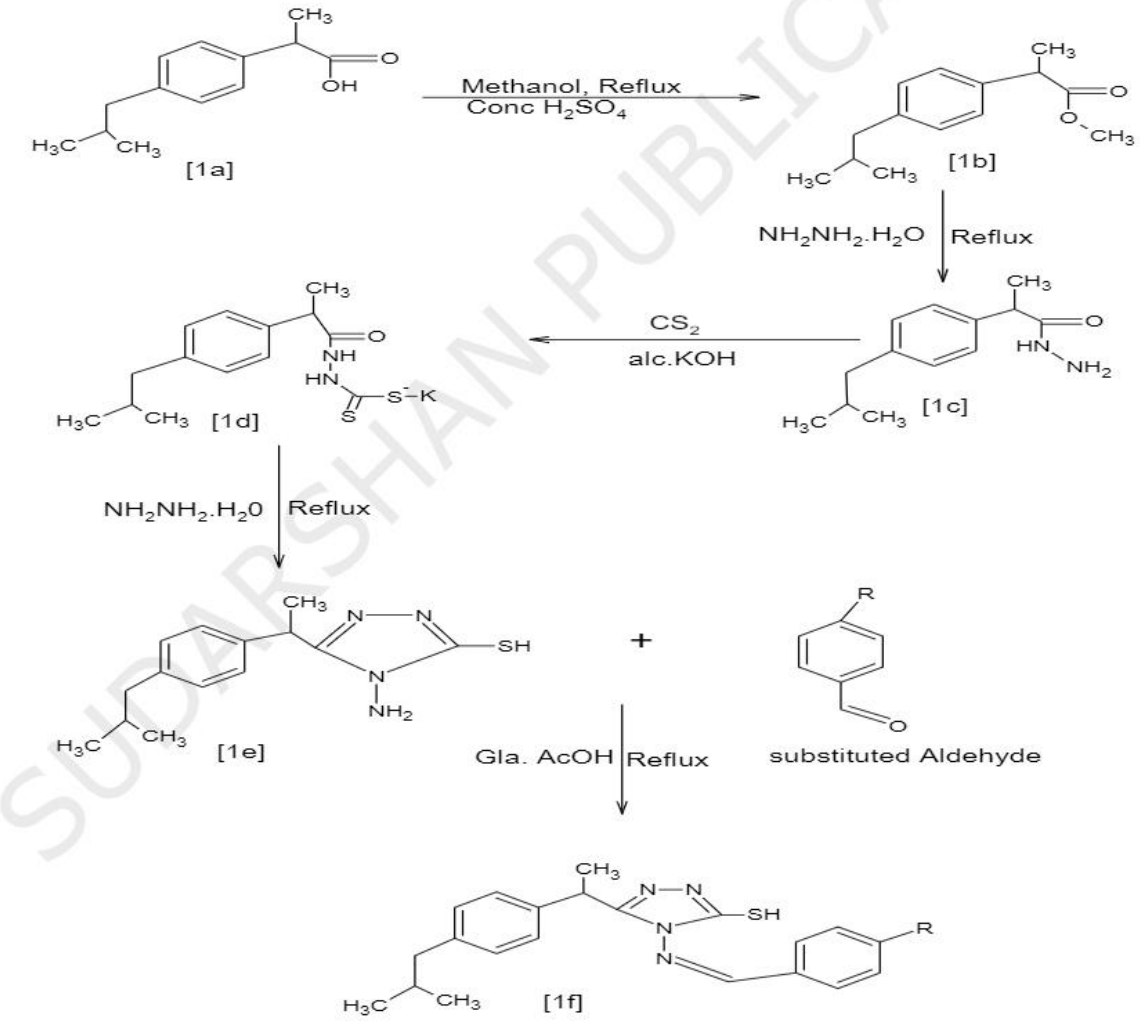
All the compounds showed satisfactory elemental analysis for C, H and N analysis. In IR spectra abs bands for aromatic C=O str. appeared in the region 1255-1260. The abs bands for N-H str. of 3200-3250, C=N stretching of Triazoles ring, and aromatic C-H stretching, SH str of thio group were observed in the range 1600-1620,3040-3050 and 2565-2570 respectively.

The ^{1}HNMR spectra of (T1-T8) in DMSO-d_6 400 MHz showed in the, range of 6.952-7.715ppm corresponding to the aromatic H (m,8H, Ar H),2.493-2.564 (s,1H.CH),1.4895(d, H, isopropyl),9.4889(s,1H,SH) and 3.8268ppm (s, 3H OCH_3) for 3H proton of methoxy group respectively.

2. EXPERIMENTAL:

The triazole derivatives were synthesis according to scheme-1.

Scheme-1



2.1 Antibacterial and antifungal activity:
All the synthesis derivatives were screened for antibacterial activity using Agar disc diffusion method. Four pathogenic strains were used viz E.coli, P.aeruginosa, S.aureus, B.subtilis. The compounds T3, T7 were more active against E.coli, T5 against P.aeruginosa, T4 against S.aureus, and B.subtilis. Ciprofloxacin used as standard for both gram positive and gram negative bacteria.
The antifungal activity were did using sabouroud dextrose agar method, two pathogenic organisms were used as Candida albicans, Aspergillus niger. Compound T5, T6, and T7 show good activity.

The melting points were determined in open glass capillary tubes and are uncorrected. Infrared (IR) spectra were recorded in KBr pellets on FT −761 Jasco. The proton nuclear magnetic resonance (^{1}HNMR) spectra were recorded on a Bruker model dpx 300 (chemical shift in δ ppm). TLC was used to monitor all the reactions and developing solvents were benzene: methanol (9:1)

2.2 Synthesis of methyl 2-(4-isobutylphenyl) propanoate [1b] and 2-(4-isobutyl phenyl) prapanohydrazide [1c]:
To a solution (0.02mole) of ibuprofen in methanol (10ml), a few drops of sulphuric acid were added and refluxed for a period of 18hrs. The mixture was then cooled to room temperature and excess of hydrazine hydrate (0.06mole) was added to it and was further refluxed for a period of 5hrs.the product was concentrated under reduced pressure and cooled. The solid obtained was washed with cold water and recrystalized from hot water. Reaction mixture was monitored during reaction by TLC using solvent system benzene: methanol (9:1).

2.3 Synthesis of potassium salt of 2-[2-(4-isobutyl phenyl) propanoyl] hydrazine-carbodithioate [1d]:
To a solution of ibuprofen acid hydrazide in methanol ,(0.02mole) carbon disulphide was added and followed by alcoholic KOH (0.015mole) dropwise.the reaction mixture was stirred for about 4hrs. Reaction mixture was monitored during reaction by TLC using solvent system benzene: methanol (9:1).after completion of reaction mixture was diluted with ether (50ml) and separated solid with dry ether 50ml and separated solid was filtered washed with dry ether to obtained potassium salt in quantitative yield.

2.4 Synthesis of 4-amino-5[(4-isobutylphenyl-1) ethyl]-1, 2, 4 Triazole-3thiol [1e]:
The potassium carbothioate salt was refluxed with (0.03mole) of hydrazine hydrate in methanol until evaluation of H2S ceased (6-8 hrs).Reaction was monitored by TLC solvent system – benzene: methanol (9:1).after completion of reaction, mixture was neutralized with dilute HCL and then poured in to the crushed ice and kept in the fridge for overnight .The solid was filtered, washed with ice cold water, dried and recrystalized in methanol.

2.5 Synthesis of 4-{[-(1Z) (2/4-substituted phenyl) methylene] amino} 5-[2-(4-isobutylphenyl]-1, 2, 4 Triazoles -3 thiol [1f]:
The aromatic aldehyde (0.01mole) was added to the solution of Triazoles (0.01mole) in glacial acetic acid 10 ml and mixture was refluxed for 24 hrs. Reaction was monitored by TLC solvent system – benzene: methanol (9:1).after completion of reaction, mixture was cooled and poured in to the ice cold water. The solid was filtered, washed with ice cold water, dried and recrystalized in methanol.

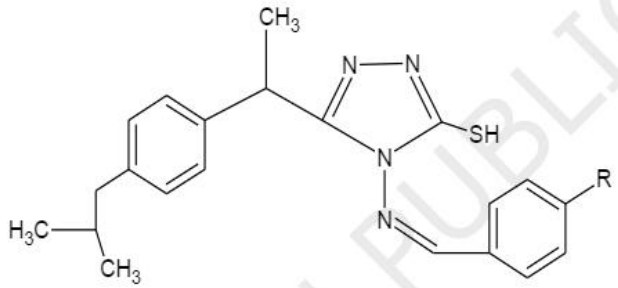
The physical and analytical data of synthesized compound are presented as followed;

2.6 Spectral data

T2 : FT-IR (KBr) (cm^{-1}) : 3332.43 (N-H), 1255 (C-O str of ether), 1602.34 (C=N str of triazole ring), 1587.13 (Ring C=C str), 2961.4 (C-H str of CH_3),3047.3(c-h str for aromatic ring), M+1 =409, 304 base peak,^{1}HNMR (DMSO-d_6) (δppm): 7.653-7.552 (m, 4H, ArH), 6.952(m, 8H, -aromatic hydrogen), 1.4885 (d, 1H, isopropyl), 9.4882 (s, 1H SH),3.8268(S,3H,OCH_3).

T1 : FT-IR (KBr) (cm^{-1}) : 3332.43 (N-H), 1255 (C-O str of ether), 1602.34 (C=Nstr of triazole ring), 1587.13 (Ring C=C str), 2961.4 (C-H str of CH_3),3047.3(c-h str for aromatic ring), M+1=395 peak, 290 base peak,^{1}HNMR (DMSO-d_6) (δppm): 7.653-7.552 (m, 4H, ArH), 6.952(m, 8H, -aromatic hydrogen), 1.4885 (d, 1H, isopropyl), 9.4882 (s, 1H SH),7.421(S,3H,OH).

Same as there other show accepted spectral data.



[1f], [T1-T7]

Physical data of newly synthesized compounds

Table-1

Code	R	Molecular formula	Recrystallizing solvent	Melting point (^{0}C)	Rf value	% yield
T1	p-OH	$C_{22}H_{26}N_4OS$	Methanol	196	0.52	70
T2	p- OCH_3	$C_{23}H_{28}N_4OS$	Methanol	180	0.48	90
T3	p-CH_3	$C_{23}H_{28}N_4S$	Methanol	214	0.56	86
T4	p-N(CH_3)	$C_{24}H_{31}N_5S$	Methanol	230	0.47	72
T5	p-F	$C_{22}H_{25}FN_4S$	Methanol	252	0.55	78
T6	p-CF_3	$C_{23}H_{25}F_3N_4S$	Methanol	264	0.49	82
T7	p-Cl	$C_{22}H_{25}ClN_4S$	Methanol	255	0.42	65

Satisfactory elemental analysis has been obtained for all the synthesized compounds

3. **RESULTS AND DISCUSSION**:

The novel synthesis 1, 2, 4 Triazole and their Schiff bases derivatives showed satisfactory

elemental analysis and FT-IR data and Proton NMR, Mass spectra. Antibacterial and antifungal activity showed by the derivative represent in their zone of inhibition.

Table-2

Organism	E.coli	S.aureus	P.aeruginosa	B.subtilis	Candida albicans	Aspergillus niger
Control	_	_	_	_	_	_
T1	-	6	9	12	11	10
T2	-	8	7	10	8	9
T3	14	10	11	10	8	9
T4	-	15	9	13	-	10
T5	11	-	16	9	10	11
T6	9	8	11	-	14	9
T7	11	10	-	7	9	15
Standard	21	18	22	21	20	22

The standard drug ciprofloxacin and fluconazole was used for antibacterial and antifungal respectively. The compounds T3, T7 were more active against E.coli, T5 against P.aeruginosa, T4 against S.aureus, and B.subtilis. The T6 show good activity against Candida albicans, and T7show against Aspergillus Niger.

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