DOI:10.7598/cst2016.1190
ISSN:2278-3458

Chemical Science Transactions
2016, **5(2),** 305-310

RESEARCH ARTICLE

Conventional Synthesis, *In Vitro* Antimicrobial Activity and Calculation of Pharmacokinetic Properties of Thioether Derivatives of Quinoxaline

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Received 13 December 2015 / Accepted 11 January 2016

Abstract: Different thioether derivatives of quinoxaline moiety have been synthesized by conventional method. All the prepared compounds were analyzed by IR and NMR spectral analysis followed by antimicrobial screening using disk diffusion (Kirby Baeur) method against pathogenic bacteria and fungi. Ciprofloxacin and fluconazole were used as a standard drug for the study. Among them compound **3i** shows better activity in comparison with standard.

Keywords: Quinoxaline, Antimicrobial activity, Pharmacokinetic property

Introduction

Heterocyclic compounds symbolize imperative set of biologically active dynamic molecules[1]. Among the diverse classes of nitrogen having heterocyclic compounds, quinoxaline derivatives are the essential components of numerous pharmacologically active compounds[2-7]. Quinoxaline exhibit a wide variety of biological activity[8] which has made them advantage structures in combinatorial drug discovery libraries[9] quinoxaline and its derivatives are very important part of numerous bioactive molecules which locate function as antimicrobial[10], anticancerous[11], antidepressant[12,13] antitubercular[14] anticonvulsant[15], analgesic[16], anti-inflammatory[17]anti-platelet[18], anti-viral[19], anti-tumoral[20] and anti-malaria[21] activities.

Quinoxaline ring is a part of diverse antibiotics, for instance Hinomycin, Levomycin and actinoleutin[22,23]. The quinoxaline is exemplified as a bioesters of quinoline, naphthalene, benzothiophene and other aromatic ring for example pyridine and pyrazine. It is one of the most significant modules of known antagonists of amino propanoic acid (AMPA). The quinoxaline moiety is too present in peptide antibiotics. Quinoxaline derivatives are double nitrogen containing heterocyclic compounds which have biological consequence.

Experimental

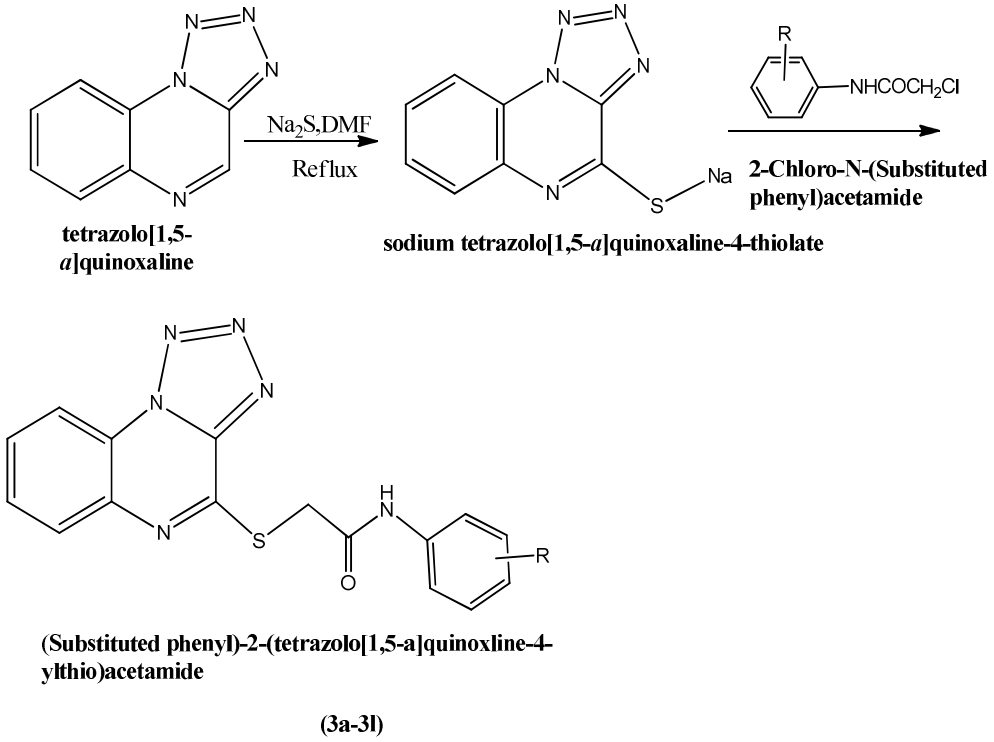
The entire chemicals and reagents in latest study were of AR grade and acquired from Merk(India). The reactions were observed by thin layer chromatography(TLC) on Merk pre-coated silica GF254 plates and envisaged under UV-chamber.Melting points (uncorrected) were concluded by open capillary tubes method. IR spectra (λ_{max} in cm^{-1}) were accomplished on a Shimadzu FTIR 8300S spectrophotometer with KBr pellets. ^1H NMR spectra were verified on a Bruker Avance II 400NMR spectrometer instrument with DMSO as solvent (chemical shift in ppm) by means of TMS as the internal standard. The elemental analysis (C, H, N) of the synthesized compounds were performed on thermo scientific (FLASH 2000) CHN Elemental Analyser. This is microprocessor based instrument which determines the CHN Analyzer percentages of C, H and N with an accuracy of 0.3%.

*Synthesis of Compound **3a-3h***

The different thioether derivatives of (substituted phenyl)-2-(tetrazolo [1, 5-a] quinoxaline-4-ylthio) acetamide (**3a-3h**) were synthesized (Scheme 1), characterized by spectral analysis as per literature method[24].

Results and Discussion

TPSA topological polar surface area is a tool for prediction of drug transport properties. TPSA was used to calculate the percentage of absorption (% ABS) by the following equation %ABS=109±0.345xTPSA. A computional study for prediction of ADME properties of all the compounds presented in Table 1.



Scheme 1. Synthetic route for the preparation of compounds

Table 1. Pharmacokinetic parameters important for good oral bioavailability of title compounds **(3a-3l)**

Compound	R	%ABS	Volume	TPSA	NROTB	HBA	HBD	LogP	MW	Lipinski's Violation
Rule		–	–	–	–	<10	<5	≤5	<500	≤1
3a	2-NO_2	63.838	301.827	130.905	5	10	1	2.662	381.377	0
3b	3-NO_2	63.838	301.827	130.905	5	10	1	2.686	381.377	0
3c	3-Cl	79.648	292.029	85.081	4	7	1	3.405	370.825	0
3d	4-Cl	79.648	292.029	85.081	4	7	1	3.429	370.825	0
3e	2-CH_3	79.648	295.054	85.081	4	7	1	3.152	350.407	0
3f	4-CH_3	79.648	295.054	85.081	4	7	1	3.2	350.407	0
3g	2-OCH_3	76.462	304.039	94.315	5	8	1	2.76	366.406	0
3h	4-OCH_3	76.462	366.406	94.315	5	8	1	2.808	366.406	0
3i	2-Cl	79.647	292.03	85.08	4	7	1	3.38	370.82	0
3j	3-Cl,4-F	79.647	296.96	85.08	4	7	1	3.52	388.81	0
3k	2,3-CH_3	79.648	305.56	85.08	4	7	1	4.01	405.27	0
3l	4-Br	79.648	296.379	85.081	4	7	1	3.56	415.276	0

%ABS:Percentage of absorption; TPSA: Topological polar surface area; NROTB: Number of rotatable bonds; MW: Molecular weight; LogP: Logarithm of compound partition coefficient between n-octanol and water; HBA: Number of hydrogen bond donors; HBD: Number of hydrogen bond acceptors

*Synthesis of N-(Substituted phenyl)-2-(tetrazolo [1,5-]quinoxaline-4-ylthio) acetamide-**3(i-l)***

Equimolar amount of sodium tetrazolo[1,5-a]quinoxaline-4-thiolate(0.01) and various 2-chloro-*N*-(Substituted phenyl)-acetamides (0.01) were added in DMF and heated under reflux for 8-10 h. The purity of the compounds was checked by TLC with toluene: acetone 8:2 as mobile phase. The mixture was kept at room temperature and relocated into ice chilled water. The solid was separated out by filteration, rinsed with water and dried out, further purified through recrystallization from ethanol.

*N-(2-Chlorophenyl)-2-(tetrazolo[1,5-]quinoxaline-4-ylthio)acetamide (**3i**)*

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-Chloro-4-fluorophenyl)-2-(tetrazolo[1,5-a]quinoxaline-4-ylthio) acetamide (**3j**)*

Elemental analysis%found C 50.39,H 2.91,N 25.71 Cal 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-CH2,), 1040(C-Cl) aryl chloride and 660(CH_2-S). ^{1}H NMR(DMSO-d6, 400 MHZ ppm) 2.637(s,3H,CH_3),4370(s,2H,CH_2),7.068-8.022(m,8H,Ar-H) and 9.648(s,1H,N-H).

*N-(2,3-Dimethylphenyl)-2-(tetrazolo[1,5-a]quinoxaline-4-ylthio)acetamide (**3k**)*

Elemental analysis % found C 51.82,H 2.99,N 22.66,Cal C 51.75,H 2.87,N 22.58, FT-IR

(KBr) in cm^{-1} 324 0(NH), 3050(C-H), 1600(C=N), 1030(C-Cl), 640(CH_2-S) ^{1}H NMR (DMSO-d6, 400 MHZ ppm) 2.745(s,3H,CH_3)4.442(s,2H,CH_3),9.166(s,1H,N-H).

*N-(4-Bromophenyl)-2-(tetrazolo[1,5-a]quinoxaline-4-ylthio)acetamide (**3l**)*

Elemental analysis % found C 51.82,H 2.99,N 22.66,Cal 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-(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).

Antimicrobial activity

The purified derivatives were screened for their antimicrobial activity by means of disc diffusion (Kirby Bauer) technique on some bacteria and fungus such as *Bacillus subtilis, Escherichia coli, Klebsiella pneumoniae* and *Staphylococcus aureus* and antifungal activity *against, Aspergillus niger, Aspergillus flavus, Trichoderma viride & Candida albicans* by standard method by calculating zone of inhibition. Firstly we obtained dilution for their dissolving solvent, thus 10 mg purified sample dissolve into 10 mL methanol. 5 Dilutions were prepared to the 5 samples. The each dilution contains concentration of samples is 1 mg/mL for the antimicrobial study. Kirby Bauer filter paper disk method is used for antimicrobial study. In this test, a number of small, sterile filter paper disks of uniform size (6 mm) that have each been impregnated with a defined concentration of an antimicrobial agent are placed on the surface of an agar plate previously inoculated with a standard amount of the organism to be tested.

Table 2. Antimicrobial screening of the title compounds (**3a-3l**)

Compound Code	Concentrations in µg/mL	Antibacterial				Antifungal			
		B. Subtilis	*E. coli*	*K. pneumoniae*	*S. aureus*	*A.niger*	*A.flavus*	*T.viride*	*C.albicans*
	1	22	20	19	18	21.7	23.5	22	21
	0.5	17	13	11	14	12.6	17.6	14	-
3i	0.25	13	12	11	12	11.5	13	12	12.9
	0.125	8	7	6	7.2	7.5	10.5	11	6.9
	0.0625	0	1	2	2.1	2	2	2.1	-
	1	20.6	19.5	17.9	16.8	22.6	15	14.9	17.4
	0.5	16.8	14.8	-	17	16.4	11	13	11
3j	0.25	13.7	-	12.8	-	-	10	11	12.8
	0.125	7.9	9.8	-	10.7	9.8	8.9	-	6.8
	0.0625	1.9	1.2	1.4	1.4	1.3	-	1.1	-
	1	16	17	16.9	12	18.9	14	14.6	17.1
	0.5	15	13	16.7	-	15.4	-	11.9	12
3k	0.25	13	15	12.4	10.4	13.7	9.3	10.8	10
	0.125	7.5	-	6.8	5.5	8.8	7.7	-	6.6
	0.0625	1.2	1	1.2	1.5	-	-	1.1	-
	1	18.6	18.9	16.8	17.8	19.1	15	21.6	16.7
	0.5	16.3	12.6	15.5	16.9	15.9	13.7	14	12.8
3l	0.25	12.5	6.3	-	8.5	13.8	5.6	8.7	11.9
	0.125	7.2	9	8.6	10.5	7.6	4.5	-	6.4
	0.0625	1.2	-	1.1	1.4	1.3	-	1.1	-

Conclusion

In the present investigation *N*-(Substituted phenyl)-2-(tetrazolo[1,5-a]quinoxaline-4-ylthio) acetamide **3(i-l)** have been synthesized and characterized by spectral analysis. They all were screened preliminary antimicrobial activity. The electronic factors exerted by the substituted and the hydrophobic nature of phenyl nucleus in the title compounds influenced the activity. In this paper Lipinski's rule of five were calculated. This rule is widely used as a filter for drug like properties. So, none of the compounds violated Lipinski's parameter making them potentially promising agents for antimicrobial therapy.

Acknowledgement

The authors acknowledge thanks to, Sophisticated Instrument facility Division(SAIF), for providing elemental analysis and NMR spectral data.Authors also admit their thankfulness to Head Department of Chemistry Dr.H.S.Gour University, Sagar for providing I.R. other necessary facilities and also thankful to scan laboratory Bhopal for providing antimicrobial data.

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