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Synthesis of Tetrazolo[1,5-a]Quinoxaline Based Thio-Ether Derivatives, Being Intoxicating Antimicrobial Agents

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ABSTRACT

In this study we have synthesized resourceful N-(Substituted phenyl)-2-(tetrazolo[1,5-a] quinoxaline-4-ylthio)acetamide, by prepration of intermediate,2-chloro -N-(substitutedphenyl)acetamide in multistep reactions process.This intermediates 2-chloro -N-(substitutedphenyl)acetamide were also synthesized by substitued anilines.TLC pointed out completion of the reaction.The structure of the compounds were authenticated by IR,^{1}NMR. the synthesized compounds were investigated for their antimicrobial activity.

Keywords: Quinoxaline, Synthesis, Antimicrobial Activity.

INTRODUCTION

Quinoxaline and Its Derivatives are of great consequence set of benzo heterocycles [1, 2] these are double nitrogen containing heterocyclic compounds. They have been stated for their application in dyes, proficient electroluminescent materials, organic semiconductors and DNA cleaving agents because of their activity adjacent to various transplantable tumors [3**]**.

Quinoxaline framework is unit for the grounding of substances with prominent biological activities, such as antimycobacterial [4], antidepressant [5] and antitumor drugs.[6] Quinoxaline derivatives have been also acknowledged for metal cation extractions[7]. They possesses recognized biological activities together with AMPA/GlyN receptor antagonis [8], antihistaminic agents [9], anti-trypanosomal activity [10], anti-herps [11], antiplasmodial activity [12]. Quinoxaline and their thio derivatives have revealed their bactericidal, neuroprotic activity .We have synthesized eight new compounds containing thio linkage.

MATERIALS AND METHODS

All chemicals and reagents in recent study were of AR grade and were procured from Merk (India). The reaction were supervised by thin layer chromatography(TLC) on Merk pre-coated silica GF254 plates and were visualized under UV-chamber. Melting points(uncorrected) were concluded by open capillary tubes method. IR spectra (λ max in cm-^{1}) were recorded on a Shimadzu FTIR 8300S spectrophotometer with KBr pellets. ^{1}H NMR spectra were recorded on a Bruker Avance II 400NMR spectrometer instrument using DMSO as solvent (chemical shift in ppm) with TMS as the internal standard. The elemental analysis

(C, H, N) of the synthesized compounds were carried out on a Heraeus Carlo Erba 1108 elemental analyzer and C, H, N values were found to be in good concurrence with the calculated values.

Sodium tetrazolo[1,5-a]quinoxaline-4-thiolate (II): Equimolar amount of compound I (0.058) and Na_2S (0.058M) was refluxed in 15 mL of acetone was refluxed until reaction have been completed (It may takes nearly 2-2.5 h) .The completion of the reaction was identified, as a result of a color change of reaction mixture from green to complete yellow color. Clarity of the compounds were ensured by TLC using toluene:acetone 8:2 as mobile phase. Reaction mixture were purified by recrystallisation by DMF Yield58%,Rf0.87,m.p310˚C,FT-IR(KBr),incm^{-1}3040(C-H), 854(aromaticC=C,bend) 1499 (aromatic C=C, str)1850,1600,1500(C-C str due to aromatic ring)1425(C-Nstr.),1600,1688(C=N,str.),1630,1570(str vibration)1386(=C-N str)1532(-NH,bend),3304(-NH,str)700(C-C bend ,out of plane.).

Synthesis of N-(substituted phenyl)-2-(tetrazolo [1, 5-a] quinoxaline-4-ylthio) acetamideIII (a-h):
Here we have taken euimolar quantity of Sodium tetrazolo[1,5-a]quinoxaline-4-thiolate(0.0077M)and different 2-Chloro-N-(Substituted Phenyl)-acetamides(0.0077M),were mixed in DMF and heating under reflux for 8-10h. The purity of the compounds was authenticated by verified TLC utilizing toluene :acetone 8:2 as mobile phase, The mixture was reserved to room temperature and transferred into ice chilled water. The solid was detached out by filtration, washed with water and dried. Further purified by recrystallisation from ethanol.

N-(2-Nitrophenyl)-2-(tetrazolo[1,5-a]quinoxaline-4-ylthio)acetamide(IIIa): Yield68%, m.p 30˚C;M.F $C_{16}H_{12}N_4O_4S$;Mol wt 381.0;Elemental Analysis % found C 50.39,H 2.91,N 25.71 Calc C 50.30,H 2.85,N 25.65 FT-IR(KBr),in cm^{-1} 3220 (N-H), 3040 (C-H), 2880(-CH_2-),1660(C=O), 1630 (C=N), 1420 and 1250 (-C-S-CH_2), 1050 (C-Cl) aryl chloride and 680 (CH_2-S). ^{1}H-NMR(DMSO-d6,400 MHZ,ppm) 2.39(s, 3H, CH_3), 4.165 (s, 2H, CH_2), 7.118--8.034 (m, 8H, Ar-H) and 8.495 (s, 1H, N-H).

N-(3-Nitrophenyl)-2-(tetrazolo[1,5-a]quinoxaline-4-ylthio)acetamide(IIIb): Yield 62%,m.p 220˚C,M.F $C_{16}H_{12}N_4O_4S$, Mol wt 381.0, Elemental Analysis % found C 50.39, H 2.91, N 25.71 Calc C 50.32,H 2.81,N 25.61, FT-IR(KBr),in cm^{-1} 3250 (N-H), 3040 (C-H), 2890(-CH_2-), 1650 (C=O), 1595 (C=N), 1340 and 1250 (-C-S-CH_2), 1040 (C-Cl) aryl chloride and 660 (CH_2-S). ^{1}H-NMR(DMSO-d6,400 MHZ,ppm) 2.637 (s,3H,CH_3) , 4.370 (s,2H,CH_2), 7.068--8.022 (m,8H, Ar-H) and 9.648(s,1H,N-H).

N-(3-Chlorophenyl)-2-(tetrazolo[1,5-a]quinoxaline-4-ylthio)acetamide(IIIc): Yield 65%, m.p 310˚C, M.F $C_{16}H_{12}ClN_3O_2S$,Mol wt 371.0, Elemental Analysis % foundC51.82,H 2.99,N 22.66, Calc C 51.75,H2.87,N22.58,FT-IR(KBr),incm^{-1}3240(NH),3050(C-H),1600(C=N),1030(C-Cl),640(CH_2-S)^{1}H-NMR(DMSO-d6,400MHZ,ppm) 2.745(s,3H,CH_3)4.422(s,2H,CH_2),9.166(s,1H,N-H).

N-(4-Chlorophenyl)-2-(tetrazolo[1,5-a]quinoxaline-4-ylthio)acetamide(IIId): Yield 50% ,m.p 290˚C, M.F $C_{16}H_{12}ClN_3O_2S$,Mol wt 371.0, Elemental Analysis % found C 51.82,H 2.99,N 22.66, Calc C 51.70,H. 2.85,N 22.54, FT-IR(KBr),in cm^{-1} 3260 (N-H), 3040 (C-H), 2880(-CH_2-),1660(C=O), 1600 (C=N), 1420 and 1250 (-C-S-CH_2), 1050 (C-Cl) aryl chloride and 680 **(CH_2-S).**)^{1}H-NMR(DMSO-d6,400 MHZ,ppm) 2.839(s, 3H, CH_3), 4.065 (s, 2H, CH_2), 7.218--8.024 (m, 8H, Ar-H) and 8.495 (s, 1H, N-H).

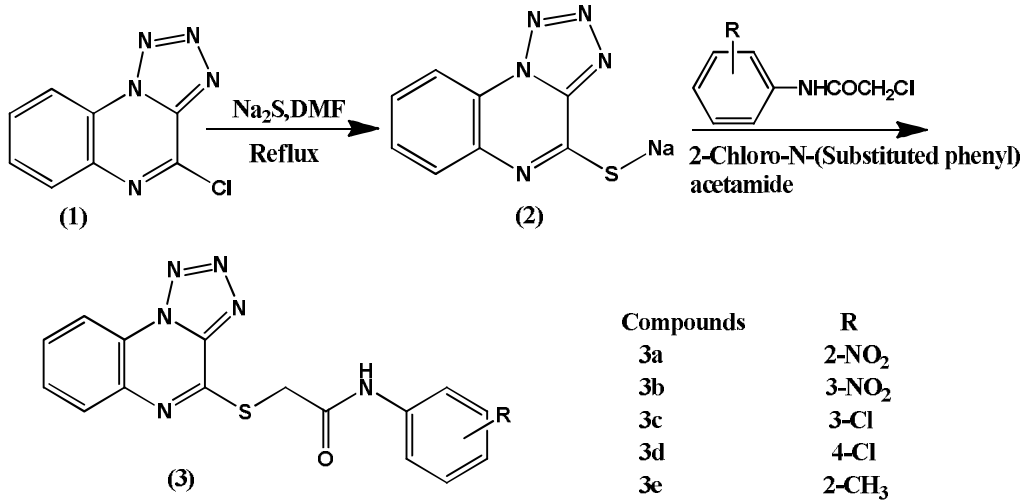
N-(o-tolylphenyl)-2-(tetrazolo[1,5-a]quinoxaline-4-ylthio)acetamide(IIIe): Yield 67%, m.p 260˚C, M.F $C_{17}H_{14}N_6OS$, Mol wt 350.0, Elemental Analysis % found C 58.27,H 4.03,N 23.98, Calc C 58.20,H. 4.17,N 22.78, , FT-IR(KBr),in cm^{-1} 3270 (N-H), 3041 (C-H), 2340(-CH_2-), 1690 (C=O), 1580 (C=N), 1400 and1130 (-C-S-CH_2), 1220, 1235 (C-O) and 720(CH_2-S). ^{1}H-NMR(DMSO-d6,400 MHZ,ppm) 2.738 (s,3H,CH_3), 3.743(s,3H,OCH_3), 4.073 (s,2H,CH_2), 6.774-8.042 (m,8H, Ar-H) and 9.487 (s,1H,N-H).

N-(p-tolylphenyl)-2-(tetrazolo[1,5-a]quinoxaline-4-ylthio)acetamide(IIIf): Yield 78%, m.p 255˚C, M.F $C_{17}H_{14}N_6OS$, Mol wt 350.0, Elemental Analysis % found C 58.27,H 4.03,N 23.98, Calc C 58.10,H. 4.27,N 22.08, FT-IR(KBr),in cm^{-1} 3270 (N-H), 3120 (C-H), 2890(-CH2-), 1630 (C=O), 1610 (C=N), 1400 and 1350 (-C-S-CH_2) and 680 (CH_2-**S).** ^{1}H-NMR(DMSO-d6,400 MHZ,ppm) 2.063 and 2.119 (d,6H,2CH_3), 3.231 (s,2H,CH_2), 6.194-7.491(m,8HAr-H) and 8.900 (s,1H,N-H).

N-(2-methoxyphenyl)-2-(tetrazolo[1,5-a]quinoxaline-4-ylthio)acetamide(IIIg): Yield 70%, m.p 285˚C, M.F $C_{17}H_{14}N_6O_2S$, Mol wt 360.0, Elemental Analysis % foundC55.73,H 3.85,N 22.94 Calc C55.70,H 3.75,N 22.90, FT-IR(KBr),in cm^{-1}3270 (N-H), 3120 (C-H), 2890(-CH2-), 1630 (C=O), 1610 (C=N), 1400 and 1350 (-C-S-CH_2**)** and 680 (CH_2-S**).** ^{1}H-NMR(DMSO-d6,400 MHZ,ppm)7.230-8.012(NH),7.08-7.26(CH),4.19-4.27(methylene proton)3.83-3.86(methylproton).

N-(4-methoxyphenyl)-2-(tetrazolo[1,5-a]quinoxaline-4-ylthio)acetamide(IIIh): Yield 61%, m.p 279˚C - 282˚C, M.F $C_{17}H_{14}N_6O_2S$,Mol wt 360.0, Elemental Analysis % foundC55.73,H 3.85,N 22.94 Calc C 55.68, H 3.70,N 22.87, FT-IR(KBr),in cm^{-1}3270 (N-H), 3120 (C-H), 2890(-CH2-), 1630 (C=O), 1610 (C=N), 1400 and 1350 (-C-S-CH_2) and 680 (CH_2-S). ^{1}H-NMR(DMSO-d6,400 MHZ,ppm) 7 .230-8.012(NH),7.08-7.26(CH),4.19-4.27(methylene proton)3.83-3.86(methyl proton)7.63-7.67(Benzene proton).

Reaction Scheme: The reaction scheme is shown in fig. 1



Compounds	R
3a	2-NO_2
3b	3-NO_2
3c	3-Cl
3d	4-Cl
3e	2-CH_3
3f	4-CH_3
3g	2-OCH_3
3h	4-OCH_3

Fig:1

RESULTS AND DISCUSSION

Starting compound 4-chlorotetrazolo[1,5a]quinoxaline[I] was synthesized according to the literature [13].and 2-Chloro-N-(Substituted Phenyl)-acetamides were prepared through literature[14].Various derivatives of N-(Substitutedphenyl)-2-(tetrazolo[1,5-a]quinoxaline-4-ylthio**)**acetamide**(**3a-3h).were synthesized by conventional procedure. These derivatives have been confirmed by their FT-IR&^{1}H-NMR spectra. Mercaptans and thiophenols absorb as a weak band in the region 2590-2580cm^{-1}C=C &C=N srt(in ring)bands occur at 1600-1420cm^{-1}.823 cm^{-1} band shows the para substituted aromatic ring str.7.252-8.012 peak shows the sec amide. All the synthesized derivatives have shown better antimicrobial activity against selected pathogens.

APPLICATIONS

Here we have applied disc diffusion methods[15] for all the synthesized quinoxaline derivative(3a-3h) evaluate the antimicrobial activity(Table 1) against chosen pathogens like antibacterial activity against *Bacillus subtilis,Escherichia coli, Klebsiella pneumoniae* and *Staphylococcus aureus* and antifungal activity *against, Aspergillus niger, Aspergillus flavus, Trichoderma viride & Candida albicans* by calculated the zone of inhibition in mm. Streptomycin and Nystatin were used as a standard drug for antibacterial and antifungal activity correspondingly. For attaining antimicrobial activity (Nutrient Agar media for bacteria) and(Potato Dextrose Agar Media for fungi)was autoclaved at 121˚,15lbs for 25 min. DMSO used as a solvent.50µL of bacterial and fungal spore suspension arranged in 1mL sterile distill water was spread on solidified agar plates using sterile glass spreader. After 25 min sterile disc loaded with 20µL of the samples were located on it under sterile condition. Culture plates were then inoculated at 28˚±1C for 72 h in case of fungi and at 30˚±1Cfor 24 h in case of bacteria. Antimicrobial property was measured and expressed as the diameter of the clearance zone in mm around the sterile disc.

Table 1. Antimicrobial data of derivatives 3a-3h

S. No.	Compound Code	Concentrations in µg/ml	Antibacterial				Antifungal			
			B. Subtilis	*E. coli*	*K. pneumoniae*	*. S. aureus*	*A. niger*	*A. flavous*	*T. viride*	*C. albicans*
1.	3a	10	-	-	-	-	-	-	-	-
		25	6.0	6.2	6.7	-	-	-	-	6.9
		50	6.2	7.0	7.5	6.3	6.8	6.6	6.0	7.0
		100	7.5	7.2	7.9	7.2	7.6	7.8	6.2	6.5
2.	3b	10	6.2	6.5	6.0	6.7	-	-	6.0	-
		25	6.6	6.7	7.1	7.2	6.8	6.4	6.4	-
		50	6.9	6.9	7.0	7.5	6.1	7.0	7.3	6.4
		100	7	6.1	7.1	7.5	6.8	7.5	7.1	6.8
3.	3c	10	-	-	-	-	6.4	6.8	6.6	-
		25	-	-	-	-	6.1	7.0	7	-
		50	7.0	-	6.2	6.1	-	7.5	7.1	7.0
		100	6.8	6.2	6.1	7.7	7.2	7.4	6.7	7
4.	3d	10	6.1	7	6.6	6.7	-	-	-	-
		25	6.4	7	6.7	6.9	-	6.6	-	6.2
		50	6.8	7.3	6.7	6.0	6.1	7.2	7.0	-
		100	6.9	7.3	7.2	6.5	6.6	7	7.7	7.3
		10	-	-	-	-	6.1	6.2	6.0	-

5.	3e	25	-	-	-	-	6.5	6.7	6.1	6.2
		50	-	6.4	-	-	6.4	6.9	6.7	-
		100	6.0	6.7	6.8	7	6.8	6.2	6.1	6.9
6.	3f	10	6.8	-	-	-	-	-	-	-
		25	6.7	7	6.2	6.1	6.2	6.9	-	6.5
		50	6.6	7	6.9	-	7.2	7.1	6.2	6.5
		100	6.9	7.1	7.2	-	7.4	7.1	7.3	6.4
7.	3g	10	6.0	6.2	6.1	6.3	-	-	-	-
		25	6.4	6.7	7.2	7.3	-	-	6.8	6.5
		50	6.7	6.8	7.1	7.2	7.5	-	6.5	6.5
		100	6.5	6.5	7.2	7.7	7.6	-	6.9	7.1
8.	3h	10	-	-	-	-	6.1	6.5	6.6	-
		25	-	-	-	6.2	6.7	6.3	6.7	6.3
		50	6.7	6.9	-	-	7.2	7.6	6.7	6.0
		100	6.8	6.7	-	-	7.6	7.7	7.4	6.9
Std. drug		Streptomycin	25	21	12	15	-	-	-	-
		Nystatin	-	-	-	-	19	20	19.5	17.5

- Zone of inhibition was measured in 6mm.against various test organism.

CONCLUSIONS

From the consequences of antimicrobial screening of whole synthesized derivatives(3a-3h) as revealed Table-1 that a good number of heterocyclic derivatives displayed modest activity against all the organism used. Among all the synthesized heterocyclic derivatives substituted by groups 2-nitro,3-chloro,4-chloro,2-methoxy and 4-methoxy group have demonstrated promising activity against preferred bacteria and fungi.

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