International Journal of Pharmacy and Biological Sciences
ISSN: 2321-3272 (Print), ISSN: 2230-7605 (Online)
IJPBS | Volume 8 | Issue 3 | JUL-SEPT | 2018 | 43-53
Research Article | Pharmaceutical Sciences | Open Access | MCI Approved| ज्ञान-विज्ञान विमुक्तये
|UGC Approved Journal |

ISONIAZID BASED 1,2,4-TRIAZOLES: DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION

Prabhu C Jalihal[a], Vaibhav Rajoriya[b], Varsha Kashaw[a] and Sushil Kumar Kashaw[b]

[a]SVN Institute of Pharmaceutical Sciences, Swami Vivekanand University, Sagar, (M.P.), India.

[b]Department of Pharmaceutical Sciences, Dr Harisingh Gour University (A Central University), Sagar, (M.P.), India

***Corresponding Author Email: varshakashaw@gmail.com**

ABSTRACT

Objective: *The objective of the present research work is to synthesize isoniazid based 1,2,4-triazole derivatives and evaluate for antimicrobial and anti-inflammatory activity.* ***Method:*** *Isoniazid based 1,2,4-triazoles derivatives has been synthesized by reaction of Isoniazid with carbon disulfide in basic medium (KOH) to form Potassium dithiocarbazinate salt and reaction with hydrazine hydrate converted into 4-amino-5-(pyridin-4-yl)-4H-1,2,4-triazole-3-thiol. This compounds was reacted with different benzaldehyde to form 4-[(substituted phenyl)-methylene]-amino-5-(pyridine-4-yl)-4H-1,2,4-triazol-3-thiol (4). The final compounds were synthesized by reaction with 2-choloro-N, N-diethylacetanilide to form 4-[substituted phenyl)-methylene]-amino-3-(N-substitutedcarboxamidomethylthio)-5-(pyridine-4-yl)-4H-1,2,4-triazoles derivatives. All these compounds characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. The antibacterial activity was determined by the cup plate method. Acute anti-inflammatory activity determined by using carrageenan induced rat paw edema model.* ***Result:*** *Antibacterial activity of synthesized compounds, compound no. PJ-B4, PJ-B9, and PJ-B13 shows more than 90%, PJ-B2, PJ-B6, PJ-B10 and PJ-B11 shows more than 80% and rest of compounds shows more than 50 and less than 70% of zone of inhibition against both Gram-positive and Gram- negative organisms. Among all these compounds only PJ-B_4 and PJ-B_{13}, shows excellent MIC against both Gram- positive and Gram- negative organisms compare to standard Norfloxacin. In antifungal activity PJ-B_4, PJ-B_7, PJ-B_9 and PJ-B_{13} showed more than 90%, PJ-B_{10}, PJ-B_{11} and PJ-B_{12} showed more than 80% and rest of compounds shows more than 50 and less than 70% of zone of inhibition. Among all these compounds only PJ-B_4 and PJ-B_{13} showed excellent MIC against all fungal strains compare to standard Clotrimazole. In all synthesized compounds, compound no. PJ-B1 to PJ-B13 showed moderate to weak anti-inflammatory activity compare to standard.* ***Conclusion:*** *All these results suggested that the isoniazid based 1,2,4-triazole derivatives has shown good antibacterial and anti-inflammatory activity.*

KEY WORDS

1,2,4-triazoles, isoniazid, antibacterial, anti-inflammatory, elemental analysis, Gram positive.

INTRODUCTION:

Isoniazid is used as first line treatment of tuberculosis, and shown to be more effective as 1,2,4-triazoles derivatives to encounter inflammation, antibacterial and antimicrobial agents[1]. These hurdles is to rectify by synthesis of the 1,2,4-triazoles derivatives that has more stable in structure. 1,2,4-triazoles has shown anti-tubercular[2,3], antimicrobial[4], hypoglycemic[5], anti-inflammatory[6], antibacterial[7,8], antioxidant[9], anticonvulsant[10], antifungal[11], anticancer[12], analgesic[13] and antidepressant activities[14]. A considerable amount of research activities are directed

towards potent, more specific and less toxic anti-inflammatory agents and it offers challenging task in the development of novel synthetic strategies.

In current scenario, microbial resistance is one of the hurdles and needs the development of newer agent to target the diseases. Literature survey indicates that triazole, thiadiazole and triazine derivatives of Indomethacin have been synthesized and tested for anti-inflammatory activity[15]. The test compounds inhibited the induction of gastric mucosal lesions and their protective effects may be related to inhibition of lipid peroxidation in gastric mucosa[16]. Prompted by these findings, it seemed of interest to synthesize new derivatives of 1,2,4-triazole and investigate their anti-inflammatory activity.

The object of the current research is to synthesize new 1,2,4-triazoles derivatives of isoniazid as potent antimicrobial and anti-inflammatory agents. In continuation with the above researches we proposed to synthesized some triazole derivatives to design and synthesize new 1,2,4-triazoles derivatives 4-[substituted phenyl)-methylene]-amino-3-(N-substituted-carboxam idmethylthio)-5-(pyridine-4-yl)-4H-1,2,4-triazoles which were expected to show anti-microbial and anti-inflammatory properties. This paper discusses the most common and useful procedure for synthesizing 4-amino-3-mercapto-1,2,4-triazoles.

In the present design, we synthesized newer di-substituted 1,2,4-triazoles derived from isonicotinic acid hydrazides (Isoniazid) by replacing 4-carbohydrazide group of isoniazid by substituting 1,2,4-triazole in a hope of getting a synergistic response of pyridine nucleus (A) and 1,2,4-triazole nucleus (B) towards antibacterial[17] and anti-inflammatory activity (Fig. 1). Mannich base derivatives and triazole fused with 6-membered rings were reported to possess significant antitubercular activity. The two nitrogen atoms of the hydrazide group of the isoniazid are complimentary to the two nitrogen atoms present at the 1 and 2 position of the triazole nucleus.

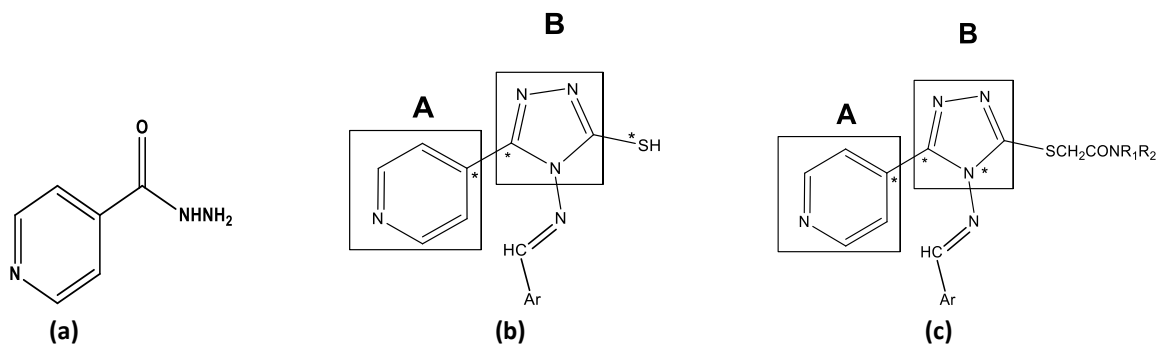


Fig. 1: Proposed pictorial representation of the proposed hypothesis. a) Chemical structure of the Isoniazid b) and c) are proposed compounds scheme for the designing of the 1,2,4-triazole compounds.

EXPERIMENTAL

MATERIAL AND METHODS

Isoniazid (Isonicotinic acid hydrazides) was purchased from CDH (Chemical Drug House), India. Carbon-disulfide, potassium hydroxide, hydrazine hydrate, ethanol, methanol, glacial acetic acid, anhydrous ether, DMSO, aldehyde compounds (benzaldehyde, *p*-anisaldehyde, 4-bromobenzaldehyde, *p*-chlorobenzaldehyde, *p*-tolualdehyde, *p*-nitrobenzaldehyde, Cinnamaldehyde) were purchased from the CDH, New Delhi, India. and Alpha-chloroacetanilides compounds (2-chloro-2,6,-dimethylacetanilides, 4-acetamido acetophenone 4-nitro-2-trifluoromethylacetanilide was purchased from the Sigma Aldrich, New Delhi, India. The chemical used for experimental work were synthetic grade. The melting points of the synthesized compounds were determined in open glass capillaries. IR spectra were recorded on ALPHA (Bruker) FTIR Spectrometer. Elemental analysis was performed and found values were within 0.4% of theoretical values. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 400 spectrophotometer at 400 MHz, 5 mm multi-nuclear inverse probe head, low and high-temperature facility and HRMAS accessory. Mass Spectra were recorded using Mass Spectrometers Jeol SX-102 (FAB) by ESI.

Synthesis of potassium dithiocarbazinate salt[18]

Isonicotinic acid hydrazide (0.10 mol) (1) was reacted with an ethanolic solution of potassium hydroxide (0.15 mol) along with carbon disulfide (0.15mol) was added

slowly to it. The reaction mixture was diluted with absolute ethanol (50 ml) and stirred continuously for 16h at room temperature on a magnetic stirrer. The precipitated potassium dithiocarbazinate salt was collected by filtration, washed with anhydrous ether and dried. The potassium dithiocarbazinate salt (2) thus obtained was used in the next step without further purification.

Synthesis of 4-amino-5-(pyridin-4-yl)-4H-1,2,4-triazole-3-thiol[19]

Potassium dithiocarbazinate salt (2) (0.079 mol) reacted with aqueous hydrazine hydrate (12 mL, 0.24 mol) solution and refluxed for 4h, hydrogen sulfide (H_2S gas) was evolved during the reaction was observed and indicated by the lead acetate solution (confirmatory test-turn lead acetate-soaked filter paper convert white to black). The reaction mixture was cooled to room temperature, diluted with ice-cold distilled water and subsequent acidification with dilute acetic acid. Obtained light yellow precipitate was filtered, washed with cold distilled water and dried. Recrystallization was done using absolute ethanol to get white crystals (3). The compound 3 exist in thione-thiol tautomeric forms, but our investigation showed that in this case, the thiol structure dominated in the solid state, as indicated by the IR and NMR data of the compound. Yield: 78%, m.p.: 214-216°C; IR (cm-1): 3160 (N-H), 3000 (C-H), 2582 (S-H), 1608 (C=N), 1571 (C=C), 709 (out of plane C-H bending), 689 (C-S). 1H NMR (ppm): 3.77 (s,1H, -NH2), 10.51 (Aromatic C-SH), 7.92 (d, 1H, Benzylidene), 8.59 (d, 1H, beta-pyridyl); 13C NMR (ppm): 151.1 (1,2,4-triazoles), 134.0 (C1-pyridine), 121.3 (C2 & C6-pyridine). 149.8 (C3 & C5-pyridine), LC-MS m/z: 193.23.

Synthesis of 4-[(substituted phenyl)-methylene]-amino-5-(pyridine-4-yl)-4H-1,2,4-triazol-3-thiol (4a-4g)

To a suspension of corresponding compound 1,2,4-triazole-3-thiol (3) (0.005 mol) in methanol (50 ml) and an equimolar quantity of aromatic aldehyde in methanol (20 ml) was mixed. This suspension was heated until a clear solution was obtained and refluxed for 3h in the presence of a few drops of concentrated hydrochloric acid in a water bath. The reaction solution was left undisturbed overnight. On the next day, the separated solid were filtered, washed with ethanol and recrystallized from ethanol to procure the product/compound (4).

Synthesis of 4-[substituted phenyl)-methylene]-amino-3-(N-substituted-carboxamidmethyl thio)-5-(pyridine-4-yl)-4H-1,2,4-triazoles

Compound 1,2,4-triazol-3-thiol (4) (0.01 mol) was dissolved in aqueous potassium hydroxide solution (0.61g in 100 ml distilled water) with stirring till a clear yellow color solution was obtained. It was filtered to remove any suspended impurities. Then various N-substituted-α-chloroacetanilides (0.01 mol) compound were dissolved in ethanol and added with shaking at 55°C stirred for 4.5 h. Then the reaction mixture was left overnight and the next day, the separated solid was filtered and washed twice with cold distilled water to remove KCl, dried and recrystallized from dilute glacial acetic acid (5). In case of aliphatic N-substituted-α-chloroacetanilides, the amide was added at room temperature.

Table 1: Elemental Analysis of synthesized final compounds

Compound code	Molecular formula	Molecular weight	Elemental analysis % found (calculated)		
			C	H	N
PJ-B_1	$C_{20}H_{22}N_6OS$	394.0	60.89 (60.87)	5.62 (5.60)	21.30 (21.31)
PJ- B_2	$C_{20}H_{21}ClN_6OS$	429.0	56.00 (56.02)	4.93 (4.94)	19.59 (19.58)
PJ-B_3	$C_{20}H_{21}ClN_6OS$	429.0	56.00 (56.02)	4.93 (4.94)	19.59 (19.58)
PJ B_4	$C_{20}H_{21}ClN_6OS$	429.0	56.00 (56.02)	4.93 (4.94)	19.59 (19.58)
PJ-B_5	$C_{20}H_{21}BrN_6OS$	473.0	50.47 (50.48)	4.47 (4.46)	17.75 (17.74)
PJ- B_6	$C_{20}H_{21}BrN_6OS$	474.0	50.47 (50.48)	4.47 (4.46)	17.75 (17.74)
PJ- B_7	$C_{21}H_{24}N_6OS$	409.0	61.74 (61.76)	5.92 (5.93)	20.57 (20.55)
PJ- B_8	$C_{21}H_{24}N_6O_2S$	425.0	59.41 (59.40)	5.70 (5.72)	19.80 (19.81)
PJ-B_9	$C_{20}H_{20}Cl_2N_6OS$	464.50	51.84 (51.82)	4.35 (4.32)	18.14 (18.13)
PJ- B_{10}	$C_{20}H_{20}Cl_2N_6OS$	464.50	51.84 (51.82)	4.35 (4.32)	18.14 (18.13)
PJ- B_{11}	$C_{22}H_{28}N_7OS$	438.0	60.39 (60.38)	6.22 (6.20)	22.41 (22.42)
PJ- B_{12}	$C_{20}H_{22}FN_6OS$	412.0	58.24 (58.22)	5.13 (5.12)	20.37 (20.36)
PJ-B_{13}	$C_{20}H_{23}N_6O_2S$	411.0	58.52 (58.54)	5.40 (5.42)	20.47 (20.48)

PJ-B1: 2-(4-(benzylidineamino)-5-(pyridine-4-yl)-4H-1,2,4triazol-3-yl thio) N,N-diethyl acetamide

Molecular formula: C20H22N6OS; Molecular weight: 394.0; TLC (Rf value): 0.62; IR (cm-1, KBr): 3050 C-H str; 2980 C-H str; 1680 C=O str; 1420 SCH2 str; 1580 C=N str; 1430 C-H def; 1470 C-C str; 1650 C=C str; 1380 C-N str; 1580 C=N str; 680 C-S str; 3050 C-H str; 1H NMR (DMSO-d6, δ ppm): 8.12 -N=CH; 7.65-8.67 aromatic protons; 3.20 SCH2; 2.25 (CH2)2; 1.25 (CH3)2; 13C NMR (DMSO-d6, δ ppm): 172.2 C=O of amide; 134 C1 of pyridine ring; 128 C2 of pyridine ring pyridine; 142 C3 & C5 of pyridine ring; 148 C2 of 1,2,4-triazole ring; 149 C5 of 1,2,4-triazole ring; 128 C1 of benzene ring; 138 C2 & C6 of benzene ring; 129 C3 & C5 of benzene ring; 168.4 C4 of benzene ring; 42.5 SCH2; 12.6 (CH3)2; 41.2(CH2)2; Mass (m/z): 396.

PJ-B2: 2,4-(2-chlorobenzylidineamino)-5-(pyridine-4-yl)-4H-1,2,4triazol-3-yl thio) N,N-diethyl acetamide

Molecular formula: C20H21ClN6OS; Molecular weight: 400; TLC (Rf value): 0.63; IR (cm-1, KBr): 3050 C-H str; 2980 C-H str; 1690 C=O str; 1420 SCH2 str; 1580 C=N str; 1430 C-H def; 1470 C-C str; 1650 C=C str; 1380 C-N str; 1580 C=N str; 680 C-S str; 3050 C-H str; 1H NMR (DMSO-d6, δ ppm): 8.12 -N=CH; 7.65-8.67 aromatic protons; 3.23 SCH2; 2.25 (CH2)2; 1.25 (CH3)2; 13C NMR (DMSO-d6, δ ppm): 172.2 C=O of amide; 134 C1 of pyridine ring; 128 C2 of pyridine ring pyridine; 142 C3 & C5 of pyridine ring; 150 C2 of 1,2,4-triazole ring; 158 C5 of 1,2,4-triazole ring; 128 C1 of benzene ring; 138 C2 & C6 of benzene ring; 129 C3 & C5 of benzene ring; 168.4 C4 of benzene ring; 42.5 SCH2; 12.6 (CH3)2; 40.2 (CH2)2; Mass (m/z): 400

PJ-B3: 2,4-(3-chlorobenzylidineamino)-5-(pyridine-4-yl)-4H-1,2,4triazol-3-yl thio) N,N-diethyl acetamide

Molecular formula: C20H21 ClN6OS; Molecular weight: 400: TLC (Rf value): 0.63; IR (cm^{-1}, KBr): 3050 C-H str; 2980 C-H str; 1690 C=O str; 1420 SCH2 str; 1580 C=N str; 1430 C-H def; 1470 C-C str; 1650C=C str 1380 C-N str; 1580 C=N str; 680 C-S str; 3050 C-H str. 1H NMR (DMSO d6, δ ppm): 8.12-N=CH; 7.65-8.67 m, 9H, aromatic protons; 3.23 SCH2; 2.25 (CH2)2; 1.25 (CH3)2; 13C NMR (DMSO-d6, δ ppm): 172.2 C=O of amide; 134 C1 of pyridine ring; 128 C2 of pyridine ring pyridine; 142 C3 & C5 of pyridine ring; 150 C2 of 1,2,4-triazole ring; 158 C5 of 1,2,4-triazole ring; 128 C1 of benzene ring; 138 C2 & C6 of benzene ring; 129 C3 & C5 of benzene ring; 168.4 C4 of benzene ring; 42.5 SCH2; 12.6 (CH3)2; 40.2 (CH2)2. Mass (m/z): 400

PJ-B4: 2,4-(4-chlorobenzylidineamino)-5-(pyridine-4-yl)-4H-1,2,4triazol-3-yl thio) N,N-diethyl acetamide

Molecular formula: C20H21 ClN6OS; Molecular weight: 400; TLC (Rf value): 0.63; IR (cm-1, KBr): 3050 C-H str; 2980 C-H str; 1690 C=O str; 1420 SCH2 str; 1580 C=N str; 1430 C-H def; 1470 C-C str; 1650 C=C str; 1380 C-N str; 1580 C=N str; 680 C-S str; 3050 C-H str; 1H NMR (DMSO-d6, δ ppm): 8.12 -N=CH; 7.65-8.67 aromatic protons; 3.23 SCH2; 2.25 (CH2)2; 1.25 (CH3)2; 13C NMR (DMSO-d6, δ ppm): 172.2 C=O of amide; 134 C1 of pyridine ring; 128 C2 of pyridine ring ; 142 C3 & C5 of pyridine ring; 150 C2 of 1,2,4-triazole ring; 158 C5 of 1,2,4-triazole ring; 128 C1 of benzene ring; 138 C2 & C6 of benzene ring; 129 C3 & C5 of benzene ring; 168 C4 of benzene ring; 42.5 SCH2; 12.6 (CH3)2; 40.2 (CH2)2. Mass (m/z): 400

PJ-B5: 2,4-(2-bomobenzylidineamino)-5-(pyridine-4-yl)-4H-1,2,4triazol-3-yl thio) N, N-diethyl acetamide

Molecular formula: C20H2 BrN6OS; Molecular weight: 474; TLC (Rf value): 0.63; IR (cm-1, KBr): 3030 C-H str; 2950 C-H str; 1690 C=O str; 1420 SCH2 str; 1580 C=N str; 1430 C-H def; 1470 C-C str; 1650 C=C str; 1380 C-N str 1590 C=N str 670 C-S str; 1H NMR (DMSO-d6, δ ppm): 9.62 -N=CH; 7.63-8.65 aromatic protons; 4.23 SCH2; 2.20 (CH2)2; 1.20 (CH3)2; 13C NMR (DMSO-d6, δ ppm): 169.2 C=O of amide; 136 C1 of pyridine ring; 146 C2 of pyridine ring pyridine; 126 C3 & C5 of pyridine ring; 150 C2 of 1,2,4-triazole ring; 159 C5 of 1,2,4-triazole ring; 136 C1 of benzene ring; 130 C2 & C6 of benzene ring; 124 C3 & C5 of benzene ring; 134 C4 of benzene ring; 40.5 SCH2; 12.6 (CH3)2; 40.2 (CH2)2 MASS (m/z): 474

PJ-B6:2,4-(3-bromobenzylidineamino)-5-(pyridine-4-yl)-4H-1,2,4triazol-3-yl thio) N, N-diethyl acetamide

Molecular formula: C20H2BrN6OS; Molecular weight: 474; TLC (Rf value): 0.65; IR (cm-1, KBr): 3060 C-H str; 2990 C-H str; 1680 C=O str; 1430 SCH2 str; 1580 C=N str; 1430 C-H def; 1470 C-C str; 1650 C=C str; 1380 C-N str; 1580 C=N str; 670 C-S str; 1H NMR (DMSO-d6, δ ppm): 9.12 -N=CH; 7.65-8.69 aromatic protons; 3.26 SCH2; 2.29 (CH2)2; 1.28 (CH3)2; 13C NMR (DMSO-d6, δ ppm): 170.2 C=O of amide; 134 C1 of pyridine ring; 129 C2 of pyridine ring pyridine; 142 C3 & C5 of pyridine ring; 150 C2 of 1,2,4-triazole ring; 158 C5 of 1,2,4-triazole ring; 130 C1 of benzene ring; 138 C2 & C6 of benzene ring; 128 C3 & C5 of benzene ring; 140 C4 of benzene ring; 42.0 SCH2; 13.6 (CH3)2; 40.2 (CH2)2; Mass (m/z): 445

PJ-B7: 2,4-(4-methylbenzylidineamino)-5-(pyridine-4-yl)-4H-1,2,4triazol-3-yl thio) N, N-diethyl acetamide

Molecular formula: C21H24N6OS; Molecular weight: 380: TLC (Rf value): 0.73; IR (cm-1, KBr): 3040 C-H str; 3035 C-H str; 1680 C=O str; 1420 SCH2 str; 1580 C=N str; 1430 C-H def; 1470 C-C str; 1650 C=C str; 1380 C-N str; 1580 C=N str; 680 C-S str; 1H NMR (DMSO-d6, δ ppm): 9.0-N=CH; 7.63-8.63 aromatic protons; 3.23 s, 2H, SCH2; 2.25 s,4H (CH2)2; 1.25 s, 6H,(CH3)2; 13C NMR (DMSO-d6, δ ppm): 172.2 C=O of amide; 155 N=CH; 134 C1 of pyridine ring; 128 C2 of pyridine ring; 142 C3 & C5 of pyridine ring; 150 C2 of 1,2,4-triazole ring; 158 C5 of 1,2,4-triazole ring; 128 C1 of benzene ring; 138 C2 & C6 of benzene ring; 129 C3 & C5 of benzene ring; 168 C4 of benzene ring; 42.5 SCH2; 15.6 (CH3)2; 40.2 (CH2)2; FAB MASS (m/z): 380

PJ-B8: 2,4-(4-methoxybenzylidineamino)-5-(pyridine-4-yl)-4H-1,2,4triazol-3-yl thio) N,N-diethyl acetamide

Molecular formula: C21H24 N6O2S; Molecular weight: 425; TLC (Rf value): 0.67; IR (cm-1, KBr): 3150 C-H str; 3135 C-H str; 1690 C=O str; 1430 SCH2; 1580 C=N str; 1430 C-H def; 1470 C-C str; 1650 C=C str; 1380 C-N str; 1580 C=N str; 680 C-S str; 3050 C-H str; 1H NMR (DMSO-d6, δ ppm): 8.9s,1H, -N=CH; 7.63-8.87 m, 9H, aromatic protons; 4.10 s, 2H, SCH2; 3.25s, 4H (CH2)2; 1.30 s, 6H,(CH3)2; 13C NMR (DMSO-d6, δ ppm): 170 C=O of amide; 136 C1 of pyridine ring; 129 C2 of pyridine ring; 140 C3 & C5 of pyridine ring; 150 C2 of 1,2,4-triazole ring; 158 C5 of 1,2,4-triazole ring; 130 C1 of benzene ring; 139 C2 & C6 of benzene ring; 128 C3 & C5 of benzene ring; 148 C4 of benzene ring; 42.0 SCH2; 12.8 (CH3)2; 40.2 (CH2)2; Mass (m/z): 425

PJ-B9: 2,4-(2,4-dichlorobenzylidineamino)-5-(pyridine-4-yl)-4H-1,2,4triazol-3-yl thio) N, N-diethyl acetamide

Molecular formula: C20H20 Cl2N6OS; Molecular weight: 465: TLC (Rf value): 0.64; IR (cm-1, KBr): 3250 C-H str; 3130 C-H str; 1690 C=O str; 1420 SCH2 str; 1580 C=N str; 1430 C-H def; 1470 C-C str; 1650 C=C str; 1320 C-N str; 1580 C=N str; 675 C-S str; 1H NMR (DMSO-d6, δ ppm): 9.6 s,1H, -N=CH; 7.45-8.83 m, 8H, aromatic protons; 4.30 s, 2H, SCH2; 3.25 s,4H (CH2)2; 1.20 s, 6H,(CH3)2; 13C NMR (DMSO-d6, δ ppm): 172.2 C=O of amide; 156.3 N=CH; 132 C1 of pyridine ring; 128 C2 of pyridine ring pyridine; 140 C3 & C5 of pyridine ring; 152 C2 of 1,2,4-triazole ring; 160 C5 of 1,2,4-triazole ring; 129 C1 of benzene ring; 140 C2 & C6 of benzene ring; 132 C3 & C5 of benzene ring; 142 C4 of benzene ring; 42.8 SCH2; 12.8 (CH3)2; 40 (CH2)2. Mass (m/z): 435

PJ-B10: 2,4-(2,6-dichlorobenzylidineamino)-5-(pyridine-4-yl)-4H-1,2,4triazol-3-yl thio) N, N-diethyl acetamide

Molecular formula: C18H16 Cl2N6OS; Molecular weight: 435; TLC (Rf value): 0.67; IR (cm-1, KBr); 3250 C-H str; 3130 C-H str; 1690 C=O str; 1420 SCH2 str; 1580 C=N str; 1430 C-H def; 1470 C-C str; 1650 C=C str; 1320 C-N str; 1580 C=N str; 675 C-S str; 1H NMR (DMSO-d6, δ ppm): 9.6 s,1H, -N=CH; 7.45-8.83 m, 8H, aromatic protons; 4.30s, 2H, SCH2; 3.25 s,4H (CH2)2; 1.20 s, 6H,(CH3)2; 13C NMR (DMSO-d6, δ ppm): 172.2 C=O of amide; 132 C1 of pyridine ring pyridine; 128 C2 of pyridine ring pyridine; 140 C3 & C5 of pyridine ring; 152 C2 of 1,2,4-triazole ring; 160C5 of 1,2,4-triazole ring; 129 C1 of benzene ring; 140C2 & C6 of benzene ring; 132 C3 & C5 of benzene ring; 142

C4 of benzene ring; 42.8 SCH2 thio alkyl 12.8 (CH3); 40 (CH2)2; Mass (m/z): 465

PJ-B11: 2,4-(N, N, Dimethylamino benzylidineamino)-5-(pyridine-4-yl)-4H-1,2,4triazol-3-yl thio) N, N-diethylacetamide

Molecular formula: C22H27 N7OS; Molecular weight: 437; TLC (Rf value): 0.68; IR (cm-1, KBr): 3050 C-H str; 2980 C-H str; 1690 C=O str; 1420 SCH2 str; 1580 C=N str; 1430 C-H def; 1470 C-C str; 1650 C=C str; 1380 C-N str; 1580 C=N str; 680 C-S str; 3050 C-H str; 1H NMR (DMSO-d6, δ ppm): 8.12 s,1H, -N=CH 7.65-8.67 m, 9H, aromatic protons; 3.23s, 2H, SCH2; 2.25 s,4H (CH2)2; 1.25 s, 6H,(CH3)2; 13C NMR (DMSO-d6, δ ppm): 172.2 C=O of amide; 134 C1 of pyridine ring; 128 C2 of pyridine ring pyridine; 142 C3 & C5 of pyridine ring; 150 C2 of 1,2,4-triazole ring; 158 C5 of 1,2,4-triazole ring; 128 C1 of benzene ring; 138 C2 & C6 of benzene ring; 129 C3 & C5 of benzene ring; 168 C4 of benzene ring; 42.5 SCH2; 12.6 (CH3)2; 40.2 (CH2)2; Mass (m/z): 400

PJ-B12: 2,4-(4-fluorobenzylidineamino)-5-(pyridine-4-yl)-4H-1,2,4triazol-3-yl thio) N,N-diethyl acetamide

Molecular formula: C20H21FN6OS; Molecular weight: 412; TLC (Rf value) 0.69: IR (cm-1, KBr): 3050C-H str; 2980 C-H str; 1690 C=O str; 1420 SCH2 str; 1580 C=N str; 1430 C-H def; 1470 C-C str; 1650 C=C str; 1380 C-N str; 1580 C=N str; 680 C-S str; 3050 C-H str; 1H NMR (DMSO-d6, δ ppm): 8.12 s,1H, -N=CH; 7.65-8.67 m, 9H, aromatic protons; 3.23, 2H, SCH2; 2.25 s,4H (CH2)2; 1.25 s, 6H,(CH3)2; 13C NMR (DMSO-d6, δ ppm): 172.2 C=O of amide; 134 C1 of pyridine ring; 128 C2 of pyridine ring

pyridine; 142 C3 & C5 of pyridine ring; 150 C2 of 1,2,4-triazole ring; 158 C5 of 1,2,4-triazole ring; 128 C1 of benzene ring; 138 C2 & C6 of benzene ring; 129 C3 & C5 of benzene ring; 168 C4 of benzene ring; 42.5 SCH2; 12.6 (CH3)2; 40.2 (CH2)2; Mass (m/z): 410

PJ-B13: 2,4-(3-hydroxybenzylidineamino)-5-(pyridine-4-yl)-4H-1,2,4triazol-3-yl thio) N, N-diethyl acetamide

Molecular formula: C20H23 N6O2S; Molecular weight: 410; TLC (Rf value): 0.7; IR (cm-1, KBr): 3050 C-H str; 2980 C-H str; 1690 C=O str; 1420 SCH2 str; 1580 C=N str; 1430 C-H def; 1470 C-C str; 1650 C=C str; 1380 C-N str; 1580 C=N str; 680 C-S str; 3050 C-H str; 1H NMR (DMSO-d6, δ ppm): 8.12 s,1H, -N=CH; 7.65-8.67 m, 9H, aromatic protons; 3.23s, 2H, SCH2; 2.25 s,4H (CH2)2; 1.25 s, 6H,(CH3)2; 13C NMR (DMSO-d6, δ ppm): 172.2 C=O of amide; 134 C1 of pyridine ring; 128 C2 of pyridine ring pyridine; 142 C3 & C5 of pyridine ring; 150 C2 of 1,2,4-triazole ring; 158 C5 of 1,2,4-triazole ring; 128 C1 of benzene ring; 138 C2 & C6 of benzene ring; 129 C3 & C5 of benzene ring; 168 C4 of benzene ring; 42.5 SCH2;12.6 (CH3)2; 40.2 (CH2)2; Mass (m/z): 410

BIOLOGICAL ACTIVITY

Antibacterial and Antifungal activity[20]

The antibacterial activity was determined by the cup plate method. Microbial strains (ATCC No): *Staphylococcus aureus* (12598); *Bacillus subtilis* (6051); *Pseudomonas aeruginosa* (25619); *Escherichia coli* (25922) is used for antibacterial activity. In this method sterilized molten nutrient agar media (20 ml) was poured aseptically and spread on the sterilized petri dishes (10 cm). The bacterial culture (CFU-10^{7}-10^{9}/ml; 0.1 ml) was added to it and mixed by swirl motion and kept aside. After setting of the culture media, a sterilized glass tube (5 mm diameter) was used aseptically to scoop out the media to make wells. Two drops (0.1 ml) of the sample solution were transferred to these wells aseptically. These were then incubated at 37±1◦C for 24 hours. Control cups contained DMSO only. The experiments were carried out in triplicate. The result (mean value n=3) were recorded by measuring the zone of growth inhibition around the cups in mm at 100 µg/ml concentration and compared with standard drug norfloxacin. The statistical analysis was carried out using student t-test, and the % of growth inhibition was calculated by taking norfloxacin as positive control with 100% inhibitions for Gram +ve and Gram-ve bacteria. Some of the compounds showed very good activity as compare to the standard drug were selected for determination of MIC. This same procedure adopted for antifungal activity. Fungal strain (ATCC No.) *Aspergillus niger* (9029); *Candida albicans* (2091); *Aspergillus fumigates*(36607) has been utilized for antifungal activity. The zone of inhibition (% inhibition) and MIC for standard drug i.e. clotrimazole and for synthesized compounds were determined by using same procedure as described under antibacterial screening.

Anti-inflammatory activity[21]

All the synthesized compounds were screened for acute anti-inflammatory activity by using carrageenan induced rat paw edema model. Male albino rats of either sex weighing (170-220) g of either sex used. The animals were divided in to four groups of six each. They were starvated overnight with water ad libitium prior to the day of experiment. Control groups received 1ml of 0.5% sodium carboxymethyl cellulose (sodium CMC), standard group received 20 mg/kg ibuprofen and test groups were received 100, 200 mg/kg of synthesized compounds orally. One hour later; a sub planar injection of 0.05 ml of 1% solution of carrageenan in sterile distilled water was administered to the left hind footpad of each animal. The paw edema volume was measured with a digital plethysmometer at 0, 1, 2, 3, 4, and 5 hr. after carrageenan injection. Paw edema volume was compared with vehicle control group and percent reduction was calculated as

$$\% \text{ edema inhibition} = 1\text{-}V_t/V_c \times 100$$

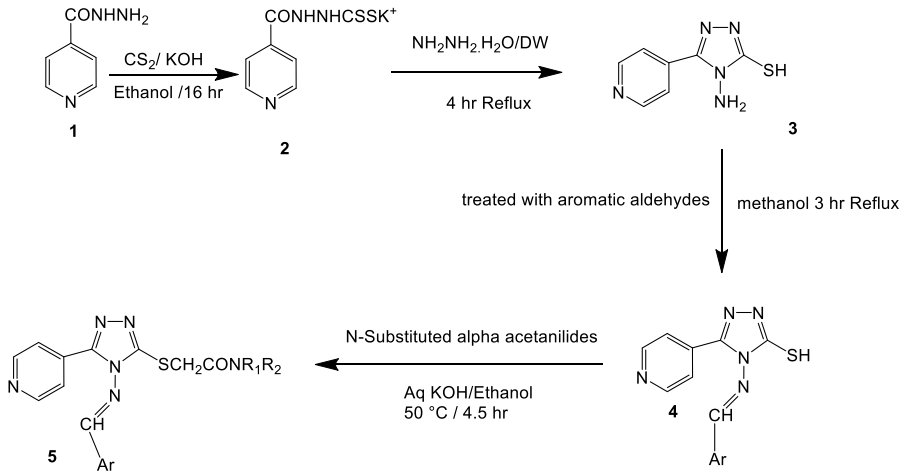
Where: V_t and V_c were oedema volume in the drug treated and the control groups respectively. The results were expressed as percentage inhibition of edema over the untreated control group.

RESULTS

Chemistry

The Synthesis of the intermediate and target compounds was accomplished according to the steps depicted in the scheme of synthesis (Fig. 2). Potassium dithiocarbazinate salt (2) was obtained from the reaction of isonicotinic acid hydrazides (1) with carbon disulfide in basic medium (KOH) and converted into 4-amino-5-(pyridin-4-yl)-4H-1,2,4-triazole-3-thiol (3) by the treatment with hydrazine hydrate. The synthesis of the other compounds was performed by the reaction of 2 with seven different benzaldehyde to form 4 [(substituted phenyl)-methylene]-amino-5-(pyridine-4-yl)-4H-1,2,4-triazol-3-thiol (4). The final compounds

were synthesized by the reaction of 3 with four different acetanilide resulting in the formation of 4 - [substituted phenyl)-methylene]-amino-3-(N-substituted carboxamidomethylthio)-5-(pyridine-4-yl)-4H-1,2,4-triazoles (5). The elemental analysis data of synthesized compounds are given in Table 1. Synthesized compounds were characterized by IR, ^{1}HNMR, ^{13}CNMR, LC-MS (FAB) and elemental analysis. All compounds were shown the solubility in DMSO, ethanol and acetonitrile and least in methanol & acetone.



1Fig 2: Scheme for the synthesis; Reagent and reaction condition: I) CS_2, ethanolic KOH, reflux 16 h; II) NH_2-$NH_2.H_2O$, reflux, 4h; III) aromatic aldehyde, methanol, reflux, 3h; IV) acetanilide, Aq. KOH, ethanol, 55°C.

Antibacterial activity

Among all compounds PJ-B4, PJ-B9, and PJ-B13 shows more than 90%, PJ-B2, PJ-B6, PJ-B10 and PJ-B11 shows more than 80% and rest of compounds shows more than 50 and less than 70% of zone of inhibition against both Gram positive and Gram-negative organisms. Among all these compounds PJ-B4, PJ-B13, shows excellent MIC against both Gram positive and Gram-negative organisms compare to standard norfloxacin. All Data of Antibacterial activity of synthesized compounds was depicted in Table 2.

Table 2: Antibacterial Activity of Synthesized Compound at 100 µg/mL

S. No.	Code No.	*S. aureus* (ATCC-12598)		*B. subtilis* (ATCC-6051)		*P.aeruginosa* (ATCC-25619)		*E. coli* (MTCC-25922)	
		In mm mean	% of Inhibition	In mm mean	% of Inhibition	In mm mean	% of Inhibition	In mm mean	% of Inhibition
1.	PJ-B_1	16.00±2.0	55.80	17..66±1.52	56.4	18.33±0.57	66.47	20.66±1.15	78.4
2.	PJ-B_2	23.00±2.0	82.6	24.66±1.15	82.0	23.66±0.58	85.15	21.33±2.51	80.76
3.	PJ-B_3	21.33±2.8	75.5	22.66±1.52	75.9	22.66±1.52	81.49	22.33±1.52	84.6
4.	PJ-B_4	26.66±1.5	92.00	27.00±1.00	92.3	25.00±2.00	90.37	24.66±2.30	92.35
5.	PJ-B_5	20.00±2.0	67.0	22.00±2.00	74.14	20.66±1.15	74.05	21.66±3.21	82.2
6.	PJ-B_6	23.33±1.5	82.00	24.33±1.15	82.7	23.00±2.00	80.30	22.66±1.52	86.06
7.	PJ-B_7	19.00±2.0	67.8	20.00±2.00	68.4	18.66±2.00	65.6	17.33±2.08	65.8
8.	PJ-B_8	18.00±1.0	62.4	20.66±0.57	68.00	21.66±2.08	77.9	19.66±2.30	74.4
9.	PJ-B_9	26.33±0.7	92.85	27.33±0.57	92.11	25.33±1.15	92.1	24.00±1.15	91.18
10.	PJ-B_{10}	25.00±1.0	89.3	26.66±1.15	90.3	24.33±1.15	88.9	25.66±1.52	97.4
11.	PJ-B_{11}	23.66±3.0	82.14	24.33±1.52	84.8	22.66±0.57	81.7	24.33±2.08	92.2
12.	PJ-B_{12}	21.00±1.0	75.6	22.66±1.52	74.4	21.66±2.08	77.5	22.66±3.21	86.1
13.	PJ-B_{13}	26.6±2.5	94.7	27.33±2.51	93.8	25.33±1.52	91.52	24.66±1.15	93.65
14.	Norfloxacin	28.6±1.1	100.0	29.67±1.15	100.0	27.66±1.15	100.0	26.33±0.57	100.0
15.	DMSO	8.33±1.15	10.3	8.33±0.57	14.1	7.33±1.00	10.3	8.00±1.00	14.1

Table 3: Minimum Inhibitory Concentration of Some Selected Compounds (Antibacterial Activity)

S. No	Code No.	MIC in µg/ml			
		S.aureus (ATCC-12598)	*B.subtilis* (ATCC-6051)	*P.aeruginosa* (ATCC-25619)	*E.coli* (MTCC-25922)
1.	PJ-B_4	20	30	50	40
2.	PJ-B_7	25	35	15	402
3.	PJ-B_9	25	35	60	50
4.	PJ-B_{11}	45	10	65	40
5.	PJ-B_{12}	30	35	65	55
6.	PJ-B_{13}	20	30	50	40
Norfloxacin		4	16	10	8

Antifungal activity:

Among all compounds, compound no. PJ-B4, PJ-B7, PJ-B9 and PJ-B13 shows more than 90% of zone of inhibition PJ-B10, PJ-B11 and PJ-B12 shows more than 80% of zone of inhibition and rest of compounds shows more than 50% and less than 70% of inhibition against all organisms. Among all these compounds only B13, shows excellent MIC against all fungal strains compare to standard Clotrimazole. Data of antifungal activity shown in Table 3 & 4.

Table 4: Antifungal Activity of Synthesized Compound at 100 µg/mL

S. No.	Code No.	Zone of Inhibition at concentration (100 µg/ml)					
		Aspergillus niger MTCC-1344		*Candida Albicans* MTCC-227		*Fusarium oxysporum* MTCC-129	
		In mm mean	% of Inhibition	In mm mean	% of Inhibition	In mm mean	% of Inhibition
1.	PJ-B_1	11.66±2.0	53.6	13.33±1.1	56.52	11.66±1.5	53.70
2.	**PJ-B_2**	19.00±2.0	86.8	20.33±2.5	86.96	19.00±1.0	87.96
3.	PJ-B_3	18.00±0.0	81.8	19.33±2.0	82.60	17.66±1.5	80.95
4.	**PJ-B_4**	21.33±3.5	96.95	22.66±3.6	97.25	21.00±1.5	96.95
5.	PJ-B_5	17.0±0.5	77.8	18.33±0.5	78.26	16.66±2.0	76.1
6.	PJ-B_6	16.33±0.5	74.8	17.33±1.5	73.3	15.66±3.0	71.41
7.	**PJ-B_7**	21.00±1.0	93.8	22.00±1.0	95.65	20.00±3.0	92.59
8.	PJ-B_8	11.66±1.0	53.0	12.66±3.2	54.33	10.66±2.3	47.76
9.	**PJ-B_9**	20.33±1.5	92.40	21.66±3.2	92.96	20.66±3.2	95.3
10.	PJ-B_{10}	18.00±1.0	81.81	19.33±3.7	82.83	18.00±1.5	83.3
11.	**PJ-B_{11}**	19.33±0.5	87.86	20.66±3.2	88.66	19.00±3.00	87.96
12.	**PJ-B_{12}**	19.0±1.0	86.8	20.66±0.5	88.66	18.66±1.5	85.71
13.	**PJ-B_{13}**	21.0±1.0	95.5	22.66±1.5	97.25	20.66±1.2	95.28
Clotrimazole		22.00±1.0	100.0	23.3±0.57	100.0	21.66±2.082	100.0
DMSO		8.0±1.0	18.8	7.66±0.58	16.3	8.33±0.57	21.3

Table 5: Minimum inhibitory concentration of some selected compounds (antifungal activity)

S. No	Code No.	MIC in µg/ml		
		A. nigers (MTCC-1344)	*C. albican* (MTCC-227)	*F. oxysporum* (MTCC-129)
1	PJ-B_4	60	30	10
2	PJ-B_7	70	40	55
3	PJ-B_9	60	35	55
4	PJ-B_{11}	65	35	55
5	PJ-B_{12}	70	40	65
6	PJ-B_{13}	60	30	40
Clotrimazole	-	12	6	10

Anti-inflammatory activity

In all compounds showed moderate to weak anti-inflammatory activity compare to standard. The anti-inflammatory activity of these compounds attributed to the inhibition of cyclooxygenase enzyme which plays vital role in the inflammation process. All Data of Antibacterial activity of synthesized compounds was depicted in Table 5.

Table 3: Anti-inflammatory activity of synthesized final compounds

Compound code	Change in paw odema volume after treatment in mL (± SEM)		Percentage inhibition of odema after treatment	
	3h	5h	3h	**5h**
Solvent control (0.5 % CMC) (1ml/kg)	0.60±0.03	0.62±0.03	-	**-**
Ibuprofen (20mg/kg) b.o	0.14±0.03	0.10±0.03	76.6	83.3
PJ-B_1 100mg/kg p,o	0.41±0.002	0.39±0.004	31.6	35.0
200 mg/kg p,o	0.38±0.02	0.36±0.04	36.6	40.0
PJ-B_2 100mg/kg p,o	0.41±0.002	0.39±0.004	31.6	35.0
200 mg/kg p,o	0.35±0.02	0.33±0.03	41.6	45.0
PJ-B_3 100mg/kg p,o	0.41±0.002	0.39±0.004	31.6	35.0
200 mg/kg p,o	0.38±0.02	0.36±0.04	36.6	40.0
PJ-B_4 100mg/kg p,o	0.35±0.02	0.33±0.03	41.6	45.0
200 mg/kg p,o	0.29±0.05	0.26±0.04	51.6	56.6
PJ-B_5 100mg/kg p,o	0.35±0.02	0.33±0.03	41.6	45.0
200 mg/kg p,o	0.32±0.04	0.30±0.05	46.6	50.0
PJ-B_6 100mg/kg p,o	0.38±0.02	0.36±0.04	36.6	40.0
200 mg/kg p,o	0.36±0.05	0.33±0.04	40.0	45.0
PJ-B_7 100mg/kg p,o	0.35±0.02	0.33±0.03	41.6	45.0
200 mg/kg p,o	0.31±0.05	0.28±0.04	48.0	53.0
PJ-B_8 100mg/kg p,o	0.36±0.05	0.33±0.04	40.0	45.0
200 mg/kg p,o	0..30±0.06	0.28±0.03	50.0	53.0
PJ-B_9 100 mg/kg p,o	0.26±0.02	0.23±0.03	56.6	61.6
200 mg/kg p,o	0.22±0.04	0.20±0.05	63.3	66.6
PJ-B_{10} 100mg/kg p,o	0.31±0.05	0.28±0.04	48.0	53.0
200 mg/kg p,o	0.26±0.02	0.23±0.03	56.6	61.6
PJ-B_{11} 100mg/kg p,o	0.36±0.05	0.33±0.04	40.0	45.0
200 mg/kg p,o	0.32±0.04	0.30±0.05	46.6	53.0
PJ-B_{12} 100mg/kg p,o	0.32±0.04	0.30±0.05	46.6	53.0
200 mg/kg p,o	0.29±0.02	0.22±0.04	51.0	63.3
PJ-B_{13} 100mg/kg p,o	0.26±0.02	0.23±0.03	56.6	61.6
200 mg/kg p,o	0.21±0.02	0.19±0.03	65.0	68.0

Values are mean ± SEM, No of animals in each group are (n = 6); *P value <0.05

DISCUSSION

Antibacterial activity

The data revealed that *p*-chloro and m-hydroxy substituted compounds shows excellent activity against all tested organisms. The presence of electron withdrawing group such as chloro in para position enhance the lipophilicity of the molecule enabling it to penetrate the microbial cell ore easily and shows the good activity. The presence of OH group on aromatic ring increases the hydrogen bonding of the compound with bacterial cell wall proteins containing free SH group and therefore it shows good activity. Un-substituted and methoxy substituted compounds shows least activity.

Antifungal activity

The data revels that *p*-chloro and *o*-hydroxy substituted compounds shows excellent activity against all tested organisms. The presence of electron withdrawing group such as chloro in para position enhance the lipophilicity of the molecule enabling it to penetrate the microbial cell more easily and shows the minimum inhibitory concentration compare to standard clotrimazole and almost equal to standard. The presence of OH group on aromatic ring increases the hydrogen bonding of the

compound with fungal cell wall proteins contain free SH group and therefore it shows good activity. Unsubstituted and methoxy substituted compounds shows least activity. Electron withdrawing group in meta position shows less MIC compare to standard.

Anti-inflammatory activity

4-chloro, 2,4-dichloro, 2,6-dichloro and hydroxyl substituted on benzylidene moiety shows weak degree of anti-inflammatory activity. It may be because of the presence of trifluoromethyl along with nitro group in para-position of benzene ring which is present on 3rd position of triazole moiety. Presence of electron withdrawing groups like chloro in para position in benzylidene ring shows more activity compare to at ortho and meta position. presence of two chlorine group at ortho and para position ie 2,4-dichloro shows more activity. Unsubstituted benzylidene ring and presence of electron donating group on benzylidene ring of triazole moiety such as methoxy group shows decreases in activity. Compounds with bulkier substitution such as nitro in para position along with trifluoro methyl group on phenyl ring 3rd position of triazole moiety showed moderate to weak activity.

CONCLUSION:

The isoniazid based 1,2,4-triazoles derivatives has been synthesized and spectral analysis data denoted that the compound is synthesized as they design. These entire synthesized compounds evaluated for the antibacterial and anti-inflammatory activity. Isoniazid based 1,2,4-triazole derivatives has shown good antibacterial and but weak anti-inflammatory activity.

REFERENCE:

1. Ahmadi F, Ghayahbashi MR, Sharifzadeh M, Alipoiur E, Ostad SN, Vosooghi M, khademi HR, Amini M. **Synthesis and evaluation of anti-inflammatory and analgesic activities of new 1,2,4-triazole derivatives.** Med Chem. 2014;11(1):69-76.
2. Fan Z, Yang Z, Zhang H, Mi N, Wang H, Cai F, Zuo X, Zheng Q, Song H. **Synthesis, Crystal Structure, and Biological Activity of 4-Methyl-1,2,3-thiadiazole-Containing 1,2,4-Triazolo[3,4-b] [1,3,4] thiadiazoles.** J Agric Food Chem, **2010**,58(5):2630-2636.
3. Gajanan S, Sandyavalli MS., Manjunath E, Kavitha NV. **Synthesis and Anti-inflammatory Activity of 3,5-Diphenyl 4-amino 1,2,4 -Triazole Derivatives.** World Journal of Pharmaceutical Research, 2017;6(8):1744-1754.
4. Godhani DR, Jogel AA, Sanghani AM, Mehta JP. **Synthesis and biological screening of 1,2,4 –triazole derivatives.** Indian Journal of chemistry, 2015;(54B):556-64.
5. Hany MD, Khaled E, Ali ZS, Ahmmed AS**. Synthesis and biological activities of some new spiro 1,2,4-triazole derivatives having sulfonamide moiety.** Organic communications, 2017; 10(4):280-287.
6. Hasan MJ, Adnan IM, Abass SJ. **Antibacterial Activity Importance of 1,2,3-triazole and 1,2,4-triazole by Click Chemistry.** Journal of Chemistry and Chemical Sciences, 2015;5(6):317-324.
7. Joshi SD, Vagdevi HM, Vaidya VP, Gadaginamath GS. **Synthesis of new 4-pyrrol-1-yl benzoic acid hydrazide analogs and some derived oxadiazole, triazole and pyrrole ring systems: A novel class of potential antibacterial and antitubercular agents**. Eur J Med Chem, **2008;**43:1989-1996.
8. Kumar A, Kashaw V, Amit V., Kashaw SK, Sahu P, Mishra V. **Synthesis, characterization and Antimycobaterial activity of some newer 1,2,4-triazole derivatives.** International Journal of Pharmacy and Biological Research, 2015; 5(2):379-392.
9. Kumar A, Mishra V, Kashaw V. **Synthesis and antimicrobial activity some new 1,2,4-triazoles.** Asian Journal of Chemistry, 2017:1317-1322.
10. Ledeti I, Bercean V, Alexa A, Foica C, Futa LM, Dehelean C, Trandafirescu C, Muntean D, Licker M, Fulia A. **Preparation and Antibacterial Properties of Substituted 1,2,4-Triazoles.** Journal of Chemistry, 2015;5:879-886.
11. Li-Jung Min, Yan-Xia Shi, Hong-Ke Wu Sun, Xing-Hai Liu, Yong-Gang Zhang. **Microwave assisted synthesis and antifungal activity of some Novel thioethers containg 1,2,4-triazole Moiety.** Applied Sciences, 2015;5:1211-1220.
12. Mehdi K, Mahboobeh S, Iraj N, Seyedeh RB. **Synthesis, Characterization and Antibacterial Activity of some Novel Thiosemicarbazides, 1,2,4-Triazol-3-thiols and their *S*-substituted Derivatives.** Iranian Journal of Pharmaceutical Research, 2015;14 (1):67-75.
13. Mishra R.K., Birendra SY, Rai AK. **Synthesis, characterization and biological evaluation of novel 1,2,4-triazole derivatives as potent antibacterial and anti-inflammatory agents.** Der Pharma Chemica. 2014;6(1):137-143.
14. Mohammad Asif. **Study of Some 1,2,4-Triazole Derivatives and Their Biological Activities.** International Journal of Pharmaceutical Drug Analysis. 2015;2(4):325-328.
15. Noha RM, Sh.El-Etrwy A. **Design, Synthesis and Biological evaluation of some 1,2,4-triazole derivatives based on Schiff's base bearing Benzimdazole moiety** Asian Journal of Pharmaceutical analysis and medicinal chemistry, 2015;3(2):62-75.

16. Rajoriya V, Kashaw V, Kashsaw SK. Design, Synthesis, Characterization and Antitubercular Screening of some New 1,2,4-Triazoles Derived from Isonicotinic Acid Hydrazides. Letters in Drug Design & Discovery, 2018;15(5):451-462.
17. Singh RJ, Singh DK. Syntheses and biological activity of some 3,5-diaryl-4H-1,2,4-triazole derivatives, IJPBS, 2010;2:1-6.
18. Singh S, Kashaw SK, Mishra VK, Mishra M, Rajoriya V, Kashaw V. **Design and Synthesis of New Bioactive 1,2,4-Triazoles, Potential Antitubercular and Antimicrobial Agents.** Indian J Pharm Sci, 2018;80(1):36-45.
19. Tozkoparan B, Kupeli E, Yesilada E, Ertan M. **Preparation of 5-aryl-3-alkylthio-l,2,4-triazoles and corresponding sulfones with antiinflammatory–analgesic activity**, Bioorg Med Chem, 2007;15:1808–1814.
20. Yasemin Ü, Sadik D, Fatih Ç, Zeynep A, Murat K. **Synthesis of new 1,2,4-triazole compounds containing Schiff and Mannich bases (morpholine) with antioxidant and antimicrobial activities.** Journal of Enzyme Inhibition and Medicinal Chemistry, 2016;31(S3):89–95.
21. Yasmin K, Mohammad S, Vijender S, Mohammad S. **Synthesis, Characterization and Anticonvulsant Activity of Some Novel 4,5-Disubstituted-1,2,4-Triazole Derivatives.** Journal of Applied Pharmaceutical Science, 2017;7(7):158-167.

Received:04.05.18, Accepted: 08.06.18, Published:01.07.2018

***Corresponding Author:**
Varsha Kashaw*
Email: varshakashaw@gmail.com