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Synthesis, Structural Elucidation and Anti Microbial Screening of *N*-(4-aryl amine)-2-{[4-phenyl-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-3-yl]sulfanyl}acetamide Derivatives

KEYWORDS: 1,2,4 triazole, Acetamide, Antifungal activity, Anti bacterial activity

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ABSTRACT *A new series of 2-[4-phenyl-5-(pyridine-4-phenyl)-4H-[1,2,4]triazole-3ylSulfanyl]-N-aryl-acetamide have been synthesized by the condensation of 4-phenyl-5-(pyridine-4-yl)-4H-1,2,4-triazole-3-thiol and 2-Chloro-N-(aryl)-acetamide in presence of anhydrous potassium Carbonate. The Structure of Synthesized compound was assigned by H¹NMR,MASS Spectra,IR Spectra and Elemental Analysis . All the compound were Screened for their in-vitro Antibacterial, Antifungal and anti tuberculosis activity.*

Introduction

The synthesis of compound containing 1,2,4 triazole ring system has attracted attention because of its wide range of pharmaceutical activity. A variety of biological compound such as anti-inflammatory, analgesic, antibacterial, antifungal, anti tubercular, antiviral, antitumor, anticonvulsant, and anti depressant have been reported for Mercapto and thione substituted 1,2,4 triazole ring system[1,2,7].

In last few decades the chemistry of 1,2,4- triazole and their fused heterocyclic derivatives has received important because of there effective biological importance. A wide number of drugs containing 1,2,4-triazole ring system are incorporated because of there wide therapeutically interests including anti inflammatory, CNS stimulants, sedatives, anti anxiety, such as fluconazole, intraconazole, Voriconazole, Also there known drug containing the 1,2,4-triazole group eg. Triazolam, Alprazolam, Etizolam and Furacylin[2,6,8].

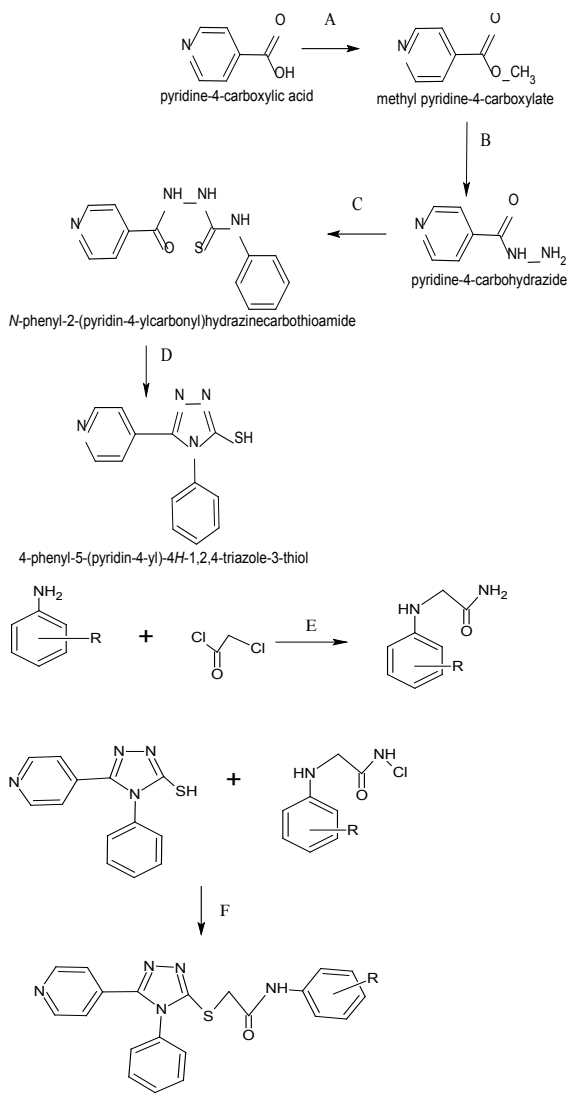
Moreover sulphur containing heterocycles represents important group of sulphur compound that are promising for use in practical application[3]. Among these heterocycles the Mercapto and Thione substituted 1,2,4-triazole ring system have been well studied[4,9].

Acetanilide derivatives are reported to exhibit a number of biological activities including anesthetic, antipyretic, anti inflammatory, and anti bacterial effects substitution including alkyl thio and alkenylthio derivatives have been carried out primarily at the third position of the 1,2,4-triazole ring as potential antimicrobial agents[5,1].

In continuation of our interest on chemistry of functionalized chloroacetamide derivatives because of the high mobility of chloride atom and reactive N-H group compound containing chlorocetamide.

Materials and Methods

All melting points were determined using open capillary tubes on electronic apparatus and were uncorrected. The IR spectra (4000-400 cm-1) of synthesized compounds were recorded on Shimadzu 8400-s FTIR spectrometer with KBr pellets. To monitor the reactions, establish the identity, purity of reactants and products, thin layer chromatography performed on TLC coated with silica gel using appropriate mobile phase system and spots visualized under UV radiation. Nuclear magnetic resonance spectra was recorded using Bruker 400 MHz model spectrometer using DMSO as a solvent and TMS as internal standard (Chemical shifts in d ppm). All new compounds subjected to elemental analysis and the results obtained were in acceptable range.



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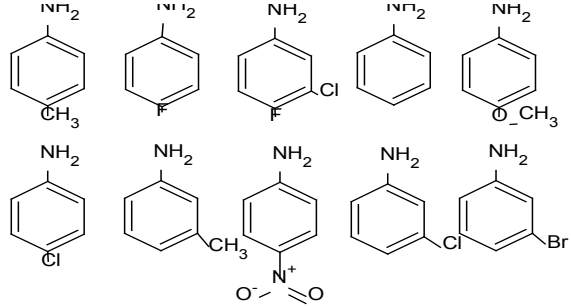

(A)CH_3OH,Conc.H_2SO_4(B)CH_3OH,HydrazineHydrate(C) Ethanol,Phenyl thioisocyanate(D)NaOH,HCl(E Benzene,Chloroacetyl Chloride(F)K_2CO_3,Acetone

step-1
Pyridine-4-carboxylic acid(0.1mole) in 200 ml methanol and 6.0ml concentrated H_2SO_4 was refluxed 12hours.and poured into The cold ice.The obtained product was filtered and was with cold water.Recrystallised from alcohol.The progress of the reaction was monitored by TLC using toluene:actone(8:2) as eluent.

Step-2
Methyl pyridine-4-carboxylate(0.1mole) and hydrazine hydrate(0.2mole) in methanol was refluxed for 15hours and poured into the ice. The obtained product is Filtered and washed with cold water. Recrystallized from ethyl alcohol. The progress of the reaction was monitoredbyTLC using toluene:acaetone(8:2) as eluent.

Step-3
The mixture of pyridine-4-carbohydrazide(0.1mole) and phenyl isothiocyanate (0.1mole) was refluxed in ethanol(220ml) for the 3hours.after cooling the formed product was collected by filtration and recystallisation from ethanol. The progress of the reaction was monitored by TLC using toluene:acetone(8:2) as eluent.

Step-4
The mixture of N-phenyl-2-(pyridine-4-ylcarbonyl)hydrazinecarbothioamide (0.05mole) and 80ml of 2N NaOH was refluxed for 4hours.The resulting solution was cooled and poured into the ice and neutralize with 2N HCl.The precipitate was filtered and washed with cold water.Dried and recrystallised from ethanol. The progress of the reaction was monitored by TLC using toluene:acetone(8:2) as eluent.

Step-5
0.02mole of chloroacetyl chloride and 2-4 drops of triethyl amine was added in the 30ml of Benzene.this mixture was stirred in ice bath.The solution of aryl amine(0.02mole) in 30ml benzene was added dropwise and refluxed for 5hours. The resulting ppt.upon cooling were filtered and wahed with benzene.recrystalllized from ehanol. The progress of the reaction was monitored by TLC using toluene:acetone(8:2) as eluent.

Step-6
The mixture of 4-phenyl-5-(pyridine-4-yl)-4H-1,2,4-triazole-3-thiol(0.01mole) and 2-chloro-N-(aryl)-acetamide(0.01mole) in 50ml dry acetone and anhydrous K_2CO_3 (0.02mole) was stirred for 4hours at room temp. and poured into ice, The product was filtered and washed with cold water. Recrystallized from alcohol.

N-(4-methylphenyl)-2-{[4-phenyl-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-3-yl]sulfanyl}acetamide

FTIR (KBr,cm^{-1}):1513cm^{-1}(C=N in triazole),3387cm^{-1}(-NH Stretching in Amide),1633 cm^{-1}(C=O in amide),1441cm^{-1}(C=C in aromatic),1601cm^{-1}(S-C=O in thioether linkage),^{1}H NMR (DMSO-d_6,ppm),2.25(s,3H,CH_3),4.21(s,2H,CH_2),7.28-7.29(d,J=4,2H,Ar-H),7.59-7.61(d,J=8,2H,Ar-H),8.55-8.57(d,J=8,2H,Ar-H),7.11-7.13(d,J=8,2H,Ar-H),7-.43-7.50(m,5H,Ar-H),10.28(s,1H,-NH), Mass spectra (m/z):402.6(M^+)

N-(4-methoxyphenyl)-2-{[4-phenyl-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-3-yl]sulfanyl}acetamide

FTIR (KBr,cm^{-1}):1517cm^{-1}(C=N in triazole),3384cm^{-1}(-NH Stretching in Amide),1635 cm^{-1}(C=O in amide),1444cm^{-1}(C=C in aromatic),1611cm^{-1}(S-C=O in thioetherlinkage),^{1}H NMR(DMSO-d_6,ppm),3.61(s,3H,OCH_3),4.27(s,2H,CH_2),7.22-7.24(d,J=4,2H,Ar-H),7.52-7.54(d,J=8,2H,Ar-H),8.52-8.54(d,J=8,2H,Ar-H),7.09-7.11(d,J=8,2H,Ar-H),7.41-7.48(m,5H,Ar-H),10.26(s,1H,-NH), Mass spectra (m/z):418.7(M^+)

N-(4-fluorophenyl)-2-{[4-phenyl-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-3-yl]sulfanyl}acetamide

FTIR (KBr,cm^{-1}):1511cm^{-1}(C=N in triazole),3347cm^{-1}(-NH Stretching in Amide),1630 cm^{-1}(C=O in amide),1451cm^{-1}(C=C in aromatic),1641cm^{-1}(S-C=O in thioether linkage),^{1}H NMR (DMSO-d_6,ppm),4.11(s,2H,CH_2),7.23-7.24(d,J=4,2H,Ar-H),7.58-7.60(d,J=8,2H,Ar-H),8.55-8.56(d,J=8,2H,Ar-H),7.14-7.15(d,J=8,2H,Ar-H),7.43-7.57(m,5H,Ar-H),10.21(s,1H,-NH), Mass spectra (m/z):427.6(M^+)

N-(3-methylphenyl)-2-{[4-phenyl-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-3-yl]sulfanyl}acetamide

FTIR (KBr,cm^{-1}):1523cm^{-1}(C=N in triazole),3337cm^{-1}(-NH Stretching in Amide),1657 cm^{-1}(C=O in amide),1447cm^{-1}(C=C in aromatic),1623cm^{-1}(S-C=O in thioether linkage),^{1}H NMR (DMSO-d_6,ppm),2.23(s,3H,CH_3),4.24(s,2H,CH_2),7.21-7.22(d,J=4,2H,Ar-H),7.52-7.53(d,J=8,2H,Ar-H),8.53-8.55(d,J=8,2H,Ar-H),7.15-7.17(d,J=8,2H,Ar-H),7-.41-7.45(m,5H,Ar-H),10.26(s,1H,-NH), Mass spectra (m/z):402.2(M^+)

N-(3-bromophenyl)-2-{[4-phenyl-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-3-yl]sulfanyl}acetamide

FTIR (KBr,cm^{-1}):1543cm^{-1}(C=N in triazole),3367cm^{-1}(-NH Stretching in Amide),1653 cm^{-1}(C=O in amide),1421cm^{-1}(C=C in aromatic),1641cm^{-1}(S-C=O in thioether linkage),^{1}H NMR (DMSO-d_6,ppm),4.28(s,2H,CH_2),7.27-7.28(d,J=4,2H,Ar-H),7.55-7.67(d,J=8,2H,Ar-H),8.53-8.55(d,J=8,2H,Ar-H),7.16-7.18(d,J=8,2H,Ar-H),7.44-7.59(m,5H,Ar-H),10.28(s,1H,-NH), Mass spectra (m/z):467.7(M^+)

N-(4-chloro-3-fluorophenyl)-2-{[4-phenyl-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-3-yl]sulfanyl}acetamide

FTIR (KBr,cm^{-1}):1516cm^{-1}(C=N in triazole),3375cm^{-1}(-NH Stretching in Amide),1663 cm^{-1}(C=O in amide),1432cm^{-1}(C=C in aromatic),1634cm^{-1}(S-C=O in thioether linkage),^{1}H NMR (DMSO-d_6,ppm),4.25(s,2H,CH_2),7.25-7.27(d,J=4,2H,Ar-H),7.54-7.56(d,J=8,2H,Ar-H),8.58-8.60(d,J=8,2H,Ar-H),7.10-7.12(d,J=8,2H,Ar-H),7.44-7.47(m,5H,Ar-H),10.21(s,1H,-NH), Mass spectra (m/z):440.2(M^+)

N-(3-fluorophenyl)-2-{[4-phenyl-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-3-yl]sulfanyl}acetamide

FTIR (KBr,cm^{-1}):1522cm^{-1}(C=N in triazole),3357cm^{-1}(-NH Stretching in Amide),1653 cm^{-1}(C=O in amide),1445cm^{-1}(C=C in aromatic),1644cm^{-1}(S-C=O in thioether linkage),^{1}H NMR (DMSO-d_6,ppm),4.26(s,2H,CH_2),7.22-7.23(d,J=4,2H,Ar-H),7.55-7.56(d,J=8,2H,Ar-H),8.57-8.59(d,J=8,2H,Ar-H),7.16-7.17(d,J=8,2H,Ar-H),7.44-7.49(m,5H,Ar-H),10.29(s,1H,-NH), Mass spectra (m/z):406.1(M^+)

N-phenyl-2-{[4-phenyl-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-3-yl]

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sulfanyl}acetamide

FTIR (KBr,cm^{-1}):1511cm^{-1}(C=N in triazole),3376cm^{-1}(-NH Stretching in Amide),1645 cm^{-1}(C=O in amide),1461cm^{-1}(C=C in aromatic),1620cm^{-1}(S-C=O in thioether linkage),^{1}H NMR (DMSO-d_6 ppm),4.28(s,2H,CH_2),7.23-7.24(d,J=4,2H,Ar-H),7.57-7.59(d,J=8,2H,Ar-H),8.53-8.55(d,J=8,2H,Ar-H),7.19-7.20(d,J=8,2H,Ar-H),7.41-7.47(m,5H,Ar-H),10.21(s,1H,-NH), Mass spectra (m/z):488.3(M^+)

N-(3-chlorophenyl)-2-{[4-phenyl-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-3-yl]sulfanyl}acetamide

FTIR (KBr,cm^{-1}):1515cm^{-1}(C=N in triazole),3447cm^{-1}(-NH Stretching in Amide),1663 cm^{-1}(C=O in amide),1456cm^{-1}(C=C in aromatic),1676cm^{-1}(S-C=O in thioether linkage),^{1}H NMR (DMSO-d_6 ppm),4.26(s,2H,CH_2),7.25-7.27(d,J=4,2H,Ar-H),7.58-7.59(d,J=8,2H,Ar-H),8.55-8.57(d,J=8,2H,Ar-H),7.16-7.18(d,J=8,2H,Ar-H),7.43-7.50(m,5H,Ar-H),10.27(s,1H,-NH), Mass spectra (m/z):422.8(M^+)

N-(4-nitrophenyl)-2-{[4-phenyl-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-3-yl]sulfanyl}acetamide

FTIR (KBr,cm^{-1}):1545cm^{-1}(C=N in triazole),3457cm^{-1}(-NH Stretching in Amide),1667 cm^{-1}(C=O in amide),1453cm^{-1}(C=C in aromatic),1634cm^{-1}(S-C=O in thioetherlinkage),^{1}HNMR(DMSO-d_6 ppm),4.20(s,2H,CH_2),7.24-7.24(d,J=4,2H,Ar-H),7.54-7.56(d,J=8,2H,Ar-H),8.57-8.59(d,J=8,2H,Ar-H),7.16-7.18(d,J=8,2H,Ar-H),7.42-7.47(m,5H,Ar-H),10.23(s,1H,-NH), Mass spectra (m/z):433.4(M^+)

Result and Discussion:

Results were obtained by reacting The mixture of 4-phenyl-5-(pyridine-4-yl)-4H-1,2,4-triazole-3-thiol and 2-chloro-N-(aryl)-acetamide The IR spectra of the compound showed absorption band at 1500 cm^{-1} which proves the presence of 1,2,4-triazole ring system , absorption band at 3400cm^{-1} proves the –NH stretching,1600cm^{-1}(S-C=Olinkagein thioether),1475(-CH_2stretching),1400cm^{-1} (C=C aromatic). The ^{1}H NMR of the compound 6(a-j) showed characteristic signal at δ 4.20(s,2H,CH_2),7.24-7.24(d,J=4,2H,Ar-H),7.54-7.56(d,J=8,2H,Ar-H),8.57-8.59(d,J=8,2H,Ar-H),7.16-7.18(d,J=8,2H,Ar-H),7.42-7.47(m,5H,Ar-H),10.23(s,1H,-NH). The mass spectrum of all the compound was obtained also in the acceptable range.

Table : 1 Physical Data of Various Synthesized Compound

Sr. No.	Com-pound	Molecular Formula	M.W.	M.P. (^{0}C)	% Yield	% of Carbon Found (Calc.)	% of Hydrogen Found (Calc.)	% of Nitrogen Found (Calc.)
1	6a	$C_{22}H_{19}N_5OS$	401.48	220-223	87	65.21 (65.88)	4.77 (4.89)	17.44 (17.62)
2	6b	$C_{22}H_{19}N_5O_2S$	417.48	230-235	89	63.29 (63.45)	4.59 (4.69)	16.78 (16.90)
3	6c	$C_{21}H_{16}FN_5OS$	426.8	205-208	85	62.21 (65.45)	3.98 (4.02)	17.27 (17.46)
4	6d	$C_{22}H_{19}N_5OS$	401.4	208-212	79	65.81 (65.91)	4.77 (4.89)	17.44 (17.56)
5	6e	$C_{21}H_{16}BrN_5OS$	466.3	215-224	75	54.08 (54.34)	3.46 (3.95)	15.02 (15.75)
6	6f	$C_{21}H_{16}ClFN_5OS$	439.8	179-181	81	57.34 (57.73)	3.44 (3.75)	15.92 (15.93)
7	6g	$C_{21}H_{16}FN_5OS$	405.4	211-214	78	62.21 (62.93)	3.98 (4.15)	17.27 (17.63)
8	6h	$C_{21}H_{17}N_5OS$	387.4	225-227	75	62.10 (62.48)	4.42 (5.22)	18.08 (18.24)
9	6i	$C_{21}H_{16}ClN_5OS$	421.9	224-226	80	59.78 (59.73)	3.82 (4.15)	16.60 (16.77)
10	6j	$C_{21}H_{16}N_6O_3S$	432.4	177-180	74	58.32 (58.95)	3.73 (3.75)	19.43 (19.52)

The compound were tested using agar cup method for antimicrobial and anti fungal activity using *E.Coli, P.Aeruginosa, S.Aureus, S.Pyogenus (bacteria) C.Albicans, A.Niger* and *A.Claycus* (fungi) are listed in below tables respectively. The table shows the anti microbial activity against gram positive, gram negative bacteria and fungi. Comparison of antimicrobial activity produced by compounds with that of standard antimicrobial drug reveals that the produced compounds shows moderate to good activity against all species of bacterial and fungal strains under study.

Drug	C.Albicans	A.Niger	A.Clavantus
-	MTCC227	MTCC282	MTCC1323
µg/ml			
Nystatin	100	100	100
Gaseofulvin	500	100	100

Table 3: Belowe Table Shows Antifungal Activity of Standard Drugs

Drug	E.Coli	P. Aeruginosa	S.Aureus	S.Pyogenus
-	MTCC443	MTCC1688	MTCC96	MTCC442
(µg/ml)				
Gentamycin	0.05	1	0.25	0.5
Ampicilin	100	100	250	100
Chloram-phinicol	50	50	50	50
Ciphrofloxa-cin	25	25	50	50
Norfloxacin	10	10	10	10

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Table 4: Shows Antibacterial Activity					
Minimum Inhibition concentration					
Sr No.	Code No.	E.Coli	P. Aeruginosa	S.Aure-us	S.Pyogenus
		MTCC443	MTCC1688	MTCC96	MTCC442
1	6a	125	500	500	1000
2	6b	200	500	100	125
3	6c	125	250	250	1000
4	6d	500	1000	500	500
5	6e	250	200	125	500
6	6f	500	200	100	500
7	6g	1000	250	500	200
8	6h	250	500	250	250
9	6i	500	1000	100	250
10	6j	500	200	500	100

Table 5: Shows Antifungal Activity				
Sr No.	Code No.	C.Albi-cans	A. -Niger	A.Clav-antus
		MTCC227	MTCC282	MTCC1323
1	6a	1000	1000	1000
2	6b	500	1000	1000
3	6c	1000	1000	500
4	6d	500	1000	1000
5	6e	1000	1000	1000
6	6f	500	1000	1000
7	6g	1000	1000	500
8	6h	1000	500	1000
9	6i	1000	1000	500
10	6j	1000	500	1000

Conclusion:

A series of 10 compound of *N*-(4-aryl amine)-2-{[4-phenyl-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-3-yl]sulfanyl}acetamide derivatives was synthesized and the structure of the compounds were well supported by the IR,1H NMR, and mass spectra. The anti bacterial and Anti fungal activity of the compounds was studied, which shows that the compounds had well to moderate activity against bacteria and fungi.Table 2:Belowe Table Shows Antibacterial Activity of Standard Drugs

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